nature medicine

Supplementary information

https://doi.org/10.1038/s41591-026-04559-4

Oral KRAS G12D inhibitor GFH375 for previously treated advanced solid tumors with *KRAS*^{G12D} mutations: a phase 1 trial

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Supplementary Table 1 All treatment-emergent adverse events by dose level

PT term, n (%)	100 mg QD (N = 1)	200 mg QD (N = 1)	300 mg BID (N = 3)	400 mg QD (N = 29)	600 mg QD (N = 29)	750 mg QD (N = 8)	900 mg QD (N = 3)	Total (N =74)
Nausea	1 (100)	0	2 (66.7)	20 (69.0)	23 (79.3)	7 (87.5)	1 (33.3)	54 (73.0)
Anemia	0	1 (100)	1 (33.3)	20 (69.0)	22 (75.9)	4 (50.0)	3 (100)	51 (68.9)
Vomiting	0	0	3 (100)	21 (72.4)	17 (58.6)	8 (100)	1 (33.3)	50 (67.6)
Diarrhea	0	1 (100)	2 (66.7)	18 (62.1)	20 (69.0)	7 (87.5)	2 (66.7)	50 (67.6)
Aspartate aminotransferase increased	1 (100)	0	2 (66.7)	13 (44.8)	16 (55.2)	5 (62.5)	0	37 (50.0)
Hypoalbuminemia	0	0	1 (33.3)	12 (41.4)	16 (55.2)	3 (37.5)	2 (66.7)	34 (45.9)
Decreased appetite	0	0	2 (66.7)	15 (51.7)	10 (34.5)	4 (50.0)	2 (66.7)	33 (44.6)
Asthenia	0	0	3 (100)	10 (34.5)	12 (41.4)	2 (25.0)	1 (33.3)	28 (37.8)
Neutrophil count decreased	0	0	1 (33.3)	10 (34.5)	12 (41.4)	4 (50.0)	0	27 (36.5)
Alanine aminotransferase increased	1 (100)	0	1 (33.3)	9 (31.0)	12 (41.4)	4 (50.0)	0	27 (36.5)
White blood cell count decreased	0	0	1 (33.3)	9 (31.0)	11 (37.9)	5 (62.5)	0	26 (35.1)
Hyponatremia	0	0	2 (66.7)	8 (27.6)	11 (37.9)	1 (12.5)	1 (33.3)	23 (31.1)
Weight decreased	0	0	0	8 (27.6)	7 (24.1)	2 (25.0)	1 (33.3)	18 (24.3)
Proteinuria	0	0	1 (33.3)	6 (20.7)	7 (24.1)	3 (37.5)	1 (33.3)	18 (24.3)
Platelet count decreased	0	0	0	7 (24.1)	7 (24.1)	1 (12.5)	0	15 (20.3)
Dizziness	0	1 (100)	1 (33.3)	3 (10.3)	7 (24.1)	3 (37.5)	0	15 (20.3)
Hypokalemia	0	0	0	7 (24.1)	5 (17.2)	1 (12.5)	1 (33.3)	14 (18.9)
Constipation	0	0	0	8 (27.6)	6 (20.7)	0	0	14 (18.9)
Blood lactate dehydrogenase increased	1 (100)	1 (100)	0	4 (13.8)	5 (17.2)	2 (25.0)	0	13 (17.6)
Blood alkaline phosphatase increased	0	0	2 (66.7)	5 (17.2)	5 (17.2)	1 (12.5)	0	13 (17.6)
Blood bilirubin increased	1 (100)	0	1 (33.3)	4 (13.8)	6 (20.7)	1 (12.5)	0	13 (17.6)
Hypertriglyceridemia	0	0	1 (33.3)	6 (20.7)	6 (20.7)	0	0	13 (17.6)

Gamma-glutamyl transferase increased	1 (100)	0	1 (33.3)	6 (20.7)	2 (6.9)	3 (37.5)	0	13 (17.6)
Fibrin D dimer increased	0	1 (100)	2 (66.7)	4 (13.8)	2 (6.9)	1 (12.5)	0	10 (13.5)
Urinary tract infection	1 (100)	0	1 (33.3)	4 (13.8)	4 (13.8)	0	0	10 (13.5)
Pyrexia	0	0	0	4 (13.8)	5 (17.2)	1 (12.5)	0	10 (13.5)
Hypocalcemia	0	0	0	2 (6.9)	7 (24.1)	1 (12.5)	0	10 (13.5)
Supraventricular extrasystoles	0	0	1 (33.3)	4 (13.8)	3 (10.3)	1 (12.5)	0	9 (12.2)
Hyperglycemia	0	0	0	4 (13.8)	3 (10.3)	1 (12.5)	0	8 (10.8)
Abdominal pain	0	0	2 (66.7)	2 (6.9)	3 (10.3)	0	1 (33.3)	8 (10.8)
Abdominal discomfort	0	0	0	3 (10.3)	4 (13.8)	1 (12.5)	0	8 (10.8)
Sinus tachycardia	0	0	1 (33.3)	4 (13.8)	3 (10.3)	0	0	8 (10.8)
Sinus bradycardia	0	1 (100)	1 (33.3)	1 (3.4)	4 (13.8)	1 (12.5)	0	8 (10.8)
Hypochloremia	0	0	1 (33.3)	3 (10.3)	3 (10.3)	0	1 (33.3)	8 (10.8)
C-reactive protein increased	0	0	0	4 (13.8)	4 (13.8)	0	0	8 (10.8)
Blood creatine phosphokinase increased	0	0	0	3 (10.3)	3 (10.3)	1 (12.5)	0	7 (9.5)
Upper respiratory tract infection	0	0	1 (33.3)	2 (6.9)	4 (13.8)	0	0	7 (9.5)
Hyperlipidemia	1 (100)	0	0	5 (17.2)	0	1 (12.5)	0	7 (9.5)
Abdominal distension	0	0	0	2 (6.9)	4 (13.8)	0	1 (33.3)	7 (9.5)
Amylase increased	0	0	2 (66.7)	2 (6.9)	2 (6.9)	1 (12.5)	0	7 (9.5)
Lymphocyte count decreased	0	0	0	1 (3.4)	4 (13.8)	1 (12.5)	0	6 (8.1)
Bilirubin conjugated increased	1 (100)	0	0	3 (10.3)	2 (6.9)	0	0	6 (8.1)
Hyperuricemia	0	0	1 (33.3)	2 (6.9)	2 (6.9)	1 (12.5)	0	6 (8.1)
Hypercholesterolemia	0	0	1 (33.3)	3 (10.3)	2 (6.9)	0	0	6 (8.1)
Back pain	0	0	0	2 (6.9)	3 (10.3)	1 (12.5)	0	6 (8.1)
Atrioventricular block first degree	0	1 (100)	0	1 (3.4)	2 (6.9)	1 (12.5)	0	5 (6.8)
Hematuria	0	0	0	2 (6.9)	1 (3.4)	2 (25.0)	0	5 (6.8)

Blood creatine phosphokinase MB increased	0	0	0	1 (3.4)	4 (13.8)	0	0	5 (6.8)
Blood creatinine increased	0	1 (100)	0	2 (6.9)	2 (6.9)	0	0	5 (6.8)
Chest discomfort	0	0	0	1 (3.4)	3 (10.3)	1 (12.5)	0	5 (6.8)
Electrocardiogram QT prolonged	0	1 (100)	1 (33.3)	2 (6.9)	0	1 (12.5)	0	5 (6.8)
Dyspepsia	0	0	0	2 (6.9)	2 (6.9)	1 (12.5)	0	5 (6.8)
Gastroesophageal reflux disease	0	0	0	1 (3.4)	2 (6.9)	2 (25.0)	0	5 (6.8)
Hepatic function abnormal	0	0	0	3 (10.3)	2 (6.9)	0	0	5 (6.8)
Lipase increased	0	0	2 (66.7)	2 (6.9)	0	0	0	4 (5.4)
Blood glucose increased	0	0	0	1 (3.4)	3 (10.3)	0	0	4 (5.4)
Electrocardiogram T wave abnormal	0	0	0	1 (3.4)	3 (10.3)	0	0	4 (5.4)
Ventricular extrasystoles	0	1 (100)	0	2 (6.9)	1 (3.4)	0	0	4 (5.4)
Pruritus	0	0	1 (33.3)	1 (3.4)	1 (3.4)	1 (12.5)	0	4 (5.4)
Rash	0	1 (100)	1 (33.3)	0	2 (6.9)	0	0	4 (5.4)
Cough	0	0	0	1 (3.4)	2 (6.9)	1 (12.5)	0	4 (5.4)
Ascites	0	0	0	1 (3.4)	3 (10.3)	0	0	4 (5.4)
Malignant neoplasm progression	0	0	0	1 (3.4)	3 (10.3)	0	0	4 (5.4)
White blood cell count increased	0	0	0	1 (3.4)	3 (10.3)	0	0	4 (5.4)
Blood urea increased	0	0	1 (33.3)	1 (3.4)	1 (3.4)	0	0	3 (4.1)
Electrocardiogram abnormal	0	0	0	0	2 (6.9)	1 (12.5)	0	3 (4.1)
Electrocardiogram ST-T change	0	0	0	0	2 (6.9)	1 (12.5)	0	3 (4.1)
Headache	0	0	0	1 (3.4)	1 (3.4)	1 (12.5)	0	3 (4.1)
Weight increased	0	0	1 (33.3)	1 (3.4)	1 (3.4)	0	0	3 (4.1)
Pain	0	0	1 (33.3)	2 (6.9)	0	0	0	3 (4.1)
Insomnia	0	0	0	1 (3.4)	1 (3.4)	1 (12.5)	0	3 (4.1)

Abdominal pain upper	0	0	0	0	2 (6.9)	1 (12.5)	0	3 (4.1)
Productive cough	0	0	0	1 (3.4)	2 (6.9)	0	0	3 (4.1)
Pneumonitis	0	0	0	2 (6.9)	0	1 (12.5)	0	3 (4.1)
Hypophosphatemia	0	0	0	1 (3.4)	2 (6.9)	0	0	3 (4.1)
Bile acids increased	1 (100)	0	0	1 (3.4)	1 (3.4)	0	0	3 (4.1)
Flatulence	0	0	0	2 (6.9)	1 (3.4)	0	0	3 (4.1)
Intestinal obstruction	0	0	0	2 (6.9)	0	1 (12.5)	0	3 (4.1)
Neutrophil count increased	0	0	0	1 (3.4)	1 (3.4)	0	0	2 (2.7)
Pain in extremity	0	0	1 (33.3)	1 (3.4)	0	0	0	2 (2.7)
Urticaria	0	0	0	1 (3.4)	1 (3.4)	0	0	2 (2.7)
Blood creatinine decreased	0	0	0	0	2 (6.9)	0	0	2 (2.7)
Pleural effusion	0	0	0	1 (3.4)	1 (3.4)	0	0	2 (2.7)
Palpitations	0	0	0	0	1 (3.4)	1 (12.5)	0	2 (2.7)
Taste disorder	0	0	0	0	2 (6.9)	0	0	2 (2.7)
Oedema peripheral	0	0	0	0	2 (6.9)	0	0	2 (2.7)
Dysphagia	0	0	0	2 (6.9)	0	0	0	2 (2.7)
Somnolence	0	1 (100)	0	0	0	1 (12.5)	0	2 (2.7)
Dry skin	0	0	0	0	2 (6.9)	0	0	2 (2.7)
Urine ketone body present	0	0	0	2 (6.9)	0	0	0	2 (2.7)
Glucose urine present	0	0	0	1 (3.4)	1 (3.4)	0	0	2 (2.7)
Urinary occult blood positive	0	0	1 (33.3)	0	1 (3.4)	0	0	2 (2.7)
Red blood cells urine positive	0	0	0	0	2 (6.9)	0	0	2 (2.7)
Protein urine present	0	0	0	2 (6.9)	0	0	0	2 (2.7)
Bilirubin urine present	0	0	0	2 (6.9)	0	0	0	2 (2.7)
White blood cells urine positive	0	0	0	1 (3.4)	1 (3.4)	0	0	2 (2.7)

Face oedema	0	0	0	0	0	2 (25.0)	0	2 (2.7)
Stomatitis	0	0	0	0	2 (6.9)	0	0	2 (2.7)
Hypothyroidism	0	0	0	1 (3.4)	1 (3.4)	0	0	2 (2.7)
Muscular weakness	0	0	0	0	1 (3.4)	1 (12.5)	0	2 (2.7)
Hypertension	0	0	0	0	2 (6.9)	0	0	2 (2.7)
Hyperkalemia	0	0	1 (33.3)	1 (3.4)	0	0	0	2 (2.7)
Hypercalcemia	1 (100)	0	0	1 (3.4)	0	0	0	2 (2.7)
Atrioventricular block	0	0	0	0	2 (6.9)	0	0	2 (2.7)
Hiccups	0	0	0	1 (3.4)	1 (3.4)	0	0	2 (2.7)
Hypomagnesaemia	0	0	0	1 (3.4)	1 (3.4)	0	0	2 (2.7)
Hypoproteinemia	0	0	0	0	2 (6.9)	0	0	2 (2.7)
Herpes zoster	1 (100)	0	0	0	0	1 (12.5)	0	2 (2.7)
Fecal occult blood positive	0	0	0	1 (3.4)	0	1 (12.5)	0	2 (2.7)
Epistaxis	0	0	0	1 (3.4)	1 (3.4)	0	0	2 (2.7)
Alpha hydroxybutyrate dehydrogenase increased	0	0	0	0	0	2 (25.0)	0	2 (2.7)
Left atrial enlargement	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Bundle branch block left	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Intervertebral disc protrusion	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Pain in extremity	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Mycoplasma infection	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Apolipoprotein A-I increased	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Syncope	0	0	1 (33.3)	0	0	0	0	1 (1.4)
Ecchymosis	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Malnutrition	0	0	0	0	0	1 (12.5)	0	1 (1.4)

Vaginal hemorrhage	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Pharyngitis	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Eye infection	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Gingival swelling	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Gingival bleeding	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Toothache	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Hypercoagulation	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Oxygen saturation decreased	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Blood iron decreased	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Chest pain	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Heart rate increased	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Electrocardiogram T wave amplitude decreased	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Electrocardiogram Q waves	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Electrocardiogram PR shortened	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Electrocardiogram PR prolongation	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Abdominal pain lower	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Temperature regulation disorder	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Temperature intolerance	0	0	1 (33.3)	0	0	0	0	1 (1.4)
Gastrointestinal hemorrhage	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Peripheral nerve injury	0	0	1 (33.3)	0	0	0	0	1 (1.4)
Peripheral artery stenosis	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Peripheral arterial occlusive disease	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Oedema	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Infusion site pain	0	0	0	0	1 (3.4)	0	0	1 (1.4)

Upper gastrointestinal hemorrhage	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Wound complication	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Ligament sprain	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Hypoxia	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Dysuria	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Rash pustular	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Urobilinogen urine increased	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Cerebrovascular accident	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Chronic gastritis	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Influenza	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Influenza like illness	0	0	0	0	0	0	1 (33.3)	1 (1.4)
Lymphocyte count increased	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Appendicitis	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Ulcerative keratitis	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Oropharyngeal pain	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Hypoaesthesia oral	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Dry mouth	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Neck pain	0	0	0	0	0	0	1 (33.3)	1 (1.4)
Conjunctivitis	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Conjunctival hemorrhage	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Procalcitonin increased	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Rotator cuff syndrome	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Myalgia	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Troponin T increased	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Ankle fracture	0	0	0	1 (3.4)	0	0	0	1 (1.4)

Dyspnea	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Laryngeal pain	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Chills	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Arteriosclerosis coronary artery	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Periarthritis	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Arthralgia	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Glutathione reductase activity increased	0	0	0	1 (3.4)	0	0	0	1 (1.4)
High density lipoprotein decreased	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Septic shock	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Pneumonia	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Hypoaesthesia	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Hepatic pain	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Abdominal infection	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Pulmonary embolism	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Noninfective gingivitis	0	0	0	0	0	1 (12.5)	0	1 (1.4)
Atrial tachycardia	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Febrile infection	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Sinoatrial block	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Chilblains	0	0	1 (33.3)	0	0	0	0	1 (1.4)
Electrolyte imbalance	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Sacral pain	0	0	1 (33.3)	0	0	0	0	1 (1.4)
Hypotension	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Cholestasis	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Bile duct stone	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Biliary tract infection	0	0	0	1 (3.4)	0	0	0	1 (1.4)

Dermatitis acneiform	0	0	0	0	1 (3.4)	0	0	1 (1.4)
Enteritis	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Aeromonas infection	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Hematochezia	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Nasopharyngitis	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Nasal obstruction	0	0	1 (33.3)	0	0	0	0	1 (1.4)
Infected fistula	0	0	0	1 (3.4)	0	0	0	1 (1.4)
Cancer pain	0	0	0	0	1 (3.4)	0	0	1 (1.4)
N-terminal prohormone brain natriuretic peptide increased	0	0	0	1 (3.4)	0	0	0	1 (1.4)
COVID-19	0	0	0	1 (3.4)	0	0	0	1 (1.4)

Supplementary Table 2 Ethics oversight and enrollment

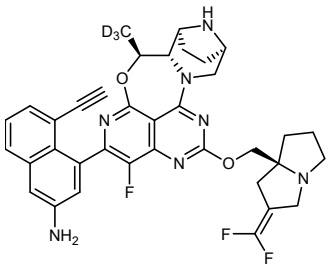
The protocol and protocol amendment was approved by the investigation sites and independent ethics committees from the list below.

Site No.	Site name	Institutional review board/ Independent ethics committee name	Principal Investigators	Enrollment
01	Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine	Ethics Committee of Shanghai Chest Hospital	Shun Lu	10
06	Zhejiang Cancer Hospital	Medical Ethics Committee of Zhejiang Cancer Hospital	Zhengbo Song	9
02	Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University	Medical Ethics Committee of Hunan Cancer Hospital	Lin Wu	8
03	National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College	Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College	Aiping Zhou	8
07	Sun Yat-sen Memorial Hospital	Medical Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University	Zhihua Li	6
09	The First Affiliated Hospital of Zhengzhou University	The Ethics Committee of Scientific Research and Clinical Trial, The First Affiliated Hospital of Zhengzhou University	Hong Zong	4
10	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	Medical Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	Heshui Wu	4
14	Shandong Cancer Hospital, Shandong First Medical University	Ethics Committee of Shandong Cancer Hospital, Shandong First Medical University	Zuoxing Niu/ Yuping Sun	4
19	The First Affiliated Hospital of Nanjing Medical	Ethics Committee of The First Affiliated Hospital of	Lingjun Zhu	4

	University	Nanjing Medical University		
20	Harbin Medical University Cancer Hospital	Ethics Committee of Harbin Medical University Cancer Hospital	Zhiwei Li	4
16	The Sixth Affiliated Hospital, Sun Yat-sen University	Ethics committee of The Sixth Affiliated hospital, Sun Yat-sen University	Yanhong Deng	4
04	The Second Affiliated Hospital, Zhejiang University School of Medicine	Human Research Ethics Committee of The Second Affiliated Hospital, Zhejiang University School of Medicine	Ying Yuan	3
05	The First Hospital of China Medical University	Clinical Research Sub-Committee of the Medical Ethics Committee of The First Affiliated Hospital of China Medical University	Xiujuan Qu	2
13	Peking Union Medical College Hospital/Chinese Academy of Medical Sciences	Drug Clinical Trial Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences	Haitao Zhao	2
12	The First Affiliated Hospital of Anhui Medical University	Clinical Research Ethics Committee of The First Affiliated Hospital of Anhui Medical University	Yingying Du	2

Supplementary Table 3 Protocol amendments

Version Number	Version Date	Summary of Protocol Amendments
1.0	March 15, 2024	Not applicable
1.1	April 08, 2023	Primary reason for amendment: To clarify the requirements for prior anti-tumor therapy for participants enrolled in Phase I to avoid ambiguity. • Updated inclusion criterion #3 regarding prior anti-tumor therapy for participants enrolled in Phase I: Either of the following criteria is met: 1) Disease progressed after standard of care and no other standard of care is available; or 2) standard of care has been confirmed to be ineffective, intolerable, or considered unsuitable.
1.2	September 13, 2024	Primary reason for amendment: To clarify the dose level of twice daily (BID) regimen in the original protocol. • Clarified the study design, operational procedures, and PK sampling related to BID regimen. • Update the definitions of DLT to be more operational. • Optimized some study operational procedures. • Corrected inconsistencies throughout the text.
1.3	November 18, 2024	Primary reason for amendment: Adjusted the Phase I protocol design, increased the number of participants for dose level backfilling. • Removed the Phase Ib expansion period. • Adjusted the maximum dose for QD. • Added ctDNA testing in the Phase I part. • Revised the GFH375 PK blood sampling time points. • Revised the list of prohibited medications in the appendix. • Corrected errors and adjusted inconsistencies.
2.0	January 24, 2025	Primary reason for amendment: Added the rationale for RP2D as completion the Phase I dose escalation part; further refined the inclusion/exclusion criteria for PDAC and NSCLC in Phase II and added Blinded Independent Central Review (BICR) assessment for efficacy evaluation. • Added the rationale for RP2D. • Further refined the inclusion/exclusion criteria for PDAC and NSCLC participants enrolled in Phase II. • Added BICR efficacy assessment to the primary endpoint analysis for PDAC and NSCLC enrolled in Phase II. • Increased the sample size for Phase II participants with PDAC and other advanced solid tumors. • Added an exploratory objective for PDAC participants enrolled in Phase II to explore the relationship between CA19-9 and treatment response.



GFH375

Supplementary Fig. 1 | Structure formula of GFH375.

Clinical Study Protocol

Study Title:	An Open-label, Phase I/II Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GFH375 in Patients with Advanced Solid Tumors with KRAS G12D Mutation
Protocol Number:	GFH375X1101
Version Number and Version Date:	Version 2.0 / January 24, 2025
Product Name:	GFH375
Study Phase:	Phase I/II
Sponsor:	GenFleet Therapeutics (Shanghai) Inc.
Sponsor Contact:	Huaqiang Zhu, Vice President of Medical Science Tel: 15601727272 Email: hqzhu@genfleet.com

Confidentiality Statement

The information contained in this clinical study protocol is confidential and is the property of GenFleet Therapeutics (Shanghai) Inc. It may not be disclosed to any third party (group or individual) without prior written permission. If you have this protocol without prior authorization, please contact GenFleet Therapeutics (Shanghai) Inc. immediately and return the protocol and any copies to the company.

Sponsor Signature Page

Study Title: An Open-label, Phase I/II Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GFH375 in Patients with Advanced Solid Tumors with KRAS G12D Mutation

Protocol Number: GFH375X1101

Position	Name	Signature (Printed)	Date
Vice President of Medical Science	Huaqiang Zhu	Huaqiang Zhu	Jan. 24, 2025

Investigator Signature Page

Study Title: An Open-label, Phase I/II Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GFH375 in Patients with Advanced Solid Tumors with KRAS G12D Mutation

Protocol Number: GFH375X1101

By signing this protocol signature page, the investigator confirms and agrees to the following:

I have read the above study protocol and its appendices. I have fully discussed the contents of this protocol with the sponsor, GenFleet Therapeutics (Shanghai) Inc. I agree to conduct the study in accordance with this study protocol and to fulfill the relevant responsibilities in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP), local regulations, and other applicable regulations. I agree to ensure that all staff involved in this study are aware of their obligations in fulfilling the above commitments.

This document contains confidential information and shall not be disclosed to anyone other than those directly involved in the conduct of the study or in ethical/regulatory review, without the written authorization of the sponsor.

I have read the entire content of this study protocol and guarantee to conduct this study as required:

Investigator's Signature: _____ Date: _____

Printed Name: _____

Investigator's Title: _____

Contact Number: _____

Site Name/Address: _____

_____

_____

Summary of Protocol Amendments

Version Number	Version Date	Summary of Protocol Amendments
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1.2	September 13, 2024	Main reason for amendment: To clarify the dose exploration of twice daily (BID) dosing regimen in the original protocol. • Clarified the study design, operational procedures, and PK sampling related to BID dose regimen. • Made the definitions of individual DLT entries more operational. • Optimized some study operational procedures. • Corrected inconsistencies throughout the text.
1.3	November 18, 2024	Main reason for amendment: Adjusted the Phase I protocol design, increased the number of participants for dose level backfilling. • Removed the Phase Ib expansion period. • Adjusted the maximum dose for QD. • Added ctDNA testing in the Phase I stage. • Revised the GFH375 PK blood sampling time points. • Revised the list of prohibited medications in the appendix. • Corrected errors and adjusted inconsistencies.
2.0	January 24, 2025	Main reason for amendment: Completed the Phase I dose escalation part, added the rationale for RP2D selection; further refined the inclusion/exclusion criteria for PDAC and NSCLC in Phase II and added Blinded Independent Central Review (BICR) assessment for efficacy evaluation. • Added the rationale for RP2D selection. • Further refined the inclusion/exclusion criteria for PDAC and NSCLC participants enrolled in Phase II. • Added BICR efficacy assessment to the primary endpoint analysis for PDAC and NSCLC enrolled in Phase II. • Increased the sample size for Phase II participants with PDAC and other advanced solid tumors. • Added an exploratory objective for PDAC participants enrolled in Phase II to explore the relationship between CA19-9 and treatment response.

Protocol Synopsis

<table>
<tr><td>Protocol Number:</td><td>GFH375X1101</td></tr>
<tr><td>Sponsor</td><td>GenFleet Therapeutics (Shanghai) Inc.</td></tr>
<tr><td>Investigational Product</td><td>Code: GFH375</td></tr>
<tr><td>Study Title</td><td>An Open-label, Phase I/II Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GFH375 in Patients with Advanced Solid Tumors with KRAS G12D Mutation</td></tr>
<tr><td>Brief Title</td><td>A Phase I/II Study to Evaluate GFH375 in Patients with Solid Tumors with KRAS G12D Mutation</td></tr>
<tr><td>Phase</td><td>Phase I/II</td></tr>
<tr><td>Version Number/Date</td><td>V2.0 / January 24, 2025</td></tr>
<tr><td>Study Duration</td><td>Approximately 48 months</td></tr>
<tr><td>Study Objectives and Endpoints</td><td>This is a Phase I/II study.
Phase I objectives and endpoints include:
<table>
<tr><th>Study Objectives</th><th>Study Endpoints</th></tr>
<tr><td>Primary Objectives</td><td>Primary Endpoints</td></tr>
<tr><td>To evaluate the safety and tolerability of GFH375 in patients with advanced solid tumors with KRAS G12D mutation</td><td>• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs); changes in vital signs, electrocardiogram (ECG), and laboratory tests</td></tr>
<tr><td>• To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of GFH375</td><td>• Incidence of dose-limiting toxicity (DLT) events</td></tr>
<tr><td>Secondary Objectives</td><td>Secondary Endpoints</td></tr>
<tr><td>• To evaluate the pharmacokinetic (PK) characteristics of GFH375 in patients with advanced solid tumors with KRAS G12D mutation.</td><td>• Plasma concentrations and PK parameters of GFH375, including but not limited to C_{max}, T_{max}, AUC, $t_{1/2}$, CL/F, V_z/F, C_{trough}</td></tr>
<tr><td>• To evaluate the preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation</td><td>• Objective response rate (ORR), duration of response (DoR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) as assessed according to Response</td></tr>
</table></td></tr>
</table>

	Evaluation Criteria in Solid Tumors (RECIST) 1.1.
Exploratory Objective	**Exploratory Endpoint**
• To explore the molecular mechanisms related to treatment sensitivity or drug resistance	• Mutation analysis of circulating tumor DNA (ctDNA) in blood at baseline and at the end of treatment
Phase II objectives and endpoints:	
Study Objectives	**Study Endpoints**
Primary Objectives	**Primary Endpoints**
• To evaluate the efficacy of GFH375 in patients with advanced non-small cell lung cancer (NSCLC), advanced ductal adenocarcinoma of pancreas (PDAC), advanced colorectal cancer (CRC), and other solid tumors with KRAS G12D mutation.	• ORR as assessed by RECIST 1.1
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation using other efficacy endpoints	• Best overall response (BOR), DoR, DCR, TTR, and PFS as assessed by RECIST 1.1 • OS
• To evaluate the safety of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation	• Incidence and severity of AEs and SAEs; changes in vital signs, ECG, and laboratory tests
• To evaluate the PK characteristics of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation	• Plasma concentrations of GFH375
Exploratory Objective	**Exploratory Endpoint**
• To explore the molecular mechanisms related to	• Mutation analysis of circulating tumor DNA (ctDNA) in blood at

	treatment sensitivity or drug resistance	baseline and at the end of treatment
	• For PDAC participants: Relationship between carbohydrate antigen 19-9 (CA19-9) and treatment response	• For PDAC participants: Change from baseline in serum CA19-9
Study Background	The RAS family is responsible for regulating signaling pathways related to cell growth, migration, survival, and differentiation. RAS proteins typically switch between GTP- and GDP-bound conformations, corresponding to the "on" and "off" states of the kinase, respectively. In various malignant tumors, oncogenic mutations in RAS lead to the inhibition of GTP hydrolysis, leaving the kinase in a constitutively active state, which results in malignant cell proliferation and changes in biological behavior. KRAS is the most common mutation type in the RAS family, accounting for approximately 90% of ductal adenocarcinomas of the pancreas, 50% of colorectal cancers, and 30% of lung adenocarcinomas. Therefore, KRAS is considered a driver oncogene for the development of many malignant tumors and for tumor metastasis. KRAS G12D is one of the most common KRAS mutation types. It is estimated that in lung adenocarcinoma, data from the United States show that the G12D mutation accounts for 4.9%, while a large-sample analysis of domestic NSCLC patients shows a KRAS G12D mutation frequency of approximately 2.2%. In pancreatic carcinoma, approximately 37% of patients carry the KRAS G12D mutation, suggesting the importance of this mutant allele at the population level in patients with pancreatic carcinoma. Preclinical studies have confirmed in multiple PDAC xenograft transplant models that KRAS G12D acts as a persistent oncogenic driver in PDAC, and KRAS G12D inhibitors have shown significant anti-tumor activity in PDAC models. In colorectal cancer, the KRAS mutation rate is approximately 40%, with KRAS G12D accounting for about 28%. In addition, studies have shown that KRAS mutation is a common factor for acquired drug resistance to cetuximab in colorectal cancer, and acquired KRAS G12D mutations have been observed in metastatic CRC tissue samples after treatment with cetuximab (or in combination with chemotherapy). Currently, several selective KRAS G12D inhibitors (such as MTRX1133 and HRS-4642) have entered clinical development, administered either orally or intravenously, but no therapy specifically targeting KRAS G12D-mutated tumors has been approved. Patients with advanced NSCLC, PDAC, CRC, and other solid tumors carrying the KRAS G12D mutation are usually first treated with chemotherapy, immunotherapy, or anti-angiogenic drugs in combination. After treatment failure with standard of care, there is a lack of effective treatment options. For example, in advanced NSCLC, although patients positive for driver genes such as EGFR and ALK can choose targeted therapies and achieve good efficacy, KRAS G12D rarely co-exists with these driver genes. Therefore, chemotherapy, such as docetaxel, remains the main treatment after failure of standard systemic therapy, with recently reported ORRs of 7.1-16.0% and a median PFS of 2.6-4.5 months. The Phase III NAPOLI-1 study, which enrolled patients with metastatic PDAC (mPDAC), showed that for mPDAC patients who had failed prior gemcitabine-based chemotherapy regimens, treatment with liposomal irinotecan in combination with 5-FU/LV (5-fluorouracil + leucovorin) resulted in significantly improved efficacy compared to those receiving only 5-FU/LV (5-fluorouracil + leucovorin): median overall survival (mOS) was 6.1 months (vs 4.2 months, HR 0.67), median PFS was 3.1 months (vs 1.5 months, HR 0.56), and ORR was 16% (vs 1%, $p < 0.0001$) . In other Phase II studies conducted in mPDAC participants who had received ≥ 1 line of therapy (most participants had received ≥ 2 lines of therapy), the reported ORR was 0%-10.7%. In CRC participants, TAS-102 +/- bevacizumab, regorafenib, and fruquintinib are common third-line treatment options, with an ORR of only 1-4%. Therefore, there is currently a lack of effective treatment methods for	

	NSCLC, PDAC, and CRC after failure of standard of care, representing a huge unmet clinical need. KRAS G12C inhibitors (sotorasib, adagrasib) have been approved for the indication of NSCLC, demonstrating good efficacy and safety in this patient population. Compared to other KRAS-mutated lung cancers, KRAS G12D mutation-positive tumors have different clinical, genomic, and immunological features. For example, in NSCLC, KRAS G12D mutation-positive status may be associated with low tumor mutation burden and low PD-(L)1 expression, often being "immune cold," which promotes tumor cell drug resistance to immunosuppressants. Clinically, separate studies are needed for these populations, and KRAS G12D inhibitors provide a great research opportunity that may bring potential benefits to these patients. GFH375 is a highly selective, oral, non-covalent small molecule inhibitor targeting the KRAS G12D mutation. In preclinical *in vitro* studies, GFH375 has shown potent inhibitory effects on KRAS-dependent signal transduction and cancer cell viability, and has demonstrated significant anti-tumor efficacy in animal models of KRAS G12D-mutated tumors. The above results support the further evaluation of the safety and efficacy of GFH375 in patients with advanced solid tumors carrying the KRAS G12D mutation.
Study Design	This is a study to evaluate the safety/tolerability, PK, and efficacy of GFH375 monotherapy in patients with advanced solid tumors with KRAS G12D mutation. The primary objective of the Phase I part is to evaluate the safety/tolerability, PK, and preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation, and to determine the MTD and/or RP2D of GFH375. The primary objective of the Phase II part is to evaluate the efficacy of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation. A Safety Monitoring Committee (SMC), composed of investigators and the sponsor, will be established during the study. For details, please refer to Chapter 10 and the SMC Charter for this study. **Phase I Part** According to the BOIN design, 3-6 participants will be enrolled in each dose cohort for treatment (except during accelerated titration). Additional participants may be enrolled if more dose levels or alternative dosing regimens need to be explored. After enrollment, participants will receive oral administration of GFH375, with each treatment cycle being 21 days. Participants will be enrolled into sequential dose-escalation cohorts, with a starting dose of 100 mg once daily (QD). A total of 7 or more dose levels are expected to be evaluated in the dose escalation part. The planned escalating doses are shown in the **table below**. The GFH375 dosing regimen will be comprehensively evaluated during dose escalation. If necessary, dose exploration with a twice daily (BID) dosing regimen will be conducted. Dose escalation can be conducted independently and in parallel for QD and BID dosing regimens. The first cycle after the first administration will serve as the DLT observation period. A DLT-evaluable case must meet one of the following two conditions: ▪ The participant experiences a DLT event, or ▪ The participant does not experience a DLT event and has received at least 15 days of the planned dosing of GFH375 in the first cycle. If no DLT event occurs, the participant will continue treatment, with dose adjustments permitted as allowed by this protocol, until progressive disease (PD), unacceptable toxicity, or discontinuation of study treatment for other reasons. If a participant experiences a DLT event during the DLT observation period, and if the investigator and sponsor assess that the participant can benefit from continuing treatment with GFH375, treatment with GFH375 will be resumed after the relevant adverse event (AE) has resolved. Refer to the corresponding section in the main text for the criteria for resumption of dosing. Participants enrolled in Phase I will undergo intensive PK sampling and have matching

ECGs collected with PK sampling to evaluate the PK characteristics and safety of GFH375. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks. Participants will return to the study site 30 (±3) days after the last study treatment for a safety follow-up, and will have survival follow-ups every 90 (±7) days thereafter. Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the Informed Consent Form (ICF), initiation of other anti-tumor therapy, or the end of the study.

	Phase I QD Dose Cohorts with Planned/Completed Escalation *
Dose Cohort 1	100 mg QD
Dose Cohort 2	200 mg QD
Dose Cohort 3	400 mg QD
Dose Cohort 4	600 mg QD
Dose Cohort 5	750 mg QD
Dose Cohort 6	1000 mg QD
Dose Cohort 7	1200 mg QD

Note: Intermediate dose exploration of the above doses, such as 150 mg, 300 mg, 500 mg, 800 mg, 900 mg, 1100 mg QD, etc., may be conducted during the escalation process based on the clinical data obtained, including safety, PK, and possible efficacy.

Based on the data obtained, including safety, PK, and preliminary efficacy results, BID dose regimen may be conducted. The starting dose for BID will be selected from one of the dose cohorts in the table below, and the total daily dose will be consistent with the QD dose being explored.

	Phase I Possible BID Dose Cohorts for Exploration*
Dose Cohort 1	100 mg BID
Dose Cohort 2	150 mg BID
Dose Cohort 3	200 mg BID
Dose Cohort 4	300 mg BID
Dose Cohort 5	400 mg BID

Note: Intermediate dose exploration of the above doses, such as 250 mg BID, etc., may be conducted.

DLT Definition

A DLT is an AE that occurs within 21 days after the first dose, is related to the investigational drug GFH375, and meets the following severity criteria. The severity of AEs is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0:

- Grade ≥ 4 absolute neutrophil count (ANC) decreased for ≥ 5 days;
- Grade ≥ 3 febrile neutropenia (ANC $<1.0 \times 10^9$/L with a single body temperature > 38.3°C or a sustained body temperature ≥38°C for more than 1 hour);
- Grade ≥ 4 platelet count decreased for ≥ 5 days;
- Grade ≥ 3 platelet count decreased with Grade ≥ 2 hemorrhage;
- Grade ≥ 4 anemia;
- If baseline ALT or AST is Grade ≤ 1: Grade ≥ 3 serum transaminases increased (ALT or AST) lasting > 7 days is considered a DLT; if baseline ALT or AST is Grade 2, then ALT or AST > 10×ULN lasting > 7 days is considered a DLT;
- Grade ≥ 3 serum bilirubin increased;
- According to Hy's Law, AST or ALT > 3×ULN (if baseline metastases to liver are

present, then > 3 times the baseline value is required), with concurrent total bilirubin > 2×ULN (causes such as biliary obstruction or other causes like hepatitis, intrahepatic tumor progression, etc., must be excluded);

- Grade ≥ 3 other toxicities (non-hepatic, non-hematologic), with the exception of the following:
  - Grade 3 nausea or vomiting, diarrhea, lasting no more than 3 days with/without symptomatic supportive care;
  - Grade 3 fatigue, lasting no more than 3 days with/without symptomatic supportive care;
  - Asymptomatic Grade 3 abnormal laboratory results lasting no more than 7 days with intervention, such as elevated cholesterol, elevated triglycerides, gamma-glutamyl transferase (GGT) increased, alkaline phosphatase (ALP) increased, blood amylase increased, etc.

Toxicities meeting the above criteria that occur after the DLT observation period will also be considered important factors in the safety evaluation. In addition, other treatment-related toxicities that may be assessed as DLTs will be determined after discussion between the sponsor and the investigator.

During the first cycle (DLT observation period), AEs that meet the DLT criteria should be reported to the sponsor within 24 hours of awareness of their occurrence.

Dose Escalation Rules and MTD Definition

Accelerated titration is permitted for the first two dose levels of the QD dosing regimen, meaning the first participant will receive treatment at the first dose level. If no Grade ≥2 treatment-related AE is observed in participants in the first two dose cohorts during the DLT observation period, 3-6 participants will be enrolled at the next higher dose level, and the BOIN design will be used for this cohort and subsequent dose escalations. Conversely, if any Grade ≥2 treatment-related AE or DLT event is reported in the first or second dose cohort, the study will switch directly to the BOIN design, starting from the lowest dose cohort where the Grade ≥2 treatment-related AE or DLT event was observed. Provided that accelerated titration is completed for the first dose, the decision on whether to use accelerated titration for the second dose level will be made by the SMC based on discussion of the PK and safety data from the first dose level. Subsequent dose levels will use the BOIN design to determine the MTD, with a target toxicity probability of 0.3. If dose exploration of the BID dosing regimen is required, the BOIN design will be used for dose escalation, with a target toxicity probability of 0.3. Each dose level will enroll 3-6 participants for treatment. Additional participants may be enrolled if more dose levels or other dosing regimens need to be explored.

The BOIN design will assign the dose level for the next group of participants according to the dose escalation/de-escalation rules shown in the table below.

Decision	**Total number of participants treated at the current dose**						
	3	**4**	**5**	**6**	**7**	**8**	**9**
Escalate, if number of participants with DLT is ≤	0	0	1	1	1	1	2
De-escalate, if number of participants with DLT is ≥	2	2	2	3	3	3	4
Eliminate dose, if number of participants with DLT is ≥	3	3	4	4	5	5	5

For specific rules, please see Section 3.1.1.2 of the main text.

After the dose escalation part is completed, isotonic regression analysis will be used based on the dose determination set (DDS) to determine the MTD. The online BOIN software at

	http://www.trialdesign.org will be used to perform isotonic regression analysis to obtain the isotonic estimates of the toxicity probability for each dose level. The dose level closest to the target toxicity rate of 0.3 is the MTD. If there are 2 or more dose levels that meet the condition simultaneously, the highest dose level with an isotonic estimate <0.3 or the lowest dose level with an isotonic estimate ≥0.3 will be selected. **Backfilling of Participants in the Dose Escalation Part** Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional participants for backfilling. These participants will be treated with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is considered to have potential clinical benefit by the investigator and sponsor, in order to better estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. If the safety of the 750 mg QD dose cohort has been explored and confirmed, backfilling of the 700 mg QD dose cohort may also be conducted. Backfilled participants will not be included in the DLT evaluation. After backfilling, no more than 30 participants will be treated in each GFH375 dose cohort (including participants enrolled in the BOIN doseescalation part). Backfilled participants will complete the relevant visits according to the Phase I part Schedule of Activities and the Phase I part PK blood sampling schedule. **Intra-participant Dose Escalation** In principle, intra-participant dose escalation will not be performed during the dose escalation part. For participants enrolled in Phase I, after agreement from the investigator and sponsor, intra-participant dose adjustment to receive RP2D monotherapy is permitted after the RP2D for this protocol has been confirmed. **Determination of RP2D** Based on all safety, tolerability, PK, and efficacy data from the Phase I dose escalation part and some backfilled participants, the RP2D was determined to be 600 mg QD. **Phase II Part** The Phase II part is an open-label, multicenter study. The overall study plan is shown in Figure 3 of the main text. The objective is to evaluate the efficacy, safety, and PK characteristics of GFH375 in patients with advanced non-small cell lung cancer, advanced pancreatic carcinoma, colorectal cancer, and other advanced solid tumors with KRAS G12D mutation. The Phase II part will enroll approximately 317 participants with advanced solid tumors with KRAS G12D mutation to receive continuous GFH375 monotherapy at the RP2D, with a treatment cycle of 21 days. Participants enrolled in this part will undergo sparse PK sampling according to the Phase II part PK blood sampling schedule and have matching ECGs collected with PK sampling. • Advanced NSCLC participant cohort: Approximately 73 participants with advanced NSCLC carrying the KRAS G12D mutation are planned for enrollment. • Advanced PDAC participant cohort: Approximately 94 participants with advanced PDAC carrying the KRAS G12D mutation are planned for enrollment. • Advanced CRC participant cohort: Approximately 50 participants with advanced CRC carrying the KRAS G12D mutation are planned for enrollment. • Other advanced solid tumor participant cohort: Approximately 100 participants with other advanced solid tumors carrying the KRAS G12D mutation are planned for enrollment, such as bile duct cancer, appendix cancer, etc., carrying the KRAS G12D mutation. Eligible participants who are screened will receive GFH375 monotherapy until PD, unacceptable toxicity, or discontinuation of study treatment for other reasons. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks. Participants will return to the study site 30 (±3) days after the last study treatment for a safety follow-up, and will have survival follow-ups every 90 (±7) days

	thereafter. Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the ICF, initiation of other anti-tumor therapy, or the end of the study.
Inclusion Criteria	**Participants must meet all of the following criteria to participate in this study:** 1. Participants who voluntarily participate in the study and sign the ICF. 2. Male or female, aged 18 - 75 years at the time of signing the ICF. 3. Participants with histologically or cytologically confirmed locally advanced or metastatic malignant tumor, who must meet the following criteria: （1）Phase I Part: Either of the following criteria is met: 1) PD after standard of care and no other standard of care is available; or 2) standard of care has been confirmed to be ineffective, intolerable, or considered unsuitable. （2）Phase II Part: a) Advanced NSCLC: ✓ Participants who have progressed after prior treatment with anti-PD-(L)1 therapy and/or platinum-based chemotherapy (unless contraindicated or intolerant), and have received no more than 3 prior lines of therapy; ✓ If prior adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy. b) Advanced PDAC: Participants who have progressed after adequate treatment with a gemcitabine-based chemotherapy regimen or FOLFIRINOX/mFOLFIRINOX regimen, or are unsuitable for standard of care due to reasons such as unacceptable toxicity, and have received no more than 3 prior lines of therapy. Those with high microsatellite instability (MSI-H) and/or deficient mismatch repair (dMMR) must have progressed after at least one prior line of anti-PD-1 therapy. If adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy. c) Advanced CRC: Participants who have progressed after at least two lines of standard of care, or are unsuitable for standard of care due to reasons such as unacceptable toxicity. Participants must have experienced PD or recurrence during or after treatment with fluorouracil, irinotecan, and oxaliplatin for metastatic disease, unless the investigator considers the participant unsuitable for the above treatment regimens. Those with known MSI-H and/or dMMR must have received prior treatment with an immune checkpoint inhibitor (if applicable). If adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy. d) Other solid tumors: Participants who have progressed after standard of care, or are unsuitable for standard of care due to reasons such as unacceptable toxicity. 4. Participants enrolled in this study must provide a written test report confirming KRAS G12D mutation-positive status. NSCLC and PDAC participants enrolled in Phase II must provide a compliant archived tumor tissue sample or undergo a biopsy during the screening period before enrollment. If a tumor tissue sample cannot be provided and a biopsy cannot be performed during the screening period, the investigator must communicate with the sponsor's medical monitor and obtain their consent before

	enrollment. 5. According to RECIST 1.1, participants enrolled in Phase I must have at least one evaluable lesion, and participants enrolled in Phase II must have at least one measurable lesion. 6. Toxicities from prior anti-tumor therapy must have resolved to baseline level (excluding alopecia) or ≤ Grade 1 (for neurological toxicity, ≤ Grade 2). 7. Investigator-assessed life expectancy ≥ 12 weeks. 8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-1 (see Appendix 2 for scoring criteria). 9. Adequate organ function, including: • Hematopoietic function: Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 75 × 10^9/L, hemoglobin ≥ 9 g/dL, with no transfusion or treatment with granulocyte colony-stimulating factor, thrombopoietin, or erythropoietin within 14 days before the blood test. • Liver function: ➢ Both AST and ALT < 2.5×ULN; for participants with baseline metastases to liver, both AST and ALT < 5×ULN; ➢ Total bilirubin (TBIL) < 1.5×ULN; for participants with Gilbert's syndrome: TBIL < 2×ULN. • Renal function: Creatinine clearance (CrCl) ≥ 50 mL/min (calculated by Cockcroft-Gault formula, see Appendix 3). • Coagulation function: Prothrombin time (PT) or activated partial thromboplastin time (APTT) < 1.5×ULN, international normalized ratio (INR) < 1.5×ULN or within the target range for anticoagulant therapy. • Albumin level ≥30 g/L (for Phase II PDAC participants only). 10. Women of childbearing potential (WOCBP) and male participants with partners who are WOCBP must agree to use effective methods of contraception from the time of signing the ICF until 30 days after the last study treatment. WOCBP must have a negative serum pregnancy test result within 7 days before dosing. 11. Participants who are able to communicate well, adhere to the follow-up schedule, and comply with the protocol requirements in the investigator's judgment.
Exclusion Criteria	**Participants who meet any of the following criteria cannot be enrolled in this study:** 1. Other malignant tumor that has progressed or required treatment within 3 years prior to enrollment, with the exception of adequately treated carcinoma in situ, basal cell carcinoma, or squamous cell carcinoma of skin. 2. Patients with unstable brain metastasis as judged by the investigator. Patients with incidentally detected brain metastasis during screening may be enrolled if they are asymptomatic and do not require therapeutic intervention; enrollment is permissible if the investigator judges the brain metastasis to be stable, the hormone dose is stable, and the prednisone dose is ≤10 mg/d (or an equivalent dose if other steroid drugs are used). 3. Phase II Part: a) Advanced NSCLC: Exclusion of known other driver gene mutations or fusions, such as EGFR, ALK, BRAF (V600E), HER2, MET (exon 14), ROS1, RET, KRAS G12C, or NTRK1/2/3 b) Advanced CRC: Exclusion of known other driver gene mutations, amplifications, or fusions, such as BRAF (V600E), HER2, NTRK, or RET c) Advanced PDAC: Exclusion of known other driver gene mutations or fusions, such as BRAF (V600E), BRCA, NTRK, or RET 4. Prior targeted therapy against KRAS G12D or pan-KRAS (with primary targeting

	effect on KRAS G12D). 5. Receipt of palliative radiation within 14 days before administration of the study drug. 6. Receipt of other anti-tumor therapy within 28 days or 5 half-lives (whichever is shorter) before dosing, including chemotherapy, targeted therapy, endocrine therapy, immunotherapy, Chinese patent medicines with definite anti-tumor effects, and other investigational drugs or devices, with the exception of endocrine maintenance therapy. 7. Concomitant clinically significant severe cardiovascular disorder: • Clinically significant severe cardiovascular events within 6 months before the first study treatment, such as myocardial infarction, angina unstable, symptomatic cardiac failure congestive (New York Heart Association Class III or IV), severe arrhythmia requiring drug therapy, or receipt of angioplasty, stenting, and coronary artery bypass graft surgery, etc. • Clinically significant QT/QTcF prolongation (based on the average of three QTcF values during the screening period, QTcF > 470 ms) or a family history of QT interval prolongation. • Hypertension that remains poorly controlled after standard treatment. 8. Stroke or other severe cerebrovascular disorder within 6 months prior to enrollment. 9. History of deep vein thrombosis or any other severe thromboembolism within 3 months prior to enrollment. 10. Concomitant pleural effusion, ascites, or pericardial effusion requiring repeated drainage or causing significant symptoms. 11. Concomitant superior vena cava syndrome. 12. History of gastrointestinal perforation and/or fistula within 6 months before the first dose of study drug that has not healed after surgery; current unstable or active gastrointestinal ulcer or other high-risk gastrointestinal hemorrhage diseases; presence of biliary or pyloric obstruction, or persistent recurrent vomiting (≥3 episodes within 24 hours); high risk of rupture, hemorrhage, or gastrointestinal/respiratory fistula due to tumor invasion of surrounding vital structures (e.g., major blood vessels, trachea); or other gastrointestinal dysfunction or diseases that may significantly affect the absorption of GFH375, or inability or unwillingness to swallow tablets. 13. Concomitant clinically significant interstitial lung disease, radiation pneumonitis, or immune-related pneumonitis requiring treatment. 14. Concomitant major acute or chronic infectious diseases, including: • Active infection requiring intravenous antibiotic therapy within 7 days prior to enrollment. • Positive for human immunodeficiency virus antibody (HIV-Ab) at baseline. • Active hepatitis b virus infection (HBsAg positive with positive HBV-DNA). • Active hepatitis c virus infection (HCV-Ab positive with positive HCV-RNA). • Active tuberculosis. 15. Other poorly controlled systemic diseases, such as diabetes mellitus. 16. Undergone or planning to undergo major surgery as judged by the investigator within 28 days before the first dose (excluding needle biopsy). 17. History of organ transplant or preparing to receive an organ transplant. 18. Need for acid-suppressing drugs, including proton pump inhibitors and novel acid-suppressing drugs (e.g., potassium-competitive acid blockers), within 7 days before or during the administration of the study drug. 19. Receipt of strong inhibitors or inducers of CYP3A or P-gp within 14 days or 5 half-lives of the drug (whichever is longer) before administration of the study drug. 20. Receipt of known sensitive substrates of CYP3A or OAT1 within 14 days or 5 half-lives of the drug (whichever is longer) before administration of the study drug. Unless

	agreed for enrollment after review by the investigator and sponsor. 21. Known allergy to the study drug or its components. 22. Severe mental or psychological illness, or history of drug abuse or severe alcoholism. 23. Pregnant or lactating women. 24. Other conditions that, in the investigator's judgment, make the participant unsuitable for the study. 25. **Phase II PDAC participants:** Numeric Rating Scale (NRS) for pain score ≥4 after standardized treatment with analgesics.
Statistical Analysis	**Analysis Sets** • Full Analysis Set (FAS): All participants who have received at least one dose of GFH375. • Safety Set (SS): All participants who have received at least one dose of GFH375 and have at least one post-treatment safety assessment. • Dose Determination Set (DDS): All Phase I participants who have received undiminished doses of GFH375 for at least 15 cumulative days during the DLT observation period and had adequate safety assessments, or who have experienced a DLT during the DLT observation period. The DDS does not include backfilled participants. • Per-Protocol Set (PPS): All Phase II participants in the FAS who are compliant with the protocol. The study team will review all protocol deviations before the final database lock and exclude participants with major protocol deviations that affect the efficacy evaluation from the PPS. • Pharmacokinetic Analysis Set (PKAS): All participants who have received at least one dose of GFH375 and have provided at least one blood sample for evaluable PK data. **Statistical Analysis Methods** Data from Phase I and Phase II will be analyzed and summarized separately. Data from the Phase I stage will be analyzed and summarized by different dose levels and dosing regimens; data from the Phase II stage will be analyzed and summarized separately by tumor type. **Safety Analysis** The incidence of AEs, treatment-related AEs, and SAEs will be summarized by System Organ Class (SOC), Preferred Term (PT), and severity. For the Phase I part, the incidence of various types of DLTs will be summarized based on the DDS, and the DLTs will be listed. Descriptive summaries will be provided for laboratory tests, vital signs, and ECGs. **Efficacy Analysis** Best overall response (BOR), ORR, and DCR will be calculated, and the two-sided 95% confidence interval (CI) for ORR and DCR will be estimated using the Clopper-Pearson method. The median DoR, PFS, and OS and their 95% Brookmeyer-Crowley CIs will be estimated using the Kaplan-Meier method. TTR will be summarized descriptively. For the Phase I stage, when the sample size of an analysis group is less than 10, DoR, TTR, PFS, and OS will be listed individually by participant, and the Kaplan-Meier method will not be used for analysis. For the Phase II stage, the primary estimand is set as follows: **Study Population**: Participants with advanced solid tumors with KRAS G12D mutation **Treatment**: GFH375 **Endpoint**: Percentage of participants who achieve CR or PR as assessed by RECIST 1.1 criteria. If a participant has no post-baseline assessment results, the participant is considered a non-responder.

	Note: For NSCLC and PDAC, this will be the percentage of participants with confirmed CR or PR based on Blinded Independent Central Review (BICR) assessment.
Intercurrent Event	Start of new anti-tumor therapy (Handling strategy: Treatment policy strategy, assessment results after the start of new anti-tumor therapy are not included in the analysis.)
Population-level Summary	ORR

PK Analysis

Plasma concentration data of GFH375 will be listed and summarized descriptively according to the sampling times specified in the protocol. The summaries will be presented by study phase, dose group, and dosing regimen. Individual participant plasma concentration-time curves of GFH375 and corresponding summary curves (mean + standard deviation) will be plotted using linear and semi-logarithmic coordinates, by study phase, dose group, and dosing regimen. Planned PK sampling times will be used to calculate summary statistics and plot summary curves (mean + standard deviation); actual PK sampling times will be used to plot individual participant curves.

Phoenix WinNonlin software (version v8.2 or later, Certara USA, Inc., New Jersey, US) will be used to perform non-compartmental analysis (NCA) to calculate the PK parameters of GFH375 based on actual blood sampling time points. The PK parameters of GFH375 after single and multiple doses in participants in the Phase I dose escalation part will be summarized descriptively, with summaries presented by dose group and dosing regimen.

Sample Size Calculation

Phase I Part

According to the BOIN design, 3-6 patients will be enrolled in each dose group for treatment (except during accelerated titration). Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional participants for backfilling. These participants will be treated with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is considered to have potential clinical benefit by the investigator and sponsor, in order to better estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. Backfilled participants will not be included in the DLT evaluation. After backfilling, no more than 30 participants will be treated in each GFH375 dose cohort (including participants enrolled in the BOIN dose-escalationpart).

Additional patients may be enrolled if more dose levels or alternative dosing regimens need to be explored.

Phase II Part

A total of approximately 317 participants are planned for enrollment, including approximately 73 patients with advanced NSCLC, approximately 94 patients with advanced PDAC, approximately 50 patients with advanced CRC, and approximately 100 patients with other advanced solid tumors.

Tumor Type	Historical Control ORR	Expected ORR	Sample Size
NSCLC	23%	40%	73
PDAC	15%	30%	94
CRC	10%	30%	50
Other			100

	<table><tr><td>Total</td><td></td><td></td><td>317</td></tr></table> For second-line advanced NSCLC, the historical control ORR is 23%, and the expected ORR in this study is 40%. The study will be considered successful if the lower limit of the 95% CI for the observed ORR is not less than the historical control of 23%. With a one-sided $\alpha = 0.025$, 73 participants are required to achieve 89% power. When at least 25 of the 73 participants have a CR/PR, the lower limit of the exact 95% CI for the observed ORR will be higher than the historical control of 23%. With 25 CR/PRs, the ORR = 34.2%, with a 95% CI of (23.5%, 46.3%). For second-line advanced PDAC, the historical control ORR is set at 15%. The expected ORR with GFH375 treatment is 30%. If the lower limit of the 95% CI for ORR after GFH375 treatment is greater than 15%, the efficacy of GFH375 will be considered statistically significant. With a one-sided $\alpha = 0.025$, 94 participants will provide 95% power to ensure that the lower limit of the 95% CI for the ORR is greater than 15%. Approximately 94 participants with PDAC are planned for enrollment. When 22 responses (PR/CR) are observed in 94 participants, the exact 95% CI for the observed ORR is (15.29%, 33.26%). Therefore, if ≥22 responses are observed in 94 participants, the efficacy of GFH375 will be considered statistically significant. For third-line CRC, the historical control ORR is 10%, and the expected ORR in this study is 30%. The study will be considered successful if the lower limit of the 95% CI for the observed ORR is not less than the historical control of 10%. It is planned to enroll 50 participants, which will provide 96% power with a one-sided $\alpha = 0.025$. When at least 10 of the 50 participants have a CR/PR, the lower limit of the exact 95% CI for the observed ORR will be higher than the historical control of 10%. With 10 CR/PRs, the ORR = 20.0%, with a 95% CI of (10.0%, 33.7%). For other solid tumors: Approximately 100 participants with advanced solid tumors with KRAS G12D mutation, such as bile duct cancer and appendix cancer with KRAS G12D mutation, are planned for enrollment.
Interim Analysis	A futility interim analysis will be performed separately for NSCLC, PDAC, and CRC. For each tumor type, the analysis is planned when approximately 35 participants (including Phase I participants treated with RP2D and Phase II participants) have had at least one post-baseline imaging tumor assessment or have withdrawn from the study early. Due to practical clinical operational reasons, the number of participants at the time of the interim analysis is allowed to differ from the planned number. During the interim analysis, enrollment will not be stopped. At the interim analysis, a futility analysis will be conducted on ORR for NSCLC, PDAC, and CRC, respectively, using the Bayesian predictive probability method. Early termination of the study for the corresponding tumor type due to lack of efficacy evidence is permitted (but not mandatory). The predictive probability of success (PPoS) will be calculated based on the observed number of Phase II participants who have achieved a response (CR/PR). If the PPoS is < 0.2, early termination of enrollment due to lack of efficacy evidence is permitted (but not mandatory). The corresponding termination criteria for PPoS < 0.2 are shown in the table below: <table><tr><th>Tumor Type</th><th>Number of Participants*</th><th>Recommended to terminate the cohort when the number of responders is ≤</th></tr><tr><td rowspan="5">NSCLC</td><td>20 ~ 21</td><td>3</td></tr><tr><td>22 ~ 25</td><td>4</td></tr><tr><td>26 ~ 29</td><td>5</td></tr><tr><td>30 ~ 33</td><td>6</td></tr><tr><td>34 ~ 37</td><td>7</td></tr></table>

	38 ~ 41	8
	42 ~ 45	9
PDAC	25 ~ 26	2
	27 ~ 33	3
	34 ~ 39	4
	40 ~ 45	5
CRC	20 ~ 23	1
	24 ~ 30	2
	31 ~ 37	3
	38 ~ 43	4
	44 ~ 48	5

*Number of participants: The sum of Phase I participants treated with RP2D and Phase II participants who have had at least one post-baseline imaging tumor assessment or have withdrawn from the study early (at least one of these must be met).

The interim analysis planned above is not mandatory. If there is sufficient comprehensive safety and efficacy data to support it before the planned time point for the interim analysis, this interim futility analysis may be omitted.

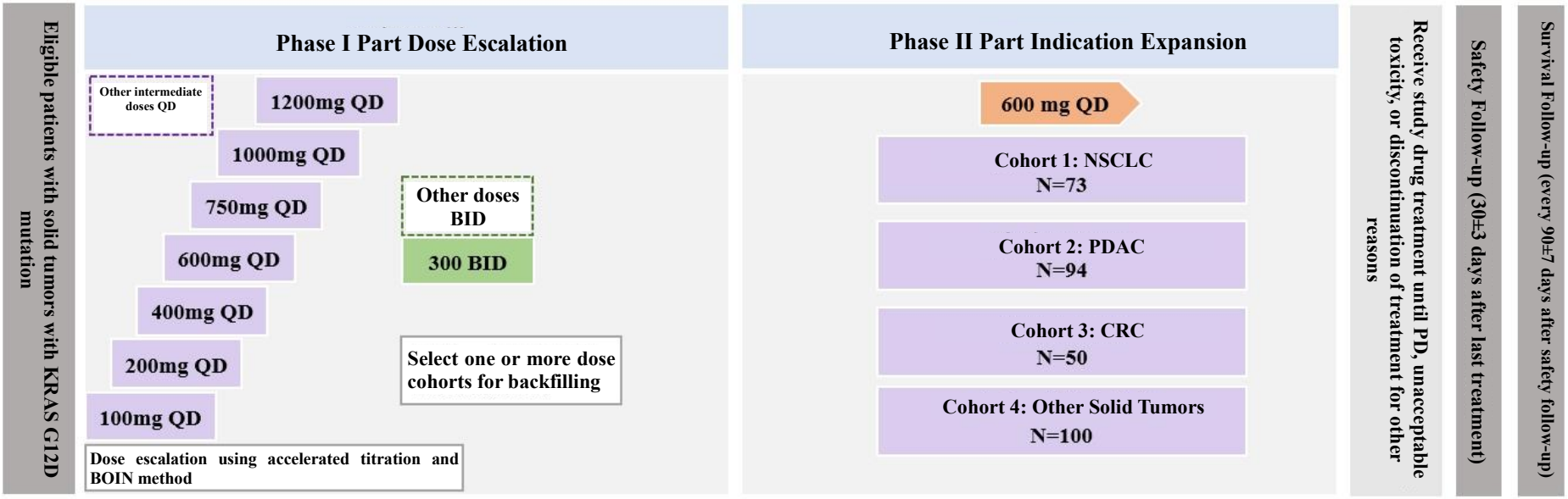

Figure 1 Overall Study Design

Abbreviations: QD: once daily; BID: twice daily; NSCLC: non-small cell lung cancer; PDAC: ductal adenocarcinoma of pancreas; CRC: colorectal cancer; BOIN: Bayesian Optimal Interval.

Schedule of Activities for Phase I Treatment Stage

Study Stage	Screening Period	Treatment Period							Remarks
		Cycle 1				Cycle 2		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D3**	**D8**	**D15**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**0**	**±3**	**±3**	**-1 ~ 3**	**±3**	**±3**	
Informed Consent	×								
Inclusion/Exclusion Criteria	×	×							Inclusion/exclusion criteria must be reviewed again on C1D1.
Demographics	×								Includes sex, age, ethnicity, etc.
Body Height/Weight	×	×				×		×	Body height is measured only once during the screening period.
Tumor History	×								Includes information on tumor diagnosis, time of diagnosis, metastatic sites, etc. For advanced NSCLC, data on prior PD-L1 expression levels should be collected (if available)
Other Medical History	×								All active medical conditions and any conditions the investigator considers clinically significant will be collected.
Prior Anti-tumor Therapy History	×								All prior anti-tumor therapy history for the study disease, including therapeutic drugs, start time, end time, best overall assessment, reason for discontinuation, etc. will be collected.
Other Prior/Concomitant Therapy	×								All prior/concomitant medications and therapeutic procedures from 30 days before the first dose until the end of the safety follow-up will be collected.
Virus Serology	×								Includes hepatitis b surface antigen (HBsAg), hepatitis b surface antibody (HBsAb), hepatitis b core antibody (HBcAb), HCV antibody, HIV antibody, and HBV-DNA and HCV-RNA tests (if necessary).
Pregnancy Test	×	×						×	Female participants of childbearing potential must undergo a serum pregnancy test within 7 days before the first dose, followed by a pregnancy test urine on D1 of every 2 cycles. If a negative urine pregnancy result cannot be confirmed, a serum pregnancy test is required.

Study Stage	Screening Period	Treatment Period							Remarks
		Cycle 1				Cycle 2		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D3**	**D8**	**D15**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**0**	**±3**	**±3**	**-1 ~ 3**	**±3**	**±3**	
Physical Examination	×	×	×	×		×	×	×	
ECOG PS	×	×				×		×	If assessed within 72 hours before the first dose, it does not need to be repeated on C1D1.
Vital Signs	×	×	×	×	×	×	×	×	
Hematology	×	×	×	×	×	×	×	×	If laboratory test results are available within 7 days before the first dose, they do not need to be repeated on C1D1. If the participant's clinical status changes significantly, laboratory tests must be repeated on C1D1.
Blood Chemistry	×	×	×	×	×	×	×	×	
Urinalysis	×	×			×	×	×	×	
Coagulation Function	×	×			×	×	×	×	
Electrocardiogram	×	×	×	×	×	×	×	×	1. If other trial procedures are combined, an ECG should be performed first to avoid the impact of study procedures on the ECG results. 2. The ECG should be performed after the participant has rested quietly for at least 10 minutes. Three ECGs will be performed at each visit during the study, with an interval of at least 5 minutes between each. 3. For ECG collection that matches PK sampling, please refer to the PK blood collection form for specific requirements.
Tumor Imaging Assessment	×	×							Compliant examination results from within 4 weeks before the first dose can be accepted as baseline and do not need to be repeated. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks.
GFH375 Administration		×							GFH375 tablets will be dispensed to participants on specified visit days and taken orally as scheduled. **Participants receiving QD**

Study Stage	Screening Period	Treatment Period							Remarks
		Cycle 1				Cycle 2		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D3**	**D8**	**D15**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**0**	**±3**	**±3**	**-1 ~ 3**	**±3**	**±3**	
									dosing should skip the dose on Day 2 and Day 3 of the first cycle; participants receiving BID dosing do not need to skip.
PK Blood Sampling		×							See PK Collection Form
Blood ctDNA	×	×							Blood samples will be collected at baseline (if collected during the screening period, no need to repeat on C1D1) for next-generation sequencing (NGS) testing
AE/SAE	×	×							AEs/SAEs will be collected from signing of ICF until 30 days after the last dose

Abbreviation: C1D1: Cycle 1 Day 1. ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; PK: Pharmacokinetics; AE/SAE, Adverse Event/Serious Adverse Event.

Schedule of Activities for Phase II Treatment Stage

Study Stage	Screening Period	Treatment Period			Remarks
		Cycle 1		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**±3**	**±3**	
Informed Consent	×				
Inclusion/Exclusion Criteria	×	×			Inclusion/exclusion criteria must be reviewed again on C1D1.
Demographics	×				Includes sex, age, ethnicity, etc.
Body Height/Weight	×	×		×	Body height is measured only once during the screening period.
Tumor Tissue Sample	×				Phase II NSCLC and PDAC participants must provide an archived formalin-fixed paraffin-embedded (FFPE) sample or a biopsy sample.
Tumor History	×				Includes information on tumor diagnosis, time of diagnosis, metastatic sites, etc. For patients with advanced NSCLC, data on prior PD-L1 expression levels should be collected (if available).
Other Medical History	×				All active medical conditions and any conditions the investigator considers clinically significant will be collected.
Prior/Concomitant Therapy	×				All prior/concomitant medications and therapeutic procedures from 30 days before the first dose until the end of the safety follow-up will be collected.
NRS Pain Score	×	×			For PDAC participants only; if assessed within 72 hours before the first dose, it does not need to be repeated on C1D1.
Virus Serology	×				Includes hepatitis b surface antigen (HBsAg), hepatitis b surface antibody (HBsAb), hepatitis b core antibody (HBcAb), HCV antibody, HIV antibody, and HBV-DNA and HCV-RNA tests (if necessary).

Study Stage	Screening Period	Treatment Period			Remarks
		Cycle 1		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**±3**	**±3**	
Pregnancy Test	×	×		×	Female participants of childbearing potential must undergo a serum pregnancy test within 7 days before the first dose, followed by a pregnancy test urine on D1 of every 2 cycles. If a negative urine pregnancy result cannot be confirmed, a serum pregnancy test is required.
Physical Examination	×	×	×	×	
ECOG PS Score	×	×		×	If assessed within 72 hours before the first dose, it does not need to be repeated on C1D1.
Vital Signs	×	×	×	×	
Hematology	×	×	×	×	If laboratory test results are available within 7 days before the first dose, they do not need to be repeated on C1D1. If the participant's clinical status changes significantly, laboratory tests must be repeated on C1D1.
Blood Chemistry	×	×	×	×	
Urinalysis	×	×	×	×	
Coagulation Function	×	×	×	×	
Electrocardiogram	×	×	×	×	1. If other trial procedures are combined, an ECG should be performed first to avoid the impact of study procedures on the ECG results. 2. The ECG should be performed after the participant has rested quietly for at least 10 minutes. Three ECGs will be performed at each visit during the study, with an interval of at least 5 minutes between each. 3. For ECG collection that matches PK sampling, please refer to the PK blood collection form for specific requirements.

Study Stage	Screening Period	Treatment Period			Remarks
		Cycle 1		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**±3**	**±3**	
CA19-9	×	×			For PDAC participants only; tested at baseline (if collected during the screening period, no need to repeat on C1D1) and every 6 ± 1 weeks during the treatment period.
Tumor Imaging Assessment	×	×			Compliant examination results from within 4 weeks before the first dose can be accepted as baseline and do not need to be repeated. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks.
GFH375 Administration		×			GFH375 tablets will be dispensed to participants on specified visit days and taken orally as scheduled
PK Blood Sampling		×			See PK Collection Form
Blood ctDNA	×	×			Blood samples will be collected at baseline (if collected during the screening period, no need to repeat on C1D1) for next-generation sequencing (NGS) testing
AE/SAE	×	×			AEs/SAEs will be collected from signing of ICF until 30 days after the last dose

Abbreviation: C1D1: Cycle 1 Day 1. ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; PK: Pharmacokinetics; AE/SAE, Adverse Event/Serious Adverse Event.

Phase I and II Parts: Schedule of Activities for End of Treatment Visit and Long-term Follow-up Visit

	End of Treatment (EOT) Visit	Safety Follow-up Visit	Survival Visit	Remarks
Visit	**Decision to end study treatment**	**30 days after last dose**	**Every 90 days after safety visit**	
Time Window (days)	+7	±3	±7	
Pregnancy Test	×	×		Pregnancy test urine will be performed; serum test will be used if necessary.
Physical Examination	×	×		
ECOG PS Score	×			
Vital Signs	×	×		
Weight	×	×		
Blood ctDNA	×			
Hematology	×	×		Tests performed within 7 days after the last dose do not need to be repeated at the EOT visit, but AE-related tests should be reviewed at the investigator's discretion
Blood Chemistry	×	×		
Urinalysis	×	×		
Coagulation Function	×	×		
Electrocardiogram	×	×		
CA19-9	×			For PDAC participants enrolled in Phase II only; no need to repeat if tested within 4 weeks before the end of treatment visit.
Imaging Assessment	×			Imaging tests performed within 4 weeks before the end of treatment visit do not need to be repeated; participants who discontinue treatment for reasons other than PD/due to PD and have not started other anti-tumor therapy need to undergo scheduled tumor imaging until PD, start of new anti-tumor therapy, or withdrawal from the study.

	End of Treatment (EOT) Visit	Safety Follow-up Visit	Survival Visit	Remarks
Visit	**Decision to end study treatment**	**30 days after last dose**	**Every 90 days after safety visit**	
Time Window (days)	**+7**	**±3**	**±7**	
Concomitant Therapy	×			Concomitant medications and therapeutic procedures will be collected
AE/SAE	×			AEs/SAEs will be collected from signing of ICF until 30 days after the last dose or start of new anti-tumor therapy
Subsequent Anti-tumor Therapy	×			Includes subsequent anti-tumor therapy, start/end time, reason for discontinuation, and BOR
Survival Status	×			

Phase I Part PK Sample and 12-Lead ECG Collection Schedule (QD/BID)

Cycle	Day	Planned Sampling Time Point (h)	Time Window	PK Sampling[1,2]	12-Lead ECG[3]
1	1	Predose	-1 h	√	√
1	1	1 h postdose	±5 min	√	
1	1	2 h postdose	±10 min	√	√
1	1	4 h postdose	±15 min	√	√
1	1	6 h postdose	±30 min	√	√
1	1	8 h postdose	±30 min	√	
1	**1**[4]	12 h postdose	±30 min	√	
1	**2**[5]	24 h postdose	±1 h	√	
1	**3**[5]	48 h postdose	±2 h	√	
1	**4**[5]	72 h post-dose (collected before dosing on D4)	±3 h	√	√
1	8	Predose	-1 h	√	√
1	15	Predose	-1 h	√	√
1	21	Predose	-1 h	√	√
1	21	1 h postdose	±5 min	√	
1	21	2 h postdose	±10 min	√	√
1	21	4 h postdose	±15 min	√	√
1	21	6 h postdose	±30 min	√	√
1	21	8 h postdose	±30 min	√	
1	**21**[4]	12 h postdose	±30 min	√	
1	**21**[5]	24 h postdose	±1 h	√	√
2	10	Predose	-1 h	√	√
4	1	Predose	-1 h	√	√
5	1	Predose	-1 h	√	√
6	1	Predose	-1 h	√	√

1. When a patient experiences a drug-related SAE, a blood sample for GFH375 plasma concentration measurement should be collected immediately upon the investigator's awareness of the event, if possible.
2. If a PK sample cannot be obtained at a planned visit, it can be postponed to the next visit for collection. It is sufficient to accurately record the dose administered, time of administration, and time of sampling.
3. ECGs matching the PK samples will be collected at qualified sites. It is recommended to perform the ECG first, then the PK blood draw. If it cannot be completed before the blood sample collection, the ECG should be performed after resting quietly for 10 minutes after the blood draw. Meanwhile, the interval between the ECG and PK sampling time needs to be kept within 30 minutes. All planned 12-ECGs should be performed after the participant has rested quietly for at least 5 min. Three measurements should be taken at each time point, with an interval of 1-2 min between each.
4. **If BID dosing, the 12 h post-dose PK samples on C1D1 and C1D21 should be collected before the second dose of the day.**
5. **Only applicable to QD dosing, collection is required before dosing.**

Phase II Part PK Sample and 12-Lead ECG Collection Schedule (QD/BID)

Cycle	Day	Planned Sampling Time Point (h)	Time Window	PK Sampling[1,2]	12-Lead ECG[3]
1	10	Predose	-1 h	√	√
1	10	Postdose	2-4 h	√	√
2	1	Predose	-1 h	√	√
2	1	Postdose	1-3 h	√	√
3	1	Predose	-1 h	√	√
3	1	Postdose	2-4 h	√	√
4	1	Predose	-1 h	√	√
5	1	Predose	-1 h	√	√
6	1	Predose	-1 h	√	√

1. When a patient experiences a drug-related SAE, a blood sample for GFH375 plasma concentration measurement should be collected immediately upon the investigator's awareness of the event, if possible.
2. If a PK sample cannot be obtained at a planned visit, it can be postponed to the next visit for collection. It is sufficient to accurately record the dose administered, time of administration, and time of sampling.
3. ECGs matching the PK samples will be collected at qualified sites. It is recommended to perform the ECG first, then the PK blood draw. If it cannot be completed before the blood sample collection, the ECG should be performed after resting quietly for 10 minutes after the blood draw. Meanwhile, the interval between the ECG and PK sampling time needs to be kept within 30 minutes. All planned 12-ECGs should be performed after the participant has rested quietly for at least 5 min. Three measurements should be taken at each time point, with an interval of 1-2 min between each.

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List of Abbreviations

Abbreviation	Full Term
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the curve
BCRP	Breast Cancer Resistance Protein
BICR	Blinded Independent Central Review
BID, bid	Bis in die
BOIN	Bayesian Optimal Interval
BOR	Best of Response
C_{max}	Maximal concentration
C_{trough}	Trough concentration
CA19-9	Carbohydrate Antigen 19-9
CI	Confidence Interval
CL	Clearance
CL_r	Renal Clearance
CNS	Central Nervous System
Cr	Creatinine
CR	Complete Response
CRC	Colorectal Cancer
CRO	Contract Research Organization
CSCO	Chinese Society of Clinical Oncology
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450 Proteins
D	Day
DCR	Disease Control Rate
DDS	Dose Determination Set
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
DRF	Dose Range Finding
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
G12D	Gly12Asp

Abbreviation	Full Term
GAP	GTPase-Activating Protein
GCP	Good Clinical Practice
GDP	Guanosine Diphosphate
GEF	Guanine Nucleotide Exchange Factor
GGT	Gamma-Glutamyl Transpeptidase
GTP	Guanosine Triphosphate
GLP	Good Laboratory Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
HR	Hazard Ratio
ICH-GCP	International Council for Harmonization
INR	International Normalized Ratio
LLOQ	Lower Limit of Quantification
K^+	Serum Potassium
KRAS	Kirsten Rat Sarcoma Viral Oncogene
MAPK	Mitogen-Activated Protein Kinase
MATE1	Multidrug and toxin extrusion 1
MATE2-K	Multidrug and toxin extrusion 2-K
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRSD	Maximal Recommended Starting Dose
MSI-H	High Microsatellite Instability
MTD	Maximum Tolerated Dose
NGS	Next Generation Sequencing
NOAEL	No-Observed-Adverse-Effect Level
NRS	Numerical Rating Scale
NSCLC	Non-Small Cell Lung Cancer
OATP1B1	Organic anion transporting polypeptide 1b1
OATP1B3	Organic anion transporting polypeptide 1b3
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OCT2	Organic cation transporter 2
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression Disease
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression Free Survival
P-gp	P-glucoprotein
PLT	Blood Platelet
PK	Pharmacokinetic
PKS	Pharmacokinetic Set

Abbreviation	Full Term
PO, po, p.o.	Oral Administration
PPoS	Predictive Probability of Success
PPS	Per Protocol Set
PR	Partial Response
PRO	Protein in Urine
PS	Physical performance
PT	Preferred Term
PT	Prothrombin Time
QD, qd	Quaque die
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SS	Safety Set
STD10	Severely Toxic Dose in 10% of the Animals
$t_{1/2}$	Elimination half-life
T_{max}	Time to reach maximum concentration
TEAE	Treatment Emergent Adverse Event
TRAE	Treatment Related Adverse Event
T-BIL	Total Bilirubin
TTP	Time to Progression
TK	Toxicokinetics
TTR	Time to Response
ULN	Upper Limits of Normal
V_d	Volume of distribution
V_{dss}	Volume of distribution at steady state

1. Introduction

1.1. Disease Background

1.1.1 Biological Mechanism of KRAS and KRAS G12D Mutation

RAS proteins are guanine nucleotide-binding proteins with GTPase enzyme activity. Their activity is switched by binding to either guanosine diphosphate (GDP) or guanosine triphosphate (GTP). They are in an inactive state when bound to GDP and become activated when bound to GTP. In cells, RAS is located at a relatively central position in signaling pathways and activates multiple downstream signaling pathways. By regulating gene transcription and protein regulation processes, RAS proteins are responsible for intercellular signaling pathways for cell growth, migration, survival, and differentiation. RAS is the most widely mutated oncogene in tumors, with approximately 30% of tumors containing RAS mutations. Mutations in all three subtypes, KRAS, HRAS, and NRAS, have been found in tumors, with KRAS mutations being the most common. KRAS mutations are most common in pancreatic carcinoma, non-small cell lung cancer (NSCLC), and colorectal cancer (CRC), reaching up to 90% in pancreatic carcinoma. KRAS mutations mainly occur at three sites: glycine (Gly, G) at positions 12 and 13, and glutamine (Gln, Q) at position 61, with the highest mutation rate at the G12 position. More than 10 different types of mutations can occur at the Gly12 position of KRAS, with mutations to aspartic acid (G12D), valine (G12V), and cysteine being the most frequent[1-3]. The role of KRAS in tumors is widely recognized, but its protein structure and extremely high affinity for GTP have hindered the development of targeted drugs against KRAS. Recent breakthroughs in covalent inhibition strategies for KRAS have led to the successful development and clinical validation of innovative small molecule drugs targeting KRAS. Among them, KRAS G12C inhibitors (sotorasib, adagrasib) have been approved for the treatment of patients with KRAS G12C-mutated NSCLC, with confirmed efficacy and an acceptable safety profile.

1.1.2 KRAS G12D-mutated Tumors

KRAS mutations are common in CRC (approx. 45% in the US, 49% in China), pancreatic carcinoma (approx. 90% in the US, 87% in China), and NSCLC (adenocarcinoma: approx. 35% in the US, 13% in China)[3]. Among them, KRAS G12D is one of the most common mutation types, with high expression in various solid tumors, including NSCLC, pancreatic carcinoma, CRC, and bile duct cancer.

Advanced NSCLC

Lung cancer is the second most common cancer and the leading cause of cancer death worldwide. NSCLC accounts for approximately 84% of lung cancer cases, and most NSCLC patients are

diagnosed at an advanced stage. Global cancer statistics reported by the International Agency for Research on Cancer show an estimated 820,000 new lung cancer diagnoses and 715,000 lung cancer-related deaths in China in 2020[4]. KRAS G12D is one of the common mutations in NSCLC. A study based on data from the American Association for Cancer Research (AACR) Project GENIE showed that the G12D mutation accounts for an estimated 4.9% of all lung adenocarcinomas in the United States[3]. A retrospective study analyzed NGS data from 150,327 NSCLC cases in the Lung Cancer Big Data Precision Treatment Collaborative Group (LANDSCAPE) project, in which the frequency of KRAS G12D mutation was approximately 2.2%[5].

The treatment of advanced NSCLC varies depending on the presence of driver gene mutations. If positive for driver genes such as EGFR, ALK, ROS, etc., corresponding targeted drugs or platinum-based doublet chemotherapy, as well as chemotherapy combined with immunotherapy, anti-angiogenic therapy, etc., can be selected. Since KRAS G12D rarely co-exists with the above-mentioned driver genes, chemotherapy, such as docetaxel, remains the main treatment after failure of standard systemic therapy, with recently reported ORRs of 13.2-16.0% and a median PFS of 2.6-4.5 months [6-8]; the ORRs for prior chemotherapy and chemotherapy plus anti-angiogenic drugs were 8.5-18.3% and 8.6%-22.9%, respectively; PFS was 2.8-4.2 months and 4.8-5.4 months, respectively; and OS was 6-11.4 months and 9.9-12.6 months, respectively[9-13]. Considering the potential for increased toxicity with combination therapy, the tolerability of patients to doublet chemotherapy and other combination therapies needs to be fully assessed in second-line and above treatments. Data on immune checkpoint inhibitor treatment for KRAS-mutated NSCLC patients mainly come from subgroup analysis reports of large Phase III clinical studies. Among them, the CheckMate057 and OAK studies reported that compared to docetaxel monotherapy, patients with KRAS mutations could achieve better overall survival (OS) benefits from nivolumab or atezolizumab treatment[14,15]. However, since most patients have already received immune checkpoint inhibitors in first-line treatment, they are not the primary choice for second-line treatment.

KRAS G12C targeted inhibitors have achieved good efficacy as monotherapy or in combination in advanced NSCLC, and it is expected that drugs targeting KRAS G12D will bring new treatment options for the subgroup of patients with this targetable mutation.

Advanced PDAC

Ductal adenocarcinoma of pancreas (PDAC) is one of the most malignant tumors with poor treatment efficacy. It is projected that pancreatic carcinoma will become the second leading cause of death from all malignant tumor by 2030, with an overall 5-year survival rate of only 10%. Furthermore, the

disease burden of pancreatic carcinoma is expected to increase globally[16]. Most PDAC patients present with metastatic disease at their initial visit and require more effective systemic therapy. With the exception of patients carrying the germline breast cancer susceptibility gene (BRCA), very few targetable mutations in PDAC have been identified to date. KRAS mutation is an early genetic driver event in its tumorigenesis process and is closely related to key biological features such as inflammation, immune evasion, and metabolic changes[17]. It is estimated that 37% of pancreatic carcinomas carry the KRAS G12D mutation, suggesting the importance of this mutant allele at the population level. Some PDAC xenograft models have shown that KRAS G12D acts as a consistent and strong oncogenic driver in PDAC, and KRAS G12D inhibitors have demonstrated significant anti-tumor activity in ductal adenocarcinoma of pancreas models.

The progress of drug therapy for PDAC has been very limited overall, especially with the limited efficacy of targeted drugs and immunotherapy. The Phase III NAPOLI-1 study, which enrolled patients with metastatic PDAC (mPDAC), showed that for mPDAC patients who had failed prior gemcitabine-based chemotherapy regimens, treatment with liposomal irinotecan in combination with 5-FU/LV (5-fluorouracil + leucovorin) resulted in significantly improved efficacy compared to those receiving only 5-FU/LV (5-fluorouracil + leucovorin): median overall survival (mOS) was 6.1 months (vs 4.2 months, HR 0.67), median PFS was 3.1 months (vs 1.5 months, HR 0.56), and ORR was 16% (vs 1%, $p < 0.0001$)[18]. Currently, there is a lack of standard or recommended treatment options for third-line therapy, with most being the reuse of first- or second-line chemotherapy drugs. A recently published French cohort study showed that among 676 patients with advanced pancreatic carcinoma who received at least one line of chemotherapy, only 37% received third-line chemotherapy, with a median PFS of only 2.03 months and a median overall survival of only 5.5 months[19,20]. Therefore, there is an urgent clinical need for effective therapeutic drugs. Currently, targeted inhibitors against KRAS G12C have achieved good efficacy in previously treated PDAC, with ORRs for sotorasib, adagrasib, and glecirasib monotherapy being 21.0%, 33.3%, and 46.4%, respectively, and median PFS being 4.0 months, 5.4 months, and 5.5 months, respectively[21-23]. It is expected that drugs targeting KRAS G12D can also provide new treatment options for the patient population with this targetable mutation.

Advanced CRC

Colorectal cancer (CRC) is currently the third most common cancer by incidence, with an estimated 1,931,590 new cases annually worldwide. CRC is also the second leading cause of cancer death, with 935,173 deaths globally in 2020. Approximately 20% of CRC patients have metastasis at diagnosis,

while up to 50% of patients with initial local disease will develop metastasis[19]. In CRC, the KRAS mutation rate is approximately 40%, with KRAS G12D accounting for about 28% [24,25]. CRC with KRAS mutations is associated with advanced disease state, poor tumor differentiation, distant metastasis, and lower survival rates, potentially indicating a poorer prognosis for PFS and OS, which has been validated in real-world clinical practice[25]. In addition, studies have shown that KRAS mutation is a common driver of acquired drug resistance to cetuximab in colorectal cancer, and acquired KRAS G12D mutations have been observed in metastatic CRC tissue samples after treatment with cetuximab (or in combination with chemotherapy)[26,27]. Targeting KRAS mutations in CRC patients holds the promise of potentially providing more effective targeted therapy and a better safety profile in this highly selected patient population.

The treatment of advanced CRC also varies depending on the presence of gene mutations such as RAS, BRAF, and HER2. When both RAS and BRAF are wild-type, the treatment used is monochemotherapy or polychemotherapy combined with cetuximab (for left-sided lesions) or bevacizumab (for right-sided lesions). Although immunotherapy has been approved for the treatment of MSI-H CRC patients, the proportion of MSI-H patients in CRC is low, and there remains a huge unmet clinical need. In the third-line or later setting, there are fewer treatment options available for patients, including palliative care, participation in clinical trials, or approved drugs (regorafenib, trifluridine/tipiracil +/- bevacizumab, and fruquintinib). However, in the late-line treatment of CRC, the currently recommended standard therapies (regorafenib, trifluridine/tipiracil, and fruquintinib) offer only limited efficacy in mCRC patients who have failed at least 2 lines of therapy, with an ORR of 1-4.7%, a median PFS of 1.9-3.7 months, and a median OS of 6.4-9.3 months[28-30]. Recently, based on a Phase III part (the SUNLIGHT study, NCT01607957), the FDA approved trifluridine/tipiracil + bevacizumab as one of the third-line treatment options. Compared to trifluridine/tipiracil monotherapy, the use of trifluridine/tipiracil combined with bevacizumab showed improved OS and PFS, but the ORR remained low at only 6.1%[31]. Therefore, there remains a significant unmet medical need in third-line and later mCRC patients. In patients with advanced CRC, the KRAS G12C-targeted inhibitors sotorasib and adagrasib have shown preliminary efficacy as monotherapy, with ORRs of 9.7% (95% CI 3.6, 19.9) and 19% (95% CI 8, 33), respectively[32,33]. Combination with an anti-EGFR antibody can further improve their efficacy. The ORR achieved with sotorasib combined with panitumumab was 26.4%-30%, with a median PFS of 5.6-5.7 months[34]. The ORR for adagrasib combined with cetuximab was 46% (95% CI 28, 66), with a median PFS of 6.7 months[33]. In addition to NSCLC, CRC, and PDAC, KRAS G12D has a high mutation frequency in various solid tumors,

including bile duct cancer, gastric cancer, and esophageal cancer. For these patients who lack effective treatment options, there are no targeted drugs against KRAS available yet.

1.1.3 Development of Drugs Targeting KRAS G12D Mutation

Currently, no therapy specifically targeting KRAS G12D-mutated tumors has been approved for marketing. Several selective KRAS G12D inhibitors are in clinical development, including MTRX1133, HRS-4642, and INCB161734.

Among them, only partial clinical data for HRS-4642, developed by Hengrui, has been disclosed. HRS-4642 is a liposomal formulation administered by intravenous injection. A total of 18 participants were enrolled in the FIH trial and treated with 15 mg QW to 300 mg QW. The overall safety was good, and preliminary efficacy was observed [37].

1.2. Investigational Product: GFH375

1.2.1 Preclinical Studies of GFH375

GFH375 is a KRAS G12D inhibitor independently developed by the sponsor, GenFleet. Comprehensive preclinical studies have been conducted, and a summary is provided below. For more detailed information, please refer to the GFH375 Investigator's Brochure.

1.2.1.1 Summary of Pharmacology Studies

GFH375 has demonstrated high activity and high selectivity in *in vitro* studies. *In vitro* biochemical studies have shown that GFH375 can effectively inhibit the transition of KRAS G12D mutant or wild-type protein from the inactive state (GDP-bound) to the active state (GTP-bound), with half-maximal inhibitory concentrations (IC_{50}) of 6 nM and 9 nM, respectively. GFH375 can also directly block the binding of activated KRAS G12D or wild-type protein to its downstream effector protein RAF1, with IC_{50} values of 2 nM and 7 nM, respectively. GFH375 has shown high activity in multiple KRAS G12D-mutated tumor cell lines, with an IC_{50} of 0.2-0.9 nM for inhibiting the phosphorylation level of the downstream pathway protein ERK1/2, and an anti-tumor cell proliferation IC_{50} of 1-10 nM. In other KRAS mutation types (KRAS G12C, G12V) of tumor cell lines, as well as KRAS wild-type and KRAS function-dependent tumor cell lines, the activity of GFH375 is relatively weak, with anti-tumor cell proliferation IC_{50} values of 159-1895 nM and 17-75 nM, respectively. GFH375 has only very weak activity in other RAS protein mutations (NRAS G12D, Q61H, HRAS Q61L) and KRAS-independent cell lines (anti-cell proliferation IC_{50}: 1636 nM-7873 nM), indicating very low off-target non-specific cytotoxicity.

Preclinical *in vivo* studies have shown that GFH375 demonstrates excellent *in vivo* activity and anti-tumor efficacy in animal models of KRAS G12D-mutated tumors. In a human pancreatic carcinoma

Panc 04.03 xenograft tumor mouse model, a single dose of GFH375 (100 mg/kg) produced strong and durable inhibition of intratumoral ERK1/2 phosphorylation levels. In the Panc 04.03 and another human pancreatic carcinoma AsPC-1 xenograft tumor mouse model, GFH375 (10 mg/kg, 30 mg/kg, and 100 mg/kg) administered orally twice daily for 14 consecutive days demonstrated dose-dependent anti-tumor efficacy, with effective doses of 5 mg/kg and 10 mg/kg, respectively, and caused significant tumor regression at the high dose (100 mg/kg).

GFH375 has high selectivity for the KRAS G12D target, with a low potential risk of off-target effects. At 10 μM, GFH375 showed no inhibitory activity against 72 representative human kinases and no inhibitory activity against 38 of 44 important safety-related targets, including G protein-coupled receptors (GPCRs), ion channels, and enzymes. For the 6 affected targets, the predicted IC_{50} concentration of GFH375 is at least >1000 nM, which is much higher than the aforementioned IC_{50} concentrations for ERK1/2 phosphorylation inhibition and anti-tumor cell proliferation in KRAS G12D cells.

The safety pharmacology studies of GFH375 included *in vitro* effects on the hERG potassium channel current and *in vivo* effects on the central nervous, respiratory, and cardiovascular systems in rats and beagle dogs, respectively.

At concentrations of 3, 6, 12, and 24 μM, GFH375 showed a concentration-dependent inhibitory effect on the hERG potassium channel current expressed in transfected human embryonic kidney cells (HEK293), with an IC_{50} value of 9.65 μM.

SD rats were given single oral gavage doses of 50, 100, and 200 mg/kg of GFH375, and the effects of the test article on the central nervous system were evaluated through a functional observation battery (FOB) while simultaneously measuring forelimb grip strength and body temperature. The results showed that the no observed adverse effect level (NOAEL) of GFH375 on the central nervous system was 200 mg/kg.

SD rats were given single oral gavage doses of 50, 100, or 200 mg/kg of GFH375, and the effects on the respiratory system were assessed using a whole-body plethysmography system. The results showed that the no observed adverse effect level (NOAEL) of GFH375 on the respiratory system in this study was 200 mg/kg.

Beagle dogs were given oral gavage doses of 5, 10, and 25 mg/kg of GFH375 according to a "crossover design", and the effects on the cardiovascular system were evaluated using telemetry. The results showed that the NOAEL of GFH375 on the cardiovascular system of Beagle dogs was 25 mg/kg/day.

1.2.1.2 Summary of PK Studies

GFH375 showed low permeability in Caco-2 cells with significant efflux transport. It can be administered orally, with a preclinical absolute bioavailability of 8.40-16.3% across species, and systemic exposure increased with increasing oral doses. There was no significant sex difference overall after administration in dogs, while there was some sex difference in rats; after repeated dosing in rats, there was no accumulation at PK doses, but accumulation was observed in female rats at TK doses; accumulation was observed in dogs after repeated dosing.

GFH375 showed very high binding in mouse plasma, high binding in rat and dog plasma, and moderate binding in monkey and human plasma. The steady-state volume of distribution (Vd_{ss}) in rats and dogs ranged from 15.7-22.5 L/kg, both showing high distribution. Total radioactivity of [^{14}C]GFH375 was widely distributed in rats, with C_{max} in descending order in the stomach wall, intestinal wall, liver, spleen, kidney, lung, heart, ovary/uterus, body fat, skeletal muscle, whole blood, and plasma. Radioactivity levels were low in the whole brain and testis/epididymis, with no significant red blood cell binding.

The main metabolic pathway of [^{14}C]GFH375 in rats was glucuronidation, with minor pathways including mono-oxidation, dehydrogenation, defluorination, cysteine conjugation, glycine conjugation, and acetylation. In beagle dog plasma, the main metabolic pathways were oxidation, dehydrogenation, defluorination, dealkylation, glucuronidation, and glutathione conjugation followed by hydrolysis to remove glutamic acid. CYP3A is its main metabolic enzyme, and the *in vivo* and *in vitro* metabolic profiles are basically consistent.

GFH375 showed moderate and low clearance in male and female rat plasma, respectively, and high clearance in dog plasma. It has a long half-life in rats and dogs, ranging from 8.18-14.3 h. Total radioactivity of [^{14}C]GFH375 in rats was mainly excreted directly in feces or via bile into feces, with urine being a minor excretion route.

GFH375 showed no inhibitory effect on CYP1A2 and CYP2C9, but had an inhibitory effect on CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP3A (with midazolam as substrate), and CYP3A (with testosterone as substrate), with IC_{50} values of 42.8, 93.2, 42.6, 26.2, 6.40, and 7.95 μM, respectively. GFH375 has significant time-dependent inhibition on CYP3A (with midazolam and testosterone as substrates, respectively). GFH375 is not an inducer of CYP1A2 and CYP2B6, but its potential as an inducer of CYP3A4 at the gene level cannot be excluded. GFH375 is not a substrate of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide 1B1 (OATP1B1), or organic anion-transporting polypeptide 1B3 (OATP1B3) transporters, but it is a substrate of P-gp. GFH375 showed

no inhibitory effect on BCRP, OATP1B1, organic cation transporter 2 (OCT2), or multidrug and toxin extrusion protein 2-K (MATE2-K), but had an inhibitory effect on P-gp, OATP1B3, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), and multidrug and toxin extrusion protein 1 (MATE1), with IC_{50} values of 16.9, 17.4, 2.56, 24.4, and 15.6 μM, respectively. This suggests that GFH375 has potential for drug-drug interactions.

1.2.1.3 Summary of Toxicology Studies

In 14-day repeated-dose toxicity dose-range finding studies conducted in SD rats and beagle dogs, the results showed that the severe toxicity dose in 10% of animals (STD_{10}) in SD rats was greater than 150 mg/kg/day. The highest non-severely toxic dose (HNSTD) in beagle dogs was 100 mg/kg/day.

In a 4-week repeated-dose Good Laboratory Practice (GLP) toxicity study in SD rats, doses of 50, 100, 200 mg/kg/day of GFH375 or blank vehicle [5% (v/v) LABRASOL + 5% (v/v) PEG400 + 90% sterile water for injection] were administered by oral gavage once daily for 28 consecutive days. At a dose of 100 mg/kg/day, 1 female animal death was observed; at a dose of 200 mg/kg/day, 2 male and 3 female animal deaths were observed. Surviving animals in the 200 mg/kg/day dose group also showed test article-related clinical signs, changes in hematology and serum chemistry parameters, and histopathological changes. At the end of the recovery period, all the above changes were reversed. Under the conditions of this study, the STD_{10} of the test article was 100 mg/kg/day.

In a 4-week repeated-dose GLP toxicity study in beagle dogs, doses of 5, 10, 25 mg/kg/day of GFH375 or blank vehicle [5% (v/v) LABRASOL + 5% (v/v) PEG400 + 90% sterile water for injection] were administered by oral gavage once daily for 28 consecutive days. No animal deaths were observed during the study. Test article-related clinical signs, changes in hematology and serum chemistry parameters, and histopathological changes were observed. After the recovery period, the changes were reversible or showed a trend toward recovery. Under the conditions of this study, the HNSTD of GFH375 for beagle dogs was 25 mg/kg/day.

The genotoxicity of GFH375 was evaluated using a standard battery of genotoxicity tests, and the results were negative.

1.3. Rationale for Study Design

1.3.1 Dose Selection

1.3.1.1 Rationale for Starting Dose Selection

The selection of the starting dose in the Phase I part is based on the results of preclinical toxicology studies, and the starting dose is calculated according to the recommendations of the ICH S9 guideline on the maximum recommended starting dose (MRSD) method.

Pivotal 4-week toxicology studies compliant with GLP were conducted in SD rats and beagle dogs. The study doses in rats were 50, 100, and 200 mg/kg/day, and the study doses in dogs were 5, 10, and 25 mg/kg/day. The study results showed that the severe toxicity dose in 10% of animals (STD10) in rats was 100 mg/kg/day, and the HNSTD in dogs was 25 mg/kg/day. According to ICH S9, based on 1/10 of the rodent STD10 or 1/6 of the non-rodent HNSTD, calculated for a patient weight of 60 kg, the corresponding human MRSDs are approximately 100 mg and 140 mg/day, respectively.

Pharmacodynamic studies showed that in an *in vivo* anti-tumor efficacy study conducted in the Panc 04.03 human pancreatic carcinoma CDX tumor mouse model, the effective dose of GFH375 was 5 mg/kg BID for 14 days. In the AsPC-1 human pancreatic carcinoma CDX tumor mouse model, the effective dose of GFH375 was 10 mg/kg BID for 14 days.

In summary, based on the safety indicated by the toxicology study results, and in combination with the GFH375 tablet strength, a dose level of 100 mg/day was selected as the starting dose for the first-in-human trial of GFH375.

1.3.1.2 Rationale for Phase II Dose Selection

After the completion of Phase I dose escalation and backfilling, the safety and RP2D will be confirmed based on a comprehensive assessment of preclinical *in vitro* and *in vivo* activity, clinical PK, clinical safety, and clinical efficacy data, and this dose will be used for the Phase II part.

1.3.2 Risk-Benefit Assessment

1.3.2.1 Potential Risks

Currently, a few small molecule inhibitors targeting KRAS G12D are in the clinical trial stage, with limited disclosure of safety and efficacy data. Among them, HRS-4642 is a KRAS G12D small molecule developed by Hengrui, administered intravenously for the treatment of patients with advanced solid tumors with KRAS G12D mutation. In its first-in-human Phase I part, a total of 18 participants were enrolled. The overall safety was good. Treatment-related AEs with a higher incidence (>2 cases) included blood cholesterol increased, infusion related reaction, proteinuria, anemia, hypertriglyceridemia, lipase increased, hypoproteinemia, blood glucose increased, alanine aminotransferase increased, platelet count decreased, hypercalcemia, hypocalcemia, pyrexia, fatigue, neutrophil count decreased, leucopenia, and aspartate aminotransferase increased[33].

Preclinical toxicology data for GFH375 suggest that its potential toxicities may include liver function impairment and gastrointestinal system adverse reactions. Based on the preclinical study results of GFH375 and data from other KRAS G12D inhibitors, the potential risks of GFH375 are as follows:

- Hepatic impairment

- Gastrointestinal system adverse reactions

1.3.2.2 Potential Benefits

The target population for this study is patients with KRAS G12D mutation-positive advanced NSCLC, PDAC, CRC, and other solid tumors. For such patients, there are no effective treatment options, and chemotherapy or chemotherapy combined with immunotherapy remains the main treatment regimen. No therapeutic drug targeting this mutation has been approved for marketing.

Currently, drugs targeting KRAS G12D have entered clinical studies and have shown preliminary clinical results. Preliminary efficacy data for the KRAS G12D small molecule inhibitor HRS-4642 show that among 18 enrolled participants with advanced solid tumors, 7 participants had target lesion shrinkage. Among them were 10 participants with NSCLC, and 5 of these participants had target lesion shrinkage.

Preclinical studies of GFH375 showed that in a human pancreatic carcinoma tumor animal model carrying the KRAS G12D mutation, a single oral gavage dose of GFH375 resulted in dose-dependent inhibition of ERK1/2 protein phosphorylation, a downstream protein in the KRAS pathway, observed in the tumor. Long-term oral gavage administration (twice daily for 14 consecutive days) showed significant anti-tumor efficacy, with an effective dose of 5-10 mg/kg, and tumor regression was observed at a high dose (100 mg/kg).

In summary, it is expected that GFH375 is worthy of further clinical research in this population to provide a new anti-tumor treatment option for these patients.

1.3.2.3 Risk-Benefit Assessment

Based on the biological characteristics of the KRAS G12D target, the product characteristics of GFH375, and the non-clinical data obtained for GFH375 as described above, this protocol has designed corresponding inclusion/exclusion criteria, lifestyle requirements, and safety examination and follow-up procedures. Through rigorous protocol design, selection of study sites, collection of drug safety information, and timely updating and communication of drug safety information, the risks to participants will be minimized as much as possible. Based on clinical data from products with the same mechanism of action, it is expected that participants who meet the inclusion/exclusion criteria are likely to benefit from GFH375 monotherapy. The overall benefit/risk assessment supports the conduct of this study.

2 Study Objectives and Endpoints

This is a Phase I/II study. The study objectives and endpoints are summarized below.

The objectives and endpoints of the Phase I part of the study include:

Study Objectives	Study Endpoints
Primary Objectives	**Primary Endpoints**
To evaluate the safety and tolerability of GFH375 in patients with advanced solid tumors with KRAS G12D mutation	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs); changes in vital signs, electrocardiogram (ECG), and laboratory tests
• To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of GFH375	• Incidence of dose-limiting toxicity (DLT) events
Secondary Objectives	**Secondary Endpoints**
• To evaluate the pharmacokinetic (PK) characteristics of GFH375 in patients with advanced solid tumors with KRAS G12D mutation.	• Plasma concentrations and PK parameters of GFH375, including but not limited to C_{max}, T_{max}, AUC, $t_{1/2}$, CL/F, V_z/F, C_{trough}
• To evaluate the preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation	• Objective response rate (ORR), duration of response (DoR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • Overall survival (OS)
Exploratory Objective	**Exploratory Endpoint**
• To explore the molecular mechanisms related to treatment sensitivity or drug resistance	• Mutation analysis of circulating tumor DNA (ctDNA) in blood at baseline and at the end of treatment

The objectives and endpoints of the Phase II part of the study include:

Study Objectives	Study Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the efficacy of GFH375 in patients with advanced non-small cell lung cancer (NSCLC), advanced pancreatic carcinoma (PDAC), advanced colorectal cancer (CRC), and other solid tumors with KRAS G12D mutation	• ORR as assessed by RECIST 1.1
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation using other efficacy endpoints	• Best overall response (BOR), DoR, DCR, TTR, and PFS as assessed by RECIST 1.1 • OS
• To evaluate the safety of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced	• Incidence and severity of AEs and SAEs • Changes in vital signs, ECGs, and laboratory tests

CRC, and other advanced solid tumors with KRAS G12D mutation	
• To evaluate the PK characteristics of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation	• Plasma concentrations of GFH375
Exploratory Objective	**Exploratory Endpoint**
• To explore the molecular mechanisms associated with treatment sensitivity or drug resistance	• Mutation analysis of blood ctDNA at baseline and at the end of treatment
• For PDAC participants: Relationship between carbohydrate antigen 19-9 (CA19-9) and treatment response	• For PDAC participants: Change from baseline in serum CA19-9

3 Study Design

3.1. Overall Design

This is a study to evaluate the safety/tolerability, PK, and efficacy of GFH375 monotherapy in patients with advanced solid tumors with KRAS G12D mutation. The primary objective of the Phase I part is to evaluate the safety/tolerability, PK, and preliminary efficacy of GFH375 in patients with advanced solid tumors carrying the KRAS G12D mutation, and to determine the MTD and RP2D of GFH375. The primary objective of the Phase II part is to evaluate the efficacy of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation.

A Safety Monitoring Committee (SMC), composed of investigators and the sponsor, will be established during the study. For details, please refer to Chapter 10 and the SMC Charter for this study.

3.1.1 Phase I Part Dose Escalation

Phase I will enroll patients with KRAS G12D-positive advanced solid tumors. The study schematic is shown in Figure 2.

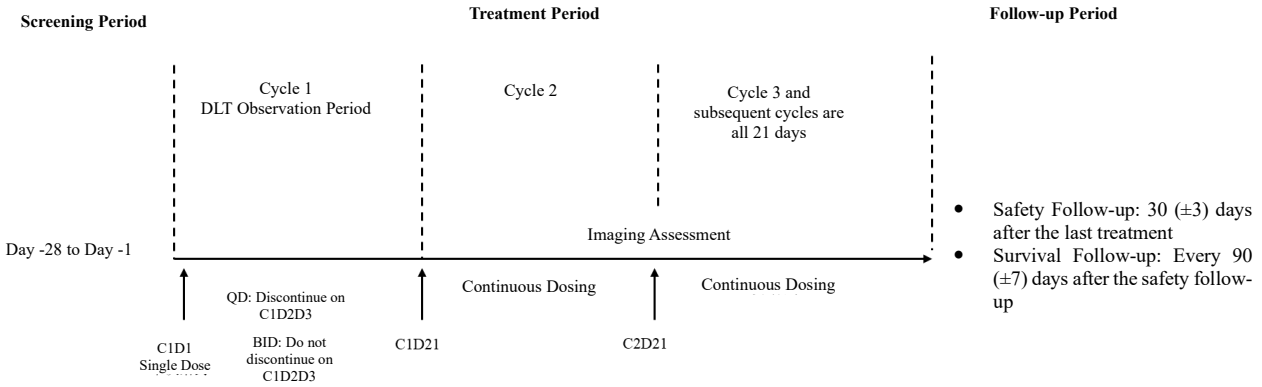

Figure 2 Phase I Part Schematic

According to the BOIN design, 3-6 participants will be enrolled in each dose cohort (except during accelerated titration) for treatment. Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional participants for backfilling. These participants will receive treatment with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is assessed by the investigator and sponsor as potentially clinically beneficial, in order to better estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. If the safety of the 750 mg QD dose cohort has been explored and confirmed, backfilling of the 700 mg QD dose cohort may also be conducted. Backfilled participants will not be included in the DLT evaluation. After backfilling, no more than 30 participants will be

treated in each GFH375 dose cohort (including participants enrolled in the BOIN dose-escalation phase).

Additional participants may be enrolled if more dose levels or alternative dosing regimens need to be explored.

After enrollment, participants will receive oral administration of GFH375, with each treatment cycle being 21 days. Participants will be enrolled into sequential dose-escalation cohorts, with a starting dose of 100 mg once daily (QD). A total of 7 or more dose levels are expected to be evaluated in the dose escalation part. The planned escalating doses are shown in Table 1.

The GFH375 dosing regimen will be comprehensively evaluated during dose escalation. If necessary, dose exploration with a twice daily (BID) dosing regimen will be conducted. Dose escalation for QD and BID dosing regimens can be conducted independently and in parallel.

The first cycle after the first administration will serve as the DLT observation period. A DLT-evaluable case must meet one of the following two conditions:

- The participant experiences a DLT event, or
- The participant does not experience a DLT event and has received at least 15 days of the planned dosing of GFH375 in the first cycle.

If no DLT event occurs, the participant will continue treatment, with dose adjustments permitted as allowed by this protocol, until progressive disease (PD), unacceptable toxicity, or discontinuation of study treatment for other reasons. If a participant experiences a DLT event during the DLT observation period, and if the investigator and sponsor assess that the participant can benefit from continuing treatment with GFH375, treatment with GFH375 will be resumed after the relevant adverse event (AE) has resolved. Refer to Table 4 and Table 5 for the criteria for resumption of dosing.

Participants enrolled in Phase I will undergo intensive PK sampling and have matching ECGs collected with PK sampling to evaluate the PK characteristics and safety of GFH375. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks. Participants will return to the study site 30 (±3) days after the last study treatment for a safety follow-up, and will have survival follow-ups every 90 (±7) days thereafter. Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the Informed Consent Form (ICF), initiation of other anti-tumor therapy, or the termination of the study.

Table 1 Phase I Part QD Dose Cohorts with Planned/Completed Escalation

	Phase I Part QD Dose Cohorts with Planned/Completed Escalation *
Dose Cohort 1	100 mg QD
Dose Cohort 2	200 mg QD
Dose Cohort 3	400 mg QD
Dose Cohort 4	600 mg QD
Dose Cohort 5	750 mg QD
Dose Cohort 6	1000 mg QD
Dose Cohort 7	1200 mg QD

Note: Intermediate dose exploration of the above doses, such as 150 mg, 300 mg, 500 mg, 800 mg, 900 mg, 1100 mg QD, etc., may be conducted during the escalation process based on the clinical data obtained, including safety, PK, and possible efficacy.

Based on the data obtained, including safety, PK, and preliminary efficacy results, BID dose regimen may be conducted. The starting dose for BID will be selected from one of the dose cohorts in the table below, and the total daily dose will be consistent with the QD dose being explored.

Table 2 Phase I Part Possible BID Dose Cohorts for Exploration

	Phase I Part Possible BID Dose Cohorts for Exploration*
Dose Cohort 1	100 mg BID
Dose Cohort 2	150 mg BID
Dose Cohort 3	200 mg BID
Dose Cohort 4	300 mg BID
Dose Cohort 5	400 mg BID

Note: Intermediate dose exploration of the above doses, such as 250 mg BID, etc., may be conducted.

3.1.1.1 DLT Definition

A DLT is an AE that occurs within 21 days after the first dose, is related to the investigational drug GFH375, and meets the following severity criteria. The severity of AEs is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0:

- Grade ≥ 4 absolute neutrophil count (ANC) decreased for ≥ 5 days;
- Grade ≥ 3 febrile neutropenia (ANC $<1.0 \times 10^9$/L with a single body temperature > 38.3°C or a sustained body temperature ≥38°C for more than 1 hour);
- Grade ≥ 4 platelet count decreased for ≥ 5 days;
- Grade ≥ 3 platelet count decreased with Grade ≥ 2 hemorrhage;
- Grade ≥ 4 anemia;
- If baseline ALT or AST is Grade ≤ 1: Grade ≥ 3 serum transaminases increased (ALT or AST) lasting > 7 days is considered a DLT; if baseline ALT or AST is Grade 2, then ALT or AST >

10×ULN lasting > 7 days is considered a DLT;

- Grade ≥ 3 serum bilirubin increased;
- According to Hy's Law, AST or ALT > 3×ULN (if baseline metastases to liver are present, then > 3 times the baseline value is required), with concurrent total bilirubin > 2×ULN (causes such as biliary obstruction or other causes like hepatitis, intrahepatic tumor progression, etc., must be excluded);
- Grade ≥ 3 other toxicities (non-hepatic, non-hematologic), with the exception of the following:
  - Grade 3 nausea or vomiting, diarrhea, lasting no more than 3 days with/without symptomatic supportive care;
  - Grade 3 fatigue, lasting no more than 3 days with/without symptomatic supportive care;
  - Asymptomatic Grade 3 abnormal laboratory results lasting no more than 7 days with intervention, such as elevated cholesterol, elevated triglycerides, gamma-glutamyl transferase (GGT) increased, alkaline phosphatase (ALP) increased, blood amylase increased, etc.

Toxicities meeting the above criteria that occur after the DLT observation period will also be considered important factors in the safety evaluation. In addition, other treatment-related toxicities that may be assessed as DLTs will be determined after discussion between the sponsor and the investigator.

During the first cycle (DLT observation period), AEs that meet the DLT criteria should be reported to the sponsor within 24 hours of awareness of their occurrence.

3.1.1.2 Dose Escalation Rules and MTD Definition

Accelerated titration is permitted for the first two dose levels of the QD dosing regimen, meaning the first participant will receive treatment at the first dose level. If no Grade ≥2 treatment-related AE is observed in participants in the first two dose cohorts during the DLT observation period, 3-6 participants will be enrolled at the next higher dose level, and the BOIN design will be used for this cohort and subsequent dose escalations. Conversely, if any Grade ≥2 treatment-related AE or DLT event is reported in the first or second dose cohort, the study will switch directly to the BOIN design, starting from the lowest dose cohort where the Grade ≥2 treatment-related AE or DLT event was observed. Provided that accelerated titration is completed for the first dose, the decision on whether to use accelerated titration for the second dose level will be made by the SMC based on discussion of the PK and safety data from the first dose level. Subsequent dose levels will use the BOIN design to

determine the MTD, with a target toxicity probability of 0.3. If dose exploration of the BID dosing regimen is required, the BOIN design will be used for dose escalation, with a target toxicity probability of 0.3. Each dose level will enroll 3-6 participants for treatment. If more dose levels or dosing regimens need to be explored, additional participants may be enrolled.

The BOIN design will assign the dose level for the next group of participants according to the dose escalation/de-escalation rules shown in Table 3.

Table 3 BOIN Design Dose Escalation/De-escalation Rules

Decision	Total number of participants treated at the current dose						
	3	**4**	**5**	**6**	**7**	**8**	**9**
Escalate, if number of participants with DLT is ≤	0	0	1	1	1	1	2
De-escalate, if number of participants with DLT is ≥	2	2	2	3	3	3	4
Eliminate dose, if number of participants with DLT is ≥	3	3	4	4	5	5	5

The specific rules are as follows:

- If the decision based on the rules in the table above is neither to escalate, de-escalate, nor eliminate the dose, then continue treating the next group of participants at the current dose.
- “Eliminate dose” in the table above means to eliminate the current and higher doses from the study.
- If the current dose is eliminated, the dose will be automatically de-escalated to the next lower level to treat participants.
- If the lowest dose level is eliminated, the study will be terminated early to ensure participant safety. In this case, the MTD cannot be determined.
- If the current dose is the lowest dose level and the rule suggests de-escalation, the next group of participants will still be treated at the current lowest dose.
- If the current dose is the highest dose level and the rule suggests escalation, newly enrolled participants will still be treated at the highest dose.
- The dose escalation part can be terminated when there are ≥6 evaluable participants at the recommended next dose level.
- There must be at least 6 evaluable participants treated at the RP2D.

After the dose escalation part is completed, isotonic regression analysis will be used based on the DDS to determine the MTD. The online BOIN software at http://www.trialdesign.org will be used to

perform isotonic regression analysis to obtain the isotonic estimates of the toxicity probability for each dose level. The dose level closest to the target toxicity rate of 0.3 is the MTD. If there are 2 or more dose levels that meet the condition simultaneously, the highest dose level with an isotonic estimate <0.3 or the lowest dose level with an isotonic estimate ≥0.3 will be selected.

3.1.1.3 Backfilling of Participants in the Dose Escalation Part

Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional participants for backfilling. These participants will receive treatment with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is assessed by the investigator and sponsor as potentially clinically beneficial, in order to better estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. If the safety of the 750 mg QD dose cohort has been explored and confirmed, backfilling of the 700 mg QD dose cohort may also be conducted. Backfilled participants will not be included in the DLT evaluation. After backfilling, no more than 30 participants will be treated in each GFH375 dose level (including participants enrolled in the BOIN dose escalation part).

Backfilled participants will complete the relevant visits according to the Phase I part Schedule of Activities and the Phase I part PK blood sampling schedule.

3.1.1.4 Intra-participant Dose Escalation

In principle, intra-participant dose escalation will not be performed during the dose escalation part. For participants enrolled in Phase I, after agreement from the investigator and sponsor, intra-participant dose adjustment to receive RP2D monotherapy is permitted after the RP2D for this protocol has been confirmed.

3.1.1.5 Rationale for Selection of Recommended Phase II Dose (RP2D)

As of January 17, 2025, a total of 33 participants have been enrolled in the Phase I part of this study (including 22 participants in the dose escalation part and 11 backfilled participants), and DLT observation has been completed for 7 dose cohorts: 100 mg, 200 mg, 400 mg, 600 mg, 750 mg, 900 mg QD, and 300 mg BID. Enrolled participants include 14 with pancreatic carcinoma, 11 with NSCLC, 5 with CRC, and 1 each with ampullary cancer, endometrial cancer, and bile duct cancer. Based on all available safety, tolerability, PK, and efficacy data, after discussion between the sponsor and key members of the SMC, the RP2D was determined to be 600 mg QD. The rationale for this selection is as follows:

Safety and tolerability:

No DLTs or Grade 5 AEs occurred in any dose cohort. In the 900 mg dose cohort, 2 of the 3 enrolled

participants discontinued treatment in Cycle 1 due to AEs and poor tolerability, indicating poor overall tolerability. The 750 mg dose cohort had a higher incidence of more severe gastrointestinal toxicity (Grade 2/3 diarrhea and vomiting), and the duration of vomiting was relatively long. In the 750 mg dose cohort, the incidence of Grade ≥2 diarrhea and Grade 2 vomiting were both 50%, including one case of Grade 3 diarrhea. In dose cohorts below 750 mg (QD), no Grade 3 diarrhea was observed, and the incidence of Grade 2 diarrhea was ≤20.0%. In the 300 mg BID dose cohort, the incidence of Grade 2 diarrhea and vomiting were 33.3% and 66.7%, respectively, which were higher than in the 600 mg QD dose cohort. The incidence of ≥ G3 treatment-emergent AEs (TEAEs) and treatment-related AEs (TRAEs) was higher in the 400 mg dose cohort than in the 600 mg QD dose cohort. There was no significant difference in the incidence of SAEs. The incidence of dose interruption due to TRAEs was also higher in the 400 mg QD dose cohort than in the 600 mg dose cohort. In the 600 mg dose cohort, only 1 participant discontinued dosing due to a TRAE, and no participants had a dose reduction due to a TRAE. The overall safety and tolerability of the 600 mg dose cohort were similar to or better than the 400 mg dose cohort. The 600 mg dose cohort was generally safe, manageable, and well-tolerated.

PK:

After oral administration of 100-900 mg of GFH375, exposure to GFH375 increased with increasing dose in the 100-400 mg range, but the increase in exposure was not significant in the 400-900 mg range. After QD oral administration of 400 mg-900 mg of GFH375, the median T_{max} was 2-4 h, the single-dose half-life was 18.5-21.6 h, and the accumulation ratio after continuous QD dosing was 0.859-1.30, with no significant accumulation observed. When the dose was higher than 400 mg, the mean trough concentration of GFH375 (34.4-50.2 ng/mL) could be sustained above the preclinical cellular IC_{90} (approximately 11 ng/mL). As mentioned earlier, overall, the safety and tolerability of the 400 mg and 600 mg cohorts were better than those of the 750 mg and 900 mg cohorts. However, the 400 mg cohort showed greater inter-individual variability (geometric CV% for C_{max} and AUC was 111%-127%). Compared to 400 mg, 600 mg can provide participants with higher and more stable exposure.

Efficacy:

Partial responses were observed in participants with pancreatic carcinoma and NSCLC starting from the 400 mg dose cohort. In the 400 mg dose cohort, the ORR and DCR for participants with pancreatic carcinoma were both 100% (2/2), while for participants with NSCLC, the ORR was 0 and the DCR was 50% (1/2). In the 600 mg QD and 300 mg BID dose cohorts, the ORR for pancreatic carcinoma was 25% (1/4) and the DCR was 100% (4/4). For NSCLC, the ORR was 75% (3/4) and the DCR was

100% (4/4). In the 750 mg dose cohort, the ORR for pancreatic carcinoma was 0 and the DCR was 100% (2/2). For NSCLC, both the ORR and DCR were 100% (1/1). In participants with NSCLC, the efficacy of the 600 mg dose cohort was superior to that of the 400 mg cohort.

Based on a comprehensive review of the above data, the RP2D was determined to be 600 mg QD.

3.1.2 Phase II Part

The Phase II part is an open-label, multicenter study. The overall study plan is shown in Figure 3. The objective is to evaluate the efficacy, safety, and PK characteristics of GFH375 in patients with advanced non-small cell lung cancer, advanced pancreatic carcinoma, colorectal cancer, and other advanced solid tumors with KRAS G12D mutation. The Phase II part will enroll approximately 317 participants with advanced solid tumors with KRAS G12D mutation to receive continuous GFH375 monotherapy at the RP2D, with a treatment cycle of 21 days. All participants enrolled in this part will undergo sparse PK sampling according to the Phase II part PK blood sampling schedule and have matching ECGs collected with PK sampling.

- Advanced NSCLC participant cohort: Approximately 73 participants with advanced NSCLC carrying the KRAS G12D mutation are planned for enrollment.
- Advanced PDAC participant cohort: Approximately 94 participants with advanced PDAC carrying the KRAS G12D mutation are planned for enrollment.
- Advanced CRC participant cohort: Approximately 50 participants with advanced CRC carrying the KRAS G12D mutation are planned for enrollment.
- Participant cohorts with other solid tumors: Approximately 100 participants with other advanced solid tumors carrying the KRAS G12D mutation are planned for enrollment, such as bile duct cancer, appendix cancer, etc., carrying the KRAS G12D mutation.

Eligible participants who are screened will receive GFH375 monotherapy until PD, unacceptable toxicity, or discontinuation of study treatment for other reasons. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks. Participants will return to the study site 30 (±3) days after the last study treatment for a safety follow-up, and will have survival follow-ups every 90 (±7) days thereafter. Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the Informed Consent Form (ICF), initiation of other anti-tumor therapy, or the termination of the study.

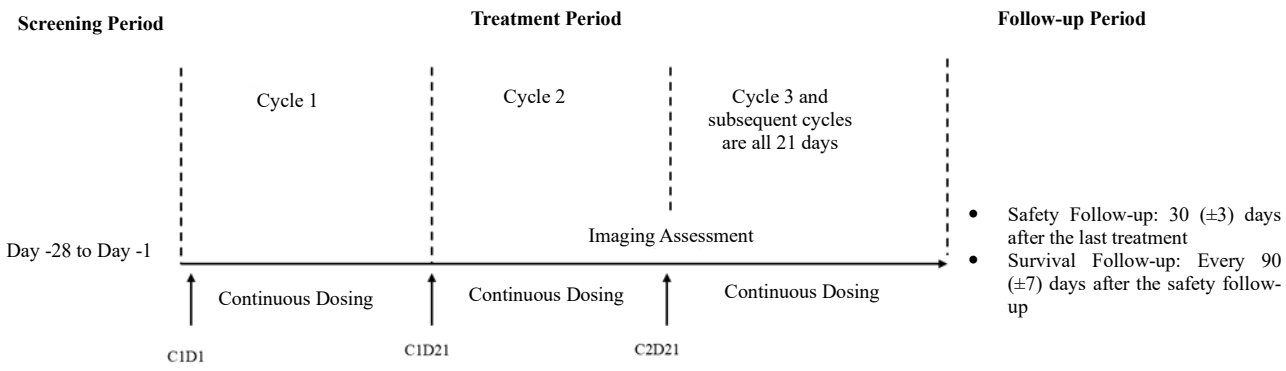

Figure 3 Phase II Part Schematic

3.2. Definition of End of Study

The end of the study is defined as the last participant having received at least 6 months of study treatment or having withdrawn early (whichever occurs first).

3.3. Early Termination of the Study

This study may be terminated or suspended early due to a decision by a regulatory authority, an opinion from an ethics committee (EC), or a judgment and decision made jointly by the sponsor and the investigator. In addition, the sponsor reserves the right to stop the development of GFH375.

Reasons for early termination or suspension of the study may include:

- Determination of an unexpected, significant, or unacceptable risk to participants;
- Existing efficacy results support early termination of the study;
- Low compliance with protocol requirements.

The party that decides to suspend/terminate the study will issue a written notice and record the reason for the study termination or suspension to the investigator, sponsor, and regulatory authorities. If the study is terminated or suspended early, the investigator should immediately notify the EC and the sponsor, and provide the relevant reasons.

Once the aforementioned issues leading to the suspension of the investigational drug, such as safety and protocol compliance, are resolved and with the consent of the sponsor, EC, and/or regulatory authorities, the study will be resumed.

4 Study Population

Participants must meet all inclusion criteria and not meet any of the exclusion criteria.

4.1. Inclusion Criteria

Participants must meet all of the following criteria to participate in this study:

1. Participants who voluntarily participate in the study and sign the ICF.
2. Male or female, aged 18 - 75 years at the time of signing the ICF.
3. Participants with histologically or cytologically confirmed locally advanced or metastatic malignant tumor, who must meet the following criteria:

（1） Phase I Part: Either of the following criteria is met: 1) PD after standard of care and no other standard of care is available; or 2) standard of care has been confirmed to be ineffective, intolerable, or considered unsuitable.

（2） Phase II Part:

a) Advanced NSCLC:

- ✓ Participants who have progressed after prior treatment with anti-PD-(L)1 therapy and/or platinum-based chemotherapy (unless contraindicated or intolerant), and have received no more than 3 prior lines of therapy;
- ✓ If prior adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy.

b) Advanced PDAC: Participants who have progressed after adequate treatment with a gemcitabine-based chemotherapy regimen or FOLFIRINOX/mFOLFIRINOX regimen, or are unsuitable for standard of care due to reasons such as unacceptable toxicity, and have received no more than 3 prior lines of therapy. Those with high microsatellite instability (MSI-H) and/or deficient mismatch repair (dMMR) must have progressed after at least one prior line of anti-PD-1 therapy. If adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy.

c) Advanced CRC: Participants who have progressed after at least two lines of standard of care, or are unsuitable for standard of care due to reasons such as unacceptable toxicity. Participants must have experienced PD or recurrence during or after

treatment with fluorouracil, irinotecan, and oxaliplatin for metastatic disease, unless the investigator considers the participant unsuitable for the above treatment regimens. Those with known MSI-H and/or dMMR must have received prior treatment with an immune checkpoint inhibitor (if applicable). If adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy.

d) Other solid tumors: Participants who have progressed after standard of care, or are unsuitable for standard of care due to reasons such as unacceptable toxicity.

4. Participants enrolled in this study must provide a written test report confirming KRAS G12D mutation-positive status. NSCLC and PDAC participants enrolled in Phase II must provide a compliant archived tumor tissue sample or undergo a biopsy during the screening period before enrollment. If a tumor tissue sample cannot be provided and a biopsy cannot be performed during the screening period, the investigator must communicate with the sponsor's medical monitor and obtain their consent before enrollment.
5. According to RECIST 1.1, participants enrolled in Phase I must have at least one evaluable lesion, and participants enrolled in Phase II must have at least one measurable lesion.
6. Toxicities from prior anti-tumor therapy must have resolved to baseline level (excluding alopecia) or ≤ Grade 1 (for neurological toxicity, ≤ Grade 2).
7. Investigator-assessed life expectancy ≥ 12 weeks.
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-1 (see Appendix 2 for scoring criteria).
9. Adequate organ function, including:
   - Hematopoietic function: Absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count ≥ 75×10^9/L, hemoglobin ≥ 9 g/dL, with no transfusion or treatment with granulocyte colony-stimulating factor, thrombopoietin, or erythropoietin within 14 days before the blood test.
   - Liver function:
     - Both AST and ALT < 2.5×ULN; for participants with baseline metastases to liver, both AST and ALT < 5×ULN;
     - Total bilirubin (TBIL) < 1.5×ULN; for participants with Gilbert's syndrome: TBIL < 2×ULN.
   - Renal function: Creatinine clearance (CrCl) ≥ 50 mL/min (calculated by Cockcroft-Gault

formula, see Appendix 3).

- Coagulation function: Prothrombin time (PT) or activated partial thromboplastin time (APTT) < 1.5×ULN, international normalized ratio (INR) < 1.5×ULN or within the target range for anticoagulant therapy.
- Albumin level ≥30 g/L (for PDAC participants enrolled in Phase II only).

10. Women of childbearing potential (WOCBP) and male participants with partners who are WOCBP must agree to use effective methods of contraception from the time of signing the ICF until 30 days after the last study treatment. WOCBP must have a negative serum pregnancy test result within 7 days before dosing.
11. Participants who are able to communicate well, adhere to the follow-up schedule, and comply with the protocol requirements in the investigator's judgment.

4.2. Exclusion Criteria

Participants who meet any of the following criteria cannot be enrolled in this study:

1. Other malignant tumor that has progressed or required treatment within 3 years prior to enrollment, with the exception of adequately treated carcinoma in situ, basal cell carcinoma, or squamous cell carcinoma of skin.
2. Patients with unstable brain metastasis as judged by the investigator. Patients with incidentally detected brain metastasis during screening may be enrolled if they are asymptomatic and do not require therapeutic intervention; enrollment is permissible if the investigator judges the brain metastasis to be stable, the hormone dose is stable, and the prednisone dose is ≤10 mg/d (or an equivalent dose if other steroid drugs are used).
3. Phase II Part:
   a) Advanced NSCLC: Exclusion of known other driver gene mutations or fusions, such as EGFR, ALK, BRAF (V600E), HER2, MET (exon 14), ROS1, RET, KRAS G12C, or NTRK1/2/3
   b) Advanced CRC: Exclusion of known other driver gene mutations, amplifications, or fusions, such as BRAF (V600E), HER2, NTRK, or RET
   c) Advanced PDAC: Exclusion of known other driver gene mutations or fusions, such as BRAF (V600E), BRCA, NTRK, or RET
4. Prior targeted therapy against KRAS G12D or pan-KRAS (with primary targeting effect on KRAS G12D).
5. Receipt of palliative radiation within 14 days before administration of the study drug.
6. Receipt of other anti-tumor therapy within 28 days or 5 half-lives (whichever is shorter) before dosing, including chemotherapy, targeted therapy, endocrine therapy, immunotherapy, Chinese patent medicines with definite anti-tumor effects, and other investigational drugs or devices, with the exception of endocrine maintenance therapy.
7. Concomitant clinically significant severe cardiovascular disorder:
   - Clinically significant severe cardiovascular events within 6 months before the first study treatment, such as myocardial infarction, angina unstable, symptomatic cardiac failure congestive (New York Heart Association Class III or IV), severe arrhythmia requiring drug therapy, or receipt of angioplasty, stenting, and coronary artery bypass graft surgery, etc.
   - Clinically significant QT/QTcF prolongation (based on the average of three QTcF values

during the screening period, QTcF > 470 ms) or a family history of QT interval prolongation.

- Hypertension that remains poorly controlled after standard treatment.

8. Stroke or other severe cerebrovascular disorder within 6 months prior to enrollment.
9. History of deep vein thrombosis or any other severe thromboembolism within 3 months prior to enrollment.
10. Concomitant pleural effusion, ascites, or pericardial effusion requiring repeated drainage or causing significant symptoms.
11. Concomitant superior vena cava syndrome.
12. History of gastrointestinal perforation and/or fistula within 6 months before the first dose of study drug that has not healed after surgery; current unstable or active gastrointestinal ulcer or other high-risk gastrointestinal hemorrhage diseases; presence of biliary or pyloric obstruction, or persistent recurrent vomiting (≥3 episodes within 24 hours); high risk of rupture, hemorrhage, or gastrointestinal/respiratory fistula due to tumor invasion of surrounding vital structures (e.g., major blood vessels, trachea); or other gastrointestinal dysfunction or diseases that may significantly affect the absorption of GFH375, or inability or unwillingness to swallow tablets.
13. Concomitant clinically significant interstitial lung disease, radiation pneumonitis, or immune-related pneumonitis requiring treatment.
14. Concomitant major acute or chronic infectious diseases, including:
    - Active infection requiring intravenous antibiotic therapy within 7 days prior to enrollment.
    - Positive for human immunodeficiency virus antibody (HIV-Ab) at baseline.
    - Active hepatitis b virus infection (HBsAg positive with positive HBV-DNA).
    - Active hepatitis c virus infection (HCV-Ab positive with positive HCV-RNA).
    - Active tuberculosis.
15. Other poorly controlled systemic diseases, such as diabetes mellitus.
16. Undergone or planning to undergo major surgery as judged by the investigator within 28 days before the first dose (excluding needle biopsy).
17. History of organ transplant or preparing to receive an organ transplant.
18. Need for acid-suppressing drugs, including proton pump inhibitors and novel acid-suppressing drugs (e.g., potassium-competitive acid blockers), within 7 days before or during the administration of the study drug.
19. Receipt of strong inhibitors or inducers of CYP3A or P-gp within 14 days or 5 half-lives of the drug (whichever is longer) before administration of the study drug.

20. Receipt of known sensitive substrates of CYP3A or OAT1 within 14 days or 5 half-lives of the drug (whichever is longer) before administration of the study drug. Unless agreed for enrollment after review by the investigator and sponsor.
21. Known allergy to the study drug or its components.
22. Severe mental or psychological illness, or history of drug abuse or severe alcoholism.
23. Pregnant or lactating women.
24. Other conditions that, in the investigator's judgment, make the participant unsuitable for the study.
25. **Phase II PDAC participants:** Numeric Rating Scale (NRS) for pain score ≥4 after standardized treatment with analgesics.

5 Study Treatment

5.1 Treatment Regimen

Phase I

The initial dose of GFH375 is 100 mg QD, with each treatment cycle being 21 days. Participants will continue treatment until PD or the occurrence of unacceptable toxicity leading to treatment discontinuation.

Phase II

Participants in Phase II will receive GFH375 at the RP2D, dosed daily. Each treatment cycle is 21 days. Participants will continue treatment until PD, unacceptable toxicity, or other reasons leading to treatment discontinuation.

5.2 Investigational Product

5.2.1 Description of Investigational Product

Investigational Product	GFH375 tablets
Active Ingredient	GFH375
Excipients	Mannitol, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, colloidal silicon dioxide, magnesium stearate, film coating premix (enteric-coated) - Opadry, purified water
Type	Oral solid dosage form
Dosage Form	Tablet
Strength	25 mg, 100 mg
Route of Administration	Oral
Storage Requirements	Store protected from light, sealed, at no more than 25°C
Shelf Life	Tentatively 24 months
Packaging and Labeling	High-density polyethylene bottles for oral solid drugs and polypropylene child-resistant combination caps for oral solid drugs, with a desiccant in a high-density polyethylene non-woven (Tyvek) bag for solid drugs inside. Each bottle will be labeled according to relevant regulatory requirements.

5.2.2 Treatment Assignment and Drug Dispensing

When a participant signs the written ICF, they will be assigned a participant number, which will be used for all study documents and Case Report Forms (CRFs). After completing the screening process,

eligibility for formal enrollment in the study will be determined based on the inclusion/exclusion criteria. All enrolled participants will receive GFH375 treatment.

The investigator or their designee must ensure that all drugs or related items for study treatment are maintained under appropriate temperature conditions during transport. If any deviation occurs, the issue must be reported and resolved before administering the study treatment.

Only participants enrolled in the study may receive the study treatment, and only authorized site personnel may provide or manage the study treatment product. All investigational intervention drugs or related items must be stored according to the storage conditions specified on the label in a secure, environmentally controlled, and monitorable (manually or automatically) area, ensuring that only the investigator and authorized site personnel have access to the study treatment product.

5.2.3 Administration of Investigational Product

GFH375 will be dispensed to participants by site personnel at scheduled visits. The quantity of drug dispensed at one time will ensure that the participant has enough medication for self-administration outside the hospital for the specified period.

GFH375 tablets are administered orally. Participants must be instructed to swallow the tablets whole and not to chew or break them. Fasting is required from 2 h before to 1 h after taking the medication, and the dosing time should be kept as consistent as possible each day. If a PK blood sample needs to be drawn in the morning, the medication should be taken after the blood draw. When dosing twice daily (BID), it is recommended to schedule the doses around 8:00 AM and 8:00 PM.

If a dose is missed, it should be taken within 4 hours of the scheduled time, the actual time of administration should be recorded, and subsequent doses should be taken as originally scheduled. If more than 4 hours have passed, the missed dose should not be taken, and the next dose should be taken as originally scheduled. If vomiting occurs after taking the medication, the dose should not be retaken. All actual dosing times should be recorded in the participant's diary, or any unexpected situations such as "missed dose" should be recorded.

5.3 Dose Adjustment

5.3.1 Permitted Dose Adjustments

In principle, dose adjustments are not permitted for participants enrolled in Phase I during the DLT observation period. The safety of participants using the investigational drug should be closely monitored during the study. It is recommended to manage TRAEs with best supportive care according to the practice of the respective study site.

Phase I participants who have completed the DLT observation period and participants enrolled in Phase II may have their doses adjusted based on actual clinical needs. Dose reduction will be performed according to the dose level settings of Phase I. A maximum of 2 dose reductions are permitted for the same participant. For participants receiving 100 mg QD of GFH375, dose reduction is not permitted in principle; for participants receiving 200 mg QD of GFH375, dose reduction is only permitted to 100 mg QD in principle. In special cases, the investigator should discuss further with the sponsor to reach an agreement. For detailed principles of dose adjustment, refer to Table 4 and Table 5.

In principle, intra-participant dose escalation will not be performed during the dose escalation part. For participants enrolled in Phase I, after agreement from the investigator and sponsor, intra-participant dose adjustment to receive RP2D monotherapy is permitted after the RP2D for this protocol has been confirmed.

5.3.2 Dose Interruption and Permanent Discontinuation

During the study, if a participant experiences an event related to the study treatment that meets any of the permanent discontinuation criteria in Table 4 or Table 5, GFH375 treatment should be stopped, and the participant should be followed up until the event resolves or returns to baseline. If the participant has shown a tumor treatment response and the investigator judges that continuing treatment is beneficial, after full communication with the sponsor, study treatment may be resumed at the same dose or a lower dose after the toxicity has recovered to the following levels, while continuing to closely monitor the relevant toxicity.

Table 4 Dose Adjustment Principles for Hematologic Toxicity

Drug-related Adverse Event	**Severity**	**Dose Adjustment**
Neutrophil count (ANC) decreased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline, resume at the same dose or reduce by 1 dose level;
	Grade 4	Interrupt dosing until recovery to ≤ Grade 1 or baseline, and reduce by 1 dose level;
	Grade 3 febrile ANC decreased	Interrupt dosing until recovery to ≤ Grade 1 or baseline, and reduce by 1 dose level;
	Grade 4 febrile ANC decreased	Interrupt dosing and withdraw from study treatment;
Platelet count (PLT) decreased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline, resume at the same dose or reduce by 1 dose level; if accompanied by hemorrhage requiring clinical intervention, reduce by 1 dose level;

Drug-related Adverse Event	**Severity**	**Dose Adjustment**
	Grade 4	Interrupt dosing until recovery to ≤ Grade 1 or baseline, and reduce by 1 dose level or interrupt dosing and withdraw from study treatment;
Anemia	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 2 or baseline, resume at the same dose or reduce by 1 dose level;
	Grade 4	Interrupt dosing until recovery to ≤ Grade 2 or baseline, and reduce by 1 dose level or interrupt dosing and withdraw from study treatment;
Other	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 2 or baseline, resume at the same dose or reduce by 1 dose level;
	Grade 4	For non-life-threatening AEs that can be controlled with treatment, dosing may be interrupted, and resumed at a reduced dose after the AE recovers to ≤ Grade 1 or baseline. For life-threatening AEs, dosing should be terminated.

Table 5 Dose Adjustment Principles for Non-hematologic Toxicity

Drug-related Adverse Event	Severity	Dose Adjustment
ALT/AST increased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline, resume at the same dose or reduce by 1 dose level; if ALT/AST >5×ULN for more than 2 weeks, or ALT/AST > 8×ULN, interrupt dosing and withdraw from study treatment;
	Grade 4/Meets Hy's Law	Interrupt dosing, withdraw from study treatment;
Blood bilirubin increased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline; if there is no concurrent elevation of transaminases or alkaline phosphatase, treatment can be resumed at the same dose or reduced by 1 dose level;
	Grade 4	Interrupt dosing, withdraw from study treatment;
Blood amylase/lipase increased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline; if asymptomatic, treatment can be resumed at the same dose or reduced by 1 dose level; if symptomatic, reduce by 1 dose level;
	Grade 4	Interrupt dosing until recovery to ≤ Grade 1 or baseline and reduce by 1 dose level, or interrupt dosing and withdraw from study treatment;
Pancreatitis	Grade 2	Interrupt dosing until amylase and imaging are normal or not clinically significant; Reduce by 1 dose level;
	Grade 3/4	Interrupt dosing, withdraw from study treatment;
Nausea/vomiting/diarrhea	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline, resume at the same dose or reduce by 1 dose level; if there is no improvement after more than 3 days of symptomatic supportive care, reduce by 1 dose level;
	Grade 4	Interrupt dosing, withdraw from study treatment;
Hypodynamia	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 2 or baseline; If recovery time is ≤ 1 week, it is recommended to resume treatment at the same dose; if >1 week, it is recommended to reduce by 1 dose level
Other systemic AEs	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline; If recovery time is ≤ 1 week, it is recommended to resume treatment at the same dose; if recovery time is >1 week, it is recommended to reduce by 1 dose level
	Grade 4	For non-life-threatening AEs that can be controlled with treatment, dosing may be interrupted, and resumed at a reduced dose after the AE recovers to ≤ Grade 1 or baseline. For life-threatening AEs, dosing should be terminated.

When the above hematologic toxicities occur, it is recommended to repeat the hematology within 3 days and then continue to closely monitor recovery. Resumption of treatment may be considered if the following criteria are met: non-hematologic toxicity recovers to ≤ Grade 1 or baseline; hematologic toxicity recovers to ANC ≥1.0×10^9/L, PLT ≥ 75×10^9/L, Hb ≥8 g/dL.

If a TRAE does not recover to a level where dosing can be resumed within 4 weeks, or if the same toxicity requiring dose interruption recurs after resuming treatment, permanent discontinuation of treatment should be considered. For the follow-up study procedures after permanent discontinuation, please refer to Section 6.4.2 of the protocol.

5.4 Prior and Concomitant Therapies

5.4.1 Prior Therapies

For prohibited prior/concomitant therapies before a participant participates in this study, please refer to Section 4 of the protocol.

After the participant signs the ICF, information on each line of prior therapy for the study disease (advanced solid tumors) will be collected, as well as other prior medications/therapies within 30 days before the first dose in this study.

5.4.2 Concomitant Therapies

From the first study treatment until the safety follow-up visit, all concomitant therapies, blood products, and non-drug interventions (such as paracentesis) received by the participant will be recorded.

5.4.2.1 Permitted/Cautionary Concomitant Therapies

During the study, the investigator must follow the principles below and use concomitant medications with caution to maximize participant safety.

Palliative and best supportive care for disease symptoms are permitted during the study, but concomitant therapies during the DLT observation period should be avoided if they may interfere with the assessment of DLTs. Palliative and supportive care for disease-related symptoms will depend on the investigator's judgment and relevant guidelines (e.g., American Society of Clinical Oncology guidelines). For example, palliative local radiation to treat painful bone lesions for symptomatic relief is permitted, provided that these lesions were known to exist at enrollment and are not the only target lesions. Before initiating radiation therapy, the investigator should assess and document whether the use of radiation is related to PD.

If a participant develops other diseases during the study, the investigator should determine whether drug therapy is necessary and should, as much as possible, avoid drugs that could significantly affect

the interpretation of study results, so as not to interfere with the assessment of the participant's safety and tolerability. If a serious adverse reaction or SAE occurs, or if the original condition aggravates or other serious diseases develop, the investigator should promptly provide concomitant and active treatment. If the criteria for participant withdrawal from the study are met, arrangements should be made for the participant's proper withdrawal.

- If the investigator is unsure whether a concomitant therapy will affect participant safety, or whether its use will affect the assessment of participant safety and tolerability, or whether its use will affect the participant's eligibility for enrollment and the evaluability of the data, they should discuss with the sponsor and reach an agreement before using the concomitant therapy.

During the study, participants should use known H2 receptor antagonists and antacids with caution, including but not limited to cimetidine, famotidine, nizatidine, and roxatidine. Antacids include hydrotalcite chewable tablets, aluminum phosphate gel, aluminum hydroxide, magnesium hydroxide, calcium carbonate, etc. If the above drugs must be used, GFH375 should be administered at least 2 hours before or after the administration of these drugs.

5.4.2.2 Prohibited Concomitant Therapies

During the study, participants should not receive the following treatments:

1) Any other anti-tumor therapy besides the study treatment (chemotherapy, immunotherapy, biological products, extensive radiotherapy, hormone therapy, targeted therapy, surgery, Chinese medicines with approved anti-tumor indications), including investigational or approved therapies. Participants receiving gonadotropin-releasing hormone (GnRH) antagonists for prostate cancer, oral contraception, or hormone replacement therapy may continue their medication.
2) The use of Chinese medicine (including Chinese patent medicine) is prohibited within 7 days before the first dose, and is not recommended until the final PK collection of the study is completed. If Chinese medicine is required to manage AEs or diseases, its use must be reviewed and approved by the sponsor beforehand.
3) Use of granulocyte colony-stimulating factor drugs as prophylactic treatment. Such drugs may only be used for the treatment of AEs at the investigator's discretion.
4) Any other investigational drugs for ongoing clinical studies, other than the study treatment.
5) The use of known strong inhibitors and inducers of CYP3A and P-gp is prohibited within 14 days before the first dose or 5 half-lives (whichever is longer) until two weeks after the last dose (see Appendix 4).

6) The use of known sensitive substrates of CYP3A or OAT1 is prohibited within 14 days before the first dose of the study drug or 5 half-lives of the drug (whichever is longer) until two weeks after the last dose (see Appendix 4). Unless the drug is reviewed and approved by the investigator and the sponsor's medical monitor during the screening period.

7) The use of known proton pump inhibitors and novel acid-suppressing drugs (e.g., potassium-competitive acid blockers), including but not limited to omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, ilaprazole, and vonoprazan, is prohibited within 7 days before the first dose of the study drug or 5 half-lives (whichever is longer) until one week after the last dose.

5.5 Treatment Compliance

Participants will follow the investigator's instructions to return all unused GFH375 tablets and packaging from the previous cycle on the specified visit day, and hand in the completed participant diary. The quantity returned by the participant will be counted, recorded, and archived, and medication compliance will be calculated based on the actual drug usage.

5.6 Drug Management

5.6.1 Receipt and Accountability of Investigational Product

The sponsor will provide GFH375 according to the expected enrollment plan of the study site. GFH375 will be shipped to the study site by a third-party logistics company with transportation qualifications. Authorized personnel at the study site will sign the shipping manifest to confirm receipt of the drug.

GFH375 can only be used for this study and can only be managed by personnel authorized by the investigator. To fully control the dispensing and use of GFH375, a quantity record must be made at each visit.

5.6.2 Storage and Management of Investigational Product

The investigator or other authorized study site personnel (e.g., pharmacist) will ensure that all investigational products are stored in a secure, access-controlled area that meets the storage conditions described in Section 5.2.1 of the protocol and that their storage complies with applicable regulatory requirements. After receiving the GFH375 tablets, participants will follow the instructions of the investigator or authorized personnel for proper storage. If any non-compliant storage situation is found, the investigator should contact the sponsor for guidance.

5.6.3 Return and Destruction of Investigational Product

Unused investigational product and packaging will be returned to and destroyed by the sponsor after

accountability, or the sponsor may authorize the study site to destroy them. The sponsor or its authorized personnel will provide the study site with instructions on how to destroy unused investigational product. If authorized to destroy at the study site, the investigator must ensure that all returns and destructions are conducted and documented in accordance with relevant regulations, guidelines, and rules.

5.6.4 Investigational Product Records

Designated personnel at the study site must promptly record the receipt, dispensing, use, inventory, destruction, return, and damage of the investigational product in accordance with relevant regulations and guidelines, and the operational procedures of this study.

5.7 Complaint Handling

To ensure participant safety and monitoring quality, and to assist in process and drug improvement, the sponsor will collect product complaints related to the investigational product used in the clinical study. For complaints related to concomitant medications, they will be reported directly to the manufacturer according to the product instructions. The investigator or their designee is responsible for completing the following product complaint process in accordance with the relevant regulations of this study:

- Use the study-specific complaint form to record the reported product complaint and a complete description of it.
- Fax or email the completed product complaint form to the sponsor or their designee within 24 hours.

If the investigator is required to return the product for investigation, the investigator should return a copy of the product complaint form along with the product.

6 Study Procedures

Before initiating any study procedures required by this protocol, the participant must read and sign the ICF approved by the EC.

All procedures should be performed within the required time windows. If, in special circumstances, a study procedure cannot be completed on time or as required, the investigator should take all necessary measures to ensure the participant's safety and well-being, and document the reason and the measures taken. In addition, the investigator must promptly notify the study team of any unexpected situations that occur.

6.1 Screening Period

Screening Period: Day -28 to Day -1 before the first study drug administration. After the participant signs the ICF, they will provide relevant information and undergo relevant examinations as required by the protocol. Baseline is defined as the last examination result before dosing. All screening period examinations and confirmations must be completed according to the Schedule of Activities. NSCLC and PDAC participants enrolled in Phase II must provide a compliant archived tumor tissue sample or undergo a biopsy during the screening period before enrollment. If a tumor tissue sample cannot be provided and a biopsy cannot be performed during the screening period, the investigator must communicate with the sponsor's medical monitor and obtain their consent before enrollment.

A screening failure is defined as a participant who, for any reason, does not ultimately start the first study drug administration. Participants who fail screening may be re-screened. If re-screening a participant is considered, the investigator must contact the sponsor's medical monitor. Consent from the sponsor's medical monitor must be obtained for re-screening. When re-screening, the participant must re-sign the ICF and will be assigned a new identification number. Assessment results from the initial screening period that are still within the study-specified time frame and meet the inclusion/exclusion criteria are still acceptable and do not need to be repeated.

The inclusion/exclusion criteria must be strictly followed. If a participant who does not meet the inclusion/exclusion criteria is found to be enrolled, the sponsor's medical monitor and the investigator must discuss and determine whether the participant should continue to participate in the study, with or without the use of the study drug. If the investigator believes that it is medically appropriate for the participant to continue participating in the study, and the sponsor's medical monitor agrees with this decision, the participant may continue to participate in the study and receive treatment with the study drug. If the investigator believes it is medically appropriate for the participant to continue participating in the study, but the sponsor's medical monitor disagrees with this decision, the participant must not

continue to participate in the study (regardless of whether they receive study drug therapy). The investigator may only allow a participant who was accidentally enrolled in this study to continue participating after receiving written approval from the sponsor.

6.2 Treatment Period

Eligible participants will receive study treatment until PD (except for participants whom the investigator judges may still benefit from continued treatment), unacceptable toxicity, withdrawal of informed consent, termination of study or early termination, initiation of new anti-tumor therapy, or death, whichever occurs first. The treatment period begins on Day 1 of study drug administration, and each treatment cycle is 21 days. During the study, participants will complete scheduled visits regularly. PK samples will be collected at the time points specified in the protocol. Efficacy will be assessed by the investigator according to RECIST 1.1. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks.

6.3 Continued Dosing After PD

After PD, if the investigator judges that the participant will continue to benefit, continued treatment with GFH375 is permitted with the participant's full informed consent, until the criteria for treatment discontinuation are met (see protocol Section 6.4).

If dosing is continued after PD, data collection must continue according to the study-designed visits.

6.4 Participant Discontinuation of Treatment and Withdrawal from the Study

6.4.1 Participant Discontinuation of Treatment

Discontinuation of study treatment does not mean withdrawal from the study. Participants who discontinue study treatment should complete the end of treatment (EOT) visit and subsequent follow-up visits as required by the protocol. Possible reasons for discontinuing study treatment include:

1) The participant experiences PD requiring treatment discontinuation, if the investigator judges that the participant may still benefit from continued dosing, study treatment may be continued after discussion with the sponsor;
2) AEs;
3) The participant starts other anti-tumor therapy;
4) The participant has serious non-compliance with the study protocol requirements;
5) Participant pregnancy;
6) Participant is lost to follow-up;
7) Participant death;

8) The participant requests to discontinue treatment but agrees to subsequent follow-up;
9) The participant withdraws informed consent;
10) The investigator believes that discontinuing study treatment is in the participant's best interest;
11) The entire clinical study is terminated or suspended.

When the above situations occur, the end of treatment (EOT) visit should be completed within 7 days of the decision to end study treatment. Investigations performed within 7 days before the EOT visit do not need to be repeated, but AE-related examinations should be re-checked at the investigator's discretion.

6.4.2 Participant Withdrawal from the Study

Participants may voluntarily withdraw from the study at any time. Reasons for withdrawal from the study may include:

1) The participant withdraws informed consent, refuses to undergo study procedures, and refuses to be contacted for future information;
2) Participant death;
3) Participant is lost to follow-up;
4) The entire study is terminated or suspended.

If a participant does not return to the site for follow-up as scheduled, every effort should be made to contact the participant promptly and reschedule the missed visit as soon as possible. The investigator should inquire about the reason for withdrawal, ask the participant to return to the site to complete the visit if possible, and follow up on any unresolved AEs. In any case, every effort should be made to document the participant's outcome if possible.

If a participant refuses to come to the study site for further visits, their disease and survival status should still be tracked and collected, unless the participant withdraws informed consent (i.e., refuses to be contacted further). In this case, no further study evaluations should be performed, and no further data should be collected.

6.5 Lost to Follow-up

A participant will be considered lost to follow-up if they fail to return to the study site for 3 consecutive scheduled visits and the site staff are unable to contact them.

If a participant does not return to the study site for a required study visit, the following actions must be taken:

- The study site will attempt to contact the participant to reschedule the missed visit, explain

the importance of adhering to the visit schedule, and confirm whether the participant is willing and/or should continue to participate in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to re-establish contact with the participant (should attempt at least two phone calls, and if still unable to make contact, a letter should be sent to the participant's most recently updated contact address). These attempts to contact the participant should be documented in the participant's medical records or study files. Before the termination of this study, the investigator should still try to contact the participant.

If the participant still cannot be contacted, they will be considered lost to follow-up. All attempts to make contact should be recorded in the source documents.

6.6 Unscheduled Visits

If the investigator judges that it is necessary for safety assessment or AE follow-up, or if clinical symptoms suggestive of PD appear, the investigator may schedule a corresponding visit for further examination and assessment.

6.7 Follow-up Period

6.7.1 Safety Follow-up

After the end of treatment visit (including participants who have completed the end of treatment/withdrawal from study visit), the follow-up period begins. Thirty days (±3 days) after the last study drug administration, participants need to return to the study site for a safety follow-up, regardless of whether they have started new anti-tumor therapy.

After the safety follow-up visit, AEs will no longer be actively collected, but all treatment-related AEs must be followed up until resolution, return to baseline, or until the investigator judges them to be stable and irreversible.

6.7.2 PD Follow-up

Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the ICF, initiation of other anti-tumor therapy, or the end of the study.

6.7.3 Survival Follow-up

After the safety follow-up is completed, participants will enter survival follow-up. Participants will undergo a survival follow-up every 90 (±7) days. The investigator will obtain the participant's survival status, disease status, and subsequent anti-tumor therapy via telephone or email, etc.

7 Study Assessments

7.1 Safety Assessment

Participants will be recorded and assessed for the safety endpoint dataset starting from the screening/baseline period. Safety endpoint assessment indicators include the incidence, severity, and type of AEs, the participant's physical examination results, vital signs measurements, and clinical laboratory test results, with assessment time points according to the visit schedule. Adverse reactions will be graded according to CTCAE v5.0. For detailed information on AE collection and reporting, please refer to Chapter 8.0 Safety Reporting and Adverse Event Management.

7.1.1 Laboratory Tests

Hematology, urinalysis, blood chemistry, coagulation function, and pregnancy tests will be performed according to the Schedule of Activities. Viral serology tests are also required during the screening period to assess eligibility for enrollment. For details, please see Table 6 Laboratory Tests.

If a participant undergoes laboratory tests outside the study site and reports a related AE, the results of that laboratory test should also be collected and entered into the electronic Case Report Form (eCRF).

Table 6 Laboratory Tests

Test Item	Observation Parameter
ematology	Red blood cell count (RBC), hemoglobin concentration (HGB), haematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell count (WBC), platelet count (PLT), absolute neutrophil count (ANC), lymphocyte (LY) count, monocyte (MO) count, eosinophil (EO) count, basophil (BA) count, neutrophil percentage, lymphocyte percentage, monocyte percentage, eosinophil percentage, basophil percentage
rinalysis	Urine white blood cells (LEU), urine nitrite (NIT), urine pH, urine specific gravity (SG), urine protein (PRO), urine glucose (GLU), urine ketone body (KET), urine urobilinogen (UBG), urine bilirubin (BIL), urinary occult blood (BLD); 24-hour urine protein (this test is required when protein urine is ≥2+)
oagulation Function	Prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR)
lood Chemistry	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), urea (UREA)/blood urea nitrogen, blood creatinine (CREA), protein total (TP), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), creatine kinase (CK), pancreatic amylase (AMY), fasting plasma glucose (FPG), total cholesterol (TCHO), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), calcium, sodium, chloride, potassium
irus Serology	Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), HBV-DNA (if necessary), hepatitis C virus antibody (HCV antibody), HCV-RNA (if necessary), HIV antibody

Test Item	Observation Parameter
·egnancy Test	Female participants of childbearing potential will undergo a serum β-HCG pregnancy test at baseline, and a urine pregnancy test at other visits

7.1.2 Physical Examination

Physical examinations will be performed at the time points specified in the corresponding Schedule of Activities.

A complete physical examination includes general condition, skin, neck (thyroid), eyes, ears, nose, throat, chest (including lungs), heart, abdomen, back, lymph nodes, extremities, and vascular and nervous systems; breast, pelvic, rectal, and external genitalia examinations will be performed if clinically indicated. A comprehensive physical examination will be performed during the screening period.

A brief physical examination will be performed before the first dose of GFH375 and at the time points specified in the protocol, based on clinical indications. The investigator may also increase the frequency of physical examinations as needed.

7.1.3 Vital Signs

The participant's vital signs (respiration, pulse, blood pressure, and body temperature) will be recorded.

7.1.4 Performance Status

Performance status assessment will be performed during the screening period, before the first dose, on D1 of each cycle, at EOT, and 30 days after the last treatment. If assessed within 72 hours before the first dose, it does not need to be repeated on C1D1. Performance status will be scored according to the Eastern Cooperative Oncology Group (ECOG) performance status scoring criteria (see Appendix 2).

7.1.5 Body Height and Weight

Body height is measured only once during the screening period. Weight will be measured during the screening period, on C1D1, C2D1, on D1 of each subsequent cycle, at EOT, and 30 days after the last treatment. Body height [centimeters (cm)] and weight [kilograms (kg), rounded to one decimal place, measured in indoor clothing without shoes] will be measured according to hospital standards.

7.1.6 12-Lead ECG

12-lead ECGs will be completed according to the date and time requirements specified in the Schedule of Activities.

The ECG examination should be performed after the participant has rested quietly for at least 10 minutes. During the screening period and the study, 3 ECG examinations will be performed, with an

interval of at least 5 minutes between each. If other trial procedures are combined, the ECG examination should be performed first to avoid the impact of trial procedures on the ECG results.

Heart rate (HR), PR interval, QRS interval, QT interval, and QTcF (Frederica's formula) interval should be assessed and collected.

12-ECG Collection of the Phase I Part Dose Escalation

Participants will undergo an ECG examination on C1D1 (pre-dose, 2 h post-dose, 4 h post-dose, 6 h post-dose), C1D4 (pre-dose, only for QD dosing), C1D8 (pre-dose), C1D15 (pre-dose), C1D21 (pre-dose, 2 h post-dose, 4 h post-dose, 6 h post-dose, 24 h post-dose [only for QD dosing]), C2D10 (pre-dose), C4D1 (pre-dose), C5D1 (pre-dose), and C6D1 (pre-dose).

12-ECG Collection of Phase II Part

Participants will undergo an ECG examination on C1D10 (pre-dose, 2-4 h post-dose), C2D1 (pre-dose, 1-3 h post-dose), C3D1 (pre-dose, 2-4 h post-dose), C4D1 (pre-dose), C5D1 (pre-dose), and C6D1 (pre-dose).

ECGs matching the PK samples will be collected at qualified sites. It is recommended to perform the ECG examination first, then the PK blood draw. If it cannot be completed before the blood sample collection, the ECG examination should be performed after resting quietly for 10 minutes after the blood draw. Meanwhile, the interval between the ECG and PK sampling time needs to be kept within 30 minutes. All planned 12-ECG examinations should be performed after the participant has rested quietly for at least 10 minutes. Three measurements should be taken at each time point, with an interval of 1-2 minutes between each.

7.1.7 Adverse Events and Concomitant Therapies

The assessment of an AE includes the event name, severity (graded according to CTCAE version 5.0), start and end time, whether it is an SAE, its relationship to the study treatment, the measures taken regarding the study treatment, and the outcome.

AEs occurring from the signing of the ICF until the completion of the study safety follow-up visit will be recorded in the source medical records and collected in the eCRF. Other drugs or treatments used by the participant during the study treatment period will be recorded as concomitant therapy in the source medical records and collected in the eCRF.

7.2 PK Assessment

7.2.1 Blood Sample Collection

Phase I Part Dose Escalation

Serial PK samples will be collected on C1D1 (single dose), C1D21 (steady state), C2D1, C2D10,

C4D1, C5D1, and C6D1 to assess the PKs of GFH375. For specific time points, see the **Phase I Part PK Sample and 12-Lead ECG Collection Schedule**.

Phase II Part

Enrolled participants will have PK samples collected pre-dose on C1D10, C2D1, C3D1, C4D1, C5D1, and C6D1. For details, see the **Phase II Part PK Sample and 12-Lead ECG Collection Schedule**.

- **Unscheduled PK Blood Draw**

When a participant experiences a drug-related SAE, a blood sample for GFH375 plasma concentration measurement should be collected immediately upon the investigator's awareness of the event, if possible.

- **Gastrointestinal AEs (Vomiting and Diarrhea) and PK Sampling**

During the study, it has been found that the incidence of gastrointestinal AEs is high after participants take GFH375, which may affect the participants' PK results. The time of occurrence and frequency of vomiting and diarrhea will be collected in the CRF for subsequent analysis.

7.2.2 Sample Analysis

The concentration of GFH375 will be determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Concentrations below the lower limit of quantitation (LLOQ) will be marked as LLOQ, and any missing samples will be marked accordingly. Sample testing will be conducted by Teddy Clinical Research Laboratory (Shanghai) Limited. Detailed information about the analysis will be recorded in the bioanalytical report.

The collection and processing methods for biological samples are detailed in the laboratory manual.

7.3 Efficacy Assessment

The assessment of tumor remission will include all known or suspected sites of disease. Imaging includes computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, or pelvis; brain CT or MRI for participants with known or suspected brain metastasis; bone scan and/or bone X-rays for participants with known or suspected metastases to bone.

A baseline CT/MRI scan should be performed within 28 days before the first administration . During the study, efficacy will be assessed by the Blinded Independent Central Review (BICR) or the investigator according to RECIST 1.1 criteria (efficacy for all participants must be assessed by the investigator, and PDAC and NSCLC participants enrolled in Phase II also require BICR assessment). Imaging and tumor assessment will be performed every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks thereafter. In subsequent tumor evaluations, the same imaging modality as used during the screening period should be used for the

same type of lesions, and the investigation should be performed on the same imaging equipment whenever possible. For participants in whom no corresponding lesions were found on baseline cranial imaging and bone scan, the investigator may decide to add corresponding examinations during the treatment period if clinically indicated.

Disease in remission assessment will be performed by the BICR or the investigator according to RECIST 1.1 (Appendix 1). All participants' radiological imaging examinations must comply with RECIST 1.1 criteria, and all data should be properly retained and be available for source verification and peer review.

If a participant discontinues study treatment for a reason other than PD and has not started subsequent other anti-tumor therapy, imaging examinations will continue until PD occurs, or subsequent anti-tumor therapy is initiated, or the participant withdraws from the study for other reasons.

7.4 Biomarker and Drug Resistance Mechanism Exploration

NSCLC and PDAC participants enrolled in Phase II must provide a compliant archived tumor tissue sample or undergo a biopsy during the screening period before enrollment, to have their baseline gene mutation status confirmed by testing at the central laboratory designated for this study (Burning Rock Biotech).

In Phase I and Phase II, blood samples will be collected from participants at baseline (if collected during the screening period, no need to repeat on C1D1) and at the end of treatment visit, and will be shipped to the central laboratory for ctDNA isolation and sequencing. The sequencing results will be correlated with efficacy to explore biomarkers related to treatment sensitivity or drug resistance.

PDAC participants enrolled in Phase II will have blood samples collected for CA19-9 testing at baseline (if collected during the screening period, no need to repeat on C1D1), every 6 ± 1 weeks during the treatment period, and at the end of treatment (no need to repeat if tested within 4 weeks before the end of treatment visit), to explore the correlation between its changes and treatment response.

7.5 Storage and Destruction of Biological Samples

Remaining samples will be disposed of or destroyed, and will be anonymized and pooled.

Sample flashback analysis (if performed) will be conducted concurrently with the bioanalysis of the study samples. These assessment results will not be reported in the Clinical Study Report (CSR), but will be provided separately in a bioanalytical report.

8. Safety Reporting and Adverse Event Management

8.1 Definition and Recording of Adverse Events

8.1.1 Definition of an Adverse Event

An AE is defined as any untoward sign, symptom, abnormal laboratory value or examination result, or medical condition that appears (or worsens) after the participant has signed the ICF, regardless of whether the event is considered to be related to the study drug. A TEAE is defined as an event that was not present before treatment and appears during the treatment period (defined as from the first dose of the study drug to 30±3 days after the last dose) or worsens relative to the pre-treatment state. AEs that begin or worsen after informed consent should be recorded in the AE eCRF. Conditions already existing at the time of informed consent should be recorded on the medical history page of the participant's eCRF. AE monitoring should continue for 30±3 days after the last dose of treatment, or until the start of new anti-tumor therapy. For details, see Section 8.2.3. AEs (including laboratory abnormalities that constitute an AE) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a definitive diagnosis cannot be made, each sign or symptom should be reported as a separate AE.

8.1.2 Criteria for Assessing the Severity of Adverse Events

AEs will be assessed using NCI-CTCAE version 5.0. If there is no corresponding AE in CTCAE v5.0, please refer to the following criteria (summarized from the grading criteria in CTCAE v5.0).

Table 7 Criteria for Assessing the Severity of Adverse Events

Grade	Clinical Description of Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), where instrumental ADL refers to preparing meals, shopping, using the telephone, managing money, etc.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; resulting in disability; limiting self-care ADL. Self-care ADL refers to bathing, dressing, undressing, eating, toileting, taking medications, etc., but not bedridden
4	Life-threatening; urgent intervention indicated
5	AE resulting in death

8.1.3 Recording and Management of Adverse Events

Each AE should be assessed as much as possible to determine:

- Name of the AE
- Severity grade
- Duration (start and end dates)
- Relationship to study treatment
- Action taken with study drug (none, dose reduced, drug interrupted, drug permanently discontinued, unknown, not applicable)
- Whether medication or treatment has been given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered, recovered, recovering, recovered with sequelae, fatal, unknown)
- Whether it is an SAE, as defined in Section **8.2** as an SAE

All AEs should be managed appropriately. If concomitant medication or non-drug therapy is given, it should be recorded in the AE eCRF. Once an AE is discovered, it should be followed up until it resolves, stabilizes, or is judged to be permanent, and changes in severity, relationship to study treatment, interventions required to treat the AE, and the outcome should be assessed at each visit (or more frequently if necessary).

8.2 Serious Adverse Events

8.2.1 Definition

An SAE is defined as an AE that occurs during any clinical study and meets one or more of the following criteria:

- Results in death;
- Is life-threatening, meaning the patient is at immediate risk of death, not that death might occur if the condition were to worsen in the future;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Other important medical events: Medical and scientific judgment must be used to decide whether to expedite reporting of other situations, such as important medical events that may not be immediately life-threatening, result in death, or require hospitalization, but are generally considered serious if medical intervention is required to prevent one of the above outcomes.

Hospitalization for the following reasons should not be reported as an SAE:

- Routine treatment or monitoring for the indication under study, not associated with any condition aggravated
- Elective or pre-planned treatment for a pre-existing disease not related to the indication under study, which has not worsened since signing the ICF
- Social reasons and respite care where there is no deterioration in the patient's general condition

Emergency outpatient treatment that does not result in hospitalization and involves an event that does not meet the above SAE definition is not an SAE.

8.2.2 Malignant Tumor Progression and Death

Clinical symptoms caused by malignant tumor progression may be recorded as an AE if it cannot be exclusively determined to be due to the progression of the study disease, or if the symptoms are inconsistent with the characteristics of the study PD. If it is clearly consistent with the suspected progression of the study disease, it is not recorded as an AE. Malignant tumor progression itself is not reported as an AE.

Clinical symptoms caused by malignant tumor progression that meet the SAE criteria and for which a relationship to the study drug cannot be completely ruled out must be reported as an SAE. If the event meets the SAE criteria (excluding death events) and is clearly consistent with the suspected progression of the study disease, it is not reported as an SAE. The collection period for SAE reporting is from the time the participant signs the ICF until 30 days after the last dose.

In a clinical study, if a participant dies during the safety follow-up period, it must be reported as an SAE, regardless of whether the investigator assesses it as possibly related to PD. The term 'death' should not be used as an SAE term, but as the outcome of an event. The medical condition/disease (including worsening of signs and symptoms) that caused or led to death should be recorded as the SAE term in the eCRF and reported as an SAE. If the cause of death cannot be determined at the time of reporting, the SAE term should be recorded as 'death of unknown cause'. The collection period for reporting SAEs with a fatal outcome is from the time the participant signs the ICF until 30 days after the last dose.

8.2.3 New Anti-tumor Therapy

If a participant starts new anti-tumor therapy during the safety follow-up period, unrelated AEs and SAEs will no longer be collected thereafter. If a death event occurs during the safety follow-up period, it must be reported as an SAE, regardless of any interventional treatment and regardless of the causal relationship of the event to the study treatment.

8.2.4 Reporting of SAEs

SAE collection will begin at the time of ICF signing, regardless of whether the participant is a screening failure. Follow-up of SAEs will continue until symptoms resolve or there is clinical improvement or stabilization.

To ensure participant safety, any SAE that occurs after the participant signs the ICF and within 30 days after the participant stops study treatment, regardless of the suspected causal relationship, must be reported to the sponsor within 24 hours of awareness of its occurrence. After 30 days following the participant's last treatment, only SAEs suspected to be related to the study treatment will be reported. Any additional information for an SAE, including complications, progression of the initial SAE, and recurrent episodes, must be reported as a follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. SAEs that occur at different time intervals or are considered completely unrelated to a previously reported SAE should be reported separately as new events.

Any SAE occurring after the safety follow-up period should only be reported to the sponsor if the investigator suspects a causal relationship with the study treatment.

Information for all SAEs will be collected and recorded on the SAE report form; to provide a complete clinical report, all applicable sections of the form must be completed. The investigator must assess and record the relationship of each SAE to the study treatment, complete the SAE report form signed by the investigator, and send the report form to the sponsor and the designated CRO pharmacovigilance department within 24 hours, and report to the relevant authorities in a timely manner according to local requirements.

- **Sponsor Pharmacovigilance Email**: drugsafety@genfleet.com
- **Tigermed Pharmacovigilance Email:** PV@TigermedGrp.com

Follow-up information should be submitted in the same manner as the original SAE report form, using a new SAE report form, indicating that it is a follow-up report to a previously reported SAE, and providing the date of the original report. The follow-up information should describe whether the event has resolved or is ongoing, how it was treated, and whether the participant continued in the study or withdrew.

8.3 Causality Assessment of Adverse Events

Causality assessment of an AE with the study treatment refers to a comprehensive evaluation to determine whether there is a reasonable possibility that the study treatment caused or contributed to the AE. Factors the investigator should consider include whether the occurrence of the AE has a

reasonable temporal relationship with the administration of the study treatment, the characteristics of the study treatment, the toxicological and pharmacological effects of the study treatment, the use of concomitant medications, the participant's pre-existing disease, medical history, family history, dechallenge (whether signs/symptoms lessen or improve after study drug discontinuation or dose reduction), and rechallenge (whether signs/symptoms reappear or worsen after re-administration of the drug), etc. The facts and rationale for determining causality should generally be provided.

The investigator should assess the relationship of the AE/SAE to the study drug according to the criteria listed below:

Table 8 Classification and Criteria for Adverse Event Relationship Assessment

Relationship	Assessment Criteria
Related	• Reasonable temporal relationship • Consistent with the known mechanism of action, characteristics, or known adverse reactions of the drug • Positive dechallenge • No other reasonable cause to explain it • Positive rechallenge
Probably related	• Reasonable temporal relationship • Consistent with the known mechanism of action, characteristics, or known adverse reactions of the drug • Positive dechallenge • No other reasonable cause to explain it • Lack of positive rechallenge evidence
Possibly related	• Reasonable temporal relationship • Lack of positive rechallenge evidence • Manifests as any of the following situations: 1) Consistent with the known mechanism of action, characteristics, or known adverse reactions of the drug, with a positive dechallenge, but can also be explained by other reasonable causes; 2) Consistent with the known mechanism of action, characteristics, or known adverse reactions of the drug, with a lack of positive dechallenge evidence, and no other reasonable cause to explain it; 3) Inconsistent with the known mechanism of action, characteristics, or known adverse reactions of the drug, with a positive dechallenge, and no other reasonable cause to explain it; 4) Inconsistent with the known mechanism of action, characteristics, or known adverse reactions, with a lack of positive dechallenge evidence, and no other reasonable cause to explain it.
Unlikely related	• Temporal relationship cannot be excluded • Lack of positive dechallenge evidence • Lack of positive rechallenge evidence • Manifests as any of the following situations: 1) Inconsistent with the known mechanism of action, characteristics, or known adverse reactions, and can be explained by other reasonable causes; 2) Consistent with the known mechanism of action, characteristics, or known adverse reactions, but can be explained by other more reasonable causes;
Not related	• No reasonable temporal relationship • Inconsistent with the known mechanism of action, characteristics, or known adverse reactions of the drug • Lack of positive dechallenge evidence • Lack of positive rechallenge evidence • Can be explained by other reasonable causes

Note: When assessing an AE, if it does not completely correspond to the criteria in the table, please refer to the professional judgment logic for the relationship between AEs and the drug in this table to make the most reasonable assessment possible.

Table 9 Summary for Adverse Event Relationship Assessment

Assessment Result / Assessment Criteria	Related	Probably related	Possibly related				Unlikely related		Not related
Reasonable temporal relationship?	+	+	+				±		-
Consistent with known drug mechanism, characteristics, or adverse reactions?	+	+	+		-		+	-	-
Dechallenge result	+	+	+	-/?	+	-/?	-/?		-/?
Rechallenge result	+	-/?	-/?				-/?		-/?
Can it be explained by other reasonable causes?	-	-	+	-	-	-	++	+	+

Note: + indicates affirmative, or positive result; - indicates negative, or negative result, or a situation where the result is not yet available; ± indicates that a temporal relationship cannot be excluded; ++ indicates that it can be explained by other 'more' reasonable causes; -/? indicates that the dechallenge/rechallenge result is negative, or dechallenge/rechallenge has not yet been performed, or dechallenge/rechallenge is not applicable.

Events assessed as related, probably related, or possibly related will be considered 'related'; events assessed as not related or unlikely related will be considered 'unrelated'. If the investigator's causality assessment is 'unknown', or if a relationship assessment cannot be made, the event should be considered related to the drug. The investigator should collect further information on the AE and provide a causality assessment based on the subsequent information.

8.4 Pregnancy Reporting

If a female participant becomes pregnant during the clinical study, the participant must discontinue study treatment and withdraw from the study; if the partner of a male participant becomes pregnant during the clinical study, the participant may continue in the clinical study. The investigator should complete the "Clinical Study Pregnancy Report/Follow-up Form" and report it to the sponsor and the designated CRO pharmacovigilance department within 24 hours of awareness of the pregnancy event. The investigator must follow up on the pregnancy event until the final outcome (including any premature termination of pregnancy or delivery), with delivery follow-up extending to 1 month after the mother gives birth. The pregnancy outcome must be reported to the sponsor. If the pregnancy outcome meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal death, death neonatal, or congenital anomaly, etc.), it must be reported following the SAE

procedure.

If a participant experiences a concurrent SAE during pregnancy, it must also be reported following the SAE reporting procedure.

8.5 Reporting of Events Meeting Hy's Law

If abnormal AST and/or ALT levels are concurrent with an abnormal elevation in total bilirubin levels, and conditions (1), (2), and (3) below are met simultaneously with no other cause for the abnormalities, such cases should always be reported as an SAE, following the SAE reporting procedure.

Table 10 Criteria for Determining Events Meeting Hy's Law

Condition Met	Assessment Criteria
(1) Abnormal ALT or AST	1) Normal baseline: ALT or AST > 3×ULN during treatment period Abnormal baseline: ALT or AST > 3× baseline level during treatment period
(2) Abnormal TBIL	2) Normal baseline: TBIL > 2×ULN during treatment period Abnormal baseline: TBIL > 2× baseline level during treatment period
(3) Alkaline phosphatase < 2×ULN (or information not available)	

Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, TBIL=total bilirubin, ULN=upper limit of normal.

If a participant has abnormal AST and/or ALT levels concurrent with an abnormal elevation in total bilirubin levels during the treatment or follow-up period, they should return to the study site for examination and assessment as soon as possible after the abnormal results are known. This should include relevant liver function laboratory tests, a detailed medical history inquiry, and a physical examination, and the possibility of liver tumors (primary or secondary) should be considered.

If a liver injury event meeting the above criteria occurs, corresponding dose adjustments or treatment discontinuation should be made according to Sections 5.3.1 and 5.3.2.

8.6 Reporting of Overdose

An overdose is defined as any accidental or intentional administration of a dose that exceeds the planned dose. If an overdose results in an AE, the AE must be recorded in the eCRF. If an overdose is associated with any SAE, please refer to Section **8.2.4 Reporting of SAEs**.

8.7 Reporting Timelines for AE/SAE/Pregnancy

Table 11 Reporting Timelines for AE/SAE/Pregnancy Events

Period	Collection Requirement
From the time the participant signs the ICF until 30±3 days after the last dose of treatment, or until the start of new anti-tumor therapy	All AE/SAE/pregnancy events Pregnancy events: Collection begins after the first dose of study treatment
After the above period	SAEs related to the study treatment

Abbreviations: AE=adverse event, SAE=serious adverse event.

9. Statistical Analysis

Detailed statistical analysis methods will be described in the Statistical Analysis Plan (SAP), and the final version of the SAP will be completed before the clinical database is locked.

9.1. Sample Size

9.1.1. Phase I Part: Dose Escalation

According to the BOIN design, 3-6 participants will be enrolled in each dose cohort (except during accelerated titration) for treatment. Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional participants for backfilling. These participants will be treated with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is considered to have potential clinical benefit by the investigator and sponsor, in order to better estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. Backfilled participants will not be included in the DLT evaluation. After backfilling, no more than 30 participants will be treated in each GFH375 dose cohort (including participants enrolled in the BOIN dose escalation part).

If more dose cohorts or alternative dosing regimens need to be explored, additional participants may be enrolled.

9.1.2. Phase II Part

A total of approximately 317 participants are planned for enrollment, including approximately 73 patients with advanced NSCLC, 94 patients with advanced PDAC, 50 patients with advanced CRC, and 100 patients with other advanced solid tumors.

Tumor Type	Historical Control ORR	Expected ORR	Sample Size
NSCLC	23%	40%	73
PDAC	15%	30%	94
CRC	10%	30%	50
Other			100
Total			317

For second-line advanced NSCLC, the historical control ORR is 23%, and the expected ORR in this study is 40%. The study will be considered successful if the lower limit of the 95% CI for the observed ORR is not less than the historical control of 23%. With a one-sided $\alpha = 0.025$, 73 participants are required to achieve 89% power. When at least 25 of the 73 participants have a CR/PR, the lower limit of the exact 95% CI for the observed ORR will be higher than the historical control of 23%. With 25 CR/PR cases, the ORR = 34.2%, with a 95% CI of (23.5%, 46.3%).

For second-line advanced PDAC, the historical control ORR is set at 15%. The expected ORR with GFH375 treatment is 30%. If the lower limit of the 95% CI for ORR after GFH375 treatment is greater than 15%, the efficacy of GFH375 will be considered statistically significant. With a one-sided α = 0.025, 94 participants will provide 95% power to ensure that the lower limit of the 95% CI for the ORR is greater than 15%. Approximately 94 participants with PDAC are planned for enrollment. When 22 responses (PR/CR) are observed in 94 participants, the exact 95% CI for the observed ORR is (15.29%, 33.26%). Therefore, if ≥22 responses are observed in 94 participants, the efficacy of GFH375 will be considered statistically significant.

For third-line CRC, the historical control ORR is 10%, and the expected ORR in this study is 30%. The study will be considered successful if the lower limit of the 95% CI for the observed ORR is not less than the historical control of 10%. It is planned to enroll 50 participants, which will provide 96% power with a one-sided α = 0.025. When at least 10 of the 50 participants have a CR/PR, the lower limit of the exact 95% CI for the observed ORR will be higher than the historical control of 10%. With 10 CR/PRs, the ORR = 20.0%, with a 95% CI of (10.0%, 33.7%).

For other solid tumors: Approximately 100 participants with advanced solid tumors with KRAS G12D mutation, such as bile duct cancer and appendix cancer with KRAS G12D mutation, are planned for enrollment.

The above sample size and ORR (and its 95% exact CI) calculations were performed using the Rsoftware. Among them, the sample size was calculated using the “nBinomial1Sample” function in the “gsDesign” package (option: conservative = TRUE); the ORR and its 95% exact CI were calculated using the “binom.exact” function in the “epitools” package (with default options).

9.2. Analysis Sets

- Full Analysis Set (FAS): All participants who have received at least one dose of GFH375.
- Safety Set (SS): All participants who have received at least one dose of GFH375 and have at least one valid post-baseline safety assessment.
- Dose Determination Set (DDS): All participants in the Phase I SS who have received undiminished doses of GFH375 for at least 15 cumulative days during the DLT observation period and had adequate safety assessments, or who have experienced a DLT during the DLT observation period. The DDS does not include backfilled participants.
- Per-Protocol Set (PPS): All Phase II participants in the FAS who are compliant with the protocol. The study team will review all protocol deviations before the final database lock and exclude participants with major protocol deviations that affect the efficacy evaluation from the PPS.

- Pharmacokinetic Analysis Set (PKAS): All participants who have received at least one dose of GFH375 and have at least one blood sample providing evaluable PK data.

9.3. Statistical Analysis Methods

Data from Phase I and Phase II will be analyzed and summarized separately. Data from the Phase I stage will be analyzed and summarized by different dose levels and dosing regimens; data from the Phase II stage will be analyzed and summarized separately by tumor type.

9.4. Safety Analysis

The incidence of AEs, treatment-related AEs, and SAEs will be summarized by System Organ Class (SOC), Preferred Term (PT), and severity. For the Phase I part, the incidence of various types of DLTs will be summarized based on the DDS, and the DLTs will be listed. Descriptive summaries will be provided for laboratory tests, vital signs, and ECGs.

9.5. Efficacy Analysis

The proportion of the respective population for BOR, ORR, and DCR will be calculated, and the two-sided 95% CI for ORR and DCR will be estimated using the Clopper-Pearson method. The median DoR, PFS, and OS and their 95% Brookmeyer-Crowley CIs will be estimated using the Kaplan-Meier method. TTR will be summarized descriptively.

For the Phase I stage, when the sample size of an analysis group is less than 10, DoR, TTR, PFS, and OS will be listed individually by participant, and the Kaplan-Meier method will not be used for analysis.

For the Phase II stage, the **primary estimand** is set as follows:

Study Population	Participants with advanced solid tumors with KRAS G12D mutation (by tumor type)
Treatment	GFH375
Endpoint	Percentage of participants who achieve CR or PR as assessed by RECIST 1.1 criteria. If a participant has no post-baseline assessment results, the participant is considered a non-responder. **Note:** For NSCLC and PDAC, this will be the percentage of participants with confirmed CR or PR based on Blinded Independent Central Review (BICR) assessment.
Intercurrent Event	Start of new anti-tumor therapy (Handling strategy: Treatment policy strategy, assessment results after the start of new anti-tumor therapy are not included in the analysis.)
Population-level Summary	ORR

9.6. PK Analysis

Plasma concentration data of GFH375 will be listed and summarized descriptively according to the sampling times specified in the protocol. The summaries will be presented by study phase, dose group, and dosing regimen. Individual participant plasma concentration-time curves of GFH375 and

corresponding summary curves (mean + standard deviation) will be plotted using linear and semi-logarithmic coordinates, by study phase, dose group, and dosing regimen. Planned PK sampling times will be used to calculate summary statistics and plot summary curves (mean + standard deviation); actual PK sampling times will be used to plot individual participant curves.

Phoenix WinNonlin software (version v8.2 or later, Certara USA, Inc., New Jersey, US) will be used to perform non-compartmental analysis (NCA) to calculate the PK parameters of GFH375 based on actual blood sampling time points. The PK parameters of GFH375 after single and multiple doses in participants in the Phase I dose escalation part will be summarized descriptively, with summaries presented by dose group and dosing regimen.

9.7 Biomarker Assessment

In Phase I and II, blood samples will be collected at baseline and at the end of treatment to isolate ctDNA for NGS testing, to explore tumor gene variations associated with treatment sensitivity or drug resistance.

Phase II PDAC participants will have CA19-9 tested at baseline, during the treatment period, and at the end of treatment to explore the correlation of its changes with treatment response.

9.8 Interim Analysis

A futility interim analysis will be performed separately for NSCLC, PDAC, and CRC. For a single tumor type, the analysis is planned when approximately 35 participants (including Phase I participants treated with RP2D and Phase II participants) have had at least one post-baseline imaging tumor assessment or have withdrawn from the study early. Due to practical clinical operational reasons, the number of participants at the time of the interim analysis is allowed to differ from the planned number. During the interim analysis, enrollment will not be stopped.

At the interim analysis, a futility analysis will be conducted for the ORR of NSCLC, PDAC, and CRC, respectively, using the Bayesian predictive probability method. Early termination of the study for the corresponding tumor type due to lack of efficacy evidence is permitted (but not mandatory).

The predictive probability of success (PPoS) will be calculated based on the observed number of Phase II participants who have achieved a response (CR/PR). If the PPoS is < 0.2, early termination of enrollment due to lack of efficacy evidence is permitted (but not mandatory). The corresponding termination criteria for PPoS < 0.2 are shown in the table below:

Tumor Type	Number of Participants*	Recommended to terminate the cohort when the number of responders is ≤
NSCLC	20 ~ 21	3
	22 ~ 25	4

Tumor Type	Number of Participants*	Recommended to terminate the cohort when the number of responders is ≤
	26 ~ 29	5
	30 ~ 33	6
	34 ~ 37	7
	38 ~ 41	8
	42 ~ 45	9
PDAC	25 ~ 26	2
	27 ~ 33	3
	34 ~ 39	4
	40 ~ 45	5
CRC	20 ~ 23	1
	24 ~ 30	2
	31 ~ 37	3
	38 ~ 43	4
	44 ~ 48	5

*Number of participants: The sum of Phase I participants treated with RP2D and Phase II participants who have had at least one post-baseline imaging tumor assessment or have withdrawn from the study early (at least one of these must be met).

The planned interim analysis above is not mandatory. If there is sufficient comprehensive safety and efficacy data to support it before the planned time point for the interim analysis, this interim futility analysis may be omitted.

10. Safety Monitoring

A Safety Monitoring Committee (SMC) composed of investigators and the sponsor will be established for this study. The SMC will continuously review safety data from the first dose of the first participant until the end of the study. During the dose escalation and expansion parts, SMC members will review safety data, PK data, etc., to decide on enrollment for the next dose or to explore potential other dose cohorts, and to recommend a suitable RP2D.

During the study, if both the investigator and the sponsor believe that a participant is at a safety risk or has reached the limit of tolerability, dose escalation or study treatment will be stopped immediately. For details, please refer to the SMC Charter.

11 Study Quality Assurance and Quality Control

According to the guiding principles of Good Clinical Practice (GCP), the sponsor is responsible for implementing and maintaining a quality assurance and quality control system according to the corresponding standard operating procedures to ensure that the clinical study is conducted and that the data is authentic, and that collection, recording, and reporting follow the protocol, GCP, and corresponding regulatory requirements.

11.1 Clinical Monitoring

The sponsor or a contract research organization (CRO) authorized by the sponsor will conduct clinical monitoring for this study. Clinical monitors should conduct monitoring according to the standard operating procedures of the sponsor or CRO and have the same rights and responsibilities as the sponsor's monitors. The monitor should maintain regular communication with the investigator, authorized study personnel, and the sponsor.

Before the start of the study, the monitor will assess the competence of each study site and report any issues related to facilities, technical equipment, or medical personnel to the sponsor. During the study, the monitor will be responsible for monitoring whether the investigator has obtained written informed consent from all participants and whether the data records are correct and complete. At the same time, the monitor will also compare the data entered into the eCRF with the source data and inform the investigator of any errors or omissions. The monitor will also control the study site's compliance with the protocol and trial procedures, arrange for the supply of the investigational drug, and ensure that the drug is stored under appropriate conditions.

Monitoring visits will be conducted in accordance with the requirements of relevant laws and regulations. From the start of participant enrollment, each site will receive regular monitoring visits. After each visit to the investigator, the monitor should submit a written report to the sponsor.

11.2 Quality Assurance Audit

During the study, the sponsor or a representative authorized by the sponsor may conduct quality assurance audits of the study site, study database, and related study documents. At the same time, the corresponding regulatory authorities may also inspect the study site, study database, and related study documents at their own discretion. When the investigator receives a notice of inspection from a regulatory authority, they must immediately inform the sponsor.

The sponsor's quality assurance department will audit the clinical study site. The audit includes: supply of the drug, required trial documents, records of the informed consent process, and the consistency of the case report forms with the source documents, etc. The content and scope of the audit may also be

increased depending on the situation. After reasonable notification, the investigator should allow auditors commissioned by the sponsor to conduct study-related audits and inspections by regulatory authorities. The main purpose of an audit or inspection is to confirm that the rights and health of the participants participating in the study are protected, that the signing of informed consent and the implementation of the trial process are conducted correctly, and that all data processing and reporting related to the evaluation of the investigational drug are consistent with the pre-planned arrangements, protocol, facilities, ethical standard operating procedures, GCP, and applicable regulatory requirements. The investigator should provide direct access to all study documents, source records, and source data.

12 Ethics

12.1 Ethics Committee

The sponsor or its authorized representative will prepare the relevant documents to be submitted to the study site's EC, including the study protocol, ICF, investigator's brochure, participant recruitment materials or advertisements, and other documents required by regulations, all of which must be submitted to the corresponding EC for approval. Before starting this study, written approval from the study site's EC must be obtained and provided to the sponsor. The EC's approval letter must specify the name, number, and version number of the study protocol, as well as the version numbers (e.g., for the ICF) and approval dates of other documents. The investigator must notify the sponsor of the EC's written opinions regarding delays, suspensions, or re-approvals.

The study site must follow the requirements of its EC. This may include submitting protocol amendments, ICF amendments, and participant recruitment material amendments to the EC for approval, local safety reporting requirements, periodic reporting and updates according to EC regulations, and submission of the final report. All the above documents and EC approval letters must be provided to the sponsor or their designee.

12.2 Ethical Conduct

The study process and the acquisition of informed consent should comply with the Declaration of Helsinki, relevant GCP requirements, and Chinese laws and regulations related to drugs and data protection.

GCP provides an ethical and scientific global quality standard for the design, conduct, recording, and reporting of clinical studies involving human participants. This study will be conducted in accordance with GCP and relevant national regulations, and will adhere to the relevant ethical principles of the Declaration of Helsinki to protect the rights, safety, and health of the participants.

The investigator must follow the procedures specified in this study protocol and may not make changes without the sponsor's permission. Any protocol deviations will be reported to the EC, the sponsor, or regulatory authorities.

12.3 Participant Information and Informed Consent

Before any study procedures begin, the potential risks and benefits of this study will be explained to potential participants using the ICF, and the language of the informed consent should be simple and easy to understand. The ICF statement should clarify that signing the informed consent is voluntary, specify the potential risks and benefits of participating in this study, and state that the participant may

withdraw from the study at any time. The investigator may only enroll a participant after fully explaining the details of the study, satisfactorily answering the participant's questions, allowing sufficient time for consideration, and obtaining written consent from the participant or their legal guardian. All signed ICFs must be kept in the investigator's files or the participant's folder.

The investigator is responsible for explaining the content of the informed consent to the participant and obtaining a signed and dated ICF from the participant or their legal guardian before the study begins. After signing, the investigator should give the participant a copy of the signed ICF. The investigator must document the informed consent process in the study source documents.

The initial ICF, any subsequent revised written ICFs, and any written information provided to participants should be reviewed by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) before use. If new information becomes available that may be relevant to the participant's willingness to continue participating in the study, the participant or their legal guardian should be informed in a timely manner. The communication of this information will be provided and documented through a revised ICF or an addendum to the original ICF (obtaining a dated signature from the participant or the participant's legal guardian).

12.4 Data Protection

The ICF will contain (or in some cases, be accompanied by a separate document with) information regarding data protection and privacy protection.

Precautions will be taken to ensure the confidentiality of documents and to prevent the identification of participants. However, in special circumstances, certain personnel may see a participant's genetic data and personal identification code. For example, in the event of a medical emergency, the sponsor, their representative physician, or the investigator will be aware of the participant's identification code and have access to that participant's genetic data. In addition, relevant regulatory authorities may require access to related documents.

12.5 Protocol Deviations

A protocol deviation is any non-compliance with the clinical study protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH GCP), or the operations manual. Non-compliance may originate from the participant, investigator, or study site staff. Corrective actions should be taken and completed in a timely manner for any violations.

13 Study Administration

13.1 Data Handling and Record Keeping

Documents in the clinical study (protocol and protocol amendments, completed eCRFs, signed ICFs, etc.) must be stored and managed in accordance with GCP requirements. The study site should retain these documents for 5 years after the end of the study.

Study documents should be properly stored for future access or data traceability. Safety and environmental risks should be considered when storing documents.

No study documents may be destroyed without the written permission of the sponsor and the investigator. Only after notifying the sponsor and obtaining their written consent may the investigator/study site transfer study documents to another party that complies with document retention requirements or move them to another location that meets the requirements for storage.

13.2 Access to Source Data/Documents

The investigator agrees to allow the sponsor, CRO, and relevant authorized regulatory authorities direct access to all study-related documents, including participant medical records.

13.3 Protocol Amendments

All amendments to the protocol during the course of the study must be communicated between the sponsor and the investigator and agreed upon. The sponsor should ensure that protocol amendments are submitted to the regulatory authorities in a timely manner.

All amendments to the protocol should be kept as protocol addenda. Any modification to the protocol must be submitted to the EC for approval or filing according to the EC's regulations. If necessary, it should also be submitted to the regulatory authorities for approval, and can only be implemented after approval by the EC and regulatory authorities (if required) (except for changes to the protocol made to eliminate an immediate hazard to study participants).

13.4 Investigator Responsibilities

The investigator will conduct this study in accordance with the protocol, the ethical principles of the Declaration of Helsinki, ICH GCP, and corresponding regulatory requirements.

The detailed responsibilities of the relevant investigators are listed in Chapter 5 of the China GCP (No. 57, 2020).

13.5 Publication Policy

All data generated from this study are confidential information of the sponsor, and the sponsor has the right to publish the study results. Information regarding the publication policy between the sponsor and the investigator will be described in the clinical study agreement.

All information related to this study (not limited to the following documents: protocol and investigator's brochure) must be kept strictly confidential. The investigator must recognize that the scientific or medical conclusions drawn from this study may have commercial value to the sponsor. The investigator should keep the information and data related to this trial confidential. If they wish to publicly publish data related to this study or conclusions drawn from the study, they must consult with the sponsor in advance and obtain the sponsor's written consent. To protect its own rights and interests, the sponsor may require the investigator not to publish relevant trial data before the study product obtains marketing approval.

The sponsor has the right to publish or release information or data related to this study, or to submit it to the drug regulatory authorities. If the sponsor needs to use the investigator's name in publications, releases, or advertising content, they should obtain the investigator's consent.

13.6 Finance and Insurance

The sponsor will purchase insurance for participants participating in this study in accordance with local regulations and minimum requirements. The relevant insurance terms will be kept in the study folder.

14 Data Management

14.1 Data Confidentiality

Information related to study participants will be kept confidential and managed in accordance with applicable laws and regulations.

Access to the data collection system will be controlled through a series of individually assigned usernames and passwords, which will only be provided to authorized personnel who have completed the necessary training.

14.2 Data Collection

Data collection for this study will be completed using an Electronic Data Capture (EDC) system.

The investigator or designated study personnel will enter data into the eCRF according to the protocol. Study site staff may only access the EDC system after receiving training. The system will use an automated check process to inspect data inconsistencies in the eCRF, allowing for modification or verification of the data entered by site staff.

When modifying data in the EDC, the reason for the modification must be entered as prompted by the system. The modification history and reasons for modification will be recorded in the audit trail of the EDC system. The investigator or their authorized personnel need to confirm the authenticity, completeness, and timeliness of the eCRF data and provide an electronic signature in the EDC system.

14.3 Data Management

The sponsor or designated CRO personnel will review the completeness and accuracy of the data entered by the study personnel. For any inconsistent or missing data, a data query will be sent to the study site. Designated study site personnel are required to answer queries in a timely manner and make necessary changes to the data.

This project will use the World Health Organization Drug Dictionary (WHODrug) to code concomitant therapies and prior medications entered into the database. MedDRA terminology will be used to code medical history/current diseases and AEs.

Before the database is locked, the study team needs to complete data cleaning, summarize all protocol deviation events that occurred during the study, and hold a data review meeting to determine the analysis sets. All decisions made during the data review meeting must be documented. After the data review meeting is passed, the study database in the EDC system will be locked upon confirmation by the study team. If any changes need to be made to the locked data, the database must be unlocked with authorization after discussion by the project team.

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16 Appendices

Appendix 1: Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

Note: This translated version is for reference only. The final version shall be the English version.

1. Measurability of Tumors at Baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be classified as either measurable or non-measurable according to the following definitions:

Measurable Lesions

Tumor lesions: At least one accurately measurable dimension (recorded as the longest diameter), with a minimum length as follows:

- CT scan 10 mm (CT scan slice thickness no greater than 5 mm)
- Conventional clinical examination instruments 10 mm (tumor lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- Chest X-ray 20 mm
- Malignant lymph nodes: Pathologically enlarged and measurable, with a short axis of a single lymph node ≥15 mm on CT scan (recommended CT scan slice thickness not to exceed 5 mm). Only the short axis is measured and followed up at baseline and during follow-up.

Non-measurable Lesions

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph node short axis ≥10 mm to <15 mm) and unmeasurable lesions. Unmeasurable lesions include: meningeal disorder, ascites, pleural or pericardial effusion, inflammatory breast cancer, lymphangiosis carcinomatosa of the skin/lung, abdominal masses that cannot be confirmed and followed up by imaging, and cystic lesions.

Special Considerations for Lesion Measurement

Bone lesions, cystic lesions, and lesions that have previously received local treatment require special notation:

Bone lesions:

- Bone scans, Positron Emission Tomography (PET) scans, or plain films are not suitable for measuring bone lesions, but can be used to confirm the presence or disappearance of bone lesions;
- Lytic or mixed lytic/blastic bone lesions with an identifiable soft tissue component that meets the

definition of measurability described above can be considered measurable lesions if they can be evaluated by tomographic imaging techniques such as CT or MRI;

- Blastic bone lesions are non-measurable.
- Cystic lesions:
- Lesions that meet the radiological criteria for a simple cyst should not be considered malignant lesions simply because they are defined as simple cysts, and are neither measurable nor non-measurable lesions;
- If they are cystic metastatic lesions and meet the definition of measurability described above, they can be considered measurable lesions. However, if non-cystic lesions exist in the same patient, non-cystic lesions should be preferentially selected as target lesions.

Locally treated lesions;

- Lesions in a previously irradiated area or an area that has undergone other local regional treatment are generally considered non-measurable, unless there is definite progression of the lesion. The study protocol should detail the conditions under which these lesions are considered measurable.

1.2 Description of Measurement Methods

Lesion Measurement

For clinical evaluation, all tumor measurements must be recorded in metric units. All baseline assessments of tumor lesion size should be completed as close as possible to the start of treatment and must be completed within 28 days (4 weeks) before the start of treatment.

Evaluation Methods

The same technique and method should be used for baseline assessment and subsequent measurements of lesions. All lesions must be evaluated using imaging examinations, except for those that cannot be evaluated by imaging and can only be evaluated by clinical investigation.

Clinical lesions: Clinical lesions can only be considered measurable if they are superficial and have a diameter ≥10 mm at the time of measurement (e.g., skin nodules). For patients with skin lesions, it is recommended to use color photographs with a ruler to measure the lesion size for archival purposes. When lesions are evaluated using both imaging and clinical investigation, imaging evaluation should be used whenever possible, as it is more objective and can be reviewed repeatedly at the end of the study.

Chest X-ray: When tumor progression is an important study endpoint, chest CT should be prioritized, as CT is more sensitive than X-ray, especially for new lesions. Chest X-ray is only applicable when the measured lesion has clear borders and the lungs are well-aerated.

CT, MRI: CT is currently the best available and repeatable method for efficacy evaluation. The definition of measurability in these guidelines is based on a CT scan slice thickness of ≤5 mm. If the CT slice thickness is greater than 5 mm, the minimum measurable lesion should be twice the slice thickness. It is recommended to use contrast-enhanced CT for efficacy assessment (unless there is a contraindication to contrast agents). MRI is also acceptable in some cases (e.g., whole body scan).

Ultrasound: Ultrasound should not be used as a method for measuring lesion size. Due to its operator dependence, ultrasound investigation is not repeatable after the measurement is completed and cannot guarantee consistency of technique and measurement between different measurements. If a new lesion is discovered using ultrasound during the study, it should be confirmed with CT or MRI. If radiation exposure from CT is a concern, MRI can be used instead.

Endoscopy, laparoscopy: The use of these techniques for objective tumor evaluation is not recommended, but they can be used to confirm CR when obtaining biopsy specimens, and also to confirm recurrence in studies where the endpoint is recurrence after CR or surgical resection.

Tumor markers: Tumor markers cannot be used alone to evaluate objective tumor response. However, if the marker level is above the upper limit of normal at baseline, it must return to the normal range for the evaluation of complete response. Because tumor markers vary by disease, this factor must be considered when writing the measurement criteria into the protocol. Specific criteria for CA-125 response (ovarian cancer recurrent) and prostate-specific antigen (PSA) response (prostate cancer recurrent) have been published. Furthermore, the Gynecologic Cancer InterGroup has developed CA-125 progression criteria, which will be incorporated into the objective tumor evaluation criteria for first-line treatment of ovarian cancer.

Cytology/Histology techniques: In specific situations defined by the protocol, these techniques can be used to identify PR and CR (e.g., residual benign tumor tissue is often present in lesions of germ cell tumors). When effusion may be a potential side effect of a certain therapy (e.g., treatment with taxane compounds or angiogenesis inhibitors), and the measurable tumor meets the criteria for response or stable disease, the appearance or worsening of tumor-related effusion during treatment can be confirmed by cytology to distinguish between response (or stable disease) and PD.

2. Assessment of Tumor Response

2.1 Target Lesion Assessment

Complete Response (CR): Disappearance of all target lesions, and all pathological lymph nodes (including target and non-target nodes) must have their short axis reduced to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as

reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest); in addition to the relative increase, the sum must also demonstrate an absolute increase of at least 5 mm (the appearance of one or more new lesions is also considered PD).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.2 Notes on Target Lesion Assessment

Lymph nodes: Even if a lymph node identified as a target lesion shrinks to within 10 mm, the actual short axis value corresponding to the baseline must still be recorded at each measurement (consistent with the anatomical plane of the baseline measurement). This means that if a lymph node is a target lesion, even if it meets the criteria for complete response, it cannot be said that the lesion has completely disappeared, because the short axis of a normal lymph node is defined as <10 mm. In the CRF or other recording methods, target lymph node lesions must be specifically recorded in a designated location: for CR, all lymph node short axes must be <10 mm; for PR, SD, and PD, the actual measured value of the target lymph node short axis will be included in the sum of diameters of target lesions.

Target lesions that are too small to measure: In clinical studies, all lesions (nodular or non-nodular) recorded at baseline should have their actual measured values recorded again in subsequent assessments, even if the lesion is very small (e.g., 2 mm). However, sometimes they may be too small, resulting in a very blurry image on the CT scan, making it difficult for the radiologist to define an exact value, and it may be reported as "too small to measure". When this occurs, it is very important to record the previous value on the CRF. If the radiologist believes the lesion may have disappeared, it should be recorded as 0 mm. If the lesion is indeed present but is blurry and an exact measurement cannot be given, a default value of 5 mm can be used. (Note: This situation is unlikely to occur with lymph nodes, as they normally have a measurable size or are often surrounded by fatty tissue, as in the retroperitoneal space; however, if a measurement cannot be given, a default of 5 mm is also used). The default value of 5 mm is derived from the slice thickness of the CT scan (this value does not change with different CT slice thicknesses). Since the chance of the same measurement value recurring is low, providing this default value will reduce the risk of incorrect assessment. However, it must be reiterated that if the radiologist can provide an exact value for the lesion size, the actual value must be recorded, even if the lesion diameter is less than 5 mm.

Fragmented or coalescent lesions: When a non-nodular lesion fragments, the longest diameters of each separate part are added together to calculate the sum of diameters of the lesion. Similarly, for coalescent lesions, they can be distinguished by the plane between each coalesced part, and then their respective longest diameters are calculated. However, if they are inseparably coalesced, the longest diameter should be the longest diameter of the entire fused lesion.

2.3 Non-target Lesion Assessment

This section defines the response criteria for non-target tumor lesions. Although some non-target lesions are actually measurable, they do not need to be measured; only a qualitative assessment at the time points specified in the protocol is required.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes are non-pathological in size (short axis <10 mm).

Non-CR/Non-PD: Presence of one or more non-target lesions and/or persistence of tumor marker levels above the normal range.

PD: Unequivocal PD of existing non-target lesions. Note: The appearance of one or more new lesions is also considered PD.

2.4 Special Notes on the Assessment of Non-target Lesion Progression

The definition of non-target lesion progression is further explained as follows: When a patient has measurable non-target lesions, even if the target lesion assessment is stable or partial response, to define unequivocal PD based on non-target lesions, the overall deterioration of the non-target lesions must have reached a degree that requires termination of treatment. A general increase in the size of one or more non-target lesions is often insufficient to meet the PD criteria. Therefore, when target lesions are stable or in partial response, it is very rare to define overall tumor PD based solely on changes in non-target lesions.

When all of a patient's non-target lesions are non-measurable: This situation occurs in some Phase III parts where the inclusion criteria do not require the presence of measurable lesions. The overall assessment still refers to the above criteria, but in this case, there is no measurable data for the lesions. Deterioration of non-target lesions is not easy to assess (by definition: all non-target lesions must be truly unmeasurable). Therefore, when changes in non-target lesions lead to an increase in overall disease burden equivalent to PD in target lesions, an effective detection method needs to be established to assess and define unequivocal PD based on non-target lesions. For example, an increase in tumor burden described as an additional 73% increase in volume (equivalent to a 20% increase in the diameter of a measurable lesion). Another example is peritoneal effusion changing from "trace" to

"massive"; lymphangiopathy from "local" to "widespread dissemination"; or described in the protocol as "sufficient to alter treatment". Examples include pleural effusion changing from trace to massive, lymphatic involvement spreading from the primary site to distant sites, or what might be described in the protocol as "necessitating a change in treatment". If unequivocal progression is found, the patient should be considered to have overall PD at that time point. It is best to have objective criteria applicable to the assessment of non-measurable lesions; note that the added criteria must be reliable.

2.5 New Lesions

The appearance of a new malignant lesion indicates PD; therefore, some evaluation of new lesions is very important. Currently, there are no specific criteria for detecting lesions by imaging; however, the discovery of a new lesion should be unequivocal. For example, progression cannot be attributed to differences in imaging techniques, changes in imaging modality, or other lesions besides the tumor (e.g., some so-called new bone lesions are merely the healing of the original lesion, or recurrence of the original lesion). This is very important when a patient's baseline lesions show a PR or CR. For example, necrosis of a liver lesion may be identified as a new cystic lesion on a CT report, when in fact it is not.

Lesions detected during follow-up that were not found at baseline will be considered new lesions and indicate PD. For example, if a patient with visceral lesions found at baseline undergoes a head CT or MRI and is found to have metastases, the patient's intracranial metastatic lesions will be considered evidence of PD, even if they did not have a head examination at baseline.

If a new lesion is equivocal, for example, due to its small size, further treatment and follow-up evaluation are needed to confirm whether it is a new lesion. If repeated examinations confirm it is a new lesion, the time of PD should be calculated from the time of its initial discovery.

Lesion assessment by Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) generally requires additional tests for supplementary confirmation. It is reasonable to combine FDG-PET examination and supplementary CT examination results to evaluate PD (especially for new suspicious disease). New lesions can be clarified by FDG-PET examination, according to the following procedure:

A negative baseline FDG-PET examination followed by a positive follow-up FDG-PET examination indicates PD.

No baseline FDG-PET examination was performed, and a subsequent FDG-PET examination is positive:

If the new lesion found on the follow-up positive FDG-PET examination is consistent with the CT examination results, it proves PD.

If the new lesion found on the follow-up positive FDG-PET examination is not confirmed by CT examination results, another CT examination is required for confirmation (if confirmed, the time of PD is calculated from the discovery of the abnormality on the previous FDG-PET examination).

If the follow-up positive FDG-PET examination result is consistent with an existing lesion on CT examination, and that lesion shows no PD on imaging, then there is no PD.

2.6 Missing Assessments and Unevaluable Descriptions

If lesion imaging or measurement cannot be performed at a specific time point, the patient is unevaluable at that time point. If only some lesions can be evaluated in an assessment, this is usually considered unevaluable at that time point, unless there is evidence that the missing lesions do not affect the efficacy response evaluation at the specified time point.

2.7 Special Notes on Efficacy Assessment

When nodular lesions are included in the overall target lesion assessment, and their size shrinks to 'normal' size (<10 mm), they will still have a lesion size scan report. To avoid over-assessing the situation reflected by an increase in nodule size, the measurement results will be recorded even if the nodule is normal. As mentioned earlier, this means that for participants with a complete response, the CRF will not record a value of 0.

If efficacy confirmation is required during the study, repeated "non-measurable" time points will complicate the assessment of BOR. The study's analysis plan must state that these missing data/assessments can be clearly explained when determining efficacy. For example, in most studies, a participant's response of PR-NE-PR can be considered as confirmed efficacy.

When a participant's overall health deteriorates, requiring discontinuation of treatment, but there is no objective evidence, it should be reported as symptomatic progression. Even after treatment discontinuation, an effort should be made to assess objective progression. Symptomatic deterioration is not a description of objective response; it is the reason for stopping treatment. The objective response of such participants will be assessed based on the status of target and non-target lesions as shown in Appendix Tables 1-3.

Cases defined as early progression, early death, and unevaluable are study-specific and should be clearly described in each protocol (depending on the treatment interval and treatment cycle).

In some cases, it is difficult to distinguish local lesions from normal tissue. When the assessment of complete response is based on such a definition, we recommend performing a biopsy before assessing the efficacy of complete response of the local lesion. When abnormal imaging results of a participant's local lesion are considered to represent lesion fibrosis or scar formation, FDG-PET is used as an

assessment standard similar to biopsy to confirm the efficacy of complete response. In this case, the use of FDG-PET should be prospectively described in the protocol, supported by reports from specialized medical literature on this situation. However, it must be recognized that the limitations of FDG-PET and biopsy themselves (including their resolution and sensitivity) will lead to false-positive results in the assessment of complete response.

Appendix Table 1. Time Point Response - Participants with Target Lesions (with or without Non-target Lesions)

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or not fully evaluable	No	PR
SD	Non-PD or not fully evaluable	No	SD
Not fully evaluable	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Not Evaluable.

Appendix Table 2. Time Point Response - Participants with Non-target Lesions Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR or Non-PD	No	Non-CR or Non-PD
Not fully evaluable	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Note: For non-target lesions, "Non-CR/Non-PD" refers to a response better than SD. Since SD is increasingly used as an endpoint for efficacy evaluation, the Non-CR/Non-PD response is established to address situations where no measurable lesions are specified.

For equivocal findings of progression (e.g., a very small, uncertain new lesion; cystic change or necrosis of an existing lesion), treatment may be continued until the next assessment. If PD is confirmed at the next assessment, the date of PD should be the date when suspected PD was first observed.

Appendix Table 3. Best Overall Response for Confirmed CR and PR

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	If SD persists for a sufficient duration, it is SD; otherwise, it should be PD
CR	PD	If SD persists for a sufficient duration, it is SD; otherwise, it should be PD
CR	NE	If SD persists for a sufficient duration, it is SD; otherwise, it should be NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	If SD persists for a sufficient duration, it is SD; otherwise, it should be PD
PR	NE	If SD persists for a sufficient duration, it is SD; otherwise, it should be NE
NE	NE	NE

Note: CR is Complete Response, PR is Partial Response, SD is Stable Disease, PD is Progressive Disease, NE is Not Evaluable. Superscript "a": If a true CR occurs at the first time point, any disease appearing at a subsequent time point will be evaluated as PD at that later time point (because the disease has reappeared after CR), even if the participant's response meets the PR criteria relative to baseline. Best response depends on whether SD occurs within the shortest treatment interval. However, sometimes the first assessment is CR, but a subsequent scan suggests that a small lesion still seems to be present; therefore, the participant's response at the first time point should actually be PR, not CR. In this case, the initial CR judgment should be revised to PR, and the best response is PR.

2.8 Confirmation of Efficacy Assessment/Duration of Response

Confirmation of Response

For non-randomized clinical studies where tumor response is the primary endpoint, the efficacy of PR and CR must be confirmed to ensure that the response is not the result of measurement error. In studies where SD or PD is the primary endpoint, confirmation of response is no longer necessary, as it has no value in the interpretation of the study results. In the case of SD, at least one measurement meeting the protocol-specified criteria for SD must be made within the shortest time interval after the start of the study (generally not less than 6-8 weeks).

Duration of Overall Response

The duration of overall response is from the time of the first measurement that meets the criteria for CR or PR (whichever is measured first) to the time of the first true record of disease recurrence or PD (using the smallest measurement recorded in the study as the reference for PD). The duration of CR

is from the time of the first measurement that meets the CR criteria to the time of the first true record of disease recurrence or PD.

Duration of Stable Disease

The time from the start of treatment to PD (in randomized studies, from the time of randomization), using the smallest sum on study as the reference (if the baseline sum is the smallest, it is used as the reference for calculating PD). The clinical relevance of the duration of SD varies between different studies and different diseases. If, in a particular study, the proportion of patients who maintain SD for a minimum duration is the study endpoint, the protocol should specify the minimum time interval between two measurements in the definition of SD.

Note: The duration of response, duration of SD, and PFS are affected by the frequency of follow-up after the baseline assessment. Defining a standard follow-up frequency is beyond the scope of these guidelines. The follow-up frequency should consider many factors, such as disease type and stage, treatment cycle, and standard practices. However, if comparisons between studies are to be made, the limitations on the accuracy of these measurement endpoints should be considered.

2.9 PFS/TTP

Many studies of advanced tumors use PFS or TTP as the primary endpoint. If the protocol requires all patients to have measurable lesions, the assessment of progression is relatively simple. An increasing number of studies allow patients with both measurable and non-measurable lesions to be enrolled. In this case, the clinical findings of PD in patients with non-measurable lesions must be described in detail and clearly. Because the date of PD often has ascertainment bias, the observation time points should be scheduled the same for all study groups.

Appendix 2: Performance Status Scoring Criteria (ECOG PS)

Score	Criteria
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Death

Appendix 3: Cockcroft-Gault Formula

Formula for serum creatinine concentration in (mg/dL):

$$\text{Male creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight})^{a}}{72 \times \text{serum creatinine}}$$

$$\text{Female creatinine clearance (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{weight})^{a}}{72 \times \text{serum creatinine}}$$

Formula for serum creatinine concentration in (μmol/L):

$$\text{Male creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight})^{a}}{0.818 \times \text{serum creatinine}}$$

$$\text{Female creatinine clearance (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{weight})^{a}}{0.818 \times \text{serum creatinine}}$$

a: Age in years, weight in kg.

Appendix 4: List of Prohibited Medications

Interaction Mechanism	Drug Name
Strong Inducers of CYP3A and P-gp	Apalutamide, carbamazepine, enzalutamide, ivosidenib, lumacaftor/ivacaftor, mitotane, phenytoin, rifampin, St. John's wort
Strong Inhibitors of CYP3A and P-gp	Ceritinib, clarithromycin, cobicistat, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir tablets, nefazodone, amiodarone, cyclosporine, dronedarone, erythromycin, lapatinib, propafenone, quinidine, ranolazine, verapamil
Sensitive Substrates of CYP3A4	Alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, isavuconazonium, ivabradine, lemborexant, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, mobocertinib, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil, venetoclax
Sensitive Substrates of OAT1	Adefovir, ciprofloxacin, furosemide, tenofovir

The table lists common strong inhibitors and inducers of CYP3A4 and P-gp, and sensitive substrates of OAT1 and CYP3A4. If there are questions about other possible concomitant medications, the investigator can communicate with the sponsor. Drug interactions can be queried on the FDA's official website at the following URL: https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems.

Appendix 5: Detailed Parameters and Simulation Performance of the BOIN Design

Using the Shiny app 'BOIN' obtained from http://www.trialdesign.org, and considering the following two scenarios:

1. Accelerated titration is used for the first two dose levels

The specific parameters of the BOIN design are as follows:

Parameter	Value
Number of dose groups	5
Starting dose	1
Number of participants per cohort	3
Number of cohorts	10
If the number of participants assigned to a dose group reaches m and the next participant is still to be assigned to that dose group, the study is terminated. m =	6
Target toxicity probability	0.3
Use default dose escalation/de-escalation boundaries (recommended)	True
Use accelerated titration	Yes
Maximum dose for accelerated titration	2
When 1 DLT is observed in 3 participants, change the decision from de-escalate to stay at the current dose	Yes
Dose elimination threshold p_K	0.95
Number of repetitions for each scenario	1000
Random number generator seed	12345

Note: Maximum sample size = Number of participants per cohort * Number of cohorts = 3 * 10 = 30.

The simulation performance of this BOIN design is as follows:

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Number of patients	Early termination %
Scenario 1							
True DLT rate	0.3	0.46	0.5	0.54	0.58		
Selection %	56.6	22.4	11.7	1.6	0		7.7
Patients treated %	44.1	35.1	17.6	2.9	0.3	12.1	
Scenario 2							
True DLT rate	0.16	0.3	0.47	0.54	0.6		
Selection %	24.8	47.5	23.8	2.9	0.1		0.9
Patients treated %	26.7	39.7	28.1	5.1	0.4	14.4	
Scenario 3							
True DLT rate	0.04	0.15	0.3	0.48	0.68		
Selection %	1.6	22.9	56.7	18	0.8		0
Patients treated %	9.8	23.3	43.4	20.7	2.8	15.3	
Scenario 4							
True DLT rate	0.02	0.07	0.12	0.3	0.45		

Selection %	0.2	3.3	23.8	51.2	21.4		0.1
Patients treated %	6.8	9.7	31.8	35.7	15.9	17	
Scenario 5							
True DLT rate	0.02	0.06	0.1	0.13	0.3		
Selection %	0.3	2.2	11.1	22.7	63.7		0
Patients treated %	7	9.2	24.3	29.5	30	16.4	

2. BOIN design considering only the last three dose levels

The specific parameters of the BOIN design are as follows:

Parameter	**Value**
Number of dose groups	5
Starting dose	1
Number of participants per cohort	3
Number of cohorts	10
If the number of participants assigned to a dose group reaches m and the next participant is still to be assigned to that dose group, the study is terminated. m =	6
Target toxicity probability	0.3
Use default dose escalation/de-escalation boundaries (recommended)	True
Use accelerated titration	No
When 1 DLT is observed in 3 participants, change the decision from de-escalate to stay at the current dose	Yes
Dose elimination threshold p_K	0.95
Number of repetitions for each scenario	1000
Random number generator seed	12345

The simulation performance of this BOIN design is as follows:

	Dose 1	Dose 2	Dose 3	Number of patients	Early termination %
Scenario 1					
True DLT rate	0.3	0.48	0.67		
Selection %	70.6	20.4	0.9		8.1
Patients treated %	63.7	32	4.3	10.4	
Scenario 2					
True DLT rate	0.13	0.3	0.44		
Selection %	27.7	50.1	21.7		0.5
Patients treated %	39.3	41.7	19	13.9	
Scenario 3					
True DLT rate	0.05	0.13	0.3		
Selection %	3.6	26.2	70.1		0.1
Patients treated %	25.1	37.4	37.5	14.7	

Based on the above simulation performance results, this design can select the correct MTD with a high probability (if an MTD exists) and will assign more patients to the dose level with a DLT rate

closest to the target probability of 0.3.

Appendix 6: Statistical Methods for Interim Analysis

The interim analysis uses the Bayesian predictive probability (PP) method to calculate the probability of success, providing a rationale for early futility assessment. Based on the efficacy data observed at the interim analysis, the probability of success (i.e., concluding that the study drug is effective) at the maximum planned sample size is calculated. Based on the observed data, a high PP indicates a high likelihood of concluding that the study treatment is effective at the end of the study, whereas a low PP suggests that the study treatment may not have sufficient efficacy.

The table below shows the relevant parameter values and calculation results set via the online software (https://www.trialdesign.org/one-page-shell.html#BEMPR):

Input Parameter	Input Value		
	NSCLC	CRC	PDAC
Reference response rate (θ_0)	0.23	0.10	0.15
Threshold for declaring efficacy at the end of the trial (p_T)	0.7		
Early Stopping for Futility	TRUE		
Probability confidence threshold for futility stopping (p_L)	0.2		
Early Stopping for Efficacy	FALSE		
Prior distribution for θ: Beta(a_0,b_0) a_0	0.5		
Prior distribution for θ: Beta(a_0,b_0) b_0	0.5		
Input Cohort Manually	FALSE		
Maximum number of patients in the trial	73	50	94
Minimum number of patients before early stopping rule applies	20		
Cohort size	1		

Appendix 7: Central Laboratory Information and Sample Destruction Company Information

Central Laboratory 1: PK Testing

Name: Teddy Clinical Research Laboratory (Shanghai) Limited

Unified Social Credit Code: 91310110MA1G83F27K

Address: Room 101-110, Block C, 3rd Floor, Building 12, No. 128 Xiangyin Road, Yangpu District, Shanghai

Central Laboratory 2: ctDNA Sequencing

Name: Guangzhou Burning Rock Biotech Co., Ltd.

Unified Social Credit Code: 91440116094098415C

Address: No. 5 Xingdao Huanbei Road, Guangzhou International Bio Island, Huangpu District, Guangzhou

Sample Destruction Company 1: PK Sample Destruction Unit

Name: Shanghai Solid Waste Disposal Co., Ltd.

Unified Social Credit Code: 913101147294906145

Address: No. 2491 Jiazhu Highway, Jiading District, Shanghai

Sample Destruction Company 2: ctDNA Sequencing Sample Destruction Unit

Name: Guangzhou GRANDTOP Group Co., Ltd.

Unified Social Credit Code: 91440101671815024A

Address: Room 1218, No. 121 Liuhua Road (South Tower), Yuexiu District, Guangzhou

Clinical Study Protocol

Study Title:	An Open-label, Phase I/II Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GFH375 in Patients with Advanced Solid Tumors with KRAS G12D Mutation
Protocol Number:	GFH375X1101
Version Number and Version Date:	Version 1.0 / March 15, 2024
Product Name:	GFH375
Study Phase:	Phase I/II
Sponsor:	GenFleet Therapeutics (Shanghai) Inc.
Sponsor Contact:	Huaqiang Zhu, Vice President of Medical Science Tel: 15601727272 Email: hqzhu@genfleet.com

Confidentiality Statement

The information contained in this clinical study protocol is confidential and is the property of GenFleet Therapeutics (Shanghai) Inc. It may not be disclosed to any third party (group or individual) without prior written permission. If you have this protocol without prior authorization, please contact GenFleet Therapeutics (Shanghai) Inc. immediately and return the protocol and any copies to the company.

Sponsor Signature Page

Study Title: An Open-label, Phase I/II Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GFH375 in Patients with Advanced Solid Tumors with KRAS G12D Mutation

Protocol Number: GFH375X1101

Position	Name	Signature (Printed)	Date
Vice President of Medical Science	Huaqiang Zhu	Huaqiang Zhu	March 15, 2024

Investigator Signature Page

Study Title: An Open-label, Phase I/II Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GFH375 in Patients with Advanced Solid Tumors with KRAS G12D Mutation

Protocol Number: GFH375X1101

By signing this protocol signature page, the investigator confirms and agrees to the following:

I have read the above study protocol and its appendices. I have fully discussed the contents of this protocol with the sponsor, GenFleet Therapeutics (Shanghai) Inc. I agree to conduct the study in accordance with this study protocol and to fulfill the relevant responsibilities in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP), local regulations, and other applicable regulations. I agree to ensure that all staff involved in this study are aware of their obligations in fulfilling the above commitments.

This document contains confidential information and shall not be disclosed to anyone other than those directly involved in the conduct of the study or in ethical/regulatory review, without the written authorization of the sponsor.

I have read the entire content of this study protocol and guarantee to conduct this study as required:

Investigator's Signature: _____ Date: _____

Printed Name: _____

Investigator's Title: _____

Contact Number: _____

Site Name/Address: _____

_____

_____

Protocol Synopsis

<table>
<tr><td>Protocol Number:</td><td>GFH375X1101</td></tr>
<tr><td>Sponsor</td><td>GenFleet Therapeutics (Shanghai) Inc.</td></tr>
<tr><td>Investigational Product</td><td>Code: GFH375</td></tr>
<tr><td>Study Title</td><td>An Open-label, Phase I/II Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GFH375 in Patients with Advanced Solid Tumors with KRAS G12D Mutation</td></tr>
<tr><td>Brief Title</td><td>A Phase I/II Study to Evaluate GFH375 in Patients with Solid Tumors with KRAS G12D Mutation</td></tr>
<tr><td>Phase</td><td>Phase I/II</td></tr>
<tr><td>Version Number/Date</td><td>V1.0 / March 15, 2024</td></tr>
<tr><td>Study Duration</td><td>Approximately 48 months</td></tr>
<tr><td>Study Objectives and Endpoints</td><td>This is a Phase I/II study.
Phase Ia objectives and endpoints include:
<table>
<tr><th>Study Objectives</th><th>Study Endpoints</th></tr>
<tr><td>Primary Objectives</td><td>Primary Endpoints</td></tr>
<tr><td>To evaluate the safety and tolerability of GFH375 in patients with advanced solid tumors with KRAS G12D mutation</td><td>• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs); changes in vital signs, electrocardiogram (ECG), and laboratory tests</td></tr>
<tr><td>• To determine the maximum tolerated dose (MTD) and recommended dose for expansiondose (RDE) of GFH375</td><td>• Incidence of dose-limiting toxicity (DLT) events</td></tr>
<tr><td>Secondary Objectives</td><td>Secondary Endpoints</td></tr>
<tr><td>• To evaluate the pharmacokinetic (PK) characteristics of GFH375 in patients with advanced solid tumors with KRAS G12D mutation.</td><td>• Plasma concentrations and PK parameters of GFH375, including but not limited to C_{max}, T_{max}, AUC, $t_{1/2}$, CL/F, V_z/F, C_{trough}</td></tr>
<tr><td>• To evaluate the preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation</td><td>• Objective response rate (ORR), duration of response (DoR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) as assessed according to Response</td></tr>
</table></td></tr>
</table>

	Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Phase Ib (Dose expansion) objectives and endpoints include:

Study Objectives	**Study Endpoints**
Primary Objectives	**Primary Endpoints**
To evaluate the safety and tolerability of GFH375 in patients with advanced solid tumors with KRAS G12D mutation ; To determine recommended phase II dose (RP2D)	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs); changes in vital signs, electrocardiogram (ECG), and laboratory tests
Secondary Objectives	**Secondary Endpoints**
• To evaluate the pharmacokinetic (PK) characteristics of GFH375 in patients with advanced solid tumors with KRAS G12D mutation.	• Plasma concentrations of GFH375
• To evaluate the preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation	• Objective response rate (ORR), duration of response (DoR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), as assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. and overall survival (OS)
Exploratory Objective	**Exploratory Endpoint**
• To explore the molecular mechanisms related to treatment sensitivity or drug resistance	• Mutation analysis of circulating tumor DNA (ctDNA) in blood at baseline and at the end of treatment

Phase II objectives and endpoints:

Study Objectives	**Study Endpoints**
Primary Objectives	**Primary Endpoints**
• To evaluate the efficacy of GFH375 in patients with advanced non-small cell lung	• ORR as assessed by RECIST 1.1

	cancer (NSCLC), advanced ductal adenocarcinoma of pancreas (PDAC), advanced colorectal cancer (CRC), and other solid tumors with KRAS G12D mutation.
	Secondary Objectives / **Secondary Endpoints** • To evaluate the efficacy of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation using other efficacy endpoints → • Best overall response (BOR), DoR, DCR, TTR, and PFS as assessed by RECIST 1.1 • OS • To evaluate the safety of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation → • Incidence and severity of AEs and SAEs; changes in vital signs, ECG, and laboratory tests • To evaluate the PK characteristics of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation → • Plasma concentrations of GFH375 **Exploratory Objective** / **Exploratory Endpoint** • To explore the molecular mechanisms related to treatment sensitivity or drug resistance → • Mutation analysis of circulating tumor DNA (ctDNA) in blood at baseline and at the end of treatment
Study Background	The RAS family is responsible for regulating signaling pathways related to cell growth, migration, survival, and differentiation. RAS proteins typically switch between GTP- and GDP-bound conformations, corresponding to the "on" and "off" states of the kinase, respectively. In various malignant tumors, oncogenic mutations in RAS lead to the inhibition of GTP hydrolysis, leaving the kinase in a constitutively active state, which results in malignant cell proliferation and changes in biological behavior. KRAS is the most common mutation type in the RAS family, accounting for approximately 90% of ductal adenocarcinomas of the pancreas, 50% of colorectal cancers, and 30% of lung adenocarcinomas. Therefore, KRAS is considered a driver oncogene for the development of many malignant tumors and for tumor metastasis. KRAS G12D is one of the most common KRAS mutation types. It is estimated that in lung adenocarcinoma, data from the United States show that the G12D mutation accounts for 4.9%, while a large-sample analysis of domestic NSCLC patients shows a KRAS G12D mutation frequency of approximately 2.2%. In pancreatic carcinoma, approximately 37% of patients carry the KRAS G12D mutation, suggesting the importance of this mutant allele at the population level in patients with pancreatic carcinoma. Preclinical studies have confirmed in multiple PDAC xenograft

	transplant models that KRAS G12D acts as a persistent oncogenic driver in PDAC, and KRAS G12D inhibitors have shown significant anti-tumor activity in PDAC models. In colorectal cancer, the KRAS mutation rate is approximately 40%, with KRAS G12D accounting for about 28%. In addition, studies have shown that KRAS mutation is a common factor for acquired drug resistance to cetuximab in colorectal cancer, and acquired KRAS G12D mutations have been observed in metastatic CRC tissue samples after treatment with cetuximab (or in combination with chemotherapy). Currently, several selective KRAS G12D inhibitors (such as MTRX1133 and HRS-4642) have entered clinical development, administered either orally or intravenously, but no therapy specifically targeting KRAS G12D-mutated tumors has been approved. Patients with advanced NSCLC, PDAC, CRC, and other solid tumors carrying the KRAS G12D mutation are usually first treated with chemotherapy, immunotherapy, or anti-angiogenic drugs in combination. After treatment failure with standard of care, there is a lack of effective treatment options. For example, in advanced NSCLC, although patients positive for driver genes such as EGFR and ALK can choose targeted therapies and achieve good efficacy, KRAS G12D rarely co-exists with these driver genes. Therefore, chemotherapy, such as docetaxel, remains the main treatment after failure of standard systemic therapy, with recently reported ORRs of 7.1-16.0% and a median PFS of 2.6-4.5 months. The Phase III NAPOLI-1 study, which enrolled patients with metastatic PDAC (mPDAC), showed that for mPDAC patients who had failed prior gemcitabine-based chemotherapy regimens, treatment with liposomal irinotecan in combination with 5-FU/LV (5-fluorouracil + leucovorin) resulted in significantly improved efficacy compared to those receiving only 5-FU/LV (5-fluorouracil + leucovorin): median overall survival (mOS) was 6.1 months (vs 4.2 months, HR 0.67), median PFS was 3.1 months (vs 1.5 months, HR 0.56), and ORR was 16% (vs 1%, $p < 0.0001$) . In other Phase II studies conducted in mPDAC participants who had received ≥ 1 line of therapy (most participants had received ≥ 2 lines of therapy), the reported ORR was 0%-10.7%. In CRC participants, TAS-102 +/- bevacizumab, regorafenib, and fruquintinib are common third-line treatment options, with an ORR of only 1-4%. Therefore, there is currently a lack of effective treatment methods for NSCLC, PDAC, and CRC after failure of standard of care, representing a huge unmet clinical need. KRAS G12C inhibitors (sotorasib, adagrasib) have been approved for the indication of NSCLC, demonstrating good efficacy and safety in this patient population. Compared to other KRAS-mutated lung cancers, KRAS G12D mutation-positive tumors have different clinical, genomic, and immunological features. For example, in NSCLC, KRAS G12D mutation-positive status may be associated with low tumor mutation burden and low PD-(L)1 expression, often being "immune cold," which promotes tumor cell drug resistance to immunosuppressants. Clinically, separate studies are needed for these populations, and KRAS G12D inhibitors provide a great research opportunity that may bring potential benefits to these patients. GFH375 is a highly selective, oral, non-covalent small molecule inhibitor targeting the KRAS G12D mutation. In preclinical *in vitro* studies, GFH375 has shown potent inhibitory effects on KRAS-dependent signal transduction and cancer cell viability, and has demonstrated significant anti-tumor efficacy in animal models of KRAS G12D-mutated tumors. The above results support the further evaluation of the safety and efficacy of GFH375 in patients with advanced solid tumors carrying the KRAS G12D mutation.
Study Design	This is a study to evaluate the safety/tolerability, PK, and efficacy of GFH375 monotherapy in patients with advanced solid tumors with KRAS G12D mutation. The primary objective of the Phase I part is to evaluate the safety/tolerability, PK, and preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation, and to determine the MTD and/or RP2D of GFH375. The primary objective of the Phase II part is to evaluate the efficacy of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation.

A Safety Monitoring Committee (SMC), composed of investigators and the sponsor, will be established during the study. For details, please refer to Chapter 10 and the SMC Charter for this study.

Phase Ia: Dose escalation Part

According to the BOIN design, 3-6 participants will be enrolled in each dose cohort for treatment (except during accelerated titration). Phase Ia will enroll approximately 30 subjects. Additional participants may be enrolled if more dose levels or alternative dosing regimens need to be explored.

After enrollment, participants will receive oral administration of GFH375, with each treatment cycle being 21 days. Participants will be enrolled into sequential dose-escalation cohorts, with a starting dose of 100 mg once daily (QD). A total of 5 or more dose levels are expected to be evaluated in the dose escalation part. The planned escalating doses are shown in the **table below**. The Investigator and Sponsor will review all available data to determine whether to explore higher dose levels or alternative dosing regimens, such as a twice-daily dosing regimen.

The first cycle after the first administration will serve as the DLT observation period. A DLT-evaluable case must meet one of the following two conditions:

- The participant experiences a DLT event, or
- The participant does not experience a DLT event and has received at least 15 days of the planned dosing of GFH375 in the first cycle.

Participants not evaluable for DLT will be replaced, with replacement subjects receiving GFH375 monotherapy at the same dose level.

If no DLT event occurs, the participant will continue treatment, with dose adjustments permitted as allowed by this protocol, until progressive disease (PD), unacceptable toxicity, or discontinuation of study treatment for other reasons. If a participant experiences a DLT event during the DLT observation period, and if the investigator and sponsor assess that the participant can benefit from continuing treatment with GFH375, treatment with GFH375 will be resumed after the relevant adverse event (AE) has resolved. Refer to the corresponding section in the main text for the criteria for resumption of dosing.

Participants enrolled in Phase Ia will undergo intensive PK sampling and have matching ECGs collected with PK sampling to evaluate the PK characteristics and safety of GFH375. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks. Participants will return to the study site 30 (±3) days after the last study treatment for a safety follow-up, and will have survival follow-ups every 90 (±7) days thereafter. Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the Informed Consent Form (ICF), initiation of other anti-tumor therapy, or the end of the study.

	Phase Ia QD Dose Cohorts with Planned/Completed Escalation *
Dose Cohort 1	100 mg QD
Dose Cohort 2	200 mg QD
Dose Cohort 3	400 mg QD
Dose Cohort 4	600 mg QD
Dose Cohort 5	900 mg QD

Note: Intermediate dose exploration of the above doses, such as 150 mg, 300 mg, 500 mg, 750 mg, QD, etc., may be conducted during the escalation process based on the clinical data obtained, including safety, PK, and possible efficacy.

DLT Definition

A DLT is an AE that occurs within 21 days after the first dose, is related to the investigational drug GFH375, and meets the following severity criteria. The severity of AEs is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0:

- Grade ≥ 4 absolute neutrophil count (ANC) decreased for ≥ 5 days;
- Grade ≥ 3 febrile neutropenia (ANC $<1.0 \times 10^9$/L with a single body temperature > 38.3°C or a sustained body temperature ≥38°C for more than 1 hour);
- Grade ≥ 4 platelet count decreased for ≥ 5 days;
- Grade ≥ 3 platelet count decreased with Grade ≥ 2 hemorrhage;
- Grade ≥ 4 anemia;
- If baseline ALT or AST is Grade ≤ 1: Grade ≥ 3 serum transaminases increased (ALT or AST) lasting > 7 days is considered a DLT; if baseline ALT or AST is Grade 2, then ALT or AST > 10×ULN lasting > 7 days is considered a DLT;
- Grade ≥ 3 serum bilirubin increased;
- According to Hy's Law, AST or ALT > 3×ULN (if baseline metastases to liver are present, then > 3 times the baseline value is required), with concurrent total bilirubin > 2×ULN (causes such as biliary obstruction or other causes like hepatitis, intrahepatic tumor progression, etc., must be excluded);
- Grade ≥ 3 other toxicities (non-hepatic, non-hematologic), with the exception of the following:
  - Grade 3 nausea or vomiting, diarrhea, lasting no more than 3 days with/without symptomatic supportive care;
  - Grade 3 fatigue, lasting no more than 3 days with/without symptomatic supportive care;
  - Asymptomatic Grade 3 abnormal laboratory and not clinically significant per Investigator assessment.

Toxicities meeting the above criteria that occur after the DLT observation period will also be considered important factors in the safety evaluation. In addition, other treatment-related toxicities that may be assessed as DLTs will be determined after discussion between the sponsor and the investigator.

During the first cycle (DLT observation period), AEs that meet the DLT criteria should be reported to the sponsor within 24 hours of awareness of their occurrence.

Dose Escalation Rules and MTD Definition

Accelerated titration is permitted for the first two dose levels of the QD dosing regimen, meaning the first participant will receive treatment at the first dose level. If no Grade ≥2 treatment-related AE is observed in participants in the first two dose cohorts during the DLT observation period, 3-6 participants will be enrolled at the next higher dose level, and the BOIN design will be used for this cohort and subsequent dose escalations. Conversely, if any Grade ≥2 treatment-related AE or DLT event is reported in the first or second dose cohort, the study will switch directly to the BOIN design, starting from the lowest dose cohort where the Grade ≥2 treatment-related AE or DLT event was observed. Provided that accelerated titration is completed for the first dose, the decision on whether to use accelerated titration for the second dose level will be made by the SMC based on discussion of the PK and safety data from the first dose level. Subsequent dose levels will use the BOIN design to determine the MTD, with a target toxicity probability of 0.3. Each dose level will enroll 3-6 participants for treatment. Phase Ia will enroll approximately 30 subjects. .

The BOIN design will assign the dose level for the next group of participants according to the dose escalation/de-escalation rules shown in the table below.

Decision	Total number of participants treated at the current dose

	3	4	5	6	7	8	9
Escalate, if number of participants with DLT is ≤	0	0	1	1	1	1	2
De-escalate, if number of participants with DLT is ≥	2	2	2	3	3	3	4
Eliminate dose, if number of participants with DLT is ≥	3	3	4	4	5	5	5

For specific rules, please see Section 3.1.1.2 of the main text.

After the dose escalation part is completed, isotonic regression analysis will be used based on the dose determination set (DDS) to determine the MTD. The online BOIN software at http://www.trialdesign.org will be used to perform isotonic regression analysis to obtain the isotonic estimates of the toxicity probability for each dose level. The dose level closest to the target toxicity rate of 0.3 is the MTD. If there are 2 or more dose levels that meet the condition simultaneously, the highest dose level with an isotonic estimate <0.3 or the lowest dose level with an isotonic estimate ≥0.3 will be selected.

Backfilling of Participants in the Dose Escalation Part

Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional participants for backfilling. These participants will be treated with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is considered to have potential clinical benefit by the investigator and sponsor, in order to better estimate the RDE/RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. If the safety of the 750 mg QD dose cohort has been explored and confirmed, backfilling of the 700 mg QD dose cohort may also be conducted. Backfilled participants will not be included in the DLT evaluation. After backfilling, no more than 9 particpants at each dose level will be treated in each GFH375 dose cohort (including participants enrolled in the BOIN doseescalation part).

Backfilled participants will complete the relevant visits according to the Phase Ia part Schedule of Activities and the Phase Ia part PK blood sampling schedule.

Intra-participant Dose Escalation

In principle, intra-participant dose escalation will not be performed during the dose escalation part. For participants enrolled in Phase Ia, after agreement from the investigator and sponsor, intra-participant dose adjustment to receive RP2D monotherapy is permitted after the RP2D for this protocol has been confirmed.

Phase Ib: Dose expansion

Upon completion of the dose-escalation phase, one or more recommended doses for expansion (RDE) will be selected based on an integration of preclinical and clinical data to conduct the dose-expansion study. Each RDE cohort is anticipated to enroll up to 30 subjects to confirm safety and establish the recommended Phase 2 dose (RP2D).

Eligible subjects will receive GFH375 monotherapy in 21-day treatment cycles until disease progression, intolerable toxicity, or study discontinuation for other reasons. Subjects enrolled in the dose-expansion portion of Phase Ib will undergo sparse pharmacokinetic (PK) sampling along with matched electrocardiogram (ECG) collection. During treatment, subjects will undergo imaging and tumor assessments every 6 weeks ±1 week for the first 48 weeks (with the first assessment to be performed after the completion of 6 weeks of study treatment), and every 12 weeks ±1 week thereafter. Subjects will return to the study site for safety follow-up 30 (±3) days after the last study treatment, followed by survival follow-ups every 90 (±7) days. Subjects who discontinue study treatment for reasons other than disease progression and who have not initiated new anticancer therapy must continue disease progression follow-up according to the prior imaging schedule until disease progression,

	withdrawal of informed consent, initiation of other anticancer therapy, or study conclusion. For subjects enrolled in Phase Ib, intra-patient dose escalation to the RP2D monotherapy may be permitted after RP2D confirmation under this protocol, contingent upon agreement between the Investigator and Sponsor. **Phase II Part** The Phase II part is an open-label, multicenter study. The overall study plan is shown in Figure 3 of the main text. The objective is to evaluate the efficacy, safety, and PK characteristics of GFH375 in patients with advanced non-small cell lung cancer, advanced pancreatic carcinoma, colorectal cancer, and other advanced solid tumors with KRAS G12D mutation. The Phase II part will enroll approximately 317 participants with advanced solid tumors with KRAS G12D mutation to receive continuous GFH375 monotherapy at the RP2D, with a treatment cycle of 21 days. Participants enrolled in this part will undergo sparse PK sampling according to the Phase II part PK blood sampling schedule and have matching ECGs collected with PK sampling. • Advanced NSCLC participant cohort: Approximately 73 participants with advanced NSCLC carrying the KRAS G12D mutation are planned for enrollment. • Advanced PDAC participant cohort: Approximately 94 participants with advanced PDAC carrying the KRAS G12D mutation are planned for enrollment. • Advanced CRC participant cohort: Approximately 50 participants with advanced CRC carrying the KRAS G12D mutation are planned for enrollment. • Other advanced solid tumor participant cohort: Approximately 100 participants with other advanced solid tumors carrying the KRAS G12D mutation are planned for enrollment, such as bile duct cancer, appendix cancer, etc., carrying the KRAS G12D mutation. Eligible participants who are screened will receive GFH375 monotherapy until PD, unacceptable toxicity, or discontinuation of study treatment for other reasons. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks. Participants will return to the study site 30 (±3) days after the last study treatment for a safety follow-up, and will have survival follow-ups every 90 (±7) days thereafter. Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the ICF, initiation of other anti-tumor therapy, or the end of the study.
Inclusion Criteria	**Participants must meet all of the following criteria to participate in this study:** 1. Participants who voluntarily participate in the study and sign the ICF. 2. Male or female, aged 18 - 75 years at the time of signing the ICF. 3. Participants with histologically or cytologically confirmed locally advanced or metastatic malignant tumor, who must meet the following criteria: （1）Phase I Part:PD after standard of care, or standard of care has been confirmed to be intolerable, or refused standard of care. （2）Phase II Part: a) Advanced NSCLC: ✓ Participants who have progressed after prior treatment with anti-PD-(L)1 therapy and/or platinum-based chemotherapy (unless contraindicated or intolerant), a; ✓ If prior adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy. b) Advanced PDAC: Participants who have progressed after adequate

	treatment with a gemcitabine-based chemotherapy regimen or FOLFIRINOX/mFOLFIRINOX regimen, or are unsuitable for standard of care due to reasons such as unacceptable toxicity, or refused standard of care.. Those with high microsatellite instability (MSI-H) and/or deficient mismatch repair (dMMR) must have progressed after at least one prior line of anti-PD-1 therapy. If adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy. c) Advanced CRC: Participants who have progressed after at least two lines of standard of care, or are unsuitable for standard of care due to reasons such as unacceptable toxicity, or refused standard of care. Participants must have experienced PD or recurrence during or after treatment with fluorouracil, irinotecan, and oxaliplatin for metastatic disease, unless the investigator considers the participant unsuitable for the above treatment regimens. Those with known MSI-H and/or dMMR must have received prior treatment with an immune checkpoint inhibitor (if applicable). If adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy. d) Other solid tumors: Participants who have progressed after standard of care, or are unsuitable for standard of care due to reasons such as unacceptable toxicity, or refused standard of care. 4. Participants enrolled in this study must provide a written test report confirming KRAS G12D mutation-positive status. 5. According to RECIST 1.1, participants enrolled in Phase Ia must have at least one evaluable lesion, and participants enrolled in Phase II must have at least one measurable lesion. 6. Toxicities from prior anti-tumor therapy must have resolved to baseline level (excluding alopecia) or ≤ Grade 1 (for neurological toxicity, ≤ Grade 2). 7. Investigator-assessed life expectancy ≥ 12 weeks. 8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-1 (see Appendix 2 for scoring criteria). 9. Adequate organ function, including: • Hematopoietic function: Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 75 × 10^9/L, hemoglobin ≥ 9 g/dL, with no transfusion or treatment with granulocyte colony-stimulating factor, thrombopoietin, or erythropoietin within 14 days before the blood test. • Liver function: ➢ Both AST and ALT < 2.5×ULN; for participants with baseline metastases to liver, both AST and ALT < 5×ULN; ➢ Total bilirubin (TBIL) < 1.5×ULN; for participants with Gilbert's syndrome: TBIL < 2×ULN. • Renal function: Creatinine clearance (CrCl) ≥ 50 mL/min (calculated by Cockcroft-Gault formula, see Appendix 3). • Coagulation function: Prothrombin time (PT) or activated partial thromboplastin time (APTT) < 1.5×ULN, international normalized ratio (INR) < 1.5×ULN or within the target range for anticoagulant therapy. 10. Women of childbearing potential (WOCBP) and male participants with partners who are WOCBP must agree to use effective methods of contraception from the time of signing the ICF until 30 days after the last study treatment. WOCBP must have a negative serum pregnancy test result within 7 days before dosing.

	11. Participants who are able to communicate well, adhere to the follow-up schedule, and comply with the protocol requirements in the investigator's judgment.
Exclusion Criteria	**Participants who meet any of the following criteria cannot be enrolled in this study:** 1. Other malignant tumor that has progressed or required treatment within 3 years prior to enrollment, with the exception of adequately treated carcinoma in situ, basal cell carcinoma, or squamous cell carcinoma of skin. 2. Patients with unstable brain metastasis as judged by the investigator. Patients with incidentally detected brain metastasis during screening may be enrolled if they are asymptomatic and do not require therapeutic intervention; enrollment is permissible if the investigator judges the brain metastasis to be stable, the hormone dose is stable, and the prednisone dose is ≤10 mg/d (or an equivalent dose if other steroid drugs are used). 3. Phase II Part: a) Advanced NSCLC: Exclusion of known other driver gene mutations or fusions, such as EGFR, ALK, BRAF (V600E), HER2, MET (exon 14), ROS1, RET, or NTRK1/2/3 b) Advanced CRC: Exclusion of known other driver gene mutations, amplifications, or fusions, such as BRAF (V600E), HER2, NTRK, or RET c) Advanced PDAC: Exclusion of known other driver gene mutations or fusions, such as BRAF (V600E), BRCA, NTRK, or RET 4. Prior targeted therapy against KRAS G12D or pan-KRAS (with primary targeting effect on KRAS G12D). 5. Receipt of palliative radiation within 14 days before administration of the study drug. 6. Receipt of other anti-tumor therapy within 28 days or 5 half-lives (whichever is shorter) before dosing, including chemotherapy, targeted therapy, endocrine therapy, immunotherapy, Chinese patent medicines with definite anti-tumor effects, and other investigational drugs or devices, with the exception of endocrine maintenance therapy. 7. Concomitant clinically significant severe cardiovascular disorder: • Clinically significant severe cardiovascular events within 6 months before the first study treatment, such as myocardial infarction, angina unstable, symptomatic cardiac failure congestive (New York Heart Association Class III or IV), severe arrhythmia requiring drug therapy, or receipt of angioplasty, stenting, and coronary artery bypass graft surgery, etc. • Clinically significant QT/QTcF prolongation (based on the average of three QTcF values during the screening period, QTcF > 470 ms) or a family history of QT interval prolongation. • Hypertension that remains poorly controlled after standard treatment. 8. Stroke or other severe cerebrovascular disorder within 6 months prior to enrollment. 9. History of deep vein thrombosis or any other severe thromboembolism within 3 months prior to enrollment. 10. Concomitant pleural effusion, ascites, or pericardial effusion requiring repeated drainage or causing significant symptoms. 11. Concomitant superior vena cava syndrome. 12. Concomitant diseases that may significantly affect the absorption of GFH375, or inability or unwillingness to swallow tablets. 13. Concomitant clinically significant interstitial lung disease, radiation pneumonitis, or immune-related pneumonitis requiring treatment. 14. Concomitant major acute or chronic infectious diseases, including: • Active infection requiring intravenous antibiotic therapy within 7 days prior to enrollment.

	• Positive for human immunodeficiency virus antibody (HIV-Ab) at baseline. • Active hepatitis b virus infection (HBsAg positive with positive HBV-DNA). • Active hepatitis c virus infection (HCV-Ab positive with positive HCV-RNA). • Active tuberculosis. 15. Other poorly controlled systemic diseases, such as diabetes mellitus. 16. Undergone or planning to undergo major surgery as judged by the investigator within 28 days before the first dose (excluding needle biopsy). 17. History of organ transplant or preparing to receive an organ transplant. 18. Need for acid-suppressing drugs, including proton pump inhibitors and novel acid-suppressing drugs (e.g., potassium-competitive acid blockers), within 7 days before or during the administration of the study drug. 19. Receipt of strong inhibitors or inducers of CYP3A or P-gp within 14 days or 5 half-lives of the drug (whichever is longer) before administration of the study drug. 20. Receipt of known sensitive substrates of CYP3A or OAT1 within 14 days or 5 half-lives of the drug (whichever is longer) before administration of the study drug. Unless agreed for enrollment after review by the investigator and sponsor. 21. Known allergy to the study drug or its components. 22. Severe mental or psychological illness, or history of drug abuse or severe alcoholism. 23. Pregnant or lactating women. 24. Other conditions that, in the investigator's judgment, make the participant unsuitable for the study. 25.
Statistical Analysis	**Analysis Sets** • Full Analysis Set (FAS): All participants who have received at least one dose of GFH375. • Safety Set (SS): All participants who have received at least one dose of GFH375 and have at least one post-treatment safety assessment. • Dose Determination Set (DDS): All Phase Ia participants who have received undiminished doses of GFH375 for at least 15 cumulative days during the DLT observation period and had adequate safety assessments, or who have experienced a DLT during the DLT observation period. The DDS does not include backfilled participants. • Per-Protocol Set (PPS): All Phase II participants in the FAS who are compliant with the protocol. The study team will review all protocol deviations before the final database lock and exclude participants with major protocol deviations that affect the efficacy evaluation from the PPS. • Pharmacokinetic Analysis Set (PKAS): All participants who have received at least one dose of GFH375 and have provided at least one blood sample for evaluable PK data. **Statistical Analysis Methods** Data from Phase Ia, Ib and Phase II will be analyzed and summarized separately. Data from the Phase I stage will be analyzed and summarized by different dose levels and dosing regimens; data from the Phase II stage will be analyzed and summarized separately by tumor type. **Safety Analysis** The incidence of AEs, treatment-related AEs, and SAEs will be summarized by System Organ Class (SOC), Preferred Term (PT), and severity. For the Phase Ia part, the incidence of various types of DLTs will be summarized based on the DDS, and the DLTs will be listed. Descriptive summaries will be provided for laboratory tests, vital signs, and ECGs. **Efficacy Analysis**

Best overall response (BOR), ORR, and DCR will be calculated, and the two-sided 95% confidence interval (CI) for ORR and DCR will be estimated using the Clopper-Pearson method. The median DoR, PFS, and OS and their 95% Brookmeyer-Crowley CIs will be estimated using the Kaplan-Meier method. TTR will be summarized descriptively.

For the Phase I stage, when the sample size of an analysis group is less than 10, DoR, TTR, PFS, and OS will be listed individually by participant, and the Kaplan-Meier method will not be used for analysis.

For the Phase II stage, the primary estimand is set as follows:

Study Population	Participants with advanced solid tumors with KRAS G12D mutation
Treatment	GFH375
Endpoint	Percentage of participants who achieve CR or PR as assessed by RECIST 1.1 criteria. If a participant has no post-baseline assessment results, the participant is considered a non-responder**.**
Intercurrent Event	Start of new anti-tumor therapy (Handling strategy: Treatment policy strategy, assessment results after the start of new anti-tumor therapy are not included in the analysis.)
Population-level Summary	ORR

PK Analysis

Plasma concentration data of GFH375 will be listed and summarized descriptively according to the sampling times specified in the protocol. The summaries will be presented by study phase, dose group, and dosing regimen. Individual participant plasma concentration-time curves of GFH375 and corresponding summary curves (mean + standard deviation) will be plotted using linear and semi-logarithmic coordinates, by study phase, dose group, and dosing regimen. Planned PK sampling times will be used to calculate summary statistics and plot summary curves (mean + standard deviation); actual PK sampling times will be used to plot individual participant curves.

Phoenix WinNonlin software (version v8.2 or later, Certara USA, Inc., New Jersey, US) will be used to perform non-compartmental analysis (NCA) to calculate the PK parameters of GFH375 based on actual blood sampling time points. The PK parameters of GFH375 after single and multiple doses in participants in the Phase Ia dose escalation part will be summarized descriptively, with summaries presented by dose group and dosing regimen.

Sample Size Calculation

Phase Ia

Phase Ia will enroll approximately 30 subjects.

According to the BOIN design, 3-6 patients will be enrolled in each dose group for treatment (except during accelerated titration). Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional participants for backfilling. These participants will be treated with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is considered to have potential clinical benefit by the investigator and sponsor, in order to better estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. Backfilled participants will not be included in the DLT evaluation. After backfilling, no more than 30 participants will be treated in each GFH375 dose cohort (including participants enrolled in the BOIN dose-escalationpart).

Additional patients may be enrolled if more dose levels or alternative dosing regimens need to be explored.

Phase Ib

One or more RDE dose cohorts are planned, with up to 30 subjects per cohort.

Phase II Part

A total of approximately 213 participants are planned for enrollment, including approximately 73 patients with advanced NSCLC, approximately 50 patients with advanced PDAC, approximately 50 patients with advanced CRC, and approximately 40 patients with other advanced solid tumors.

Tumor Type	Historical Control ORR	Expected ORR	Sample Size
NSCLC	23%	40%	73
PDAC	15%	30%	50
CRC	10%	30%	50
Other			40
Total			213

For second-line advanced NSCLC, the historical control ORR is 23%, and the expected ORR in this study is 40%. The study will be considered successful if the lower limit of the 95% CI for the observed ORR is not less than the historical control of 23%. With a one-sided $\alpha = 0.025$, 73 participants are required to achieve 85% power. When at least 25 of the 73 participants have a CR/PR, the lower limit of the exact 95% CI for the observed ORR will be higher than the historical control of 23%. With 25 CR/PRs, the ORR = 34.2%, with a 95% CI of (23.5%, 46.3%).

For advanced PDAC and CRC, the historical control ORR is 10% for both; an ORR of 30% is anticipated for both tumor types in this study.The study will be considered successful if the lower limit of the 95% CI for the observed ORR is not less than the historical control of 10%. It is planned to enroll 50 participants, which will provide 96% power with a one-sided $\alpha = 0.025$. When at least 10 of the 50 participants have a CR/PR, the lower limit of the exact 95% CI for the observed ORR will be higher than the historical control of 10%. With 10 CR/PRs, the ORR = 20.0%, with a 95% CI of (10.0%, 33.7%).

For other solid tumors: Approximately 40 participants with advanced solid tumors with KRAS G12D mutation, such as bile duct cancer and appendix cancer with KRAS G12D mutation, are planned for enrollment.

Interim Analysis

A futility interim analysis will be performed separately for NSCLC, PDAC, and CRC in phase II. For each tumor type, the analysis is planned when approximately 25 participants (including Phase I participants treated with RP2D and Phase II participants) have had at least one post-baseline imaging tumor assessment or have withdrawn from the study early. Due to practical clinical operational reasons, the number of participants at the time of the interim analysis is allowed to differ from the planned number. During the interim analysis, enrollment will not be stopped.

At the interim analysis, a futility analysis will be conducted on ORR for NSCLC, PDAC, and CRC, respectively, using the Bayesian predictive probability method. Early termination of the study for the corresponding tumor type due to lack of efficacy evidence is permitted (but not mandatory).

The predictive probability of success (PPoS) will be calculated based on the observed number of Phase II participants who have achieved a response (CR/PR). If the PPoS is < 0.2, early termination of enrollment due to lack of efficacy evidence is permitted (but not

mandatory). The corresponding termination criteria for PPoS < 0.2 are shown in the table below:

Tumor Type	Number of Participants*	Recommended to terminate the cohort when the number of responders is ≤
NSCLC	20 ~ 21	3
	22 ~ 25	4
	26 ~ 29	5
	30	6
PDAC, CRC	20 ~ 23	1
	24 ~ 30	2

*Number of participants: The sum of Phase I participants treated with RP2D and Phase II participants who have had at least one post-baseline imaging tumor assessment or have withdrawn from the study early (at least one of these must be met).

The interim analysis planned above is not mandatory. If there is sufficient comprehensive safety and efficacy data to support it before the planned time point for the interim analysis, this interim futility analysis may be omitted.

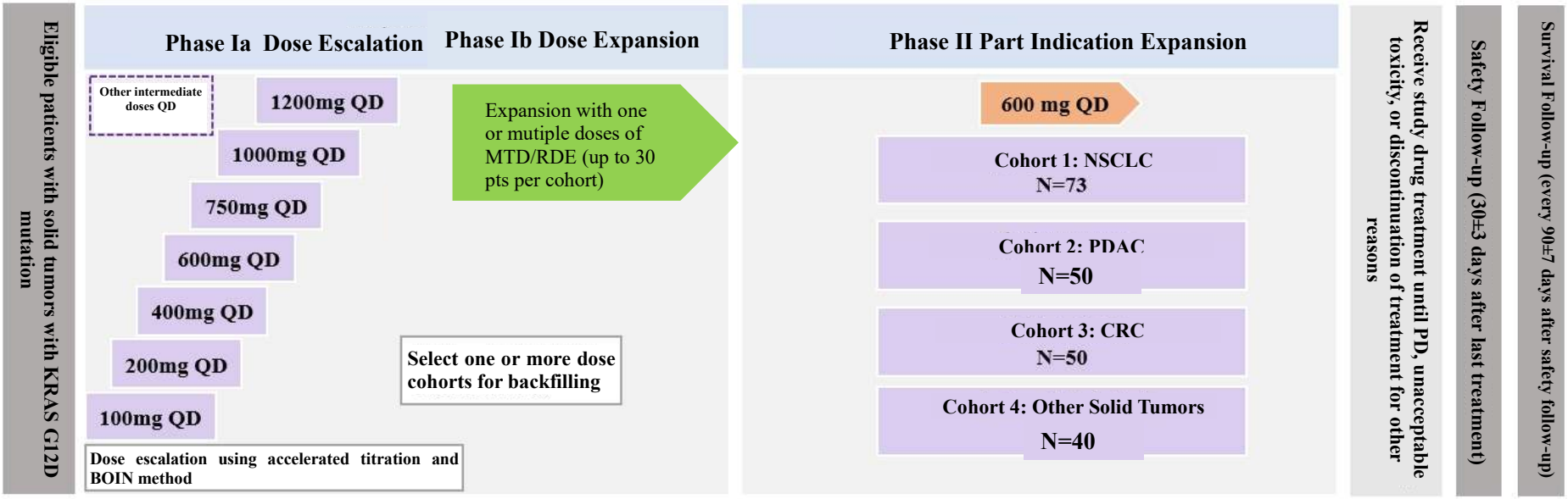

Figure 1 Overall Study Design

Abbreviations: QD: once daily; BID: twice daily; NSCLC: non-small cell lung cancer; PDAC: ductal adenocarcinoma of pancreas; CRC: colorectal cancer; BOIN: Bayesian Optimal Interval.

Schedule of Activities for Phase Ia Treatment Stage

Study Stage	Screening Period	Treatment Period							Remarks
		Cycle 1				Cycle 2		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D3**	**D8**	**D15**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**0**	**±3**	**±3**	**-1 ~ 3**	**±3**	**±3**	
Informed Consent	×								
Inclusion/Exclusion Criteria	×	×							Inclusion/exclusion criteria must be reviewed again on C1D1.
Demographics	×								Includes sex, age, ethnicity, etc.
Body Height/Weight	×	×				×		×	Body height is measured only once during the screening period.
Tumor History	×								Includes information on tumor diagnosis, time of diagnosis, metastatic sites, etc. For advanced NSCLC, data on prior PD-L1 expression levels should be collected (if available)
Other Medical History	×								All active medical conditions and any conditions the investigator considers clinically significant will be collected.
Prior Anti-tumor Therapy History	×								All prior anti-tumor therapy history for the study disease, including therapeutic drugs, start time, end time, best overall assessment, reason for discontinuation, etc. will be collected.
Other Prior/Concomitant Therapy	×								All prior/concomitant medications and therapeutic procedures from 30 days before the first dose until the end of the safety follow-up will be collected.
Virus Serology	×								Includes hepatitis b surface antigen (HBsAg), hepatitis b surface antibody (HBsAb), hepatitis b core antibody (HBcAb), HCV antibody, HIV antibody, and HBV-DNA and HCV-RNA tests (if necessary).
Pregnancy Test	×	×						×	Female participants of childbearing potential must undergo a serum pregnancy test within 7 days before the first dose, followed by a pregnancy test urine on D1 of every 2 cycles. If a negative urine pregnancy result cannot be confirmed, a serum pregnancy test is required.

Study Stage	Screening Period	Treatment Period							Remarks
		Cycle 1				Cycle 2		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D3**	**D8**	**D15**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**0**	**±3**	**±3**	**-1 ~ 3**	**±3**	**±3**	
Physical Examination	×	×	×	×		×	×	×	
ECOG PS	×	×				×		×	If assessed within 72 hours before the first dose, it does not need to be repeated on C1D1.
Vital Signs	×	×	×	×	×	×	×	×	
Hematology	×	×	×	×	×	×	×	×	If laboratory test results are available within 7 days before the first dose, they do not need to be repeated on C1D1. If the participant's clinical status changes significantly, laboratory tests must be repeated on C1D1.
Blood Chemistry	×	×	×	×	×	×	×	×	
Urinalysis	×	×			×	×	×	×	
Coagulation Function	×	×			×	×	×	×	
Electrocardiogram	×	×	×	×	×	×	×	×	1. If other trial procedures are combined, an ECG should be performed first to avoid the impact of study procedures on the ECG results. 2. The ECG should be performed after the participant has rested quietly for at least 10 minutes. Three ECGs will be performed at each visit during the study, with an interval of at least 5 minutes between each. 3. For ECG collection that matches PK sampling, please refer to the PK blood collection form for specific requirements.
Tumor Imaging Assessment	×	×							Compliant examination results from within 4 weeks before the first dose can be accepted as baseline and do not need to be repeated. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks.
GFH375 Administration		×							GFH375 tablets will be dispensed to participants on specified visit days and taken orally as scheduled. **Participants receiving QD**

Study Stage	Screening Period	Treatment Period							Remarks
		Cycle 1				Cycle 2		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D3**	**D8**	**D15**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**0**	**±3**	**±3**	**-1 ~ 3**	**±3**	**±3**	
									dosing should skip the dose on Day 2 and Day 3 of the first cycle; participants receiving BID dosing do not need to skip.
PK Blood Sampling		×							See PK Collection Form
AE/SAE	×	×							AEs/SAEs will be collected from signing of ICF until 30 days after the last dose

Abbreviation: C1D1: Cycle 1 Day 1. ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; PK: Pharmacokinetics; AE/SAE, Adverse Event/Serious Adverse Event.

Schedule of Activities for Phase Ib Treatment Stage

Stage stage	Screen period	Treatment period					Remarks
		Cycle 1		Cycle 2		Subsequent cylces	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit day	**D-28~D-1**	**D1**	**D10**	**D1**	**D10**	**D1**	
Time window (day)	**NA**	**0**	**±3**	**±3**	**±3**	**±3**	
Informed Consent	×						
Inclusion/exclusion criteria	×	×					Inclusion/exclusion criteria must be reviewed again on C1D1.
Demographics	×						Includes sex, age, ethnicity, etc.
Body height/weight	×	×		×		×	Body height is measured only once during the screening period.
Tumor history	×						Includes information on tumor diagnosis, time of diagnosis, metastatic sites, etc. For advanced NSCLC, data on prior PD-L1 expression levels should be collected (if available)
Other medical history	×						All active medical conditions and any conditions the investigator considers clinically significant will be collected.
Prior anti-tumor therapy history	×						All prior anti-tumor therapy history for the study disease, including therapeutic drugs, start time, end time, best overall assessment, reason for discontinuation, etc. will be collected.
Other prior/concomitant therapy	×						All prior/concomitant medications and therapeutic procedures from 30 days before the first dose until the end of the safety follow-up will be collected.
Virus serology	×						Includes hepatitis b surface antigen (HBsAg), hepatitis b surface antibody (HBsAb), hepatitis b core antibody (HBcAb), HCV antibody, HIV antibody, and HBV-DNA and HCV-RNA tests (if necessary).
Pregnancy test	×	×				×	Female participants of childbearing potential must undergo a serum pregnancy test within 7 days before the first dose, followed by a pregnancy test urine on D1 of every 2 cycles. If a negative urine pregnancy result cannot be confirmed, a serum pregnancy test is required.
Physical Examination	×	×	×	×	×	×	

Stage stage	Screen period	Treatment period					Remarks
		Cycle 1		Cycle 2		Subsequent cylces	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit day	**D-28~D-1**	**D1**	**D10**	**D1**	**D10**	**D1**	
Time window (day)	**NA**	**0**	**±3**	**±3**	**±3**	**±3**	
ECOG PS	×	×		×		×	If assessed within 72 hours before the first dose, it does not need to be repeated on C1D1.
Vital Signs	×	×	×	×	×	×	
Hematology	×	×	×	×	×	×	If laboratory test results are available within 7 days before the first dose, they do not need to be repeated on C1D1. If the participant's clinical status changes significantly, laboratory tests must be repeated on C1D1.
Blood Chemistry	×	×	×	×	×	×	
Urinalysis	×	×	×	×	×	×	
Coagulation Function	×	×	×	×	×	×	
ECG	×	×	×	×	×	×	1. If other trial procedures are combined, an ECG should be performed first to avoid the impact of study procedures on the ECG results. 2. The ECG should be performed after the participant has rested quietly for at least 10 minutes. Three ECGs will be performed at each visit during the study, with an interval of at least 5 minutes between each. 3. For ECG collection that matches PK sampling, please refer to the PK blood collection form for specific requirements.
Tumor Imaging Assessment	×	×					Compliant examination results from within 4 weeks before the first dose can be accepted as baseline and do not need to be repeated. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks.
GFH375 Administration		×					GFH375 tablets will be dispensed to participants on specified visit days and taken orally as scheduled.
PK Blood Sampling		×					See PK Collection Form
Blood ctDNA		×					Blood samples will be collected at baseline (if collected during the screening period, no need to repeat on C1D1) for next-generation sequencing (NGS) testing
AE/SAE	×	×					AEs/SAEs will be collected from signing of ICF until 30 days after the last dose

缩写：C1D1：第 1 周期第 1 天。ECOG：东部肿瘤协作组；PS：体能状况；PK：药代动力学；AE/SAE，不良事件/严重不良事件。

Schedule of Activities for Phase II Treatment Stage

Study Stage	Screening Period	Treatment Period			Remarks
		Cycle 1		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**±3**	**±3**	
Informed Consent	×				
Inclusion/Exclusion Criteria	×	×			Inclusion/exclusion criteria must be reviewed again on C1D1.
Demographics	×				Includes sex, age, ethnicity, etc.
Body Height/Weight	×	×		×	Body height is measured only once during the screening period.
Tumor History	×				Includes information on tumor diagnosis, time of diagnosis, metastatic sites, etc. For patients with advanced NSCLC, data on prior PD-L1 expression levels should be collected (if available).
Other Medical History	×				All active medical conditions and any conditions the investigator considers clinically significant will be collected.
Prior/Concomitant Therapy	×				All prior/concomitant medications and therapeutic procedures from 30 days before the first dose until the end of the safety follow-up will be collected.
Virus Serology	×				Includes hepatitis b surface antigen (HBsAg), hepatitis b surface antibody (HBsAb), hepatitis b core antibody (HBcAb), HCV antibody, HIV antibody, and HBV-DNA and HCV-RNA tests (if necessary).
Pregnancy Test	×	×		×	Female participants of childbearing potential must undergo a serum pregnancy test within 7 days before the first dose, followed by a pregnancy test urine on D1 of every 2 cycles. If a negative urine pregnancy result cannot be confirmed, a serum pregnancy test is required.
Physical Examination	×	×	×	×	

Study Stage	Screening Period	Treatment Period			Remarks
		Cycle 1		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**±3**	**±3**	
ECOG PS Score	×	×		×	If assessed within 72 hours before the first dose, it does not need to be repeated on C1D1.
Vital Signs	×	×	×	×	
Hematology	×	×	×	×	If laboratory test results are available within 7 days before the first dose, they do not need to be repeated on C1D1. If the participant's clinical status changes significantly, laboratory tests must be repeated on C1D1.
Blood Chemistry	×	×	×	×	
Urinalysis	×	×	×	×	
Coagulation Function	×	×	×	×	
Electrocardiogram	×	×	×	×	1. If other trial procedures are combined, an ECG should be performed first to avoid the impact of study procedures on the ECG results. 2. The ECG should be performed after the participant has rested quietly for at least 10 minutes. Three ECGs will be performed at each visit during the study, with an interval of at least 5 minutes between each. 3. For ECG collection that matches PK sampling, please refer to the PK blood collection form for specific requirements.
Tumor Imaging Assessment	×	×			Compliant examination results from within 4 weeks before the first dose can be accepted as baseline and do not need to be repeated. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks.
GFH375 Administration		×			GFH375 tablets will be dispensed to participants on specified visit days and taken orally as scheduled
PK Blood Sampling		×			See PK Collection Form

Study Stage	Screening Period	Treatment Period			Remarks
		Cycle 1		Subsequent Cycles	1. Every 21 days/cycle: Visit windows are calculated based on the first study drug administration date, C1D1. 2. In addition to the visits and examinations specified in the protocol, the investigator may schedule examinations as needed based on clinical indications.
Visit Day	**D-28~D-1**	**D1**	**D10**	**D1**	
Time Window (days)	**NA**	**0**	**±3**	**±3**	
Blood ctDNA	×	×			Blood samples will be collected at baseline (if collected during the screening period, no need to repeat on C1D1) for next-generation sequencing (NGS) testing
AE/SAE	×	×			AEs/SAEs will be collected from signing of ICF until 30 days after the last dose

Abbreviation: C1D1: Cycle 1 Day 1. ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; PK: Pharmacokinetics; AE/SAE, Adverse Event/Serious Adverse Event.

Phase I and II Parts: Schedule of Activities for End of Treatment Visit and Long-term Follow-up Visit

	End of Treatment (EOT) Visit	Safety Follow-up Visit	Survival Visit	Remarks
Visit	**Decision to end study treatment**	**30 days after last dose**	**Every 90 days after safety visit**	
Time Window (days)	+7	±3	±7	
Pregnancy Test	×	×		Pregnancy test urine will be performed; serum test will be used if necessary.
Physical Examination	×	×		
ECOG PS Score	×			
Vital Signs	×	×		
Weight	×	×		
Blood ctDNA	×			
Hematology	×	×		Tests performed within 7 days after the last dose do not need to be repeated at the EOT visit, but AE-related tests should be reviewed at the investigator's discretion
Blood Chemistry	×	×		
Urinalysis	×	×		
Coagulation Function	×	×		
Electrocardiogram	×	×		
Imaging Assessment	×			Imaging tests performed within 4 weeks before the end of treatment visit do not need to be repeated; participants who discontinue treatment for reasons other than PD/due to PD and have not started other anti-tumor therapy need to undergo scheduled tumor imaging until PD, start of new anti-tumor therapy, or withdrawal from the study.
Concomitant Therapy	×			Concomitant medications and therapeutic procedures will be collected

	End of Treatment (EOT) Visit	Safety Follow-up Visit	Survival Visit	Remarks
Visit	**Decision to end study treatment**	**30 days after last dose**	**Every 90 days after safety visit**	
Time Window (days)	**+7**	**±3**	**±7**	
AE/SAE	×			AEs/SAEs will be collected from signing of ICF until 30 days after the last dose or start of new anti-tumor therapy
Subsequent Anti-tumor Therapy	×			Includes subsequent anti-tumor therapy, start/end time, reason for discontinuation, and BOR
Survival Status	×			

Phase Ia Part PK Sample and 12-Lead ECG Collection Schedule

Cycle	Day	Planned Sampling Time Point (h)	Time Window	PK Sampling[1,2]	12-Lead ECG[3]
1	1	Predose	-1 h	√	√
		给药后0.5h	±5min	√	
1	1	1 h postdose	±5 min	√	
1	1	2 h postdose	±10 min	√	√
1	1	4 h postdose	±15 min	√	√
1	1	6 h postdose	±30 min	√	√
1	1	8 h postdose	±30 min	√	
1	**1[4]**	12 h postdose	±30 min	√	
1	**2[5]**	24 h postdose	±1 h	√	
1	**3[5]**	48 h postdose	±2 h	√	
1	**4[5]**	72 h post-dose (collected before dosing on D4)	±3 h	√	√
1	8	Predose	-1 h	√	√
1	15	Predose	-1 h	√	√
1	21	Predose	-1 h	√	√
1	21	1 h postdose	±5 min	√	
1	21	2 h postdose	±10 min	√	√
1	21	4 h postdose	±15 min	√	√
1	21	6 h postdose	±30 min	√	√
1	21	8 h postdose	±30 min	√	
1	**21[4]**	12 h postdose	±30 min	√	
1	**21[5]**	24 h postdose	±1 h	√	√
2	10	Predose	-1 h	√	√
4	1	Predose	-1 h	√	√
5	1	Predose	-1 h	√	√
6	1	Predose	-1 h	√	√

1. When a patient experiences a drug-related SAE, a blood sample for GFH375 plasma concentration measurement should be collected immediately upon the investigator's awareness of the event, if possible.
2. If a PK sample cannot be obtained at a planned visit, it can be postponed to the next visit for collection. It is sufficient to accurately record the dose administered, time of administration, and time of sampling.
3. ECGs matching the PK samples will be collected at qualified sites. It is recommended to perform the ECG first, then the PK blood draw. If it cannot be completed before the blood sample collection, the ECG should be performed after resting quietly for 10 minutes after the blood draw. Meanwhile, the interval between the ECG and PK sampling time needs to be kept within 30 minutes. All planned 12-ECGs should be performed after the participant has rested quietly for at least 5 min. Three measurements should be taken at each time point, with an interval of 1-2 min between each.
4. **If BID dosing, the 12 h post-dose PK samples on C1D1 and C1D21 should be collected before the second dose of the day.**
5. **Only applicable to QD dosing, collection is required before dosing.**

Phase Ib/II Part PK Sample and 12-Lead ECG Collection Schedule (QD/BID)

Cycle	Day	Planned Sampling Time Point (h)	Time Window	PK Sampling[1,2]	12-Lead ECG[3]
1	10	Predose	-1 h	√	√
1	10	Postdose	2-4 h	√	√
2	1	Predose	-1 h	√	√
2	1	Postdose	1-3 h	√	√
3	1	Predose	-1 h	√	√
3	1	Postdose	2-4 h	√	√
4	1	Predose	-1 h	√	√

1. When a patient experiences a drug-related SAE, a blood sample for GFH375 plasma concentration measurement should be collected immediately upon the investigator's awareness of the event, if possible.
2. If a PK sample cannot be obtained at a planned visit, it can be postponed to the next visit for collection. It is sufficient to accurately record the dose administered, time of administration, and time of sampling.
3. ECGs matching the PK samples will be collected at qualified sites. It is recommended to perform the ECG first, then the PK blood draw. If it cannot be completed before the blood sample collection, the ECG should be performed after resting quietly for 10 minutes after the blood draw. Meanwhile, the interval between the ECG and PK sampling time needs to be kept within 30 minutes. All planned 12-ECGs should be performed after the participant has rested quietly for at least 5 min. Three measurements should be taken at each time point, with an interval of 1-2 min between each.

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List of Abbreviations

Abbreviation	Full Term
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the curve
BCRP	Breast Cancer Resistance Protein
BICR	Blinded Independent Central Review
BID, bid	Bis in die
BOIN	Bayesian Optimal Interval
BOR	Best of Response
C_{max}	Maximal concentration
C_{trough}	Trough concentration
CA19-9	Carbohydrate Antigen 19-9
CI	Confidence Interval
CL	Clearance
CL_r	Renal Clearance
CNS	Central Nervous System
Cr	Creatinine
CR	Complete Response
CRC	Colorectal Cancer
CRO	Contract Research Organization
CSCO	Chinese Society of Clinical Oncology
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450 Proteins
D	Day
DCR	Disease Control Rate
DDS	Dose Determination Set
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
DRF	Dose Range Finding
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
G12D	Gly12Asp

Abbreviation	Full Term
GAP	GTPase-Activating Protein
GCP	Good Clinical Practice
GDP	Guanosine Diphosphate
GEF	Guanine Nucleotide Exchange Factor
GGT	Gamma-Glutamyl Transpeptidase
GTP	Guanosine Triphosphate
GLP	Good Laboratory Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
HR	Hazard Ratio
ICH-GCP	International Council for Harmonization
INR	International Normalized Ratio
LLOQ	Lower Limit of Quantification
K^+	Serum Potassium
KRAS	Kirsten Rat Sarcoma Viral Oncogene
MAPK	Mitogen-Activated Protein Kinase
MATE1	Multidrug and toxin extrusion 1
MATE2-K	Multidrug and toxin extrusion 2-K
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRSD	Maximal Recommended Starting Dose
MSI-H	High Microsatellite Instability
MTD	Maximum Tolerated Dose
NGS	Next Generation Sequencing
NOAEL	No-Observed-Adverse-Effect Level
NRS	Numerical Rating Scale
NSCLC	Non-Small Cell Lung Cancer
OATP1B1	Organic anion transporting polypeptide 1b1
OATP1B3	Organic anion transporting polypeptide 1b3
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OCT2	Organic cation transporter 2
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression Disease
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression Free Survival
P-gp	P-glucoprotein
PLT	Blood Platelet
PK	Pharmacokinetic
PKS	Pharmacokinetic Set

Abbreviation	Full Term
PO, po, p.o.	Oral Administration
PPoS	Predictive Probability of Success
PPS	Per Protocol Set
PR	Partial Response
PRO	Protein in Urine
PS	Physical performance
PT	Preferred Term
PT	Prothrombin Time
QD, qd	Quaque die
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SS	Safety Set
STD10	Severely Toxic Dose in 10% of the Animals
$t_{1/2}$	Elimination half-life
T_{max}	Time to reach maximum concentration
TEAE	Treatment Emergent Adverse Event
TRAE	Treatment Related Adverse Event
T-BIL	Total Bilirubin
TTP	Time to Progression
TK	Toxicokinetics
TTR	Time to Response
ULN	Upper Limits of Normal
V_d	Volume of distribution
V_{dss}	Volume of distribution at steady state

1. Introduction

1.1. Disease Background

1.1.1 Biological Mechanism of KRAS and KRAS G12D Mutation

RAS proteins are guanine nucleotide-binding proteins with GTPase enzyme activity. Their activity is switched by binding to either guanosine diphosphate (GDP) or guanosine triphosphate (GTP). They are in an inactive state when bound to GDP and become activated when bound to GTP. In cells, RAS is located at a relatively central position in signaling pathways and activates multiple downstream signaling pathways. By regulating gene transcription and protein regulation processes, RAS proteins are responsible for intercellular signaling pathways for cell growth, migration, survival, and differentiation. RAS is the most widely mutated oncogene in tumors, with approximately 30% of tumors containing RAS mutations. Mutations in all three subtypes, KRAS, HRAS, and NRAS, have been found in tumors, with KRAS mutations being the most common. KRAS mutations are most common in pancreatic carcinoma, non-small cell lung cancer (NSCLC), and colorectal cancer (CRC), reaching up to 90% in pancreatic carcinoma. KRAS mutations mainly occur at three sites: glycine (Gly, G) at positions 12 and 13, and glutamine (Gln, Q) at position 61, with the highest mutation rate at the G12 position. More than 10 different types of mutations can occur at the Gly12 position of KRAS, with mutations to aspartic acid (G12D), valine (G12V), and cysteine being the most frequent[1-3]. The role of KRAS in tumors is widely recognized, but its protein structure and extremely high affinity for GTP have hindered the development of targeted drugs against KRAS. Recent breakthroughs in covalent inhibition strategies for KRAS have led to the successful development and clinical validation of innovative small molecule drugs targeting KRAS. Among them, KRAS G12C inhibitors (sotorasib, adagrasib) have been approved for the treatment of patients with KRAS G12C-mutated NSCLC, with confirmed efficacy and an acceptable safety profile.

1.1.2 KRAS G12D-mutated Tumors

KRAS mutations are common in CRC (approx. 45% in the US, 49% in China), pancreatic carcinoma (approx. 90% in the US, 87% in China), and NSCLC (adenocarcinoma: approx. 35% in the US, 13% in China)[3]. Among them, KRAS G12D is one of the most common mutation types, with high expression in various solid tumors, including NSCLC, pancreatic carcinoma, CRC, and bile duct cancer.

Advanced NSCLC

Lung cancer is the second most common cancer and the leading cause of cancer death worldwide. NSCLC accounts for approximately 84% of lung cancer cases, and most NSCLC patients are

diagnosed at an advanced stage. Global cancer statistics reported by the International Agency for Research on Cancer show an estimated 820,000 new lung cancer diagnoses and 715,000 lung cancer-related deaths in China in 2020[4]. KRAS G12D is one of the common mutations in NSCLC. A study based on data from the American Association for Cancer Research (AACR) Project GENIE showed that the G12D mutation accounts for an estimated 4.9% of all lung adenocarcinomas in the United States[3]. A retrospective study analyzed NGS data from 150,327 NSCLC cases in the Lung Cancer Big Data Precision Treatment Collaborative Group (LANDSCAPE) project, in which the frequency of KRAS G12D mutation was approximately 2.2%[5].

The treatment of advanced NSCLC varies depending on the presence of driver gene mutations. If positive for driver genes such as EGFR, ALK, ROS, etc., corresponding targeted drugs or platinum-based doublet chemotherapy, as well as chemotherapy combined with immunotherapy, anti-angiogenic therapy, etc., can be selected. Since KRAS G12D rarely co-exists with the above-mentioned driver genes, chemotherapy, such as docetaxel, remains the main treatment after failure of standard systemic therapy, with recently reported ORRs of 13.2-16.0% and a median PFS of 2.6-4.5 months [6-8]; the ORRs for prior chemotherapy and chemotherapy plus anti-angiogenic drugs were 8.5-18.3% and 8.6%-22.9%, respectively; PFS was 2.8-4.2 months and 4.8-5.4 months, respectively; and OS was 6-11.4 months and 9.9-12.6 months, respectively[9-13]. Considering the potential for increased toxicity with combination therapy, the tolerability of patients to doublet chemotherapy and other combination therapies needs to be fully assessed in second-line and above treatments. Data on immune checkpoint inhibitor treatment for KRAS-mutated NSCLC patients mainly come from subgroup analysis reports of large Phase III clinical studies. Among them, the CheckMate057 and OAK studies reported that compared to docetaxel monotherapy, patients with KRAS mutations could achieve better overall survival (OS) benefits from nivolumab or atezolizumab treatment[14,15]. However, since most patients have already received immune checkpoint inhibitors in first-line treatment, they are not the primary choice for second-line treatment.

KRAS G12C targeted inhibitors have achieved good efficacy as monotherapy or in combination in advanced NSCLC, and it is expected that drugs targeting KRAS G12D will bring new treatment options for the subgroup of patients with this targetable mutation.

Advanced PDAC

Ductal adenocarcinoma of pancreas (PDAC) is one of the most malignant tumors with poor treatment efficacy. It is projected that pancreatic carcinoma will become the second leading cause of death from all malignant tumor by 2030, with an overall 5-year survival rate of only 10%. Furthermore, the

disease burden of pancreatic carcinoma is expected to increase globally[16]. Most PDAC patients present with metastatic disease at their initial visit and require more effective systemic therapy. With the exception of patients carrying the germline breast cancer susceptibility gene (BRCA), very few targetable mutations in PDAC have been identified to date. KRAS mutation is an early genetic driver event in its tumorigenesis process and is closely related to key biological features such as inflammation, immune evasion, and metabolic changes[17]. It is estimated that 37% of pancreatic carcinomas carry the KRAS G12D mutation, suggesting the importance of this mutant allele at the population level. Some PDAC xenograft models have shown that KRAS G12D acts as a consistent and strong oncogenic driver in PDAC, and KRAS G12D inhibitors have demonstrated significant anti-tumor activity in ductal adenocarcinoma of pancreas models.

The progress of drug therapy for PDAC has been very limited overall, especially with the limited efficacy of targeted drugs and immunotherapy. The Phase III NAPOLI-1 study, which enrolled patients with metastatic PDAC (mPDAC), showed that for mPDAC patients who had failed prior gemcitabine-based chemotherapy regimens, treatment with liposomal irinotecan in combination with 5-FU/LV (5-fluorouracil + leucovorin) resulted in significantly improved efficacy compared to those receiving only 5-FU/LV (5-fluorouracil + leucovorin): median overall survival (mOS) was 6.1 months (vs 4.2 months, HR 0.67), median PFS was 3.1 months (vs 1.5 months, HR 0.56), and ORR was 16% (vs 1%, $p < 0.0001$)[18]. Currently, there is a lack of standard or recommended treatment options for third-line therapy, with most being the reuse of first- or second-line chemotherapy drugs. A recently published French cohort study showed that among 676 patients with advanced pancreatic carcinoma who received at least one line of chemotherapy, only 37% received third-line chemotherapy, with a median PFS of only 2.03 months and a median overall survival of only 5.5 months[19,20]. Therefore, there is an urgent clinical need for effective therapeutic drugs. Currently, targeted inhibitors against KRAS G12C have achieved good efficacy in previously treated PDAC, with ORRs for sotorasib, adagrasib, and glecirasib monotherapy being 21.0%, 33.3%, and 46.4%, respectively, and median PFS being 4.0 months, 5.4 months, and 5.5 months, respectively[21-23]. It is expected that drugs targeting KRAS G12D can also provide new treatment options for the patient population with this targetable mutation.

Advanced CRC

Colorectal cancer (CRC) is currently the third most common cancer by incidence, with an estimated 1,931,590 new cases annually worldwide. CRC is also the second leading cause of cancer death, with 935,173 deaths globally in 2020. Approximately 20% of CRC patients have metastasis at diagnosis,

while up to 50% of patients with initial local disease will develop metastasis[19]. In CRC, the KRAS mutation rate is approximately 40%, with KRAS G12D accounting for about 28% [24,25]. CRC with KRAS mutations is associated with advanced disease state, poor tumor differentiation, distant metastasis, and lower survival rates, potentially indicating a poorer prognosis for PFS and OS, which has been validated in real-world clinical practice[25]. In addition, studies have shown that KRAS mutation is a common driver of acquired drug resistance to cetuximab in colorectal cancer, and acquired KRAS G12D mutations have been observed in metastatic CRC tissue samples after treatment with cetuximab (or in combination with chemotherapy)[26,27]. Targeting KRAS mutations in CRC patients holds the promise of potentially providing more effective targeted therapy and a better safety profile in this highly selected patient population.

The treatment of advanced CRC also varies depending on the presence of gene mutations such as RAS, BRAF, and HER2. When both RAS and BRAF are wild-type, the treatment used is monochemotherapy or polychemotherapy combined with cetuximab (for left-sided lesions) or bevacizumab (for right-sided lesions). Although immunotherapy has been approved for the treatment of MSI-H CRC patients, the proportion of MSI-H patients in CRC is low, and there remains a huge unmet clinical need. In the third-line or later setting, there are fewer treatment options available for patients, including palliative care, participation in clinical trials, or approved drugs (regorafenib, trifluridine/tipiracil +/- bevacizumab, and fruquintinib). However, in the late-line treatment of CRC, the currently recommended standard therapies (regorafenib, trifluridine/tipiracil, and fruquintinib) offer only limited efficacy in mCRC patients who have failed at least 2 lines of therapy, with an ORR of 1-4.7%, a median PFS of 1.9-3.7 months, and a median OS of 6.4-9.3 months[28-30]. Recently, based on a Phase III part (the SUNLIGHT study, NCT01607957), the FDA approved trifluridine/tipiracil + bevacizumab as one of the third-line treatment options. Compared to trifluridine/tipiracil monotherapy, the use of trifluridine/tipiracil combined with bevacizumab showed improved OS and PFS, but the ORR remained low at only 6.1%[31]. Therefore, there remains a significant unmet medical need in third-line and later mCRC patients. In patients with advanced CRC, the KRAS G12C-targeted inhibitors sotorasib and adagrasib have shown preliminary efficacy as monotherapy, with ORRs of 9.7% (95% CI 3.6, 19.9) and 19% (95% CI 8, 33), respectively[32,33]. Combination with an anti-EGFR antibody can further improve their efficacy. The ORR achieved with sotorasib combined with panitumumab was 26.4%-30%, with a median PFS of 5.6-5.7 months[34]. The ORR for adagrasib combined with cetuximab was 46% (95% CI 28, 66), with a median PFS of 6.7 months[33]. In addition to NSCLC, CRC, and PDAC, KRAS G12D has a high mutation frequency in various solid tumors,

including bile duct cancer, gastric cancer, and esophageal cancer. For these patients who lack effective treatment options, there are no targeted drugs against KRAS available yet.

1.1.3 Development of Drugs Targeting KRAS G12D Mutation

Currently, no therapy specifically targeting KRAS G12D-mutated tumors has been approved for marketing. Several selective KRAS G12D inhibitors are in clinical development, including MTRX1133, HRS-4642, and INCB161734.

Among them, only partial clinical data for HRS-4642, developed by Hengrui, has been disclosed. HRS-4642 is a liposomal formulation administered by intravenous injection. A total of 18 participants were enrolled in the FIH trial and treated with 15 mg QW to 300 mg QW. The overall safety was good, and preliminary efficacy was observed [37].

1.2. Investigational Product: GFH375

1.2.1 Preclinical Studies of GFH375

GFH375 is a KRAS G12D inhibitor independently developed by the sponsor, GenFleet. Comprehensive preclinical studies have been conducted, and a summary is provided below. For more detailed information, please refer to the GFH375 Investigator's Brochure.

1.2.1.1 Summary of Pharmacology Studies

GFH375 has demonstrated high activity and high selectivity in *in vitro* studies. *In vitro* biochemical studies have shown that GFH375 can effectively inhibit the transition of KRAS G12D mutant or wild-type protein from the inactive state (GDP-bound) to the active state (GTP-bound), with half-maximal inhibitory concentrations (IC_{50}) of 6 nM and 9 nM, respectively. GFH375 can also directly block the binding of activated KRAS G12D or wild-type protein to its downstream effector protein RAF1, with IC_{50} values of 2 nM and 7 nM, respectively. GFH375 has shown high activity in multiple KRAS G12D-mutated tumor cell lines, with an IC_{50} of 0.2-0.9 nM for inhibiting the phosphorylation level of the downstream pathway protein ERK1/2, and an anti-tumor cell proliferation IC_{50} of 1-10 nM. In other KRAS mutation types (KRAS G12C, G12V) of tumor cell lines, as well as KRAS wild-type and KRAS function-dependent tumor cell lines, the activity of GFH375 is relatively weak, with anti-tumor cell proliferation IC_{50} values of 159-1895 nM and 17-75 nM, respectively. GFH375 has only very weak activity in other RAS protein mutations (NRAS G12D, Q61H, HRAS Q61L) and KRAS-independent cell lines (anti-cell proliferation IC_{50}: 1636 nM-7873 nM), indicating very low off-target non-specific cytotoxicity.

Preclinical *in vivo* studies have shown that GFH375 demonstrates excellent *in vivo* activity and anti-tumor efficacy in animal models of KRAS G12D-mutated tumors. In a human pancreatic carcinoma

Panc 04.03 xenograft tumor mouse model, a single dose of GFH375 (100 mg/kg) produced strong and durable inhibition of intratumoral ERK1/2 phosphorylation levels. In the Panc 04.03 and another human pancreatic carcinoma AsPC-1 xenograft tumor mouse model, GFH375 (10 mg/kg, 30 mg/kg, and 100 mg/kg) administered orally twice daily for 14 consecutive days demonstrated dose-dependent anti-tumor efficacy, with effective doses of 5 mg/kg and 10 mg/kg, respectively, and caused significant tumor regression at the high dose (100 mg/kg).

GFH375 has high selectivity for the KRAS G12D target, with a low potential risk of off-target effects. At 10 μM, GFH375 showed no inhibitory activity against 72 representative human kinases and no inhibitory activity against 38 of 44 important safety-related targets, including G protein-coupled receptors (GPCRs), ion channels, and enzymes. For the 6 affected targets, the predicted IC_{50} concentration of GFH375 is at least >1000 nM, which is much higher than the aforementioned IC_{50} concentrations for ERK1/2 phosphorylation inhibition and anti-tumor cell proliferation in KRAS G12D cells.

The safety pharmacology studies of GFH375 included *in vitro* effects on the hERG potassium channel current and *in vivo* effects on the central nervous, respiratory, and cardiovascular systems in rats and beagle dogs, respectively.

At concentrations of 3, 6, 12, and 24 μM, GFH375 showed a concentration-dependent inhibitory effect on the hERG potassium channel current expressed in transfected human embryonic kidney cells (HEK293), with an IC_{50} value of 9.65 μM.

SD rats were given single oral gavage doses of 50, 100, and 200 mg/kg of GFH375, and the effects of the test article on the central nervous system were evaluated through a functional observation battery (FOB) while simultaneously measuring forelimb grip strength and body temperature. The results showed that the no observed adverse effect level (NOAEL) of GFH375 on the central nervous system was 200 mg/kg.

SD rats were given single oral gavage doses of 50, 100, or 200 mg/kg of GFH375, and the effects on the respiratory system were assessed using a whole-body plethysmography system. The results showed that the no observed adverse effect level (NOAEL) of GFH375 on the respiratory system in this study was 200 mg/kg.

Beagle dogs were given oral gavage doses of 5, 10, and 25 mg/kg of GFH375 according to a "crossover design", and the effects on the cardiovascular system were evaluated using telemetry. The results showed that the NOAEL of GFH375 on the cardiovascular system of Beagle dogs was 25 mg/kg/day.

1.2.1.2 Summary of PK Studies

GFH375 showed low permeability in Caco-2 cells with significant efflux transport. It can be administered orally, with a preclinical absolute bioavailability of 8.40-16.3% across species, and systemic exposure increased with increasing oral doses. There was no significant sex difference overall after administration in dogs, while there was some sex difference in rats; after repeated dosing in rats, there was no accumulation at PK doses, but accumulation was observed in female rats at TK doses; accumulation was observed in dogs after repeated dosing.

GFH375 showed very high binding in mouse plasma, high binding in rat and dog plasma, and moderate binding in monkey and human plasma. The steady-state volume of distribution (Vd_{ss}) in rats and dogs ranged from 15.7-22.5 L/kg, both showing high distribution. Total radioactivity of [^{14}C]GFH375 was widely distributed in rats, with C_{max} in descending order in the stomach wall, intestinal wall, liver, spleen, kidney, lung, heart, ovary/uterus, body fat, skeletal muscle, whole blood, and plasma. Radioactivity levels were low in the whole brain and testis/epididymis, with no significant red blood cell binding.

The main metabolic pathway of [^{14}C]GFH375 in rats was glucuronidation, with minor pathways including mono-oxidation, dehydrogenation, defluorination, cysteine conjugation, glycine conjugation, and acetylation. In beagle dog plasma, the main metabolic pathways were oxidation, dehydrogenation, defluorination, dealkylation, glucuronidation, and glutathione conjugation followed by hydrolysis to remove glutamic acid. CYP3A is its main metabolic enzyme, and the *in vivo* and *in vitro* metabolic profiles are basically consistent.

GFH375 showed moderate and low clearance in male and female rat plasma, respectively, and high clearance in dog plasma. It has a long half-life in rats and dogs, ranging from 8.18-14.3 h. Total radioactivity of [^{14}C]GFH375 in rats was mainly excreted directly in feces or via bile into feces, with urine being a minor excretion route.

GFH375 showed no inhibitory effect on CYP1A2 and CYP2C9, but had an inhibitory effect on CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP3A (with midazolam as substrate), and CYP3A (with testosterone as substrate), with IC_{50} values of 42.8, 93.2, 42.6, 26.2, 6.40, and 7.95 μM, respectively. GFH375 has significant time-dependent inhibition on CYP3A (with midazolam and testosterone as substrates, respectively). GFH375 is not an inducer of CYP1A2 and CYP2B6, but its potential as an inducer of CYP3A4 at the gene level cannot be excluded. GFH375 is not a substrate of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide 1B1 (OATP1B1), or organic anion-transporting polypeptide 1B3 (OATP1B3) transporters, but it is a substrate of P-gp. GFH375 showed

no inhibitory effect on BCRP, OATP1B1, organic cation transporter 2 (OCT2), or multidrug and toxin extrusion protein 2-K (MATE2-K), but had an inhibitory effect on P-gp, OATP1B3, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), and multidrug and toxin extrusion protein 1 (MATE1), with IC_{50} values of 16.9, 17.4, 2.56, 24.4, and 15.6 μM, respectively. This suggests that GFH375 has potential for drug-drug interactions.

1.2.1.3 Summary of Toxicology Studies

In 14-day repeated-dose toxicity dose-range finding studies conducted in SD rats and beagle dogs, the results showed that the severe toxicity dose in 10% of animals (STD_{10}) in SD rats was greater than 150 mg/kg/day. The highest non-severely toxic dose (HNSTD) in beagle dogs was 100 mg/kg/day.

In a 4-week repeated-dose Good Laboratory Practice (GLP) toxicity study in SD rats, doses of 50, 100, 200 mg/kg/day of GFH375 or blank vehicle [5% (v/v) LABRASOL + 5% (v/v) PEG400 + 90% sterile water for injection] were administered by oral gavage once daily for 28 consecutive days. At a dose of 100 mg/kg/day, 1 female animal death was observed; at a dose of 200 mg/kg/day, 2 male and 3 female animal deaths were observed. Surviving animals in the 200 mg/kg/day dose group also showed test article-related clinical signs, changes in hematology and serum chemistry parameters, and histopathological changes. At the end of the recovery period, all the above changes were reversed. Under the conditions of this study, the STD_{10} of the test article was 100 mg/kg/day.

In a 4-week repeated-dose GLP toxicity study in beagle dogs, doses of 5, 10, 25 mg/kg/day of GFH375 or blank vehicle [5% (v/v) LABRASOL + 5% (v/v) PEG400 + 90% sterile water for injection] were administered by oral gavage once daily for 28 consecutive days. No animal deaths were observed during the study. Test article-related clinical signs, changes in hematology and serum chemistry parameters, and histopathological changes were observed. After the recovery period, the changes were reversible or showed a trend toward recovery. Under the conditions of this study, the HNSTD of GFH375 for beagle dogs was 25 mg/kg/day.

The genotoxicity of GFH375 was evaluated using a standard battery of genotoxicity tests, and the results were negative.

1.3. Rationale for Study Design

1.3.1 Dose Selection

1.3.1.1 Rationale for Starting Dose Selection

The selection of the starting dose in the Phase I part is based on the results of preclinical toxicology studies, and the starting dose is calculated according to the recommendations of the ICH S9 guideline on the maximum recommended starting dose (MRSD) method.

Pivotal 4-week toxicology studies compliant with GLP were conducted in SD rats and beagle dogs. The study doses in rats were 50, 100, and 200 mg/kg/day, and the study doses in dogs were 5, 10, and 25 mg/kg/day. The study results showed that the severe toxicity dose in 10% of animals (STD10) in rats was 100 mg/kg/day, and the HNSTD in dogs was 25 mg/kg/day. According to ICH S9, based on 1/10 of the rodent STD10 or 1/6 of the non-rodent HNSTD, calculated for a patient weight of 60 kg, the corresponding human MRSDs are approximately 100 mg and 140 mg/day, respectively.

Pharmacodynamic studies showed that in an *in vivo* anti-tumor efficacy study conducted in the Panc 04.03 human pancreatic carcinoma CDX tumor mouse model, the effective dose of GFH375 was 5 mg/kg BID for 14 days. In the AsPC-1 human pancreatic carcinoma CDX tumor mouse model, the effective dose of GFH375 was 10 mg/kg BID for 14 days.

In summary, based on the safety indicated by the toxicology study results, and in combination with the GFH375 tablet strength, a dose level of 100 mg/day was selected as the starting dose for the first-in-human trial of GFH375.

1.3.1.2 Rationale for Phase II Dose Selection

After the completion of Phase I dose escalation and backfilling, the safety and RP2D will be confirmed based on a comprehensive assessment of preclinical *in vitro* and *in vivo* activity, clinical PK, clinical safety, and clinical efficacy data, and this dose will be used for the Phase II part.

1.3.2 Risk-Benefit Assessment

1.3.2.1 Potential Risks

Currently, a few small molecule inhibitors targeting KRAS G12D are in the clinical trial stage, with limited disclosure of safety and efficacy data. Among them, HRS-4642 is a KRAS G12D small molecule developed by Hengrui, administered intravenously for the treatment of patients with advanced solid tumors with KRAS G12D mutation. In its first-in-human Phase I part, a total of 18 participants were enrolled. The overall safety was good. Treatment-related AEs with a higher incidence (>2 cases) included blood cholesterol increased, infusion related reaction, proteinuria, anemia, hypertriglyceridemia, lipase increased, hypoproteinemia, blood glucose increased, alanine aminotransferase increased, platelet count decreased, hypercalcemia, hypocalcemia, pyrexia, fatigue, neutrophil count decreased, leucopenia, and aspartate aminotransferase increased[33].

Preclinical toxicology data for GFH375 suggest that its potential toxicities may include liver function impairment and gastrointestinal system adverse reactions. Based on the preclinical study results of GFH375 and data from other KRAS G12D inhibitors, the potential risks of GFH375 are as follows:

- Hepatic impairment

- Gastrointestinal system adverse reactions

1.3.2.2 Potential Benefits

The target population for this study is patients with KRAS G12D mutation-positive advanced NSCLC, PDAC, CRC, and other solid tumors. For such patients, there are no effective treatment options, and chemotherapy or chemotherapy combined with immunotherapy remains the main treatment regimen. No therapeutic drug targeting this mutation has been approved for marketing.

Currently, drugs targeting KRAS G12D have entered clinical studies and have shown preliminary clinical results. Preliminary efficacy data for the KRAS G12D small molecule inhibitor HRS-4642 show that among 18 enrolled participants with advanced solid tumors, 7 participants had target lesion shrinkage. Among them were 10 participants with NSCLC, and 5 of these participants had target lesion shrinkage.

Preclinical studies of GFH375 showed that in a human pancreatic carcinoma tumor animal model carrying the KRAS G12D mutation, a single oral gavage dose of GFH375 resulted in dose-dependent inhibition of ERK1/2 protein phosphorylation, a downstream protein in the KRAS pathway, observed in the tumor. Long-term oral gavage administration (twice daily for 14 consecutive days) showed significant anti-tumor efficacy, with an effective dose of 5-10 mg/kg, and tumor regression was observed at a high dose (100 mg/kg).

In summary, it is expected that GFH375 is worthy of further clinical research in this population to provide a new anti-tumor treatment option for these patients.

1.3.2.3 Risk-Benefit Assessment

Based on the biological characteristics of the KRAS G12D target, the product characteristics of GFH375, and the non-clinical data obtained for GFH375 as described above, this protocol has designed corresponding inclusion/exclusion criteria, lifestyle requirements, and safety examination and follow-up procedures. Through rigorous protocol design, selection of study sites, collection of drug safety information, and timely updating and communication of drug safety information, the risks to participants will be minimized as much as possible. Based on clinical data from products with the same mechanism of action, it is expected that participants who meet the inclusion/exclusion criteria are likely to benefit from GFH375 monotherapy. The overall benefit/risk assessment supports the conduct of this study.

2 Study Objectives and Endpoints

This is a Phase I/II study. The study objectives and endpoints are summarized below.

The objectives and endpoints of the Phase Ia part of the study include:

Study Objectives	Study Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and tolerability of GFH375 in patients with advanced solid tumors with KRAS G12D mutation	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs); changes in vital signs, electrocardiogram (ECG), and laboratory tests
• To determine the maximum tolerated dose (MTD) and recommended dose for expansiondose (RDE) of GFH375	• Incidence of dose-limiting toxicity (DLT) events
Secondary Objectives	**Secondary Endpoints**
• To evaluate the pharmacokinetic (PK) characteristics of GFH375 in patients with advanced solid tumors with KRAS G12D mutation.	• Plasma concentrations and PK parameters of GFH375, including but not limited to C_{max}, T_{max}, AUC, $t_{1/2}$, CL/F, V_z/F, C_{trough}
• To evaluate the preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation	• Objective response rate (ORR), duration of response (DoR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) as assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Phase Ib (Dose expansion) objectives and endpoints include：

Study Objectives	Study Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and tolerability of GFH375 in patients with advanced solid tumors with KRAS G12D mutation； To determine recommended phase II dose (RP2D)	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs); changes in vital signs, electrocardiogram (ECG), and laboratory tests
Secondary Objectives	**Secondary Endpoints**
• To evaluate the pharmacokinetic (PK) characteristics of GFH375 in patients with	• Plasma concentrations of GFH375

advanced solid tumors with KRAS G12D mutation.	
• To evaluate the preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation	• Objective response rate (ORR), duration of response (DoR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), as assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. and overall survival (OS)
Exploratory Objective	**Exploratory Endpoint**
• To explore the molecular mechanisms related to treatment sensitivity or drug resistance	• Mutation analysis of circulating tumor DNA (ctDNA) in blood at baseline and at the end of treatment

The objectives and endpoints of the Phase II part of the study include:

Study Objectives	**Study Endpoints**
Primary Objectives	**Primary Endpoints**
• To evaluate the efficacy of GFH375 in patients with advanced non-small cell lung cancer (NSCLC), advanced ductal adenocarcinoma of pancreas (PDAC), advanced colorectal cancer (CRC), and other solid tumors with KRAS G12D mutation.	• ORR as assessed by RECIST 1.1
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation using other efficacy endpoints	• Best overall response (BOR), DoR, DCR, TTR, and PFS as assessed by RECIST 1.1 • OS
• To evaluate the safety of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation	• Incidence and severity of AEs and SAEs; changes in vital signs, ECG, and laboratory tests
• To evaluate the PK characteristics of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other	• Plasma concentrations of GFH375

advanced solid tumors with KRAS G12D mutation	
Exploratory Objective	**Exploratory Endpoint**
• To explore the molecular mechanisms related to treatment sensitivity or drug resistance	• Mutation analysis of circulating tumor DNA (ctDNA) in blood at baseline and at the end of treatment

3 Study Design

3.1. Overall Design

This is a study to evaluate the safety/tolerability, PK, and efficacy of GFH375 monotherapy in patients with advanced solid tumors with KRAS G12D mutation. The primary objective of the Phase I part is to evaluate the safety/tolerability, PK, and preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation, and to determine the MTD and/or RP2D of GFH375. The primary objective of the Phase II part is to evaluate the efficacy of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation.

A Safety Monitoring Committee (SMC), composed of investigators and the sponsor, will be established during the study. For details, please refer to Chapter 10 and the SMC Charter for this study..

3.1.1 Phase Ia Part Dose Escalation

Phase Ia will enroll patients with KRAS G12D-positive advanced solid tumors. The study schematic is shown in Figure 2.

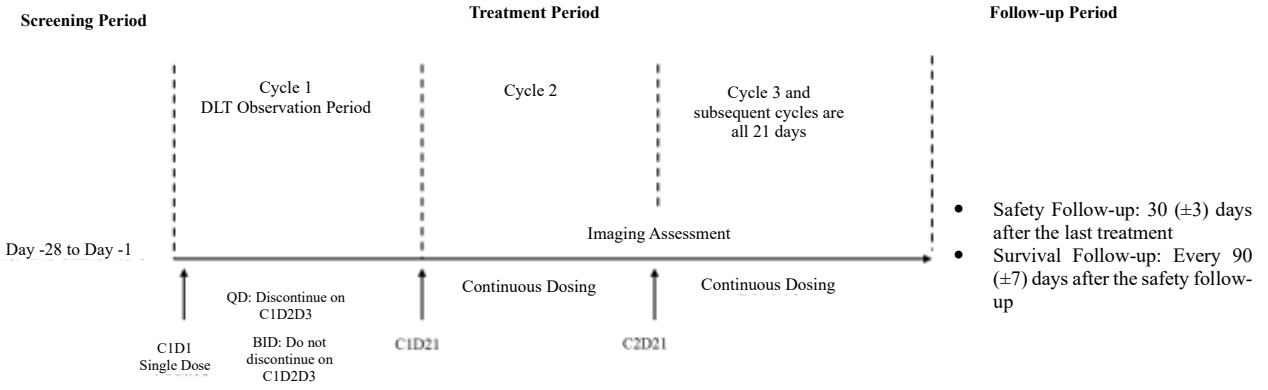

Figure 2 Phase Ia Part Schematic

According to the BOIN design, 3-6 participants will be enrolled in each dose cohort (except during accelerated titration) for treatment. Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional participants for backfilling.

These participants will receive treatment with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is assessed by the investigator and sponsor as potentially clinically beneficial, in order to better estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. If the safety of the 750 mg QD dose cohort has been explored and confirmed, backfilling of the 700 mg QD dose cohort may also be conducted. Backfilled participants will not be included in the DLT evaluation. After backfilling, no more than 30 participants will be treated in each GFH375 dose cohort (including participants enrolled in the BOIN dose-escalation phase).

Additional participants may be enrolled if more dose levels or alternative dosing regimens need to be explored.

After enrollment, participants will receive oral administration of GFH375, with each treatment cycle being 21 days. Participants will be enrolled into sequential dose-escalation cohorts, with a starting dose of 100 mg once daily (QD). A total of 7 or more dose levels are expected to be evaluated in the dose escalation part. The planned escalating doses are shown in Table 1.

The GFH375 dosing regimen will be comprehensively evaluated during dose escalation. If necessary, dose exploration with a twice daily (BID) dosing regimen will be conducted. Dose escalation for QD and BID dosing regimens can be conducted independently and in parallel.

The first cycle after the first administration will serve as the DLT observation period. A DLT-evaluable case must meet one of the following two conditions:

- The participant experiences a DLT event, or
- The participant does not experience a DLT event and has received at least 15 days of the planned dosing of GFH375 in the first cycle.

If no DLT event occurs, the participant will continue treatment, with dose adjustments permitted as allowed by this protocol, until progressive disease (PD), unacceptable toxicity, or discontinuation of study treatment for other reasons. If a participant experiences a DLT event during the DLT observation period, and if the investigator and sponsor assess that the participant can benefit from continuing treatment with GFH375, treatment with GFH375 will be resumed after the relevant adverse event (AE) has resolved. Refer to Table 4 and Table 5 for the criteria for resumption of dosing.

Participants enrolled in Phase I will undergo intensive PK sampling and have matching ECGs collected with PK sampling to evaluate the PK characteristics and safety of GFH375. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks. Participants

will return to the study site 30 (±3) days after the last study treatment for a safety follow-up, and will have survival follow-ups every 90 (±7) days thereafter. Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the Informed Consent Form (ICF), initiation of other anti-tumor therapy, or the termination of the study.

Table 1 Phase Ia Part QD Dose Cohorts with Planned/Completed Escalation

	Phase I Part QD Dose Cohorts with Planned/Completed Escalation *
Dose Cohort 1	100 mg QD
Dose Cohort 2	200 mg QD
Dose Cohort 3	400 mg QD
Dose Cohort 4	600 mg QD
Dose Cohort 5	900 mg QD

Note: Intermediate dose exploration of the above doses, such as 150 mg, 300 mg, 500 mg, 750 mg, QD, etc., may be conducted during the escalation process based on the clinical data obtained, including safety, PK, and possible efficacy.

3.1.1.1 DLT Definition

A DLT is an AE that occurs within 21 days after the first dose, is related to the investigational drug GFH375, and meets the following severity criteria. The severity of AEs is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0:

- Grade ≥ 4 absolute neutrophil count (ANC) decreased for ≥ 5 days;
- Grade ≥ 3 febrile neutropenia (ANC <1.0 × 109/L with a single body temperature > 38.3° C or a sustained body temperature ≥38° C for more than 1 hour);
- Grade ≥ 4 platelet count decreased for ≥ 5 days;
- Grade ≥ 3 platelet count decreased with Grade ≥ 2 hemorrhage;
- Grade ≥ 4 anemia;
- If baseline ALT or AST is Grade ≤ 1: Grade ≥ 3 serum transaminases increased (ALT or AST) lasting > 7 days is considered a DLT; if baseline ALT or AST is Grade 2, then ALT or AST > 10×ULN lasting > 7 days is considered a DLT;
- Grade ≥ 3 serum bilirubin increased;
- According to Hy's Law, AST or ALT > 3×ULN (if baseline metastases to liver are present, then > 3 times the baseline value is required), with concurrent total bilirubin > 2×ULN (causes such as biliary obstruction or other causes like hepatitis, intrahepatic tumor progression, etc., must be excluded);
- Grade ≥ 3 other toxicities (non-hepatic, non-hematologic), with the exception of the following:
- Grade 3 nausea or vomiting, diarrhea, lasting no more than 3 days with/without

symptomatic supportive care;

- Grade 3 fatigue, lasting no more than 3 days with/without symptomatic supportive care;
- Asymptomatic Grade 3 abnormal laboratory and not clinically significant per Investigator assessment.

Toxicities meeting the above criteria that occur after the DLT observation period will also be considered important factors in the safety evaluation. In addition, other treatment-related toxicities that may be assessed as DLTs will be determined after discussion between the sponsor and the investigator.

During the first cycle (DLT observation period), AEs that meet the DLT criteria should be reported to the sponsor within 24 hours of awareness of their occurrence.

3.1.1.2 Dose Escalation Rules and MTD Definition

Accelerated titration is permitted for the first two dose levels of the QD dosing regimen, meaning the first participant will receive treatment at the first dose level. If no Grade ≥2 treatment-related AE is observed in participants in the first two dose cohorts during the DLT observation period, 3-6 participants will be enrolled at the next higher dose level, and the BOIN design will be used for this cohort and subsequent dose escalations. Conversely, if any Grade ≥2 treatment-related AE or DLT event is reported in the first or second dose cohort, the study will switch directly to the BOIN design, starting from the lowest dose cohort where the Grade ≥2 treatment-related AE or DLT event was observed. Provided that accelerated titration is completed for the first dose, the decision on whether to use accelerated titration for the second dose level will be made by the SMC based on discussion of the PK and safety data from the first dose level. Subsequent dose levels will use the BOIN design to determine the MTD, with a target toxicity probability of 0.3. If dose exploration of the BID dosing regimen is required, the BOIN design will be used for dose escalation, with a target toxicity probability of 0.3. Each dose level will enroll 3-6 participants for treatment. If more dose levels or dosing regimens need to be explored, additional participants may be enrolled.

The BOIN design will assign the dose level for the next group of participants according to the dose escalation/de-escalation rules shown in Table 3.

Table 3 BOIN Design Dose Escalation/De-escalation Rules

Decision	Total number of participants treated at the current dose

	3	4	5	6	7	8	9
Escalate, if number of participants with DLT is ≤	0	0	1	1	1	1	2
De-escalate, if number of participants with DLT is ≥	2	2	2	3	3	3	4
Eliminate dose, if number of participants with DLT is ≥	3	3	4	4	5	5	5

The specific rules are as follows:

- If the decision based on the rules in the table above is neither to escalate, de-escalate, nor eliminate the dose, then continue treating the next group of participants at the current dose.
- "Eliminate dose" in the table above means to eliminate the current and higher doses from the study.
- If the current dose is eliminated, the dose will be automatically de-escalated to the next lower level to treat participants.
- If the lowest dose level is eliminated, the study will be terminated early to ensure participant safety. In this case, the MTD cannot be determined.
- If the current dose is the lowest dose level and the rule suggests de-escalation, the next group of participants will still be treated at the current lowest dose.
- If the current dose is the highest dose level and the rule suggests escalation, newly enrolled participants will still be treated at the highest dose.
- The dose escalation part can be terminated when there are ≥6 evaluable participants at the recommended next dose level.
- There must be at least 6 evaluable participants treated at the RDE/RP2D.

After the dose escalation part is completed, isotonic regression analysis will be used based on the DDS to determine the MTD. The online BOIN software at http://www.trialdesign.org will be used to perform isotonic regression analysis to obtain the isotonic estimates of the toxicity probability for each dose level. The dose level closest to the target toxicity rate of 0.3 is the MTD. If there are 2 or more dose levels that meet the condition simultaneously, the highest dose level with an isotonic estimate <0.3 or the lowest dose level with an isotonic estimate ≥0.3 will be selected.

3.1.1.3 Backfilling of Participants in the Dose Escalation Part

Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional participants for backfilling. These participants will receive treatment with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is assessed by the investigator and sponsor as potentially clinically beneficial, in order to better

estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. If the safety of the 750 mg QD dose cohort has been explored and confirmed, backfilling of the 700 mg QD dose cohort may also be conducted. Backfilled participants will not be included in the DLT evaluation. After backfilling, no more than 30 participants will be treated in each GFH375 dose level (including participants enrolled in the BOIN dose escalation part).

Backfilled participants will complete the relevant visits according to the Phase I part Schedule of Activities and the Phase I part PK blood sampling schedule.

3.1.1.4 Intra-participant Dose Escalation

In principle, intra-participant dose escalation will not be performed during the dose escalation part. For participants enrolled in Phase I, after agreement from the investigator and sponsor, intra-participant dose adjustment to receive RP2D monotherapy is permitted after the RP2D for this protocol has been confirmed.

3.1.1.5 Rationale for Selection of Recommended Phase II Dose (RP2D)

As of January 17, 2025, a total of 33 participants have been enrolled in the Phase I part of this study (including 22 participants in the dose escalation part and 11 backfilled participants), and DLT observation has been completed for 7 dose cohorts: 100 mg, 200 mg, 400 mg, 600 mg, 750 mg, 900 mg QD, and 300 mg BID. Enrolled participants include 14 with pancreatic carcinoma, 11 with NSCLC, 5 with CRC, and 1 each with ampullary cancer, endometrial cancer, and bile duct cancer. Based on all available safety, tolerability, PK, and efficacy data, after discussion between the sponsor and key members of the SMC, the RP2D was determined to be 600 mg QD. The rationale for this selection is as follows:

Safety and tolerability:

No DLTs or Grade 5 AEs occurred in any dose cohort. In the 900 mg dose cohort, 2 of the 3 enrolled participants discontinued treatment in Cycle 1 due to AEs and poor tolerability, indicating poor overall tolerability. The 750 mg dose cohort had a higher incidence of more severe gastrointestinal toxicity (Grade 2/3 diarrhea and vomiting), and the duration of vomiting was relatively long. In the 750 mg dose cohort, the incidence of Grade ≥2 diarrhea and Grade 2 vomiting were both 50%, including one case of Grade 3 diarrhea. In dose cohorts below 750 mg (QD), no Grade 3 diarrhea was observed, and the incidence of Grade 2 diarrhea was ≤20.0%. In the 300 mg BID dose cohort, the incidence of Grade 2 diarrhea and vomiting were 33.3% and 66.7%, respectively, which were higher than in the 600 mg QD dose cohort. The incidence of ≥ G3 treatment-emergent AEs (TEAEs) and treatment-related AEs (TRAEs) was higher in the 400 mg dose cohort than in the 600 mg QD dose cohort. There was no

significant difference in the incidence of SAEs. The incidence of dose interruption due to TRAEs was also higher in the 400 mg QD dose cohort than in the 600 mg dose cohort. In the 600 mg dose cohort, only 1 participant discontinued dosing due to a TRAE, and no participants had a dose reduction due to a TRAE. The overall safety and tolerability of the 600 mg dose cohort were similar to or better than the 400 mg dose cohort. The 600 mg dose cohort was generally safe, manageable, and well-tolerated.

PK:

After oral administration of 100-900 mg of GFH375, exposure to GFH375 increased with increasing dose in the 100-400 mg range, but the increase in exposure was not significant in the 400-900 mg range. After QD oral administration of 400 mg-900 mg of GFH375, the median T_{max} was 2-4 h, the single-dose half-life was 18.5-21.6 h, and the accumulation ratio after continuous QD dosing was 0.859-1.30, with no significant accumulation observed. When the dose was higher than 400 mg, the mean trough concentration of GFH375 (34.4-50.2 ng/mL) could be sustained above the preclinical cellular IC_{90} (approximately 11 ng/mL). As mentioned earlier, overall, the safety and tolerability of the 400 mg and 600 mg cohorts were better than those of the 750 mg and 900 mg cohorts. However, the 400 mg cohort showed greater inter-individual variability (geometric CV% for C_{max} and AUC was 111%-127%). Compared to 400 mg, 600 mg can provide participants with higher and more stable exposure.

Efficacy:

Partial responses were observed in participants with pancreatic carcinoma and NSCLC starting from the 400 mg dose cohort. In the 400 mg dose cohort, the ORR and DCR for participants with pancreatic carcinoma were both 100% (2/2), while for participants with NSCLC, the ORR was 0 and the DCR was 50% (1/2). In the 600 mg QD and 300 mg BID dose cohorts, the ORR for pancreatic carcinoma was 25% (1/4) and the DCR was 100% (4/4). For NSCLC, the ORR was 75% (3/4) and the DCR was 100% (4/4). In the 750 mg dose cohort, the ORR for pancreatic carcinoma was 0 and the DCR was 100% (2/2). For NSCLC, both the ORR and DCR were 100% (1/1). In participants with NSCLC, the efficacy of the 600 mg dose cohort was superior to that of the 400 mg cohort.

Based on a comprehensive review of the above data, the RP2D was determined to be 600 mg QD.

Phase Ib: Dose expansion

Phase Ib design shown in Figure 3.

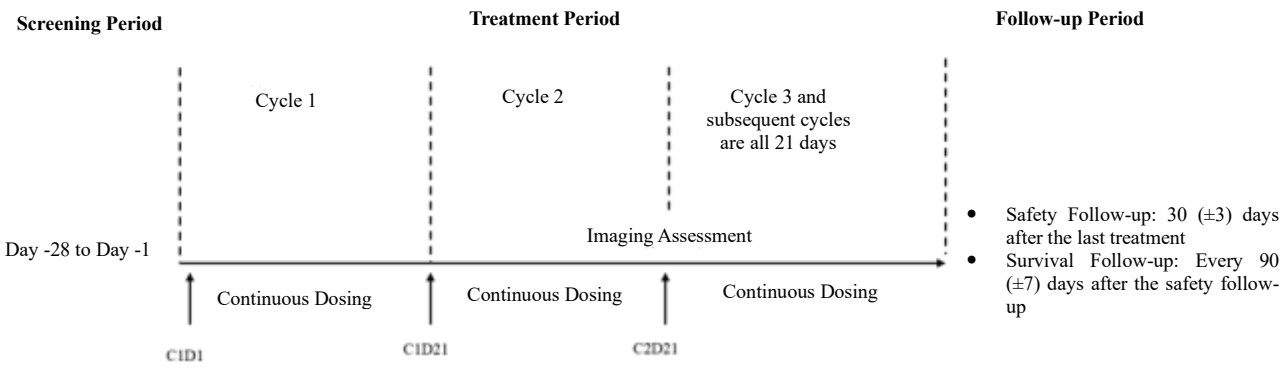

Figure 3 Phase Ib/II Part Schematic

Upon completion of the dose-escalation phase, one or more recommended doses for expansion (RDE) will be selected based on an integration of preclinical and clinical data to conduct the dose-expansion study. Each RDE cohort is anticipated to enroll up to 30 subjects to confirm safety and establish the recommended Phase 2 dose (RP2D).

Eligible subjects will receive GFH375 monotherapy in 21-day treatment cycles until disease progression, intolerable toxicity, or study discontinuation for other reasons. Subjects enrolled in the dose-expansion portion of Phase Ib will undergo sparse pharmacokinetic (PK) sampling along with matched electrocardiogram (ECG) collection. During treatment, subjects will undergo imaging and tumor assessments every 6 weeks ±1 week for the first 48 weeks (with the first assessment to be performed after the completion of 6 weeks of study treatment), and every 12 weeks ±1 week thereafter. Subjects will return to the study site for safety follow-up 30 (±3) days after the last study treatment, followed by survival follow-ups every 90 (±7) days. Subjects who discontinue study treatment for reasons other than disease progression and who have not initiated new anticancer therapy must continue disease progression follow-up according to the prior imaging schedule until disease progression, withdrawal of informed consent, initiation of other anticancer therapy, or study conclusion.

For subjects enrolled in Phase Ib, intra-patient dose escalation to the RP2D monotherapy may be permitted after RP2D confirmation under this protocol, contingent upon agreement between the Investigator and Sponsor.

3.1.2 Phase II Part

The Phase II part is an open-label, multicenter study. The overall study plan is shown in Figure 3 of the main text. The objective is to evaluate the efficacy, safety, and PK characteristics of GFH375 in

patients with advanced non-small cell lung cancer, advanced pancreatic carcinoma, colorectal cancer, and other advanced solid tumors with KRAS G12D mutation. The Phase II part will enroll approximately 317 participants with advanced solid tumors with KRAS G12D mutation to receive continuous GFH375 monotherapy at the RP2D, with a treatment cycle of 21 days. Participants enrolled in this part will undergo sparse PK sampling according to the Phase II part PK blood sampling schedule and have matching ECGs collected with PK sampling.

- Advanced NSCLC participant cohort: Approximately 73 participants with advanced NSCLC carrying the KRAS G12D mutation are planned for enrollment.
- Advanced PDAC participant cohort: Approximately 50 participants with advanced PDAC carrying the KRAS G12D mutation are planned for enrollment.
- Advanced CRC participant cohort: Approximately 50 participants with advanced CRC carrying the KRAS G12D mutation are planned for enrollment.
- Other advanced solid tumor participant cohort: Approximately 40 participants with other advanced solid tumors carrying the KRAS G12D mutation are planned for enrollment, such as bile duct cancer, appendix cancer, etc., carrying the KRAS G12D mutation.

3.2. Definition of End of Study

The end of the study is defined as the last participant having received at least 6 months of study treatment or having withdrawn early (whichever occurs first).

3.3. Early Termination of the Study

This study may be terminated or suspended early due to a decision by a regulatory authority, an opinion from an ethics committee (EC), or a judgment and decision made jointly by the sponsor and the investigator. In addition, the sponsor reserves the right to stop the development of GFH375.

Reasons for early termination or suspension of the study may include:

- Determination of an unexpected, significant, or unacceptable risk to participants;
- Existing efficacy results support early termination of the study;
- Low compliance with protocol requirements.

The party that decides to suspend/terminate the study will issue a written notice and record the reason for the study termination or suspension to the investigator, sponsor, and regulatory authorities. If the study is terminated or suspended early, the investigator should immediately notify the EC and the sponsor, and provide the relevant reasons.

Once the aforementioned issues leading to the suspension of the investigational drug, such as safety and protocol compliance, are resolved and with the consent of the sponsor, EC, and/or regulatory authorities, the study will be resumed.

4 Study Population

Participants must meet all inclusion criteria and not meet any of the exclusion criteria.

4.1. Inclusion Criteria

Participants must meet all of the following criteria to participate in this study:

1. Participants who voluntarily participate in the study and sign the ICF.
2. Male or female, aged 18 - 75 years at the time of signing the ICF.
3. Participants with histologically or cytologically confirmed locally advanced or metastatic malignant tumor, who must meet the following criteria:
   ⑶ Phase I Part:PD after standard of care, or standard of care has been confirmed to be intolerable, or refused standard of care.
   ⑷ Phase II Part:
      e) Advanced NSCLC:
         ✓ Participants who have progressed after prior treatment with anti-PD-(L)1 therapy and/or platinum-based chemotherapy (unless contraindicated or intolerant), a;
         ✓ If prior adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy.
      f) Advanced PDAC: Participants who have progressed after adequate treatment with a gemcitabine-based chemotherapy regimen or FOLFIRINOX/mFOLFIRINOX regimen, or are unsuitable for standard of care due to reasons such as unacceptable toxicity, or refused standard of care.. Those with high microsatellite instability (MSI-H) and/or deficient mismatch repair (dMMR) must have progressed after at least one prior line of anti-PD-1 therapy. If adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy.
      g) Advanced CRC: Participants who have progressed after at least two lines of standard of care, or are unsuitable for standard of care due to reasons such as unacceptable toxicity, or refused standard of care. Participants must have experienced PD or recurrence during or after treatment with fluorouracil, irinotecan, and oxaliplatin for metastatic disease, unless the investigator considers the participant unsuitable for the above treatment regimens. Those with known MSI-H and/or dMMR must have received prior treatment with an immune checkpoint inhibitor (if applicable). If adjuvant or neoadjuvant therapy was received and recurrence/progression occurred during or within 6 months after stopping treatment, this therapy can be counted as one line of therapy.
      h) Other solid tumors: Participants who have progressed after standard of care, or are unsuitable for standard of care due to reasons such as unacceptable toxicity, or refused standard of care.
4. Participants enrolled in this study must provide a written test report confirming KRAS G12D mutation-positive status.
5. According to RECIST 1.1, participants enrolled in Phase Ia must have at least one evaluable lesion,

and participants enrolled in Phase II must have at least one measurable lesion.

6. Toxicities from prior anti-tumor therapy must have resolved to baseline level (excluding alopecia) or ≤ Grade 1 (for neurological toxicity, ≤ Grade 2).
7. Investigator-assessed life expectancy ≥ 12 weeks.
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-1 (see Appendix 2 for scoring criteria).
9. Adequate organ function, including:
   - Hematopoietic function: Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 75 × 10^9/L, hemoglobin ≥ 9 g/dL, with no transfusion or treatment with granulocyte colony-stimulating factor, thrombopoietin, or erythropoietin within 14 days before the blood test.
   - Liver function:
     - Both AST and ALT < 2.5×ULN; for participants with baseline metastases to liver, both AST and ALT < 5×ULN;
     - Total bilirubin (TBIL) < 1.5×ULN; for participants with Gilbert's syndrome: TBIL < 2×ULN.
   - Renal function: Creatinine clearance (CrCl) ≥ 50 mL/min (calculated by Cockcroft-Gault formula, see Appendix 3).
   - Coagulation function: Prothrombin time (PT) or activated partial thromboplastin time (APTT) < 1.5×ULN, international normalized ratio (INR) < 1.5×ULN or within the target range for anticoagulant therapy.
10. Women of childbearing potential (WOCBP) and male participants with partners who are WOCBP must agree to use effective methods of contraception from the time of signing the ICF until 30 days after the last study treatment. WOCBP must have a negative serum pregnancy test result within 7 days before dosing.
11. Participants who are able to communicate well, adhere to the follow-up schedule, and comply with the protocol requirements in the investigator's judgment.

4.2. Exclusion Criteria

Participants who meet any of the following criteria cannot be enrolled in this study:

1. Other malignant tumor that has progressed or required treatment within 3 years prior to enrollment, with the exception of adequately treated carcinoma in situ, basal cell carcinoma, or squamous cell carcinoma of skin.
2. Patients with unstable brain metastasis as judged by the investigator. Patients with incidentally detected brain metastasis during screening may be enrolled if they are asymptomatic and do not require therapeutic intervention; enrollment is permissible if the investigator judges the brain metastasis to be stable, the hormone dose is stable, and the prednisone dose is ≤10 mg/d (or an equivalent dose if other steroid drugs are used).
3. Phase II Part:
   d) Advanced NSCLC: Exclusion of known other driver gene mutations or fusions, such as EGFR, ALK, BRAF (V600E), HER2, MET (exon 14), ROS1, RET, or NTRK1/2/3
   e) Advanced CRC: Exclusion of known other driver gene mutations, amplifications, or fusions, such as BRAF (V600E), HER2, NTRK, or RET
   f) Advanced PDAC: Exclusion of known other driver gene mutations or fusions, such as BRAF (V600E), BRCA, NTRK, or RET
4. Prior targeted therapy against KRAS G12D or pan-KRAS (with primary targeting effect on KRAS G12D).
5. Receipt of palliative radiation within 14 days before administration of the study drug.
6. Receipt of other anti-tumor therapy within 28 days or 5 half-lives (whichever is shorter) before dosing, including chemotherapy, targeted therapy, endocrine therapy, immunotherapy, Chinese patent medicines with definite anti-tumor effects, and other investigational drugs or devices, with the exception of endocrine maintenance therapy.
7. Concomitant clinically significant severe cardiovascular disorder:
   - Clinically significant severe cardiovascular events within 6 months before the first study treatment, such as myocardial infarction, angina unstable, symptomatic cardiac failure congestive (New York Heart Association Class III or IV), severe arrhythmia requiring drug therapy, or receipt of angioplasty, stenting, and coronary artery bypass graft surgery, etc.
   - Clinically significant QT/QTcF prolongation (based on the average of three QTcF values during the screening period, QTcF > 470 ms) or a family history of QT interval prolongation.
   - Hypertension that remains poorly controlled after standard treatment.
8. Stroke or other severe cerebrovascular disorder within 6 months prior to enrollment.
9. History of deep vein thrombosis or any other severe thromboembolism within 3 months prior to enrollment.
10. Concomitant pleural effusion, ascites, or pericardial effusion requiring repeated drainage or causing significant symptoms.
11. Concomitant superior vena cava syndrome.
12. Concomitant diseases that may significantly affect the absorption of GFH375, or inability or unwillingness to swallow tablets.
13. Concomitant clinically significant interstitial lung disease, radiation pneumonitis, or immune-related pneumonitis requiring treatment.
14. Concomitant major acute or chronic infectious diseases, including:

- Active infection requiring intravenous antibiotic therapy within 7 days prior to enrollment.
- Positive for human immunodeficiency virus antibody (HIV-Ab) at baseline.
- Active hepatitis b virus infection (HBsAg positive with positive HBV-DNA).
- Active hepatitis c virus infection (HCV-Ab positive with positive HCV-RNA).
- Active tuberculosis.

15. Other poorly controlled systemic diseases, such as diabetes mellitus.
16. Undergone or planning to undergo major surgery as judged by the investigator within 28 days before the first dose (excluding needle biopsy).
17. History of organ transplant or preparing to receive an organ transplant.
18. Need for acid-suppressing drugs, including proton pump inhibitors and novel acid-suppressing drugs (e.g., potassium-competitive acid blockers), within 7 days before or during the administration of the study drug.
19. Receipt of strong inhibitors or inducers of CYP3A or P-gp within 14 days or 5 half-lives of the drug (whichever is longer) before administration of the study drug.
20. Receipt of known sensitive substrates of CYP3A or OAT1 within 14 days or 5 half-lives of the drug (whichever is longer) before administration of the study drug. Unless agreed for enrollment after review by the investigator and sponsor.
21. Known allergy to the study drug or its components.
22. Severe mental or psychological illness, or history of drug abuse or severe alcoholism.
23. Pregnant or lactating women.
24. Other conditions that, in the investigator's judgment, make the participant unsuitable for the study.

5 Study Treatment

5.1 Treatment Regimen

Phase Ia

The initial dose of GFH375 is 100 mg QD, with each treatment cycle being 21 days. Participants will continue treatment until PD or the occurrence of unacceptable toxicity leading to treatment discontinuation.

Phase Ib and II

Participants in Phase Ib/II will receive GFH375 at the RP2D, dosed daily. Each treatment cycle is 21 days. Participants will continue treatment until PD, unacceptable toxicity, or other reasons leading to treatment discontinuation.

5.2 Investigational Product

5.2.1 Description of Investigational Product

Investigational Product	GFH375 tablets
Active Ingredient	GFH375
Excipients	Mannitol, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, colloidal silicon dioxide, magnesium stearate, film coating premix (enteric-coated) - Opadry, purified water
Type	Oral solid dosage form
Dosage Form	Tablet
Strength	25 mg, 100 mg
Route of Administration	Oral
Storage Requirements	Store protected from light, sealed, at no more than 25°C
Shelf Life	Tentatively 24 months
Packaging and Labeling	High-density polyethylene bottles for oral solid drugs and polypropylene child-resistant combination caps for oral solid drugs, with a desiccant in a high-density polyethylene non-woven (Tyvek) bag for solid drugs inside. Each bottle will be labeled according to relevant regulatory requirements.

5.2.2 Treatment Assignment and Drug Dispensing

When a participant signs the written ICF, they will be assigned a participant number, which will be used for all study documents and Case Report Forms (CRFs). After completing the screening process,

eligibility for formal enrollment in the study will be determined based on the inclusion/exclusion criteria. All enrolled participants will receive GFH375 treatment.

The investigator or their designee must ensure that all drugs or related items for study treatment are maintained under appropriate temperature conditions during transport. If any deviation occurs, the issue must be reported and resolved before administering the study treatment.

Only participants enrolled in the study may receive the study treatment, and only authorized site personnel may provide or manage the study treatment product. All investigational intervention drugs or related items must be stored according to the storage conditions specified on the label in a secure, environmentally controlled, and monitorable (manually or automatically) area, ensuring that only the investigator and authorized site personnel have access to the study treatment product.

5.2.3 Administration of Investigational Product

GFH375 will be dispensed to participants by site personnel at scheduled visits. The quantity of drug dispensed at one time will ensure that the participant has enough medication for self-administration outside the hospital for the specified period.

GFH375 tablets are administered orally. Participants must be instructed to swallow the tablets whole and not to chew or break them. Fasting is required from 2 h before to 1 h after taking the medication, and the dosing time should be kept as consistent as possible each day. If a PK blood sample needs to be drawn in the morning, the medication should be taken after the blood draw. When dosing twice daily (BID), it is recommended to schedule the doses around 8:00 AM and 8:00 PM.

If a dose is missed, it should be taken within 4 hours of the scheduled time, the actual time of administration should be recorded, and subsequent doses should be taken as originally scheduled. If more than 4 hours have passed, the missed dose should not be taken, and the next dose should be taken as originally scheduled. If vomiting occurs after taking the medication, the dose should not be retaken. All actual dosing times should be recorded in the participant's diary, or any unexpected situations such as "missed dose" should be recorded.

5.3 Dose Adjustment

5.3.1 Permitted Dose Adjustments

In principle, dose adjustments are not permitted for participants enrolled in Phase I during the DLT observation period. The safety of participants using the investigational drug should be closely monitored during the study. It is recommended to manage TRAEs with best supportive care according to the practice of the respective study site.

Phase I participants who have completed the DLT observation period and participants enrolled in Phase II may have their doses adjusted based on actual clinical needs. Dose reduction will be performed according to the dose level settings of Phase I. A maximum of 2 dose reductions are permitted for the same participant. For participants receiving 100 mg QD of GFH375, dose reduction is not permitted in principle; for participants receiving 200 mg QD of GFH375, dose reduction is only permitted to 100 mg QD in principle. In special cases, the investigator should discuss further with the sponsor to reach an agreement. For detailed principles of dose adjustment, refer to Table 4 and Table 5.

In principle, intra-participant dose escalation will not be performed during the dose escalation part. For participants enrolled in Phase I, after agreement from the investigator and sponsor, intra-participant dose adjustment to receive RP2D monotherapy is permitted after the RP2D for this protocol has been confirmed.

5.3.2 Dose Interruption and Permanent Discontinuation

During the study, if a participant experiences an event related to the study treatment that meets any of the permanent discontinuation criteria in Table 4 or Table 5, GFH375 treatment should be stopped, and the participant should be followed up until the event resolves or returns to baseline. If the participant has shown a tumor treatment response and the investigator judges that continuing treatment is beneficial, after full communication with the sponsor, study treatment may be resumed at the same dose or a lower dose after the toxicity has recovered to the following levels, while continuing to closely monitor the relevant toxicity.

Table 4 Dose Adjustment Principles for Hematologic Toxicity

Drug-related Adverse Event	Severity	Dose Adjustment
Neutrophil count (ANC) decreased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline, resume at the same dose or reduce by 1 dose level;
	Grade 4	Interrupt dosing until recovery to ≤ Grade 1 or baseline, and reduce by 1 dose level;
	Grade 3 febrile ANC decreased	Interrupt dosing until recovery to ≤ Grade 1 or baseline, and reduce by 1 dose level;
	Grade 4 febrile ANC decreased	Interrupt dosing and withdraw from study treatment;
Platelet count (PLT) decreased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline, resume at the same dose or reduce by 1 dose level; if accompanied by hemorrhage requiring clinical intervention, reduce by 1 dose level;

Drug-related Adverse Event	**Severity**	**Dose Adjustment**
	Grade 4	Interrupt dosing until recovery to ≤ Grade 1 or baseline, and reduce by 1 dose level or interrupt dosing and withdraw from study treatment;
Anemia	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 2 or baseline, resume at the same dose or reduce by 1 dose level;
	Grade 4	Interrupt dosing until recovery to ≤ Grade 2 or baseline, and reduce by 1 dose level or interrupt dosing and withdraw from study treatment;
Other	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 2 or baseline, resume at the same dose or reduce by 1 dose level;
	Grade 4	For non-life-threatening AEs that can be controlled with treatment, dosing may be interrupted, and resumed at a reduced dose after the AE recovers to ≤ Grade 1 or baseline. For life-threatening AEs, dosing should be terminated.

Table 5 Dose Adjustment Principles for Non-hematologic Toxicity

Drug-related Adverse Event	Severity	Dose Adjustment
ALT/AST increased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline, resume at the same dose or reduce by 1 dose level; if ALT/AST >5×ULN for more than 2 weeks, or ALT/AST > 8×ULN, interrupt dosing and withdraw from study treatment;
	Grade 4/Meets Hy's Law	Interrupt dosing, withdraw from study treatment;
Blood bilirubin increased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline; if there is no concurrent elevation of transaminases or alkaline phosphatase, treatment can be resumed at the same dose or reduced by 1 dose level;
	Grade 4	Interrupt dosing, withdraw from study treatment;
Blood amylase/lipase increased	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline; if asymptomatic, treatment can be resumed at the same dose or reduced by 1 dose level; if symptomatic, reduce by 1 dose level;
	Grade 4	Interrupt dosing until recovery to ≤ Grade 1 or baseline and reduce by 1 dose level, or interrupt dosing and withdraw from study treatment;
Pancreatitis	Grade 2	Interrupt dosing until amylase and imaging are normal or not clinically significant; Reduce by 1 dose level;
	Grade 3/4	Interrupt dosing, withdraw from study treatment;
Nausea/vomiting/diarrhea	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline, resume at the same dose or reduce by 1 dose level; if there is no improvement after more than 3 days of symptomatic supportive care, reduce by 1 dose level;
	Grade 4	Interrupt dosing, withdraw from study treatment;
Hypodynamia	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 2 or baseline; If recovery time is ≤ 1 week, it is recommended to resume treatment at the same dose; if >1 week, it is recommended to reduce by 1 dose level
Other systemic AEs	Grade 1/2	Continue at the same dose;
	Grade 3	Interrupt dosing until recovery to ≤ Grade 1 or baseline; If recovery time is ≤ 1 week, it is recommended to resume treatment at the same dose; if recovery time is >1 week, it is recommended to reduce by 1 dose level
	Grade 4	For non-life-threatening AEs that can be controlled with treatment, dosing may be interrupted, and resumed at a reduced dose after the AE recovers to ≤ Grade 1 or baseline. For life-threatening AEs, dosing should be terminated.

When the above hematologic toxicities occur, it is recommended to repeat the hematology within 3 days and then continue to closely monitor recovery. Resumption of treatment may be considered if the following criteria are met: non-hematologic toxicity recovers to ≤ Grade 1 or baseline; hematologic toxicity recovers to ANC ≥1.0×10^9/L, PLT ≥ 75×10^9/L, Hb ≥8 g/dL.

If a TRAE does not recover to a level where dosing can be resumed within 4 weeks, or if the same toxicity requiring dose interruption recurs after resuming treatment, permanent discontinuation of treatment should be considered. For the follow-up study procedures after permanent discontinuation, please refer to Section 6.4.2 of the protocol.

5.4 Prior and Concomitant Therapies

5.4.1 Prior Therapies

For prohibited prior/concomitant therapies before a participant participates in this study, please refer to Section 4 of the protocol.

After the participant signs the ICF, information on each line of prior therapy for the study disease (advanced solid tumors) will be collected, as well as other prior medications/therapies within 30 days before the first dose in this study.

5.4.2 Concomitant Therapies

From the first study treatment until the safety follow-up visit, all concomitant therapies, blood products, and non-drug interventions (such as paracentesis) received by the participant will be recorded.

5.4.2.1 Permitted/Cautionary Concomitant Therapies

During the study, the investigator must follow the principles below and use concomitant medications with caution to maximize participant safety.

Palliative and best supportive care for disease symptoms are permitted during the study, but concomitant therapies during the DLT observation period should be avoided if they may interfere with the assessment of DLTs. Palliative and supportive care for disease-related symptoms will depend on the investigator's judgment and relevant guidelines (e.g., American Society of Clinical Oncology guidelines). For example, palliative local radiation to treat painful bone lesions for symptomatic relief is permitted, provided that these lesions were known to exist at enrollment and are not the only target lesions. Before initiating radiation therapy, the investigator should assess and document whether the use of radiation is related to PD.

If a participant develops other diseases during the study, the investigator should determine whether drug therapy is necessary and should, as much as possible, avoid drugs that could significantly affect

the interpretation of study results, so as not to interfere with the assessment of the participant's safety and tolerability. If a serious adverse reaction or SAE occurs, or if the original condition aggravates or other serious diseases develop, the investigator should promptly provide concomitant and active treatment. If the criteria for participant withdrawal from the study are met, arrangements should be made for the participant's proper withdrawal.

- If the investigator is unsure whether a concomitant therapy will affect participant safety, or whether its use will affect the assessment of participant safety and tolerability, or whether its use will affect the participant's eligibility for enrollment and the evaluability of the data, they should discuss with the sponsor and reach an agreement before using the concomitant therapy.

During the study, participants should use known H2 receptor antagonists and antacids with caution, including but not limited to cimetidine, famotidine, nizatidine, and roxatidine. Antacids include hydrotalcite chewable tablets, aluminum phosphate gel, aluminum hydroxide, magnesium hydroxide, calcium carbonate, etc. If the above drugs must be used, GFH375 should be administered at least 2 hours before or after the administration of these drugs.

5.4.2.2 Prohibited Concomitant Therapies

During the study, participants should not receive the following treatments:

1) Any other anti-tumor therapy besides the study treatment (chemotherapy, immunotherapy, biological products, extensive radiotherapy, hormone therapy, targeted therapy, surgery, Chinese medicines with approved anti-tumor indications), including investigational or approved therapies. Participants receiving gonadotropin-releasing hormone (GnRH) antagonists for prostate cancer, oral contraception, or hormone replacement therapy may continue their medication.
2) The use of Chinese medicine (including Chinese patent medicine) is prohibited within 7 days before the first dose, and is not recommended until the final PK collection of the study is completed. If Chinese medicine is required to manage AEs or diseases, its use must be reviewed and approved by the sponsor beforehand.
3) Use of granulocyte colony-stimulating factor drugs as prophylactic treatment. Such drugs may only be used for the treatment of AEs at the investigator's discretion.
4) Any other investigational drugs for ongoing clinical studies, other than the study treatment.
5) The use of known strong inhibitors and inducers of CYP3A and P-gp is prohibited within 14 days before the first dose or 5 half-lives (whichever is longer) until two weeks after the last dose (see Appendix 4).

6) The use of known sensitive substrates of CYP3A or OAT1 is prohibited within 14 days before the first dose of the study drug or 5 half-lives of the drug (whichever is longer) until two weeks after the last dose (see Appendix 4). Unless the drug is reviewed and approved by the investigator and the sponsor's medical monitor during the screening period.

7) The use of known proton pump inhibitors and novel acid-suppressing drugs (e.g., potassium-competitive acid blockers), including but not limited to omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, ilaprazole, and vonoprazan, is prohibited within 7 days before the first dose of the study drug or 5 half-lives (whichever is longer) until one week after the last dose.

5.5 Treatment Compliance

Participants will follow the investigator's instructions to return all unused GFH375 tablets and packaging from the previous cycle on the specified visit day, and hand in the completed participant diary. The quantity returned by the participant will be counted, recorded, and archived, and medication compliance will be calculated based on the actual drug usage.

5.6 Drug Management

5.6.1 Receipt and Accountability of Investigational Product

The sponsor will provide GFH375 according to the expected enrollment plan of the study site. GFH375 will be shipped to the study site by a third-party logistics company with transportation qualifications. Authorized personnel at the study site will sign the shipping manifest to confirm receipt of the drug.

GFH375 can only be used for this study and can only be managed by personnel authorized by the investigator. To fully control the dispensing and use of GFH375, a quantity record must be made at each visit.

5.6.2 Storage and Management of Investigational Product

The investigator or other authorized study site personnel (e.g., pharmacist) will ensure that all investigational products are stored in a secure, access-controlled area that meets the storage conditions described in Section 5.2.1 of the protocol and that their storage complies with applicable regulatory requirements. After receiving the GFH375 tablets, participants will follow the instructions of the investigator or authorized personnel for proper storage. If any non-compliant storage situation is found, the investigator should contact the sponsor for guidance.

5.6.3 Return and Destruction of Investigational Product

Unused investigational product and packaging will be returned to and destroyed by the sponsor after

accountability, or the sponsor may authorize the study site to destroy them. The sponsor or its authorized personnel will provide the study site with instructions on how to destroy unused investigational product. If authorized to destroy at the study site, the investigator must ensure that all returns and destructions are conducted and documented in accordance with relevant regulations, guidelines, and rules.

5.6.4 Investigational Product Records

Designated personnel at the study site must promptly record the receipt, dispensing, use, inventory, destruction, return, and damage of the investigational product in accordance with relevant regulations and guidelines, and the operational procedures of this study.

5.7 Complaint Handling

To ensure participant safety and monitoring quality, and to assist in process and drug improvement, the sponsor will collect product complaints related to the investigational product used in the clinical study. For complaints related to concomitant medications, they will be reported directly to the manufacturer according to the product instructions. The investigator or their designee is responsible for completing the following product complaint process in accordance with the relevant regulations of this study:

- Use the study-specific complaint form to record the reported product complaint and a complete description of it.
- Fax or email the completed product complaint form to the sponsor or their designee within 24 hours.

If the investigator is required to return the product for investigation, the investigator should return a copy of the product complaint form along with the product.

6 Study Procedures

Before initiating any study procedures required by this protocol, the participant must read and sign the ICF approved by the EC.

All procedures should be performed within the required time windows. If, in special circumstances, a study procedure cannot be completed on time or as required, the investigator should take all necessary measures to ensure the participant's safety and well-being, and document the reason and the measures taken. In addition, the investigator must promptly notify the study team of any unexpected situations that occur.

6.1 Screening Period

Screening Period: Day -28 to Day -1 before the first study drug administration. After the participant signs the ICF, they will provide relevant information and undergo relevant examinations as required by the protocol. Baseline is defined as the last examination result before dosing. All screening period examinations and confirmations must be completed according to the Schedule of Activities. NSCLC and PDAC participants enrolled in Phase II must provide a compliant archived tumor tissue sample or undergo a biopsy during the screening period before enrollment. If a tumor tissue sample cannot be provided and a biopsy cannot be performed during the screening period, the investigator must communicate with the sponsor's medical monitor and obtain their consent before enrollment.

A screening failure is defined as a participant who, for any reason, does not ultimately start the first study drug administration. Participants who fail screening may be re-screened. If re-screening a participant is considered, the investigator must contact the sponsor's medical monitor. Consent from the sponsor's medical monitor must be obtained for re-screening. When re-screening, the participant must re-sign the ICF and will be assigned a new identification number. Assessment results from the initial screening period that are still within the study-specified time frame and meet the inclusion/exclusion criteria are still acceptable and do not need to be repeated.

The inclusion/exclusion criteria must be strictly followed. If a participant who does not meet the inclusion/exclusion criteria is found to be enrolled, the sponsor's medical monitor and the investigator must discuss and determine whether the participant should continue to participate in the study, with or without the use of the study drug. If the investigator believes that it is medically appropriate for the participant to continue participating in the study, and the sponsor's medical monitor agrees with this decision, the participant may continue to participate in the study and receive treatment with the study drug. If the investigator believes it is medically appropriate for the participant to continue participating in the study, but the sponsor's medical monitor disagrees with this decision, the participant must not

continue to participate in the study (regardless of whether they receive study drug therapy). The investigator may only allow a participant who was accidentally enrolled in this study to continue participating after receiving written approval from the sponsor.

6.2 Treatment Period

Eligible participants will receive study treatment until PD (except for participants whom the investigator judges may still benefit from continued treatment), unacceptable toxicity, withdrawal of informed consent, termination of study or early termination, initiation of new anti-tumor therapy, or death, whichever occurs first. The treatment period begins on Day 1 of study drug administration, and each treatment cycle is 21 days. During the study, participants will complete scheduled visits regularly. PK samples will be collected at the time points specified in the protocol. Efficacy will be assessed by the investigator according to RECIST 1.1. During treatment, participants will undergo imaging and tumor assessment every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks after 48 weeks.

6.3 Continued Dosing After PD

After PD, if the investigator judges that the participant will continue to benefit, continued treatment with GFH375 is permitted with the participant's full informed consent, until the criteria for treatment discontinuation are met (see protocol Section 6.4).

If dosing is continued after PD, data collection must continue according to the study-designed visits.

6.4 Participant Discontinuation of Treatment and Withdrawal from the Study

6.4.1 Participant Discontinuation of Treatment

Discontinuation of study treatment does not mean withdrawal from the study. Participants who discontinue study treatment should complete the end of treatment (EOT) visit and subsequent follow-up visits as required by the protocol. Possible reasons for discontinuing study treatment include:

1) The participant experiences PD requiring treatment discontinuation, if the investigator judges that the participant may still benefit from continued dosing, study treatment may be continued after discussion with the sponsor;
2) AEs;
3) The participant starts other anti-tumor therapy;
4) The participant has serious non-compliance with the study protocol requirements;
5) Participant pregnancy;
6) Participant is lost to follow-up;
7) Participant death;

8) The participant requests to discontinue treatment but agrees to subsequent follow-up;
9) The participant withdraws informed consent;
10) The investigator believes that discontinuing study treatment is in the participant's best interest;
11) The entire clinical study is terminated or suspended.

When the above situations occur, the end of treatment (EOT) visit should be completed within 7 days of the decision to end study treatment. Investigations performed within 7 days before the EOT visit do not need to be repeated, but AE-related examinations should be re-checked at the investigator's discretion.

6.4.2 Participant Withdrawal from the Study

Participants may voluntarily withdraw from the study at any time. Reasons for withdrawal from the study may include:

1) The participant withdraws informed consent, refuses to undergo study procedures, and refuses to be contacted for future information;
2) Participant death;
3) Participant is lost to follow-up;
4) The entire study is terminated or suspended.

If a participant does not return to the site for follow-up as scheduled, every effort should be made to contact the participant promptly and reschedule the missed visit as soon as possible. The investigator should inquire about the reason for withdrawal, ask the participant to return to the site to complete the visit if possible, and follow up on any unresolved AEs. In any case, every effort should be made to document the participant's outcome if possible.

If a participant refuses to come to the study site for further visits, their disease and survival status should still be tracked and collected, unless the participant withdraws informed consent (i.e., refuses to be contacted further). In this case, no further study evaluations should be performed, and no further data should be collected.

6.5 Lost to Follow-up

A participant will be considered lost to follow-up if they fail to return to the study site for 3 consecutive scheduled visits and the site staff are unable to contact them.

If a participant does not return to the study site for a required study visit, the following actions must be taken:

- The study site will attempt to contact the participant to reschedule the missed visit, explain

the importance of adhering to the visit schedule, and confirm whether the participant is willing and/or should continue to participate in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to re-establish contact with the participant (should attempt at least two phone calls, and if still unable to make contact, a letter should be sent to the participant's most recently updated contact address). These attempts to contact the participant should be documented in the participant's medical records or study files. Before the termination of this study, the investigator should still try to contact the participant.

If the participant still cannot be contacted, they will be considered lost to follow-up. All attempts to make contact should be recorded in the source documents.

6.6 Unscheduled Visits

If the investigator judges that it is necessary for safety assessment or AE follow-up, or if clinical symptoms suggestive of PD appear, the investigator may schedule a corresponding visit for further examination and assessment.

6.7 Follow-up Period

6.7.1 Safety Follow-up

After the end of treatment visit (including participants who have completed the end of treatment/withdrawal from study visit), the follow-up period begins. Thirty days (±3 days) after the last study drug administration, participants need to return to the study site for a safety follow-up, regardless of whether they have started new anti-tumor therapy.

After the safety follow-up visit, AEs will no longer be actively collected, but all treatment-related AEs must be followed up until resolution, return to baseline, or until the investigator judges them to be stable and irreversible.

6.7.2 PD Follow-up

Participants who discontinue study treatment for reasons other than PD and have not yet started new anti-tumor therapy must continue PD follow-up according to the previous imaging assessment schedule until PD, withdrawal of the ICF, initiation of other anti-tumor therapy, or the end of the study.

6.7.3 Survival Follow-up

After the safety follow-up is completed, participants will enter survival follow-up. Participants will undergo a survival follow-up every 90 (±7) days. The investigator will obtain the participant's survival status, disease status, and subsequent anti-tumor therapy via telephone or email, etc.

7 Study Assessments

7.1 Safety Assessment

Participants will be recorded and assessed for the safety endpoint dataset starting from the screening/baseline period. Safety endpoint assessment indicators include the incidence, severity, and type of AEs, the participant's physical examination results, vital signs measurements, and clinical laboratory test results, with assessment time points according to the visit schedule. Adverse reactions will be graded according to CTCAE v5.0. For detailed information on AE collection and reporting, please refer to Chapter 8.0 Safety Reporting and Adverse Event Management.

7.1.1 Laboratory Tests

Hematology, urinalysis, blood chemistry, coagulation function, and pregnancy tests will be performed according to the Schedule of Activities. Viral serology tests are also required during the screening period to assess eligibility for enrollment. For details, please see Table 6 Laboratory Tests.

If a participant undergoes laboratory tests outside the study site and reports a related AE, the results of that laboratory test should also be collected and entered into the electronic Case Report Form (eCRF).

Table 6 Laboratory Tests

Test Item	Observation Parameter
ematology	Red blood cell count (RBC), hemoglobin concentration (HGB), haematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell count (WBC), platelet count (PLT), absolute neutrophil count (ANC), lymphocyte (LY) count, monocyte (MO) count, eosinophil (EO) count, basophil (BA) count, neutrophil percentage, lymphocyte percentage, monocyte percentage, eosinophil percentage, basophil percentage
rinalysis	Urine white blood cells (LEU), urine nitrite (NIT), urine pH, urine specific gravity (SG), urine protein (PRO), urine glucose (GLU), urine ketone body (KET), urine urobilinogen (UBG), urine bilirubin (BIL), urinary occult blood (BLD); 24-hour urine protein (this test is required when protein urine is ≥2+)
oagulation Function	Prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR)
lood Chemistry	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), urea (UREA)/blood urea nitrogen, blood creatinine (CREA), protein total (TP), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), creatine kinase (CK), pancreatic amylase (AMY), fasting plasma glucose (FPG), total cholesterol (TCHO), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), calcium, sodium, chloride, potassium
irus Serology	Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), HBV-DNA (if necessary), hepatitis C virus antibody (HCV antibody), HCV-RNA (if necessary), HIV antibody

Test Item	Observation Parameter
·egnancy Test	Female participants of childbearing potential will undergo a serum β-HCG pregnancy test at baseline, and a urine pregnancy test at other visits

7.1.2 Physical Examination

Physical examinations will be performed at the time points specified in the corresponding Schedule of Activities.

A complete physical examination includes general condition, skin, neck (thyroid), eyes, ears, nose, throat, chest (including lungs), heart, abdomen, back, lymph nodes, extremities, and vascular and nervous systems; breast, pelvic, rectal, and external genitalia examinations will be performed if clinically indicated. A comprehensive physical examination will be performed during the screening period.

A brief physical examination will be performed before the first dose of GFH375 and at the time points specified in the protocol, based on clinical indications. The investigator may also increase the frequency of physical examinations as needed.

7.1.3 Vital Signs

The participant's vital signs (respiration, pulse, blood pressure, and body temperature) will be recorded.

7.1.4 Performance Status

Performance status assessment will be performed during the screening period, before the first dose, on D1 of each cycle, at EOT, and 30 days after the last treatment. If assessed within 72 hours before the first dose, it does not need to be repeated on C1D1. Performance status will be scored according to the Eastern Cooperative Oncology Group (ECOG) performance status scoring criteria (see Appendix 2).

7.1.5 Body Height and Weight

Body height is measured only once during the screening period. Weight will be measured during the screening period, on C1D1, C2D1, on D1 of each subsequent cycle, at EOT, and 30 days after the last treatment. Body height [centimeters (cm)] and weight [kilograms (kg), rounded to one decimal place, measured in indoor clothing without shoes] will be measured according to hospital standards.

7.1.6 12-Lead ECG

12-lead ECGs will be completed according to the date and time requirements specified in the Schedule of Activities.

The ECG examination should be performed after the participant has rested quietly for at least 10 minutes. During the screening period and the study, 3 ECG examinations will be performed, with an

interval of at least 5 minutes between each. If other trial procedures are combined, the ECG examination should be performed first to avoid the impact of trial procedures on the ECG results.

Heart rate (HR), PR interval, QRS interval, QT interval, and QTcF (Frederica's formula) interval should be assessed and collected.

12-ECG Collection of the Phase I Part Dose Escalation

Participants will undergo an ECG examination on C1D1 (pre-dose, 2 h post-dose, 4 h post-dose, 6 h post-dose), C1D4 (pre-dose, only for QD dosing), C1D8 (pre-dose), C1D15 (pre-dose), C1D21 (pre-dose, 2 h post-dose, 4 h post-dose, 6 h post-dose, 24 h post-dose [only for QD dosing]), C2D10 (pre-dose), C4D1 (pre-dose), C5D1 (pre-dose), and C6D1 (pre-dose).

12-ECG Collection of Phase II Part

Participants will undergo an ECG examination on C1D10 (pre-dose, 2-4 h post-dose), C2D1 (pre-dose, 1-3 h post-dose), C3D1 (pre-dose, 2-4 h post-dose), C4D1 (pre-dose), C5D1 (pre-dose), and C6D1 (pre-dose).

ECGs matching the PK samples will be collected at qualified sites. It is recommended to perform the ECG examination first, then the PK blood draw. If it cannot be completed before the blood sample collection, the ECG examination should be performed after resting quietly for 10 minutes after the blood draw. Meanwhile, the interval between the ECG and PK sampling time needs to be kept within 30 minutes. All planned 12-ECG examinations should be performed after the participant has rested quietly for at least 10 minutes. Three measurements should be taken at each time point, with an interval of 1-2 minutes between each.

7.1.7 Adverse Events and Concomitant Therapies

The assessment of an AE includes the event name, severity (graded according to CTCAE version 5.0), start and end time, whether it is an SAE, its relationship to the study treatment, the measures taken regarding the study treatment, and the outcome.

AEs occurring from the signing of the ICF until the completion of the study safety follow-up visit will be recorded in the source medical records and collected in the eCRF. Other drugs or treatments used by the participant during the study treatment period will be recorded as concomitant therapy in the source medical records and collected in the eCRF.

7.2 PK Assessment

7.2.1 Blood Sample Collection

Phase I Part Dose Escalation

Serial PK samples will be collected on C1D1 (single dose), C1D21 (steady state), C2D1, C2D10,

C4D1, C5D1, and C6D1 to assess the PKs of GFH375. For specific time points, see the **Phase I Part PK Sample and 12-Lead ECG Collection Schedule**.

Phase Ib/II Part

Enrolled participants will have PK samples collected pre-dose on C1D10, C2D1, C3D1, C4D1, C5D1, and C6D1. For details, see the **Phase II Part PK Sample and 12-Lead ECG Collection Schedule**.

- **Unscheduled PK Blood Draw**

When a participant experiences a drug-related SAE, a blood sample for GFH375 plasma concentration measurement should be collected immediately upon the investigator's awareness of the event, if possible.

- **Gastrointestinal AEs (Vomiting and Diarrhea) and PK Sampling**

During the study, it has been found that the incidence of gastrointestinal AEs is high after participants take GFH375, which may affect the participants' PK results. The time of occurrence and frequency of vomiting and diarrhea will be collected in the CRF for subsequent analysis.

7.2.2 Sample Analysis

The concentration of GFH375 will be determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Concentrations below the lower limit of quantitation (LLOQ) will be marked as LLOQ, and any missing samples will be marked accordingly. Sample testing will be conducted by Teddy Clinical Research Laboratory (Shanghai) Limited. Detailed information about the analysis will be recorded in the bioanalytical report.

The collection and processing methods for biological samples are detailed in the laboratory manual.

7.3 Efficacy Assessment

The assessment of tumor remission will include all known or suspected sites of disease. Imaging includes computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, or pelvis; brain CT or MRI for participants with known or suspected brain metastasis; bone scan and/or bone X-rays for participants with known or suspected metastases to bone.

A baseline CT/MRI scan should be performed within 28 days before the first administration . During the study, efficacy will be assessed by the Blinded Independent Central Review (BICR) or the investigator according to RECIST 1.1 criteria (efficacy for all participants must be assessed by the investigator, and PDAC and NSCLC participants enrolled in Phase II also require BICR assessment). Imaging and tumor assessment will be performed every 6 ± 1 weeks for the first 48 weeks (the first assessment after 6 weeks of study treatment), and every 12 ± 1 weeks thereafter. In subsequent tumor evaluations, the same imaging modality as used during the screening period should be used for the

same type of lesions, and the investigation should be performed on the same imaging equipment whenever possible. For participants in whom no corresponding lesions were found on baseline cranial imaging and bone scan, the investigator may decide to add corresponding examinations during the treatment period if clinically indicated.

Disease in remission assessment will be performed by the BICR or the investigator according to RECIST 1.1 (Appendix 1). All participants' radiological imaging examinations must comply with RECIST 1.1 criteria, and all data should be properly retained and be available for source verification and peer review.

If a participant discontinues study treatment for a reason other than PD and has not started subsequent other anti-tumor therapy, imaging examinations will continue until PD occurs, or subsequent anti-tumor therapy is initiated, or the participant withdraws from the study for other reasons.

7.4 Biomarker and Drug Resistance Mechanism Exploration

NSCLC and PDAC participants enrolled in Phase II must provide a compliant archived tumor tissue sample or undergo a biopsy during the screening period before enrollment, to have their baseline gene mutation status confirmed by testing at the central laboratory designated for this study (Burning Rock Biotech).

In Phase I and Phase II, blood samples will be collected from participants at baseline (if collected during the screening period, no need to repeat on C1D1) and at the end of treatment visit, and will be shipped to the central laboratory for ctDNA isolation and sequencing. The sequencing results will be correlated with efficacy to explore biomarkers related to treatment sensitivity or drug resistance.

PDAC participants enrolled in Phase II will have blood samples collected for CA19-9 testing at baseline (if collected during the screening period, no need to repeat on C1D1), every 6 ± 1 weeks during the treatment period, and at the end of treatment (no need to repeat if tested within 4 weeks before the end of treatment visit), to explore the correlation between its changes and treatment response.

7.5 Storage and Destruction of Biological Samples

Remaining samples will be disposed of or destroyed, and will be anonymized and pooled.

Sample flashback analysis (if performed) will be conducted concurrently with the bioanalysis of the study samples. These assessment results will not be reported in the Clinical Study Report (CSR), but will be provided separately in a bioanalytical report.

8. Safety Reporting and Adverse Event Management

8.1 Definition and Recording of Adverse Events

8.1.1 Definition of an Adverse Event

An AE is defined as any untoward sign, symptom, abnormal laboratory value or examination result, or medical condition that appears (or worsens) after the participant has signed the ICF, regardless of whether the event is considered to be related to the study drug. A TEAE is defined as an event that was not present before treatment and appears during the treatment period (defined as from the first dose of the study drug to 30±3 days after the last dose) or worsens relative to the pre-treatment state. AEs that begin or worsen after informed consent should be recorded in the AE eCRF. Conditions already existing at the time of informed consent should be recorded on the medical history page of the participant's eCRF. AE monitoring should continue for 30±3 days after the last dose of treatment, or until the start of new anti-tumor therapy. For details, see Section 8.2.3. AEs (including laboratory abnormalities that constitute an AE) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a definitive diagnosis cannot be made, each sign or symptom should be reported as a separate AE.

8.1.2 Criteria for Assessing the Severity of Adverse Events

AEs will be assessed using NCI-CTCAE version 5.0. If there is no corresponding AE in CTCAE v5.0, please refer to the following criteria (summarized from the grading criteria in CTCAE v5.0).

Table 7 Criteria for Assessing the Severity of Adverse Events

Grade	Clinical Description of Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), where instrumental ADL refers to preparing meals, shopping, using the telephone, managing money, etc.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; resulting in disability; limiting self-care ADL. Self-care ADL refers to bathing, dressing, undressing, eating, toileting, taking medications, etc., but not bedridden
4	Life-threatening; urgent intervention indicated
5	AE resulting in death

8.1.3 Recording and Management of Adverse Events

Each AE should be assessed as much as possible to determine:

- Name of the AE
- Severity grade
- Duration (start and end dates)
- Relationship to study treatment
- Action taken with study drug (none, dose reduced, drug interrupted, drug permanently discontinued, unknown, not applicable)
- Whether medication or treatment has been given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered, recovered, recovering, recovered with sequelae, fatal, unknown)
- Whether it is an SAE, as defined in Section **8.2** as an SAE

All AEs should be managed appropriately. If concomitant medication or non-drug therapy is given, it should be recorded in the AE eCRF. Once an AE is discovered, it should be followed up until it resolves, stabilizes, or is judged to be permanent, and changes in severity, relationship to study treatment, interventions required to treat the AE, and the outcome should be assessed at each visit (or more frequently if necessary).

8.2 Serious Adverse Events

8.2.1 Definition

An SAE is defined as an AE that occurs during any clinical study and meets one or more of the following criteria:

- Results in death;
- Is life-threatening, meaning the patient is at immediate risk of death, not that death might occur if the condition were to worsen in the future;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Other important medical events: Medical and scientific judgment must be used to decide whether to expedite reporting of other situations, such as important medical events that may not be immediately life-threatening, result in death, or require hospitalization, but are generally considered serious if medical intervention is required to prevent one of the above outcomes.

Hospitalization for the following reasons should not be reported as an SAE:

- Routine treatment or monitoring for the indication under study, not associated with any condition aggravated
- Elective or pre-planned treatment for a pre-existing disease not related to the indication under study, which has not worsened since signing the ICF
- Social reasons and respite care where there is no deterioration in the patient's general condition

Emergency outpatient treatment that does not result in hospitalization and involves an event that does not meet the above SAE definition is not an SAE.

8.2.2 Malignant Tumor Progression and Death

Clinical symptoms caused by malignant tumor progression may be recorded as an AE if it cannot be exclusively determined to be due to the progression of the study disease, or if the symptoms are inconsistent with the characteristics of the study PD. If it is clearly consistent with the suspected progression of the study disease, it is not recorded as an AE. Malignant tumor progression itself is not reported as an AE.

Clinical symptoms caused by malignant tumor progression that meet the SAE criteria and for which a relationship to the study drug cannot be completely ruled out must be reported as an SAE. If the event meets the SAE criteria (excluding death events) and is clearly consistent with the suspected progression of the study disease, it is not reported as an SAE. The collection period for SAE reporting is from the time the participant signs the ICF until 30 days after the last dose.

In a clinical study, if a participant dies during the safety follow-up period, it must be reported as an SAE, regardless of whether the investigator assesses it as possibly related to PD. The term 'death' should not be used as an SAE term, but as the outcome of an event. The medical condition/disease (including worsening of signs and symptoms) that caused or led to death should be recorded as the SAE term in the eCRF and reported as an SAE. If the cause of death cannot be determined at the time of reporting, the SAE term should be recorded as 'death of unknown cause'. The collection period for reporting SAEs with a fatal outcome is from the time the participant signs the ICF until 30 days after the last dose.

8.2.3 New Anti-tumor Therapy

If a participant starts new anti-tumor therapy during the safety follow-up period, unrelated AEs and SAEs will no longer be collected thereafter. If a death event occurs during the safety follow-up period, it must be reported as an SAE, regardless of any interventional treatment and regardless of the causal relationship of the event to the study treatment.

8.2.4 Reporting of SAEs

SAE collection will begin at the time of ICF signing, regardless of whether the participant is a screening failure. Follow-up of SAEs will continue until symptoms resolve or there is clinical improvement or stabilization.

To ensure participant safety, any SAE that occurs after the participant signs the ICF and within 30 days after the participant stops study treatment, regardless of the suspected causal relationship, must be reported to the sponsor within 24 hours of awareness of its occurrence. After 30 days following the participant's last treatment, only SAEs suspected to be related to the study treatment will be reported. Any additional information for an SAE, including complications, progression of the initial SAE, and recurrent episodes, must be reported as a follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. SAEs that occur at different time intervals or are considered completely unrelated to a previously reported SAE should be reported separately as new events.

Any SAE occurring after the safety follow-up period should only be reported to the sponsor if the investigator suspects a causal relationship with the study treatment.

Information for all SAEs will be collected and recorded on the SAE report form; to provide a complete clinical report, all applicable sections of the form must be completed. The investigator must assess and record the relationship of each SAE to the study treatment, complete the SAE report form signed by the investigator, and send the report form to the sponsor and the designated CRO pharmacovigilance department within 24 hours, and report to the relevant authorities in a timely manner according to local requirements.

- **Sponsor Pharmacovigilance Email**: drugsafety@genfleet.com
- **Tigermed Pharmacovigilance Email:** PV@TigermedGrp.com

Follow-up information should be submitted in the same manner as the original SAE report form, using a new SAE report form, indicating that it is a follow-up report to a previously reported SAE, and providing the date of the original report. The follow-up information should describe whether the event has resolved or is ongoing, how it was treated, and whether the participant continued in the study or withdrew.

8.3 Causality Assessment of Adverse Events

Causality assessment of an AE with the study treatment refers to a comprehensive evaluation to determine whether there is a reasonable possibility that the study treatment caused or contributed to the AE. Factors the investigator should consider include whether the occurrence of the AE has a

reasonable temporal relationship with the administration of the study treatment, the characteristics of the study treatment, the toxicological and pharmacological effects of the study treatment, the use of concomitant medications, the participant's pre-existing disease, medical history, family history, dechallenge (whether signs/symptoms lessen or improve after study drug discontinuation or dose reduction), and rechallenge (whether signs/symptoms reappear or worsen after re-administration of the drug), etc. The facts and rationale for determining causality should generally be provided.

The investigator should assess the relationship of the AE/SAE to the study drug according to the criteria listed below:

Table 8 Classification and Criteria for Adverse Event Relationship Assessment

Relationship	Assessment Criteria
Related	• Reasonable temporal relationship • Consistent with the known mechanism of action, characteristics, or known adverse reactions of the drug • Positive dechallenge • No other reasonable cause to explain it • Positive rechallenge
Probably related	• Reasonable temporal relationship • Consistent with the known mechanism of action, characteristics, or known adverse reactions of the drug • Positive dechallenge • No other reasonable cause to explain it • Lack of positive rechallenge evidence
Possibly related	• Reasonable temporal relationship • Lack of positive rechallenge evidence • Manifests as any of the following situations: 1) Consistent with the known mechanism of action, characteristics, or known adverse reactions of the drug, with a positive dechallenge, but can also be explained by other reasonable causes; 2) Consistent with the known mechanism of action, characteristics, or known adverse reactions of the drug, with a lack of positive dechallenge evidence, and no other reasonable cause to explain it; 3) Inconsistent with the known mechanism of action, characteristics, or known adverse reactions of the drug, with a positive dechallenge, and no other reasonable cause to explain it; 4) Inconsistent with the known mechanism of action, characteristics, or known adverse reactions, with a lack of positive dechallenge evidence, and no other reasonable cause to explain it.
Unlikely related	• Temporal relationship cannot be excluded • Lack of positive dechallenge evidence • Lack of positive rechallenge evidence • Manifests as any of the following situations: 1) Inconsistent with the known mechanism of action, characteristics, or known adverse reactions, and can be explained by other reasonable causes; 2) Consistent with the known mechanism of action, characteristics, or known adverse reactions, but can be explained by other more reasonable causes;
Not related	• No reasonable temporal relationship • Inconsistent with the known mechanism of action, characteristics, or known adverse reactions of the drug • Lack of positive dechallenge evidence • Lack of positive rechallenge evidence • Can be explained by other reasonable causes

Note: When assessing an AE, if it does not completely correspond to the criteria in the table, please refer to the professional judgment logic for the relationship between AEs and the drug in this table to make the most reasonable assessment possible.

Table 9 Summary for Adverse Event Relationship Assessment

Assessment Result / Assessment Criteria	Related	Probably related	Possibly related				Unlikely related		Not related
Reasonable temporal relationship?	+	+	+				±		-
Consistent with known drug mechanism, characteristics, or adverse reactions?	+	+	+		-		+	-	-
Dechallenge result	+	+	+	-/?	+	-/?	-/?		-/?
Rechallenge result	+	-/?	-/?				-/?		-/?
Can it be explained by other reasonable causes?	-	-	+	-	-	-	++	+	+

Note: + indicates affirmative, or positive result; - indicates negative, or negative result, or a situation where the result is not yet available; ± indicates that a temporal relationship cannot be excluded; ++ indicates that it can be explained by other 'more' reasonable causes; -/? indicates that the dechallenge/rechallenge result is negative, or dechallenge/rechallenge has not yet been performed, or dechallenge/rechallenge is not applicable.

Events assessed as related, probably related, or possibly related will be considered 'related'; events assessed as not related or unlikely related will be considered 'unrelated'. If the investigator's causality assessment is 'unknown', or if a relationship assessment cannot be made, the event should be considered related to the drug. The investigator should collect further information on the AE and provide a causality assessment based on the subsequent information.

8.4 Pregnancy Reporting

If a female participant becomes pregnant during the clinical study, the participant must discontinue study treatment and withdraw from the study; if the partner of a male participant becomes pregnant during the clinical study, the participant may continue in the clinical study. The investigator should complete the "Clinical Study Pregnancy Report/Follow-up Form" and report it to the sponsor and the designated CRO pharmacovigilance department within 24 hours of awareness of the pregnancy event. The investigator must follow up on the pregnancy event until the final outcome (including any premature termination of pregnancy or delivery), with delivery follow-up extending to 1 month after the mother gives birth. The pregnancy outcome must be reported to the sponsor. If the pregnancy outcome meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal death, death neonatal, or congenital anomaly, etc.), it must be reported following the SAE

procedure.

If a participant experiences a concurrent SAE during pregnancy, it must also be reported following the SAE reporting procedure.

8.5 Reporting of Events Meeting Hy's Law

If abnormal AST and/or ALT levels are concurrent with an abnormal elevation in total bilirubin levels, and conditions (1), (2), and (3) below are met simultaneously with no other cause for the abnormalities, such cases should always be reported as an SAE, following the SAE reporting procedure.

Table 10 Criteria for Determining Events Meeting Hy's Law

Condition Met	Assessment Criteria
(1) Abnormal ALT or AST	1) Normal baseline: ALT or AST > 3×ULN during treatment period Abnormal baseline: ALT or AST > 3× baseline level during treatment period
(2) Abnormal TBIL	2) Normal baseline: TBIL > 2×ULN during treatment period Abnormal baseline: TBIL > 2× baseline level during treatment period
(3) Alkaline phosphatase < 2×ULN (or information not available)	

Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, TBIL=total bilirubin, ULN=upper limit of normal.

If a participant has abnormal AST and/or ALT levels concurrent with an abnormal elevation in total bilirubin levels during the treatment or follow-up period, they should return to the study site for examination and assessment as soon as possible after the abnormal results are known. This should include relevant liver function laboratory tests, a detailed medical history inquiry, and a physical examination, and the possibility of liver tumors (primary or secondary) should be considered.

If a liver injury event meeting the above criteria occurs, corresponding dose adjustments or treatment discontinuation should be made according to Sections 5.3.1 and 5.3.2.

8.6 Reporting of Overdose

An overdose is defined as any accidental or intentional administration of a dose that exceeds the planned dose. If an overdose results in an AE, the AE must be recorded in the eCRF. If an overdose is associated with any SAE, please refer to Section **8.2.4 Reporting of SAEs**.

8.7 Reporting Timelines for AE/SAE/Pregnancy

Table 11 Reporting Timelines for AE/SAE/Pregnancy Events

Period	Collection Requirement
From the time the participant signs the ICF until 30±3 days after the last dose of treatment, or until the start of new anti-tumor therapy	All AE/SAE/pregnancy events Pregnancy events: Collection begins after the first dose of study treatment
After the above period	SAEs related to the study treatment

Abbreviations: AE=adverse event, SAE=serious adverse event.

9. Statistical Analysis

Detailed statistical analysis methods will be described in the Statistical Analysis Plan (SAP), and the final version of the SAP will be completed before the clinical database is locked.

9.1. Sample Size

9.1.1. Phase Ia Part

Phase Ia will enroll approximately 30 subjects.

According to the BOIN design, 3-6 participants will be enrolled in each dose cohort (except during accelerated titration) for treatment. Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional participants for backfilling. These participants will be treated with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is considered to have potential clinical benefit by the investigator and sponsor, in order to better estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. Backfilled participants will not be included in the DLT evaluation. After backfilling, no more than 30 participants will be treated in each GFH375 dose cohort (including participants enrolled in the BOIN dose escalation part).

If more dose cohorts or alternative dosing regimens need to be explored, additional participants may be enrolled.

9.1.2.Phase Ib

One or more RDE dose cohorts are planned, with up to 30 subjects per cohort.

9.1.3. Phase II Part

A total of approximately 213 participants are planned for enrollment, including approximately 73 patients with advanced NSCLC, approximately 50 patients with advanced PDAC, approximately 50 patients with advanced CRC, and approximately 40 patients with other advanced solid tumors.

Tumor Type	Historical Control ORR	Expected ORR	Sample Size
NSCLC	23%	40%	73
PDAC	15%	30%	50
CRC	10%	30%	50
Other			40
Total			213

For second-line advanced NSCLC, the historical control ORR is 23%, and the expected ORR in this study is 40%. The study will be considered successful if the lower limit of the 95% CI for the observed ORR is not less than the historical control of 23%. With a one-sided $\alpha = 0.025$, 73 participants are required to achieve 85% power. When at least 25 of the 73 participants have a CR/PR, the lower limit of the exact 95% CI for the observed ORR will be higher than the historical control of 23%. With 25 CR/PRs, the ORR = 34.2%, with a 95% CI of (23.5%, 46.3%).

For advanced PDAC and CRC, the historical control ORR is 10% for both; an ORR of 30% is anticipated for both tumor types in this study.The study will be considered successful if the lower limit of the 95% CI for the observed ORR is not less than the historical control of 10%. It is planned to enroll 50 participants, which will provide 96% power with a one-sided $\alpha = 0.025$. When at least 10 of the 50 participants have a CR/PR, the lower limit of the exact 95% CI for the observed ORR will be higher than the historical control of 10%. With 10 CR/PRs, the ORR = 20.0%, with a 95% CI of (10.0%, 33.7%).

For other solid tumors: Approximately 40 participants with advanced solid tumors with KRAS G12D mutation, such as bile duct cancer and appendix cancer with KRAS G12D mutation, are planned for enrollment.

9.2. Analysis Sets

- Full Analysis Set (FAS): All participants who have received at least one dose of GFH375.
- Safety Set (SS): All participants who have received at least one dose of GFH375 and have at least one valid post-baseline safety assessment.
- Dose Determination Set (DDS): All participants in the Phase Ia SS who have received undiminished doses of GFH375 for at least 15 cumulative days during the DLT observation period and had adequate safety assessments, or who have experienced a DLT during the DLT observation period. The DDS does not include backfilled participants.
- Per-Protocol Set (PPS): All Phase II participants in the FAS who are compliant with the protocol. The study team will review all protocol deviations before the final database lock and exclude participants with major protocol deviations that affect the efficacy evaluation from the PPS.
- Pharmacokinetic Analysis Set (PKAS): All participants who have received at least one dose of GFH375 and have at least one blood sample providing evaluable PK data.

9.3. Statistical Analysis Methods

Data from Phase Ia, Ib and Phase II will be analyzed and summarized separately. Data from the Phase I stage will be analyzed and summarized by different dose levels and dosing regimens; data from the Phase II stage will be analyzed and summarized separately by tumor type.

9.4. Safety Analysis

The incidence of AEs, treatment-related AEs, and SAEs will be summarized by System Organ Class (SOC), Preferred Term (PT), and severity. For the Phase Ia part, the incidence of various types of

DLTs will be summarized based on the DDS, and the DLTs will be listed. Descriptive summaries will be provided for laboratory tests, vital signs, and ECGs.

9.5. Efficacy Analysis

The proportion of the respective population for BOR, ORR, and DCR will be calculated, and the two-sided 95% CI for ORR and DCR will be estimated using the Clopper-Pearson method. The median DoR, PFS, and OS and their 95% Brookmeyer-Crowley CIs will be estimated using the Kaplan-Meier method. TTR will be summarized descriptively.

For the Phase I stage, when the sample size of an analysis group is less than 10, DoR, TTR, PFS, and OS will be listed individually by participant, and the Kaplan-Meier method will not be used for analysis.

For the Phase II stage, the **primary estimand** is set as follows:

Study Population	Participants with advanced solid tumors with KRAS G12D mutation (by tumor type)
Treatment	GFH375
Endpoint	Percentage of participants who achieve CR or PR as assessed by RECIST 1.1 criteria. If a participant has no post-baseline assessment results, the participant is considered a non-responder. **Note:** For NSCLC and PDAC, this will be the percentage of participants with confirmed CR or PR based on Blinded Independent Central Review (BICR) assessment.
Intercurrent Event	Start of new anti-tumor therapy (Handling strategy: Treatment policy strategy, assessment results after the start of new anti-tumor therapy are not included in the analysis.)
Population-level Summary	ORR

9.6. PK Analysis

Plasma concentration data of GFH375 will be listed and summarized descriptively according to the sampling times specified in the protocol. The summaries will be presented by study phase, dose group, and dosing regimen. Individual participant plasma concentration-time curves of GFH375 and corresponding summary curves (mean + standard deviation) will be plotted using linear and semi-logarithmic coordinates, by study phase, dose group, and dosing regimen. Planned PK sampling times will be used to calculate summary statistics and plot summary curves (mean + standard deviation); actual PK sampling times will be used to plot individual participant curves.

Phoenix WinNonlin software (version v8.2 or later, Certara USA, Inc., New Jersey, US) will be used to perform non-compartmental analysis (NCA) to calculate the PK parameters of GFH375 based on actual blood sampling time points. The PK parameters of GFH375 after single and multiple doses in participants in the Phase I dose escalation part will be summarized descriptively, with summaries presented by dose group and dosing regimen.

9.7 Biomarker Assessment

In Phase I and II, blood samples will be collected at baseline and at the end of treatment to isolate ctDNA for NGS testing, to explore tumor gene variations associated with treatment sensitivity or drug resistance.

9.8 Interim Analysis

A futility interim analysis will be performed separately for NSCLC, PDAC, and CRC. For a single tumor type, the analysis is planned when approximately 35 participants (including Phase I participants treated with RP2D and Phase II participants) have had at least one post-baseline imaging tumor assessment or have withdrawn from the study early. Due to practical clinical operational reasons, the number of participants at the time of the interim analysis is allowed to differ from the planned number. During the interim analysis, enrollment will not be stopped.

At the interim analysis, a futility analysis will be conducted for the ORR of NSCLC, PDAC, and CRC, respectively, using the Bayesian predictive probability method. Early termination of the study for the corresponding tumor type due to lack of efficacy evidence is permitted (but not mandatory).

The predictive probability of success (PPoS) will be calculated based on the observed number of Phase II participants who have achieved a response (CR/PR). If the PPoS is < 0.2, early termination of enrollment due to lack of efficacy evidence is permitted (but not mandatory). The corresponding termination criteria for PPoS < 0.2 are shown in the table below:

Tumor Type	Number of Participants*	Recommended to terminate the cohort when the number of responders is ≤
NSCLC	20 ~ 21	3
	22 ~ 25	4
	26 ~ 29	5
	30	6
PDAC, CRC	20 ~ 23	1
	24 ~ 30	2

*Number of participants: The sum of Phase I participants treated with RP2D and Phase II participants who have had at least one post-baseline imaging tumor assessment or have withdrawn from the study early (at least one of these must be met).

The planned interim analysis above is not mandatory. If there is sufficient comprehensive safety and efficacy data to support it before the planned time point for the interim analysis, this interim futility analysis may be omitted.

10. Safety Monitoring

A Safety Monitoring Committee (SMC) composed of investigators and the sponsor will be established for this study. The SMC will continuously review safety data from the first dose of the first participant until the end of the study. During the dose escalation and expansion parts, SMC members will review safety data, PK data, etc., to decide on enrollment for the next dose or to explore potential other dose cohorts, and to recommend a suitable RP2D.

During the study, if both the investigator and the sponsor believe that a participant is at a safety risk or has reached the limit of tolerability, dose escalation or study treatment will be stopped immediately. For details, please refer to the SMC Charter.

11 Study Quality Assurance and Quality Control

According to the guiding principles of Good Clinical Practice (GCP), the sponsor is responsible for implementing and maintaining a quality assurance and quality control system according to the corresponding standard operating procedures to ensure that the clinical study is conducted and that the data is authentic, and that collection, recording, and reporting follow the protocol, GCP, and corresponding regulatory requirements.

11.1 Clinical Monitoring

The sponsor or a contract research organization (CRO) authorized by the sponsor will conduct clinical monitoring for this study. Clinical monitors should conduct monitoring according to the standard operating procedures of the sponsor or CRO and have the same rights and responsibilities as the sponsor's monitors. The monitor should maintain regular communication with the investigator, authorized study personnel, and the sponsor.

Before the start of the study, the monitor will assess the competence of each study site and report any issues related to facilities, technical equipment, or medical personnel to the sponsor. During the study, the monitor will be responsible for monitoring whether the investigator has obtained written informed consent from all participants and whether the data records are correct and complete. At the same time, the monitor will also compare the data entered into the eCRF with the source data and inform the investigator of any errors or omissions. The monitor will also control the study site's compliance with the protocol and trial procedures, arrange for the supply of the investigational drug, and ensure that the drug is stored under appropriate conditions.

Monitoring visits will be conducted in accordance with the requirements of relevant laws and regulations. From the start of participant enrollment, each site will receive regular monitoring visits. After each visit to the investigator, the monitor should submit a written report to the sponsor.

11.2 Quality Assurance Audit

During the study, the sponsor or a representative authorized by the sponsor may conduct quality assurance audits of the study site, study database, and related study documents. At the same time, the corresponding regulatory authorities may also inspect the study site, study database, and related study documents at their own discretion. When the investigator receives a notice of inspection from a regulatory authority, they must immediately inform the sponsor.

The sponsor's quality assurance department will audit the clinical study site. The audit includes: supply of the drug, required trial documents, records of the informed consent process, and the consistency of the case report forms with the source documents, etc. The content and scope of the audit may also be

increased depending on the situation. After reasonable notification, the investigator should allow auditors commissioned by the sponsor to conduct study-related audits and inspections by regulatory authorities. The main purpose of an audit or inspection is to confirm that the rights and health of the participants participating in the study are protected, that the signing of informed consent and the implementation of the trial process are conducted correctly, and that all data processing and reporting related to the evaluation of the investigational drug are consistent with the pre-planned arrangements, protocol, facilities, ethical standard operating procedures, GCP, and applicable regulatory requirements. The investigator should provide direct access to all study documents, source records, and source data.

12 Ethics

12.1 Ethics Committee

The sponsor or its authorized representative will prepare the relevant documents to be submitted to the study site's EC, including the study protocol, ICF, investigator's brochure, participant recruitment materials or advertisements, and other documents required by regulations, all of which must be submitted to the corresponding EC for approval. Before starting this study, written approval from the study site's EC must be obtained and provided to the sponsor. The EC's approval letter must specify the name, number, and version number of the study protocol, as well as the version numbers (e.g., for the ICF) and approval dates of other documents. The investigator must notify the sponsor of the EC's written opinions regarding delays, suspensions, or re-approvals.

The study site must follow the requirements of its EC. This may include submitting protocol amendments, ICF amendments, and participant recruitment material amendments to the EC for approval, local safety reporting requirements, periodic reporting and updates according to EC regulations, and submission of the final report. All the above documents and EC approval letters must be provided to the sponsor or their designee.

12.2 Ethical Conduct

The study process and the acquisition of informed consent should comply with the Declaration of Helsinki, relevant GCP requirements, and Chinese laws and regulations related to drugs and data protection.

GCP provides an ethical and scientific global quality standard for the design, conduct, recording, and reporting of clinical studies involving human participants. This study will be conducted in accordance with GCP and relevant national regulations, and will adhere to the relevant ethical principles of the Declaration of Helsinki to protect the rights, safety, and health of the participants.

The investigator must follow the procedures specified in this study protocol and may not make changes without the sponsor's permission. Any protocol deviations will be reported to the EC, the sponsor, or regulatory authorities.

12.3 Participant Information and Informed Consent

Before any study procedures begin, the potential risks and benefits of this study will be explained to potential participants using the ICF, and the language of the informed consent should be simple and easy to understand. The ICF statement should clarify that signing the informed consent is voluntary, specify the potential risks and benefits of participating in this study, and state that the participant may

withdraw from the study at any time. The investigator may only enroll a participant after fully explaining the details of the study, satisfactorily answering the participant's questions, allowing sufficient time for consideration, and obtaining written consent from the participant or their legal guardian. All signed ICFs must be kept in the investigator's files or the participant's folder.

The investigator is responsible for explaining the content of the informed consent to the participant and obtaining a signed and dated ICF from the participant or their legal guardian before the study begins. After signing, the investigator should give the participant a copy of the signed ICF. The investigator must document the informed consent process in the study source documents.

The initial ICF, any subsequent revised written ICFs, and any written information provided to participants should be reviewed by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) before use. If new information becomes available that may be relevant to the participant's willingness to continue participating in the study, the participant or their legal guardian should be informed in a timely manner. The communication of this information will be provided and documented through a revised ICF or an addendum to the original ICF (obtaining a dated signature from the participant or the participant's legal guardian).

12.4 Data Protection

The ICF will contain (or in some cases, be accompanied by a separate document with) information regarding data protection and privacy protection.

Precautions will be taken to ensure the confidentiality of documents and to prevent the identification of participants. However, in special circumstances, certain personnel may see a participant's genetic data and personal identification code. For example, in the event of a medical emergency, the sponsor, their representative physician, or the investigator will be aware of the participant's identification code and have access to that participant's genetic data. In addition, relevant regulatory authorities may require access to related documents.

12.5 Protocol Deviations

A protocol deviation is any non-compliance with the clinical study protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH GCP), or the operations manual. Non-compliance may originate from the participant, investigator, or study site staff. Corrective actions should be taken and completed in a timely manner for any violations.

13 Study Administration

13.1 Data Handling and Record Keeping

Documents in the clinical study (protocol and protocol amendments, completed eCRFs, signed ICFs, etc.) must be stored and managed in accordance with GCP requirements. The study site should retain these documents for 5 years after the end of the study.

Study documents should be properly stored for future access or data traceability. Safety and environmental risks should be considered when storing documents.

No study documents may be destroyed without the written permission of the sponsor and the investigator. Only after notifying the sponsor and obtaining their written consent may the investigator/study site transfer study documents to another party that complies with document retention requirements or move them to another location that meets the requirements for storage.

13.2 Access to Source Data/Documents

The investigator agrees to allow the sponsor, CRO, and relevant authorized regulatory authorities direct access to all study-related documents, including participant medical records.

13.3 Protocol Amendments

All amendments to the protocol during the course of the study must be communicated between the sponsor and the investigator and agreed upon. The sponsor should ensure that protocol amendments are submitted to the regulatory authorities in a timely manner.

All amendments to the protocol should be kept as protocol addenda. Any modification to the protocol must be submitted to the EC for approval or filing according to the EC's regulations. If necessary, it should also be submitted to the regulatory authorities for approval, and can only be implemented after approval by the EC and regulatory authorities (if required) (except for changes to the protocol made to eliminate an immediate hazard to study participants).

13.4 Investigator Responsibilities

The investigator will conduct this study in accordance with the protocol, the ethical principles of the Declaration of Helsinki, ICH GCP, and corresponding regulatory requirements.

The detailed responsibilities of the relevant investigators are listed in Chapter 5 of the China GCP (No. 57, 2020).

13.5 Publication Policy

All data generated from this study are confidential information of the sponsor, and the sponsor has the right to publish the study results. Information regarding the publication policy between the sponsor and the investigator will be described in the clinical study agreement.

All information related to this study (not limited to the following documents: protocol and investigator's brochure) must be kept strictly confidential. The investigator must recognize that the scientific or medical conclusions drawn from this study may have commercial value to the sponsor. The investigator should keep the information and data related to this trial confidential. If they wish to publicly publish data related to this study or conclusions drawn from the study, they must consult with the sponsor in advance and obtain the sponsor's written consent. To protect its own rights and interests, the sponsor may require the investigator not to publish relevant trial data before the study product obtains marketing approval.

The sponsor has the right to publish or release information or data related to this study, or to submit it to the drug regulatory authorities. If the sponsor needs to use the investigator's name in publications, releases, or advertising content, they should obtain the investigator's consent.

13.6 Finance and Insurance

The sponsor will purchase insurance for participants participating in this study in accordance with local regulations and minimum requirements. The relevant insurance terms will be kept in the study folder.

14 Data Management

14.1 Data Confidentiality

Information related to study participants will be kept confidential and managed in accordance with applicable laws and regulations.

Access to the data collection system will be controlled through a series of individually assigned usernames and passwords, which will only be provided to authorized personnel who have completed the necessary training.

14.2 Data Collection

Data collection for this study will be completed using an Electronic Data Capture (EDC) system.

The investigator or designated study personnel will enter data into the eCRF according to the protocol. Study site staff may only access the EDC system after receiving training. The system will use an automated check process to inspect data inconsistencies in the eCRF, allowing for modification or verification of the data entered by site staff.

When modifying data in the EDC, the reason for the modification must be entered as prompted by the system. The modification history and reasons for modification will be recorded in the audit trail of the EDC system. The investigator or their authorized personnel need to confirm the authenticity, completeness, and timeliness of the eCRF data and provide an electronic signature in the EDC system.

14.3 Data Management

The sponsor or designated CRO personnel will review the completeness and accuracy of the data entered by the study personnel. For any inconsistent or missing data, a data query will be sent to the study site. Designated study site personnel are required to answer queries in a timely manner and make necessary changes to the data.

This project will use the World Health Organization Drug Dictionary (WHODrug) to code concomitant therapies and prior medications entered into the database. MedDRA terminology will be used to code medical history/current diseases and AEs.

Before the database is locked, the study team needs to complete data cleaning, summarize all protocol deviation events that occurred during the study, and hold a data review meeting to determine the analysis sets. All decisions made during the data review meeting must be documented. After the data review meeting is passed, the study database in the EDC system will be locked upon confirmation by the study team. If any changes need to be made to the locked data, the database must be unlocked with authorization after discussion by the project team.

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16 Appendices

Appendix 1: Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

Note: This translated version is for reference only. The final version shall be the English version.

1. Measurability of Tumors at Baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be classified as either measurable or non-measurable according to the following definitions:

Measurable Lesions

Tumor lesions: At least one accurately measurable dimension (recorded as the longest diameter), with a minimum length as follows:

- CT scan 10 mm (CT scan slice thickness no greater than 5 mm)
- Conventional clinical examination instruments 10 mm (tumor lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- Chest X-ray 20 mm
- Malignant lymph nodes: Pathologically enlarged and measurable, with a short axis of a single lymph node ≥15 mm on CT scan (recommended CT scan slice thickness not to exceed 5 mm). Only the short axis is measured and followed up at baseline and during follow-up.

Non-measurable Lesions

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph node short axis ≥10 mm to <15 mm) and unmeasurable lesions. Unmeasurable lesions include: meningeal disorder, ascites, pleural or pericardial effusion, inflammatory breast cancer, lymphangiosis carcinomatosa of the skin/lung, abdominal masses that cannot be confirmed and followed up by imaging, and cystic lesions.

Special Considerations for Lesion Measurement

Bone lesions, cystic lesions, and lesions that have previously received local treatment require special notation:

Bone lesions:

- Bone scans, Positron Emission Tomography (PET) scans, or plain films are not suitable for measuring bone lesions, but can be used to confirm the presence or disappearance of bone lesions;
- Lytic or mixed lytic/blastic bone lesions with an identifiable soft tissue component that meets the

definition of measurability described above can be considered measurable lesions if they can be evaluated by tomographic imaging techniques such as CT or MRI;

- Blastic bone lesions are non-measurable.
- Cystic lesions:
- Lesions that meet the radiological criteria for a simple cyst should not be considered malignant lesions simply because they are defined as simple cysts, and are neither measurable nor non-measurable lesions;
- If they are cystic metastatic lesions and meet the definition of measurability described above, they can be considered measurable lesions. However, if non-cystic lesions exist in the same patient, non-cystic lesions should be preferentially selected as target lesions.

Locally treated lesions;

- Lesions in a previously irradiated area or an area that has undergone other local regional treatment are generally considered non-measurable, unless there is definite progression of the lesion. The study protocol should detail the conditions under which these lesions are considered measurable.

1.2 Description of Measurement Methods

Lesion Measurement

For clinical evaluation, all tumor measurements must be recorded in metric units. All baseline assessments of tumor lesion size should be completed as close as possible to the start of treatment and must be completed within 28 days (4 weeks) before the start of treatment.

Evaluation Methods

The same technique and method should be used for baseline assessment and subsequent measurements of lesions. All lesions must be evaluated using imaging examinations, except for those that cannot be evaluated by imaging and can only be evaluated by clinical investigation.

Clinical lesions: Clinical lesions can only be considered measurable if they are superficial and have a diameter ≥10 mm at the time of measurement (e.g., skin nodules). For patients with skin lesions, it is recommended to use color photographs with a ruler to measure the lesion size for archival purposes. When lesions are evaluated using both imaging and clinical investigation, imaging evaluation should be used whenever possible, as it is more objective and can be reviewed repeatedly at the end of the study.

Chest X-ray: When tumor progression is an important study endpoint, chest CT should be prioritized, as CT is more sensitive than X-ray, especially for new lesions. Chest X-ray is only applicable when the measured lesion has clear borders and the lungs are well-aerated.

CT, MRI: CT is currently the best available and repeatable method for efficacy evaluation. The definition of measurability in these guidelines is based on a CT scan slice thickness of ≤5 mm. If the CT slice thickness is greater than 5 mm, the minimum measurable lesion should be twice the slice thickness. It is recommended to use contrast-enhanced CT for efficacy assessment (unless there is a contraindication to contrast agents). MRI is also acceptable in some cases (e.g., whole body scan).

Ultrasound: Ultrasound should not be used as a method for measuring lesion size. Due to its operator dependence, ultrasound investigation is not repeatable after the measurement is completed and cannot guarantee consistency of technique and measurement between different measurements. If a new lesion is discovered using ultrasound during the study, it should be confirmed with CT or MRI. If radiation exposure from CT is a concern, MRI can be used instead.

Endoscopy, laparoscopy: The use of these techniques for objective tumor evaluation is not recommended, but they can be used to confirm CR when obtaining biopsy specimens, and also to confirm recurrence in studies where the endpoint is recurrence after CR or surgical resection.

Tumor markers: Tumor markers cannot be used alone to evaluate objective tumor response. However, if the marker level is above the upper limit of normal at baseline, it must return to the normal range for the evaluation of complete response. Because tumor markers vary by disease, this factor must be considered when writing the measurement criteria into the protocol. Specific criteria for CA-125 response (ovarian cancer recurrent) and prostate-specific antigen (PSA) response (prostate cancer recurrent) have been published. Furthermore, the Gynecologic Cancer InterGroup has developed CA-125 progression criteria, which will be incorporated into the objective tumor evaluation criteria for first-line treatment of ovarian cancer.

Cytology/Histology techniques: In specific situations defined by the protocol, these techniques can be used to identify PR and CR (e.g., residual benign tumor tissue is often present in lesions of germ cell tumors). When effusion may be a potential side effect of a certain therapy (e.g., treatment with taxane compounds or angiogenesis inhibitors), and the measurable tumor meets the criteria for response or stable disease, the appearance or worsening of tumor-related effusion during treatment can be confirmed by cytology to distinguish between response (or stable disease) and PD.

2. Assessment of Tumor Response

2.1 Target Lesion Assessment

Complete Response (CR): Disappearance of all target lesions, and all pathological lymph nodes (including target and non-target nodes) must have their short axis reduced to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as

reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest); in addition to the relative increase, the sum must also demonstrate an absolute increase of at least 5 mm (the appearance of one or more new lesions is also considered PD).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.2 Notes on Target Lesion Assessment

Lymph nodes: Even if a lymph node identified as a target lesion shrinks to within 10 mm, the actual short axis value corresponding to the baseline must still be recorded at each measurement (consistent with the anatomical plane of the baseline measurement). This means that if a lymph node is a target lesion, even if it meets the criteria for complete response, it cannot be said that the lesion has completely disappeared, because the short axis of a normal lymph node is defined as <10 mm. In the CRF or other recording methods, target lymph node lesions must be specifically recorded in a designated location: for CR, all lymph node short axes must be <10 mm; for PR, SD, and PD, the actual measured value of the target lymph node short axis will be included in the sum of diameters of target lesions.

Target lesions that are too small to measure: In clinical studies, all lesions (nodular or non-nodular) recorded at baseline should have their actual measured values recorded again in subsequent assessments, even if the lesion is very small (e.g., 2 mm). However, sometimes they may be too small, resulting in a very blurry image on the CT scan, making it difficult for the radiologist to define an exact value, and it may be reported as "too small to measure". When this occurs, it is very important to record the previous value on the CRF. If the radiologist believes the lesion may have disappeared, it should be recorded as 0 mm. If the lesion is indeed present but is blurry and an exact measurement cannot be given, a default value of 5 mm can be used. (Note: This situation is unlikely to occur with lymph nodes, as they normally have a measurable size or are often surrounded by fatty tissue, as in the retroperitoneal space; however, if a measurement cannot be given, a default of 5 mm is also used). The default value of 5 mm is derived from the slice thickness of the CT scan (this value does not change with different CT slice thicknesses). Since the chance of the same measurement value recurring is low, providing this default value will reduce the risk of incorrect assessment. However, it must be reiterated that if the radiologist can provide an exact value for the lesion size, the actual value must be recorded, even if the lesion diameter is less than 5 mm.

Fragmented or coalescent lesions: When a non-nodular lesion fragments, the longest diameters of each separate part are added together to calculate the sum of diameters of the lesion. Similarly, for coalescent lesions, they can be distinguished by the plane between each coalesced part, and then their respective longest diameters are calculated. However, if they are inseparably coalesced, the longest diameter should be the longest diameter of the entire fused lesion.

2.3 Non-target Lesion Assessment

This section defines the response criteria for non-target tumor lesions. Although some non-target lesions are actually measurable, they do not need to be measured; only a qualitative assessment at the time points specified in the protocol is required.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes are non-pathological in size (short axis <10 mm).

Non-CR/Non-PD: Presence of one or more non-target lesions and/or persistence of tumor marker levels above the normal range.

PD: Unequivocal PD of existing non-target lesions. Note: The appearance of one or more new lesions is also considered PD.

2.4 Special Notes on the Assessment of Non-target Lesion Progression

The definition of non-target lesion progression is further explained as follows: When a patient has measurable non-target lesions, even if the target lesion assessment is stable or partial response, to define unequivocal PD based on non-target lesions, the overall deterioration of the non-target lesions must have reached a degree that requires termination of treatment. A general increase in the size of one or more non-target lesions is often insufficient to meet the PD criteria. Therefore, when target lesions are stable or in partial response, it is very rare to define overall tumor PD based solely on changes in non-target lesions.

When all of a patient's non-target lesions are non-measurable: This situation occurs in some Phase III parts where the inclusion criteria do not require the presence of measurable lesions. The overall assessment still refers to the above criteria, but in this case, there is no measurable data for the lesions. Deterioration of non-target lesions is not easy to assess (by definition: all non-target lesions must be truly unmeasurable). Therefore, when changes in non-target lesions lead to an increase in overall disease burden equivalent to PD in target lesions, an effective detection method needs to be established to assess and define unequivocal PD based on non-target lesions. For example, an increase in tumor burden described as an additional 73% increase in volume (equivalent to a 20% increase in the diameter of a measurable lesion). Another example is peritoneal effusion changing from "trace" to

"massive"; lymphangiopathy from "local" to "widespread dissemination"; or described in the protocol as "sufficient to alter treatment". Examples include pleural effusion changing from trace to massive, lymphatic involvement spreading from the primary site to distant sites, or what might be described in the protocol as "necessitating a change in treatment". If unequivocal progression is found, the patient should be considered to have overall PD at that time point. It is best to have objective criteria applicable to the assessment of non-measurable lesions; note that the added criteria must be reliable.

2.5 New Lesions

The appearance of a new malignant lesion indicates PD; therefore, some evaluation of new lesions is very important. Currently, there are no specific criteria for detecting lesions by imaging; however, the discovery of a new lesion should be unequivocal. For example, progression cannot be attributed to differences in imaging techniques, changes in imaging modality, or other lesions besides the tumor (e.g., some so-called new bone lesions are merely the healing of the original lesion, or recurrence of the original lesion). This is very important when a patient's baseline lesions show a PR or CR. For example, necrosis of a liver lesion may be identified as a new cystic lesion on a CT report, when in fact it is not.

Lesions detected during follow-up that were not found at baseline will be considered new lesions and indicate PD. For example, if a patient with visceral lesions found at baseline undergoes a head CT or MRI and is found to have metastases, the patient's intracranial metastatic lesions will be considered evidence of PD, even if they did not have a head examination at baseline.

If a new lesion is equivocal, for example, due to its small size, further treatment and follow-up evaluation are needed to confirm whether it is a new lesion. If repeated examinations confirm it is a new lesion, the time of PD should be calculated from the time of its initial discovery.

Lesion assessment by Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) generally requires additional tests for supplementary confirmation. It is reasonable to combine FDG-PET examination and supplementary CT examination results to evaluate PD (especially for new suspicious disease). New lesions can be clarified by FDG-PET examination, according to the following procedure:

A negative baseline FDG-PET examination followed by a positive follow-up FDG-PET examination indicates PD.

No baseline FDG-PET examination was performed, and a subsequent FDG-PET examination is positive:

If the new lesion found on the follow-up positive FDG-PET examination is consistent with the CT examination results, it proves PD.

If the new lesion found on the follow-up positive FDG-PET examination is not confirmed by CT examination results, another CT examination is required for confirmation (if confirmed, the time of PD is calculated from the discovery of the abnormality on the previous FDG-PET examination).

If the follow-up positive FDG-PET examination result is consistent with an existing lesion on CT examination, and that lesion shows no PD on imaging, then there is no PD.

2.6 Missing Assessments and Unevaluable Descriptions

If lesion imaging or measurement cannot be performed at a specific time point, the patient is unevaluable at that time point. If only some lesions can be evaluated in an assessment, this is usually considered unevaluable at that time point, unless there is evidence that the missing lesions do not affect the efficacy response evaluation at the specified time point.

2.7 Special Notes on Efficacy Assessment

When nodular lesions are included in the overall target lesion assessment, and their size shrinks to 'normal' size (<10 mm), they will still have a lesion size scan report. To avoid over-assessing the situation reflected by an increase in nodule size, the measurement results will be recorded even if the nodule is normal. As mentioned earlier, this means that for participants with a complete response, the CRF will not record a value of 0.

If efficacy confirmation is required during the study, repeated "non-measurable" time points will complicate the assessment of BOR. The study's analysis plan must state that these missing data/assessments can be clearly explained when determining efficacy. For example, in most studies, a participant's response of PR-NE-PR can be considered as confirmed efficacy.

When a participant's overall health deteriorates, requiring discontinuation of treatment, but there is no objective evidence, it should be reported as symptomatic progression. Even after treatment discontinuation, an effort should be made to assess objective progression. Symptomatic deterioration is not a description of objective response; it is the reason for stopping treatment. The objective response of such participants will be assessed based on the status of target and non-target lesions as shown in Appendix Tables 1-3.

Cases defined as early progression, early death, and unevaluable are study-specific and should be clearly described in each protocol (depending on the treatment interval and treatment cycle).

In some cases, it is difficult to distinguish local lesions from normal tissue. When the assessment of complete response is based on such a definition, we recommend performing a biopsy before assessing the efficacy of complete response of the local lesion. When abnormal imaging results of a participant's local lesion are considered to represent lesion fibrosis or scar formation, FDG-PET is used as an

assessment standard similar to biopsy to confirm the efficacy of complete response. In this case, the use of FDG-PET should be prospectively described in the protocol, supported by reports from specialized medical literature on this situation. However, it must be recognized that the limitations of FDG-PET and biopsy themselves (including their resolution and sensitivity) will lead to false-positive results in the assessment of complete response.

Appendix Table 1. Time Point Response - Participants with Target Lesions (with or without Non-target Lesions)

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or not fully evaluable	No	PR
SD	Non-PD or not fully evaluable	No	SD
Not fully evaluable	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Not Evaluable.

Appendix Table 2. Time Point Response - Participants with Non-target Lesions Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR or Non-PD	No	Non-CR or Non-PD
Not fully evaluable	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Note: For non-target lesions, "Non-CR/Non-PD" refers to a response better than SD. Since SD is increasingly used as an endpoint for efficacy evaluation, the Non-CR/Non-PD response is established to address situations where no measurable lesions are specified.

For equivocal findings of progression (e.g., a very small, uncertain new lesion; cystic change or necrosis of an existing lesion), treatment may be continued until the next assessment. If PD is confirmed at the next assessment, the date of PD should be the date when suspected PD was first observed.

Appendix Table 3. Best Overall Response for Confirmed CR and PR

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	If SD persists for a sufficient duration, it is SD; otherwise, it should be PD
CR	PD	If SD persists for a sufficient duration, it is SD; otherwise, it should be PD
CR	NE	If SD persists for a sufficient duration, it is SD; otherwise, it should be NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	If SD persists for a sufficient duration, it is SD; otherwise, it should be PD
PR	NE	If SD persists for a sufficient duration, it is SD; otherwise, it should be NE
NE	NE	NE

Note: CR is Complete Response, PR is Partial Response, SD is Stable Disease, PD is Progressive Disease, NE is Not Evaluable. Superscript "a": If a true CR occurs at the first time point, any disease appearing at a subsequent time point will be evaluated as PD at that later time point (because the disease has reappeared after CR), even if the participant's response meets the PR criteria relative to baseline. Best response depends on whether SD occurs within the shortest treatment interval. However, sometimes the first assessment is CR, but a subsequent scan suggests that a small lesion still seems to be present; therefore, the participant's response at the first time point should actually be PR, not CR. In this case, the initial CR judgment should be revised to PR, and the best response is PR.

2.8 Confirmation of Efficacy Assessment/Duration of Response

Confirmation of Response

For non-randomized clinical studies where tumor response is the primary endpoint, the efficacy of PR and CR must be confirmed to ensure that the response is not the result of measurement error. In studies where SD or PD is the primary endpoint, confirmation of response is no longer necessary, as it has no value in the interpretation of the study results. In the case of SD, at least one measurement meeting the protocol-specified criteria for SD must be made within the shortest time interval after the start of the study (generally not less than 6-8 weeks).

Duration of Overall Response

The duration of overall response is from the time of the first measurement that meets the criteria for CR or PR (whichever is measured first) to the time of the first true record of disease recurrence or PD (using the smallest measurement recorded in the study as the reference for PD). The duration of CR

is from the time of the first measurement that meets the CR criteria to the time of the first true record of disease recurrence or PD.

Duration of Stable Disease

The time from the start of treatment to PD (in randomized studies, from the time of randomization), using the smallest sum on study as the reference (if the baseline sum is the smallest, it is used as the reference for calculating PD). The clinical relevance of the duration of SD varies between different studies and different diseases. If, in a particular study, the proportion of patients who maintain SD for a minimum duration is the study endpoint, the protocol should specify the minimum time interval between two measurements in the definition of SD.

Note: The duration of response, duration of SD, and PFS are affected by the frequency of follow-up after the baseline assessment. Defining a standard follow-up frequency is beyond the scope of these guidelines. The follow-up frequency should consider many factors, such as disease type and stage, treatment cycle, and standard practices. However, if comparisons between studies are to be made, the limitations on the accuracy of these measurement endpoints should be considered.

2.9 PFS/TTP

Many studies of advanced tumors use PFS or TTP as the primary endpoint. If the protocol requires all patients to have measurable lesions, the assessment of progression is relatively simple. An increasing number of studies allow patients with both measurable and non-measurable lesions to be enrolled. In this case, the clinical findings of PD in patients with non-measurable lesions must be described in detail and clearly. Because the date of PD often has ascertainment bias, the observation time points should be scheduled the same for all study groups.

Appendix 2: Performance Status Scoring Criteria (ECOG PS)

Score	Criteria
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Death

Appendix 3: Cockcroft-Gault Formula

Formula for serum creatinine concentration in (mg/dL):

$$\text{Male creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight})^{a}}{72 \times \text{serum creatinine}}$$

$$\text{Female creatinine clearance (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{weight})^{a}}{72 \times \text{serum creatinine}}$$

Formula for serum creatinine concentration in (μmol/L):

$$\text{Male creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight})^{a}}{0.818 \times \text{serum creatinine}}$$

$$\text{Female creatinine clearance (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{weight})^{a}}{0.818 \times \text{serum creatinine}}$$

a: Age in years, weight in kg.

Appendix 4: List of Prohibited Medications

Interaction Mechanism	Drug Name
Strong Inducers of CYP3A and P-gp	Apalutamide, carbamazepine, enzalutamide, ivosidenib, lumacaftor/ivacaftor, mitotane, phenytoin, rifampin, St. John's wort
Strong Inhibitors of CYP3A and P-gp	Ceritinib, clarithromycin, cobicistat, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir tablets, nefazodone, amiodarone, cyclosporine, dronedarone, erythromycin, lapatinib, propafenone, quinidine, ranolazine, verapamil
Sensitive Substrates of CYP3A4	Alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, isavuconazonium, ivabradine, lemborexant, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, mobocertinib, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil, venetoclax
Sensitive Substrates of OAT1	Adefovir, ciprofloxacin, furosemide, tenofovir

The table lists common strong inhibitors and inducers of CYP3A4 and P-gp, and sensitive substrates of OAT1 and CYP3A4. If there are questions about other possible concomitant medications, the investigator can communicate with the sponsor. Drug interactions can be queried on the FDA's official website at the following URL: https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems.

Appendix 5: Detailed Parameters and Simulation Performance of the BOIN Design

Using the Shiny app 'BOIN' obtained from http://www.trialdesign.org, and considering the following two scenarios:

1. Accelerated titration is used for the first two dose levels

The specific parameters of the BOIN design are as follows:

Parameter	Value
Number of dose groups	5
Starting dose	1
Number of participants per cohort	3
Number of cohorts	10
If the number of participants assigned to a dose group reaches m and the next participant is still to be assigned to that dose group, the study is terminated. m =	6
Target toxicity probability	0.3
Use default dose escalation/de-escalation boundaries (recommended)	True
Use accelerated titration	Yes
Maximum dose for accelerated titration	2
When 1 DLT is observed in 3 participants, change the decision from de-escalate to stay at the current dose	Yes
Dose elimination threshold p_K	0.95
Number of repetitions for each scenario	1000
Random number generator seed	12345

Note: Maximum sample size = Number of participants per cohort * Number of cohorts = 3 * 10 = 30.

The simulation performance of this BOIN design is as follows:

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Number of patients	Early termination %
Scenario 1							
True DLT rate	0.3	0.46	0.5	0.54	0.58		
Selection %	56.6	22.4	11.7	1.6	0		7.7
Patients treated %	44.1	35.1	17.6	2.9	0.3	12.1	
Scenario 2							
True DLT rate	0.16	0.3	0.47	0.54	0.6		
Selection %	24.8	47.5	23.8	2.9	0.1		0.9
Patients treated %	26.7	39.7	28.1	5.1	0.4	14.4	
Scenario 3							
True DLT rate	0.04	0.15	0.3	0.48	0.68		
Selection %	1.6	22.9	56.7	18	0.8		0
Patients treated %	9.8	23.3	43.4	20.7	2.8	15.3	
Scenario 4							
True DLT rate	0.02	0.07	0.12	0.3	0.45		

Selection %	0.2	3.3	23.8	51.2	21.4		0.1
Patients treated %	6.8	9.7	31.8	35.7	15.9	17	
Scenario 5							
True DLT rate	0.02	0.06	0.1	0.13	0.3		
Selection %	0.3	2.2	11.1	22.7	63.7		0
Patients treated %	7	9.2	24.3	29.5	30	16.4	

2. BOIN design considering only the last three dose levels

The specific parameters of the BOIN design are as follows:

Parameter	**Value**
Number of dose groups	5
Starting dose	1
Number of participants per cohort	3
Number of cohorts	10
If the number of participants assigned to a dose group reaches m and the next participant is still to be assigned to that dose group, the study is terminated. m =	6
Target toxicity probability	0.3
Use default dose escalation/de-escalation boundaries (recommended)	True
Use accelerated titration	No
When 1 DLT is observed in 3 participants, change the decision from de-escalate to stay at the current dose	Yes
Dose elimination threshold p_K	0.95
Number of repetitions for each scenario	1000
Random number generator seed	12345

The simulation performance of this BOIN design is as follows:

	Dose 1	Dose 2	Dose 3	Number of patients	Early termination %
Scenario 1					
True DLT rate	0.3	0.48	0.67		
Selection %	70.6	20.4	0.9		8.1
Patients treated %	63.7	32	4.3	10.4	
Scenario 2					
True DLT rate	0.13	0.3	0.44		
Selection %	27.7	50.1	21.7		0.5
Patients treated %	39.3	41.7	19	13.9	
Scenario 3					
True DLT rate	0.05	0.13	0.3		
Selection %	3.6	26.2	70.1		0.1
Patients treated %	25.1	37.4	37.5	14.7	

Based on the above simulation performance results, this design can select the correct MTD with a high probability (if an MTD exists) and will assign more patients to the dose level with a DLT rate

closest to the target probability of 0.3.

Appendix 6: Statistical Methods for Interim Analysis

The interim analysis uses the Bayesian predictive probability (PP) method to calculate the probability of success, providing a rationale for early futility assessment. Based on the efficacy data observed at the interim analysis, the probability of success (i.e., concluding that the study drug is effective) at the maximum planned sample size is calculated. Based on the observed data, a high PP indicates a high likelihood of concluding that the study treatment is effective at the end of the study, whereas a low PP suggests that the study treatment may not have sufficient efficacy.

The table below shows the relevant parameter values and calculation results set via the online software (https://www.trialdesign.org/one-page-shell.html#BEMPR):

Input Parameter	Input Value		
	NSCLC	CRC	PDAC
Reference response rate (θ_0)	0.23	0.10	0.15
Threshold for declaring efficacy at the end of the trial (p_T)	0.7		
Early Stopping for Futility	TRUE		
Probability confidence threshold for futility stopping (p_L)	0.2		
Early Stopping for Efficacy	FALSE		
Prior distribution for θ: Beta(a_0,b_0) a_0	0.5		
Prior distribution for θ: Beta(a_0,b_0) b_0	0.5		
Input Cohort Manually	FALSE		
Maximum number of patients in the trial	73	50	94
Minimum number of patients before early stopping rule applies	20		
Cohort size	1		

Appendix 7: Central Laboratory Information and Sample Destruction Company Information

Central Laboratory 1: PK Testing

Name: Teddy Clinical Research Laboratory (Shanghai) Limited

Unified Social Credit Code: 91310110MA1G83F27K

Address: Room 101-110, Block C, 3rd Floor, Building 12, No. 128 Xiangyin Road, Yangpu District, Shanghai

Central Laboratory 2: ctDNA Sequencing

Name: Guangzhou Burning Rock Biotech Co., Ltd.

Unified Social Credit Code: 91440116094098415C

Address: No. 5 Xingdao Huanbei Road, Guangzhou International Bio Island, Huangpu District, Guangzhou

Sample Destruction Company 1: PK Sample Destruction Unit

Name: Shanghai Solid Waste Disposal Co., Ltd.

Unified Social Credit Code: 913101147294906145

Address: No. 2491 Jiazhu Highway, Jiading District, Shanghai

Sample Destruction Company 2: ctDNA Sequencing Sample Destruction Unit

Name: Guangzhou GRANDTOP Group Co., Ltd.

Unified Social Credit Code: 91440101671815024A

Address: Room 1218, No. 121 Liuhua Road (South Tower), Yuexiu District, Guangzhou

临床研究方案

研究标题：	一项评估 GFH375 治疗 KRAS G12D 突变型晚期实体瘤患者的安全性、耐受性、药代动力学和疗效的开放标签、I/II 期临床研究
方案编号：	GFH375X1101
版本号及版本日期：	2.0 版/2025 年 1 月 24 日
产品名称：	GFH375
研究分期：	I/II 期
申办方：	劲方医药科技（上海）股份有限公司
申办方联系人：	朱华强，医学科学副总裁 电话：15601727272 Email：hqzhu@genfleet.com

保密声明

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申办方签字页

研究标题：一项评估 GFH375 治疗 KRAS G12D 突变型晚期实体瘤患者的安全性、耐受性、药代动力学和疗效的开放标签、I/II 期临床研究

方案编号：GFH375X1101

职位	姓名	签名（正楷）	日期
医学科学副总裁	朱华强		2025.01.24.

研究者签字页

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通过签署此方案签字页，研究者确认并同意：

我已阅读了上述研究方案及其附件。我已与申办方劲方医药科技（上海）股份有限公司充分讨论了该方案的内容。我同意按照此研究方案开展研究，以及国际人用药品注册技术要求协调会-药物临床研究质量管理规范（ICH-GCP）、当地法规和其他适用的法规履行相关的职责。我同意将确保所有参与本研究的工作人员了解他们在履行上述承诺方面的义务。

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我已阅读本研究方案的全部内容并保证按要求开展本研究：

研究者签名：_____ 日期：_____

打印体姓名：_____

研究者职称：_____

联系电话：_____

中心名称/地址：_____

_____

_____

方案修订小结

版本号	版本日期	方案修订小结
1.0	2024 年 03 月 15 日	不适用
1.1	2023 年 04 月 08 日	主要修改原因：明确针对入组 I 期受试者的既往抗肿瘤治疗的要求，避免产生歧义。 • 更新针对 I 期受试者既往抗肿瘤治疗的入选标准#3：符合以下任意一条标准：1)接受标准治疗后疾病进展，且没有其他标准治疗可用；或 2)已证实标准治疗无效、不耐受或认为不适合。
1.2	2024 年 9 月 13 日	主要修改原因：明确原方案中给药频率每日两次（BID）的剂量探索。 • 明确 BID 剂量探索相关的研究设计、操作流程和 PK 采集 • 个别 DLT 条目的定义更具可操作性 • 优化部分研究操作流程 • 对全文不一致的地方进行勘误
1.3	2024 年 11 月 18 日	主要修改原因：调整 I 期部分方案设计、增加剂量组回填人数 • 不再设置 Ib 扩展期 • 调整 QD 的最高剂量 • 增加 I 期阶段 ctDNA 检测 • 修改 GFH375 PK 血样采集时间点 • 修改附录禁用药列表 • 勘误和调整不一致的地方
2.0	2025 年 1 月 24 日	主要修改原因：完成 I 期剂量递增阶段，增加 RP2D 选择依据；II 期针对 PDAC 和 NSCLC 进一步细化入排标准并对疗效评估增加 BICR 评估。 • 增加 RP2D 选择依据 • 针对 II 期 PDAC 和 NSCLC 受试者进一步细化入排标准 • II 期 PDAC 和 NSCLC 主要终点分析增加 BICR 评估疗效 • 增加 II 期 PDAC 和其他晚期实体瘤受试者的样本量

		• II 期 PDAC 受试者增加探索目的，探索 CA19-9 和治疗应答的关系

方案摘要

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I 期目的和终点包括：
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<tr><td>• 评估 GFH375 在 KRAS G12D 突变型晚期实体瘤患者中的初步疗效</td><td>• 根据实体瘤疗效评价标准 (RECIST) 1.1 评估的客观缓解率 (ORR)、缓解持续时间 (DoR)、疾病控制率 (DCR)、</td></tr>
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	至缓解时间 (TTR)、无进展生存期 (PFS) 和总生存期 (OS)
探索目的	**探索终点**
• 探索与治疗敏感或耐药相关的分子机制	• 基线和治疗结束时血液循环肿瘤 DNA（ctDNA）的突变分析

II 期部分的研究目的和终点：

研究目的	**研究终点**
主要目的	**主要终点**
• 评估 GFH375 在 KRAS G12D 突变的晚期非小细胞肺癌（NSCLC）、晚期胰腺导管腺癌 (PDAC)、晚期结直肠癌 (CRC)和其他实体瘤患者中的疗效	• 根据 RECIST 1.1 评估的 ORR
次要目的	**次要终点**
• 使用其他疗效指标评估 GFH375 在 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的疗效	• 根据 RECIST 1.1 评估的最佳总体缓解（BOR）、DoR、DCR、TTR、PFS • OS
• 评估 GFH375 在 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的安全性	• AE、SAE 的发生率和严重程度；生命体征、ECG 和实验室检查的改变
• 评估 GFH375 在 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的 PK 特征	• GFH375 的血浆浓度
探索目的	**探索终点**
• 探索与治疗敏感或耐药相关的分子机制	• 基线和治疗结束时血液循环肿瘤 DNA（ctDNA）的突变分析
• 针对 PDAC 受试者：糖类抗原 19-9（CA19-9）与治疗应答的关系	• 针对 PDAC 受试者：血清CA19-9相对基线的变化

研究背景	RAS 家族负责调节细胞的生长、迁移、存活和分化相关的信号通路。RAS 蛋白通常在 GTP 和 GDP 结合构象之间进行切换，分别对应激酶的“开启”和“关闭”状态。在各种恶性肿瘤中，RAS 的致癌突变导致 GTP 水解被抑制，使激酶处于变构激活状态，从而导致细胞恶性增殖和生物行为学的改变。 KRAS 是 RAS 家族中最常见的突变类型，约占胰腺导管腺癌的 90%、结直肠癌的 50%和肺腺癌的 30%。因此，KRAS 被认为是许多恶性肿瘤发生和肿瘤转移的驱动癌基因。KRAS G12D 为 KRAS 最常见的突变类型之一，据估计在肺腺癌中美国的数据显示 G12D 突变占 4.9%，而国内 NSCLC 患者的大样本量分析显示 KRAS G12D 突变频率约为 2.2%。在胰腺癌中，约 37%的患者携带 KRAS G12D 突变，提示该突变等位基因在胰腺癌患者人群水平的重要性。临床前研究中已在多个 PDAC 异种移植模型中证实，KRAS G12D 在 PDAC 中作为一种持续发挥作用的致癌驱动基因，KRAS G12D 抑制剂在 PDAC 模型中显示出显著的抗肿瘤活性。在结直肠癌中，KRAS 突变率约为 40%，其中 KRAS G12D 约占 28%。此外，研究表明 KRAS 突变是结直肠癌对西妥昔单抗获得性耐药的常见因素，在经西妥昔单抗（或联合化疗）治疗后的 CRC 转移组织样本中观察到获得性的 KRAS G12D 突变。目前，已有数款 KRAS G12D 选择性的抑制剂（如 MTRX1133 和 HRS-4642 等）进入临床开发中，分别通过口服或静脉给药，尚未有特异性靶向 KRAS G12D 突变肿瘤的疗法获批。 晚期 NSCLC、 PDAC 、CRC 以及其他携带 KRAS G12D 突变的实体瘤患者通常首选接受化疗、免疫治疗或抗血管生成药物联合治疗，在标准治疗失败后，均缺乏有效的治疗手段。如晚期 NSCLC 虽然 EGFR、ALK 等驱动基因阳性的患者可以选用针对性的靶向治疗，获得较好的疗效，但由于 KRAS G12D 极少与上述驱动基因同时存在，因此仍以化疗如多西他赛等作为标准系统治疗失败的主要治疗药物，近期报告的 ORR：7.1-16.0%; 中位 PFS: 2.6-4.5 个月。在入组转移性 PDAC（mPDAC）患者的 III 期 NAPOLI-1 研究显示，对于既往以吉西他滨为基础的化疗方案治疗失败后的 mPDAC 患者，相较于仅接受 5-FU/LV（5-氟尿嘧啶+亚叶酸），患者接受伊立替康脂质体联合 5-FU/LV（5-氟尿嘧啶+亚叶酸）后，疗效得到明显改善：中位总生存期（mOS）为 6.1 月（vs 4.2 月，HR 0.67）中位 PFS 为 3.1 个月 （vs 1.5 月，HR 0.56），ORR 为 16%（vs 1%，$p < 0.0001$） 。在接受≥1 线治疗后的 mPDAC 受试者中开展的其他 II 期研究中（多数受试者接受过≥2 线治疗），

	报告的 ORR 为 0%-10.7%。在 CRC 受试者中，TAS-102+/-贝伐珠单抗、瑞戈非尼和呋喹替尼等通常作为三线治疗的选择，ORR 仅为 1 - 4%。因此，标准治疗失败的 NSCLC、PDAC 和 CRC 目前均缺乏有效的治疗方法，有巨大的未被满足的临床需求。 KRAS G12C 抑制剂（索托拉西布、阿达格拉西布）获批 NSCLC 的适应症，在此类患者中证实了良好的疗效和安全性。而与其他 KRAS 突变肺癌相比，KRAS G12D 突变阳性的肿瘤具有不同的临床、基因组和免疫学特征，如在 NSCLC 中，KRAS G12D 突变阳性状态可能与低肿瘤突变负荷和低 PD-(L)1 表达相关，多为“immune cold”，从而促进肿瘤细胞对免疫抑制剂治疗耐药，临床上需要针对这些人群单独开展研究，KRAS G12D 抑制剂提供了很好的研究机会，可能为这些患者带来潜在获益。 GFH375 是一种靶向 KRAS G12D 突变的高选择性、口服、非共价小分子抑制剂。GFH375 在临床前体外研究中显示出对 KRAS 依赖性的信号转导和癌细胞活力的强效抑制作用，并在 KRAS G12D 突变肿瘤动物模型上体现了显著的抗肿瘤药效。上述结果支持在携带 KRAS G12D 突变的晚期实体瘤患者中进一步评估 GFH375 的安全性和疗效。
研究设计	本研究是一项评估 GFH375 单药在携带 KRAS G12D 突变的晚期实体瘤患者中的安全性/耐受性、PK 及有效性。I 期研究的主要目的是评估 GFH375 在携带 KRAS G12D 突变的晚期实体瘤患者中的安全性/耐受性、PK 和初步有效性，并确定 GFH375 的 MTD 和/或 RP2D。II 期研究的主要目的是评估 GFH375 在携带 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的有效性。 研究期间将设立由研究者及申办方组成的安全监查委员会（SMC），详细信息可参考第 10 章节及本研究的 SMC 章程。 **I 期部分** 将根据 BOIN 设计，在每个剂量组入组 3-6 例受试者（加速滴定时除外）接受治疗。如果需要探索更多的剂量水平或替代给药方案，则可以入组额外的受试者。 受试者入组后将接受 GFH375 口服给药治疗，每 21 天为一个治疗周期。受试者将入组至顺序递增的不同剂量组，起始剂量为 100 mg 每日一次（QD）。预计在剂量递增部分共进行 7 个或更多给药剂量的评估，计划的递增剂量参见**下表**。

剂量递增过程中将综合评估 GFH375 给药方案，必要时将进行给药频率为每日 2 次（BID）的剂量探索，剂量递增可在 QD 和 BID 给药方案上独立并行进行。

首次治疗后的第一个周期将作为剂量限制性毒性（DLT）观察期，DLT 可评估病例需要满足以下两个条件之一：

- 受试者发生 DLT 事件，或
- 受试者未发生 DLT 事件，且在第一周期至少接受了 15 天 GFH375 的计划给药。

如未发生 DLT 事件，受试者将继续接受治疗，并允许在符合本方案准许情况下的剂量调整，直至出现疾病进展、不可耐受的毒性或因其他原因结束研究治疗。若受试者在 DLT 观察期发生 DLT 事件，经研究者与申办方评估继续接受 GFH375 的治疗能够获益，将在相关的不良事件缓解后恢复 GFH375 治疗。恢复给药标准可参考正文相应章节。

入组 I 期的受试者将进行密集 PK 采样并收集与 PK 采样相匹配的心电图，以评估 GFH375 的药代动力学特征和安全性。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。受试者将在末次研究治疗后 30 (±3) 天返回研究中心完成安全性随访，之后每 90 (±7) 天进行一次生存随访。受试者因疾病进展以外的原因结束研究治疗且尚未开始新的抗肿瘤治疗，需按照之前的影像学评估计划继续进行疾病进展随访，直至疾病进展、撤回 ICF、开始其他抗肿瘤治疗或研究结束。

	I期计划/完成递增的QD剂量组*
剂量组1	100 mg QD
剂量组2	200 mg QD
剂量组3	400 mg QD
剂量组4	600 mg QD
剂量组5	750 mg QD
剂量组6	1000 mg QD
剂量组7	1200 mg QD

注：可能会在爬坡过程中基于获得的临床数据包括安全性、PK、可能的有效性，进行上述剂量的中间剂量探索，如 150mg、300mg、500mg、800mg、900mg、1100mg QD 等。

基于所获得的数据包括安全性、PK、初步疗效结果，可能会进行 BID 剂量探索。BID 起始剂量将选择下表其中一个剂量组，每日总剂量与正在探

索的 QD 剂量一致。

	I期可能探索的BID剂量组*
剂量组1	100 mg BID
剂量组2	150 mg BID
剂量组3	200 mg BID
剂量组4	300 mg BID
剂量组5	400 mg BID

注：可能会进行上述剂量的中间剂量探索，如 250mg BID 等。

DLT 定义

DLT 是指在首次用药后 21 天内出现的、与研究药物 GFH375 相关且符合以下严重程度的不良事件。不良事件的严重程度根据不良事件通用术语评价标准（CTCAE）5.0 版进行分级：

- ≥4级中性粒细胞绝对计数（ANC）降低≥5天；
- ≥ 3级发热性中性粒细胞减少症（ANC <1.0 × 10^9/L 伴单次体温 > 38.3℃或持续体温≥38℃超过1小时）；
- ≥4级血小板计数降低持续≥5天；
- ≥3级血小板计数降低合并≥2级出血；
- ≥4级贫血；
- 若基线ALT或AST ≤ 1级：≥ 3级血清转氨酶升高（ALT或AST）持续 > 7天被视作DLT；若基线ALT或AST为2级，则 ALT或AST> 10x ULN持续 > 7天被视作DLT；
- 血清胆红素升高≥3级；
- 根据海氏法则，AST或ALT > 3xULN（若基线合并肝转移，则要求 > 3倍基线值），且同时合并总胆红素 > 2xULN（需排除胆道梗阻或其他原因导致的如肝炎、肝内肿瘤进展等病因）；
- ≥3级其他毒性（非肝脏、非血液学），除外以下情况：
  - 3 级的恶心或呕吐、腹泻，在接受/不接受对症支持治疗的情况下持续时间不长于3天；
  - 3 级的疲乏，在接受/不接受对症支持治疗的情况下持续时间不长于3天；
  - 无症状的3级实验室结果异常，经干预治疗持续时间不长于7

天，如胆固醇升高、甘油三酯升高、谷氨酰转肽酶（GGT）升高、碱性磷酸酶（ALP）升高、血淀粉酶升高等。

在 DLT 观察期后出现的符合上述标准的毒性也将被视为评价安全性的重要因素。此外，将在申办方和研究者讨论后确定可能被评估为 DLT 的其他治疗相关毒性。

在第一周期（DLT 观察期）内，对于符合 DLT 标准的 AE，应于获知其发生之后的 24 小时之内报告至申办方。

剂量递增规则与 MTD 定义

允许在 QD 给药方案下的前两个剂量采用加速滴定法，即首例受试者将接受第一个剂量水平的治疗。如果前两个剂量组的受试者在 DLT 观察期内均未观察到≥2 级治疗相关 AE，则在下一个较高剂量水平纳入 3~6 例受试者，并使用 BOIN 设计进行本组和后续剂量递增；反之，如果在第一个或第二个剂量组报告任何≥2 级治疗相关 AE 或 DLT 事件，则从观察到≥2 级治疗相关 AE 或 DLT 事件的最低剂量组开始，直接转为 BOIN 设计。在第一个剂量完成加速滴定的前提下，对于第二个剂量水平是否采用加速滴定，将由 SMC 基于第一个剂量水平的 PK 及安全性数据进行讨论决定。后续剂量水平采用 BOIN 设计确定 MTD，目标毒性概率为 0.3。如需对 BID 给药方案进行剂量探索，则使用 BOIN 设计进行剂量递增，目标毒性概率为 0.3。每个剂量水平将入组 3~6 例受试者接受治疗，如需探索更多剂量水平或其他给药方案，则可以入组额外的受试者。

BOIN 设计将根据下表所示的剂量升降规则，为下一组受试者分配剂量水平。

决策	当前剂量上治疗的受试者总数						
	3	**4**	**5**	**6**	**7**	**8**	**9**
升剂量，若发生 DLT 的受试者例数≤	0	0	1	1	1	1	2
降剂量，若发生 DLT 的受试者例数≥	2	2	2	3	3	3	4
剔除剂量，若 DLT受试者例数≥	3	3	4	4	5	5	5

具体规则请见正文章节 3.1.1.2。

剂量递增阶段结束后，将基于剂量确定分析集（DDS）采用保序回归分析以确定 MTD。使用 http://www.trialdesign.org 的在线 BOIN 软件进行保序回归分析，得到每个剂量水平毒性概率的保序估计值。最接近目标毒性率 0.3 的剂量水平即为 MTD。如果有 2 个或以上同时满足条件的剂量水平，选择保序估计值<0.3 的最高剂量水平或保序估计值≥0.3 的最低剂量水平。

剂量递增阶段受试者回填

将根据已获得的安全性/耐受性、PK 及初步有效性数据，可能选择一个或多个剂量组入组额外的受试者作为回填，接受已确认安全且耐受性良好的、经研究者及申办方评估可能临床获益的 GFH375 单药剂量组进行治疗，以更好地估计 GFH375 单药的 RP2D 以及表征其安全性\耐受性、PK 及有效性。如探索并确认过 750mg QD 剂量组的安全性，亦可进行 700mg QD 剂量组回填。回填的受试者不被纳入 DLT 的评估。回填后，接受 GFH375 每个剂量组治疗的受试者不超过 30 例（包括 BOIN 剂量递增阶段入组的受试者）。

回填的受试者将根据 I 期的流程访视表及 I 期的 PK 采血表完成相关访视。

受试者个体内剂量递增

剂量递增研究期间原则上不进行个体内剂量递增。对于入组 I 期的受试者，经研究者和申办方同意后，允许在本方案的 RP2D 剂量确认后，进行个体内剂量调整，接受 RP2D 的单药治疗。

RP2D 的确定

根据 I 期剂量递增部分以及部分回填受试者的所有安全性、耐受性、PK 和疗效数据，确定 RP2D 为 600 mg QD。

II 期部分

II 期研究为开放标签、多中心的研究，总体研究计划见正文图 3。目的是评估 GFH375 治疗携带 KRAS G12D 突变的晚期非小细胞肺癌、晚期胰腺癌、结直肠癌和其他晚期实体瘤患者的有效性、安全性和 PK 特征。II 期研究将入组约 317 例 KRAS G12D 突变的晚期实体瘤受试者，以接受 RP2D 的 GFH375 连续单药治疗，治疗周期为 21 天。该部分入组的受试者将根据 II 期 PK 采血表进行稀疏 PK 采样，并收集与 PK 采样相匹配的心电图。

- 晚期NSLCL受试者队列：计划入组约 73 例携带KRAS G12D 突变

	的晚期NSCLC受试者。 • 晚期 PDAC受试者队列：计划入组约 94 例携带KRAS G12D 突变的晚期PDAC受试者。 • 晚期 CRC 受试者队列：计划入组约 50 例携带KRAS G12D 突变的晚期CRC受试者。 • 其他晚期实体瘤受试者队列：计划入组约 100 例携带 KRAS G12D 突变的晚期实体瘤受试者，如携带 KRAS G12D 突变的胆管癌、阑尾癌等。 筛选合格的受试者将接受 GFH375 单药治疗，直至疾病进展、出现不可耐受的毒性或因其他原因结束研究治疗。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。受试者将在末次研究治疗后 30 (±3) 天返回研究中心完成安全性随访，之后每 90 (±7) 天进行一次生存随访。受试者因疾病进展以外的原因结束研究治疗且尚未开始新的抗肿瘤治疗，需按照之前的影像学评估计划继续进行疾病进展随访，直至疾病进展、撤回 ICF、开始其他抗肿瘤治疗或研究结束。
入选标准	**参加本研究的受试者需符合所有以下标准：** 1. 自愿参加研究并签署知情同意书。 2. 在签署知情同意书时年龄为 18 - 75 周岁的男性或女性。 3. 经组织学或细胞学病理确认的局部晚期或转移性恶性肿瘤受试者，需符合以下标准： （1） I 期部分：符合以下任意一条标准：1)接受标准治疗后疾病进展，且没有其他标准治疗可用；或 2)已证实标准治疗无效、不耐受或认为不适合。 （2） II 期部分： a) 晚期 NSCLC： ✓ 既往接受过抗 PD-（L）1 治疗和/或以铂类为基础的化疗后进展（除非有使用禁忌或不耐受），且既往治疗线数不超过 3 线； ✓ 若既往接受过辅助或新辅助治疗且在治疗期间或治疗停止后 6 个月内出现复发/进展，则可将该治疗计

	入一个线数的治疗。 b) 晚期 PDAC：既往经过基于吉西他滨的化疗方案或 FOLFIRINOX/mFOLFIRINOX 方案的充分治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗，且既往治疗线数不超过 3 线。存在微卫星高度不稳定（MSI-H）及错配修复基因缺陷型（dMMR）者需既往经过至少一线抗 PD-1 治疗后进展。如果接受过辅助或新辅助治疗且在治疗期间或治疗停止后 6 个月内出现复发/进展，则可将该治疗计入一个线数的治疗。 c) 晚期 CRC：经至少二线标准治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗。受试者须既往在接受氟尿嘧啶、伊立替康和奥沙利铂治疗转移性疾病期间或之后发生疾病进展或复发，除非研究者认为受试者不适合接受以上治疗方案。已知有微卫星高度不稳定（MSI-H）及错配修复基因缺陷型（dMMR）的受试者必须既往接受过免疫检查点抑制剂治疗（如适用）。如果接受过辅助或新辅助治疗且在治疗期间或治疗停止后 6 个月内出现复发/进展，则可将该治疗计入一个线数的治疗。 d) 其他实体瘤：经标准治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗。 4. 入组本研究的受试者需提供确认 KRAS G12D 突变阳性的书面检测报告。II 期 NSCLC 和 PDAC 受试者需在入组前提供符合要求的存档肿瘤组织样本或在筛选期接受活检。若无法提供肿瘤组织样本亦无法在筛选期接受活检，研究者需与申办方医学沟通，获得申办方医学同意后方可入组。 5. 根据 RECIST 1.1，I 期受试者必须至少有一个可评估病灶， II 期受试者必须至少有一个可测量病灶。 6. 既往抗肿瘤治疗的毒性反应必须缓解至基线水平（不包括脱发）或≤1 级（对于神经系统毒性，≤2 级）。 7. 研究者判断预期生存时间≥ 12 周。 8. 美国东部肿瘤协作组（ECOG）体能状态评分（PS）0~1 分（评分标准参见附录 2）。

	9. 具有充分的器官功能，包括： • 造血功能：中性粒细胞绝对计数 (ANC) ≥ 1.5 × 10 ^{9}/L，血小板计数 ≥ 75 × 10 ^{9}/L，血红蛋白 ≥ 9 g/dL，在血液检查前 14 天内未输血或未接受粒细胞集落刺激因子、血小板生成素或促红细胞生成素治疗。 • 肝功能： ➢ AST 和 ALT 均< 2.5×ULN；对于基线存在肝转移的受试者，要求 AST 和 ALT 均< 5×ULN； ➢ 总胆红素（TBIL）< 1.5×ULN；Gilbert 综合征受试者：TBIL < 2×ULN。 • 肾功能：肌酐清除率（CrCl）≥ 50 mL/min（Cockcroft-Gault 公式计算，参考附录 3）。 • 凝血功能：凝血酶原时间（PT）或活化部分凝血活酶时间（APTT）< 1.5×ULN，国际标准化比值（INR） < 1.5×ULN 或处于抗凝治疗的目标范围内。 • 白蛋白水平 ≥30 g/L（仅针对 II 期 PDAC 受试者）。 10. 有生育能力的女性（WOCBP）和伴侣为 WOCBP 的男性受试者必须同意从签署知情同意书至末次研究治疗后 30 天内采取有效的避孕方法。WOCBP 在给药前 7 天内的血清妊娠试验结果必须为阴性。 11. 根据研究者的判断，受试者能够良好沟通、按计划随访并遵守方案的要求。
排除标准	**符合以下任意一条标准的受试者不能入组本研究：** 1. 入组前 3 年内发生进展或需要治疗的其他恶性肿瘤，除外经充分治疗的原位癌、基底细胞癌或皮肤鳞状细胞癌。 2. 研究者判断不稳定的脑转移患者。对于在筛选过程中无意检出的伴脑转移的患者，如果未引起临床症状且不需要治疗干预， 可允许入组；如果研究者判断脑转移控制稳定，激素剂量使用稳定，且强的松剂量 ≤10mg/d（若使用其他类固醇药物，则为相应等效剂量），可允许入组。 3. II 期部分： a) 晚期 NSCLC：排除已知的其他驱动基因突变或融合，如 EGFR、ALK、 BRAF (V600E)、HER2、MET (exon 14)、 ROS1、RET、

	KRAS G12C 或 NTRK1/2/3 b) 晚期 CRC：排除已知的其他驱动基因突变、扩增或融合，如 BRAF (V600E)、HER2、NTRK 或 RET c) 晚期 PDAC：排除已知的其他驱动基因突变或融合，如 BRAF (V600E)、BRCA、NTRK 或 RET 4. 既往接受过 KRAS G12D 或者泛 KRAS （具有主要靶向 KRAS G12D 作用）的靶向治疗。 5. 在研究药物给药前 14 天内接受姑息性放疗。 6. 在给药前 28 天内或 5 个半衰期内（以较短者为准）接受过其他抗肿瘤治疗，包括化疗、靶向治疗、内分泌治疗、免疫治疗、具有明确抗肿瘤作用的中成药及其他试验用药物或器械，内分泌维持治疗除外。 7. 合并具有临床意义的严重心血管疾病： • 首次研究治疗前 6 个月内发生具有临床意义的严重心血管事件，如心肌梗死、不稳定型心绞痛、症状性充血性心力衰竭（纽约心脏病协会 III 或 IV 级）、需要药物治疗的重度心律失常或接受血管成形术、支架植入术和冠状动脉旁路移植术等。 • 具有临床意义 QT/QTcF 延长（基于筛选期三次 QTcF 的平均值，QTcF > 470 ms）或合并 QT 间期延长的家族史。 • 经标准治疗后仍控制不佳的高血压。 8. 入组前 6 个月内发生卒中或其他严重脑血管疾病。 9. 入组前 3 个月内有深静脉血栓或其它任何严重血栓栓塞的病史。 10. 伴随需要反复引流或有明显症状的胸腔积液、腹水或心包积液。 11. 合并上腔静脉综合征。 12. 在研究药物首次给药前 6 个月内有胃肠道穿孔和/或瘘管病史、且经手术治疗未痊愈；当前不稳定或活动性消化道溃疡或合并其他高风险消化道出血疾病；存在胆道或幽门梗阻，或持续性反复呕吐（24 小时内呕吐 ≥3 次）；因肿瘤侵犯周围重要结构（如大血管、气管等）而存在较高的破裂出血或胃肠道/呼吸道瘘风险；或合并其他可能显著影响 GFH375 吸收的胃肠道功能受损或胃肠道疾病，或无法或不愿意吞咽片剂。 13. 合并具有临床意义并需要治疗的间质性肺病、放射性肺炎或免疫相关

	性肺炎。 14. 合并重大急性或慢性感染性疾病，包括： • 入组前 7 天内需要静脉使用抗生素治疗的活动性感染。 • 基线时人类免疫缺陷病毒抗体 (HIV-Ab) 阳性。 • 活动性乙型肝炎病毒感染（HBsAg 阳性伴 HBV-DNA 阳性）。 • 活动性丙型肝炎病毒感染（HCV-Ab 阳性伴 HCV-RNA 阳性）。 • 活动性结核病。 15. 合并其他控制不佳的系统性疾病，如糖尿病。 16. 在首次给药前 28 天内接受或计划进行由研究者判断的重大手术（穿刺活检除外）。 17. 既往有器官移植病史或准备接受器官移植。 18. 在研究药物给药前 7 天内或接受研究药物期间需使用抑酸类药物，包括质子泵抑制剂和新型抑酸类药物（如钾离子竞争性酸阻滞剂）。 19. 在研究药物给药前 14 天内或药物的 5 个半衰期内（以较长者为准）接受了 CYP3A 或 P-gp 的强抑制剂或强诱导剂。 20. 在研究药物给药前 14 天内或药物的 5 个半衰期内（以较长者为准）接受过已知敏感的 CYP3A 或 OAT1 底物。除非经研究者和申办方审阅后同意入组。 21. 已知对研究药物或成分过敏。 22. 有严重的精神、心理疾病或有药物滥用史或有严重酗酒史。 23. 妊娠或哺乳期女性。 24. 研究者判断不适合参加研究的其他情况。 25. **II 期 PDAC 受试者：**经过止痛药物规范治疗后疼痛数字分级法（NRS）评分 ≥4 分。
统计分析	**分析集** • 全分析集（FAS）：至少接受过 1 次 GFH375 给药的所有受试者。 • 安全性分析集（SS）：至少接受过 1 次 GFH375 给药且至少有 1 次治疗后安全性评估的所有受试者。

- 剂量确定分析集（DDS）：I 期在 DLT 观察期间至少累计 15 天接受未减量 的 GFH375、有充分的安全性评估的所有受试者，或在 DLT 观察期间发生 DLT。DDS 不包含回填（backfill）的受试者。
- 符合方案集（PPS）：FAS 中符合方案的所有 II 期受试者。研究团队将在最终数据库锁定前对所有方案偏离进行审查，据此将发生影响疗效评价的重大方案偏离的受试者从 PPS 中排除。
- 药代动力学分析集 (PKAS)：至少接受过 1 次 GFH375 给药且至少有 1 份血样提供可评价 PK 数据的所有受试者。

统计分析方法

将对 I 期、 II 期的数据分别单独进行分析汇总。其中，I 期阶段的数据将按照不同剂量水平和给药方案进行分析汇总；II 期阶段的数据将按照肿瘤类型分别进行分析汇总。

安全性分析

按系统器官分类、首选术语、严重程度汇总 AE、治疗相关 AE 、 SAE 的发生率。对于 I 期部分，基于 DDS 汇总各类 DLT 的发生率，并对 DLT 进行列表。对实验室检查、生命体征、 ECG 进行描述性汇总。

有效性分析

计算最佳总体缓解（BOR）、ORR、DCR，并采用 Clopper-Pearson 方法估计 ORR 和 DCR 的双侧 95%置信区间（CI）。采用 Kaplan-Meier 方法估计 DoR、PFS、OS 的中位数及其 95% Brookmeyer-Crowley CI。对 TTR 进行描述性汇总。

对于 I 期阶段，当分析组的样本量小于 10 例时，将按受试者单独列出 DoR、TTR、PFS、OS，不采用 Kaplan-Meier 方法进行分析。

对于 II 期阶段，设置主要估计目标如下：

研究人群	KRAS G12D 突变型晚期实体瘤受试者
治疗	GFH375
终点	根据 RECIST 1.1 标准评估达到 CR 或 PR 的受试者百分比。若受试者基线后无任何评价结果，则认为该受试者未缓解。 **注：**对于 NSCLC 和 PDAC，将基于盲态独立中心审查委员会（BICR）评估的确认的 CR 或 PR 的受试者百分比。

伴发事件	开始新的抗肿瘤治疗（处理策略：在治策略，开始新的抗肿瘤治疗后的评估结果不纳入分析。）
群体层面汇总	ORR

药代动力学分析

将对血浆中 GFH375 的浓度数据按照方案规定的采样时间进行列表和描述性统计汇总，汇总将按照研究分期、剂量组和给药频率呈现。将使用线性和半对数坐标，按研究分期、剂量组和给药频率绘制个体受试者的血浆中 GFH375 浓度-时间曲线和相应的汇总曲线（平均值 + 标准差）。使用计划 PK 采样时间计算汇总统计量及绘制汇总曲线（平均值 + 标准差）；将使用实际 PK 采样时间，绘制个体受试者曲线。

将使用 Phoenix WinNonlin 软件（v8.2 版或以上版本, Certara USA, Inc., New Jersey, US）采用非房室模型分析（NCA），按实际采血时间点计算 GFH375 的 PK 参数。对 I 期剂量递增阶段受试者单次和多次给药后 GFH375 的 PK 参数进行描述性统计汇总，汇总按照剂量组和给药频率呈现。

样本量计算

I 期

将根据 BOIN 设计，在每个剂量组入组 3-6 例患者（加速滴定时除外）接受治疗。将根据已获得的安全性/耐受性、PK 及初步有效性数据，可能选择一个或多个剂量组入组额外的受试者作为回填， 接受已确认安全且耐受性良好的、经研究者及申办方评估可能临床获益的 GFH375 单药剂量进行治疗，以更好的估计 GFH375 单药的 RP2D 以及表征其安全性\耐受性、PK 及有效性。回填的受试者不被纳入 DLT 的评估。回填后，接受 GFH375 每个剂量组治疗的受试者不超过 30 例（包括 BOIN 剂量递增阶段入组的受试者）。

如果需要探索更多的剂量水平或替代给药方案，则可以入组额外的患者。

II 期

总共预计入组约 317 例受试者，其中约 73 例晚期 NSCLC 患者、约 94 例晚期 PDAC 患者、约 50 例晚期 CRC 患者、约 100 例晚期其他实体瘤患者。

肿瘤类型	历史对照 ORR	预期 ORR	样本量
NSCLC	23%	40%	73
PDAC	15%	30%	94
CRC	10%	30%	50
其他			100
合计			317

对于晚期二线NSCLC，ORR的历史对照值为23%，预计本研究ORR可达到40%。若观测到的ORR的95% CI下限不低于历史对照23%，则视为成功。单侧α＝0.025，要达到89%把握度，则需要73例受试者。当73例受试者中有至少25例CR/PR时，ORR观测值的exact 95% CI下限高于历史对照23%。25例CR/PR时，ORR = 34.2%，其95% CI为(23.5%, 46.3%)。

对于晚期二线PDAC，ORR的历史对照值设定值为15%，预计GFH375治疗下ORR可达到30%，若采用GFH375治疗后ORR的95%CI下限大于15%，则认为GFH375的疗效具有统计学显著意义。当单侧α＝0.025，94例受试者可获得95%的把握度以保证试验数据获得ORR的95%CI下限大于15%。计划入组PDAC受试者约94例。当94例受试者中观察到22例获得缓解（PR/CR）时，ORR观测值的exact 95%为（15.29%，33.26%）。因此94例受试者中观察到≥22例缓解时，则认为GFH375的疗效具有统计学意义。

对于三线CRC，ORR的历史对照值为10%，预计本研究ORR可以达到30%。若观测到的ORR的95% CI下限不低于历史对照10%，则视为成功。计划入组50例受试者，在单侧α＝0.025的情况下，把握度可达到96%。当50例受试者中有至少10例CR/PR时，ORR观测值的exact 95% CI下限高于历史对照10%。10例CR/PR时，ORR = 20.0%，其95% CI为(10.0%, 33.7%)。

对于其他实体瘤：计划入组约100例KRAS G12D突变的晚期实体瘤受试者，如携带KRAS G12D突变的胆管癌、阑尾癌等。

期中分析

将分别对NSCLC、PDAC、CRC进行无效性中期分析。对于单个瘤种，计划在约35例受试者（包括I期接受RP2D治疗的受试者和II期受试者）至少有一次基线后影像学肿瘤评估或提前退出研究时进行。考虑实际临床操作的原因，允许中期分析时的受试者例数与计划例数有所差别。期中分析过

程中，项目不停止入组。

期中分析时，将分别针对 NSCLC、PDAC、CRC 的 ORR，采用贝叶斯预测概率的方法进行无效性分析。允许（但不强制）因缺乏有效性证据而提前终止对相应瘤种的研究。

基于观察到的获得缓解（CR/PR）的 II 期受试者例数计算预测成功概率（PPoS），如果 PPoS < 0.2，则允许（但不强制）因为缺少有效性证据而提前终止入组。PPoS < 0.2 的对应的终止标准见下表：

瘤种	受试者例数*	建议终止试验，当缓解受试者例数 ≤
NSCLC	20 ~ 21	3
	22 ~ 25	4
	26 ~ 29	5
	30 ~ 33	6
	34 ~ 37	7
	38 ~ 41	8
	42 ~ 45	9
PDAC	25 ~ 26	2
	27 ~ 33	3
	34 ~ 39	4
	40 ~ 45	5
CRC	20 ~ 23	1
	24 ~ 30	2
	31 ~ 37	3
	38 ~ 43	4
	44 ~ 48	5

*受试者例数：至少有一次基线后影像学肿瘤评估或提前退出研究（至少满足其一）的 I 期接受 RP2D 治疗的受试者和 II 期受试者数之和。

上述计划的中期分析不强制进行，在达到中期分析计划的时间点前，如果有足够的安全性和有效性综合数据支持，可以省略该中期无效性分析。

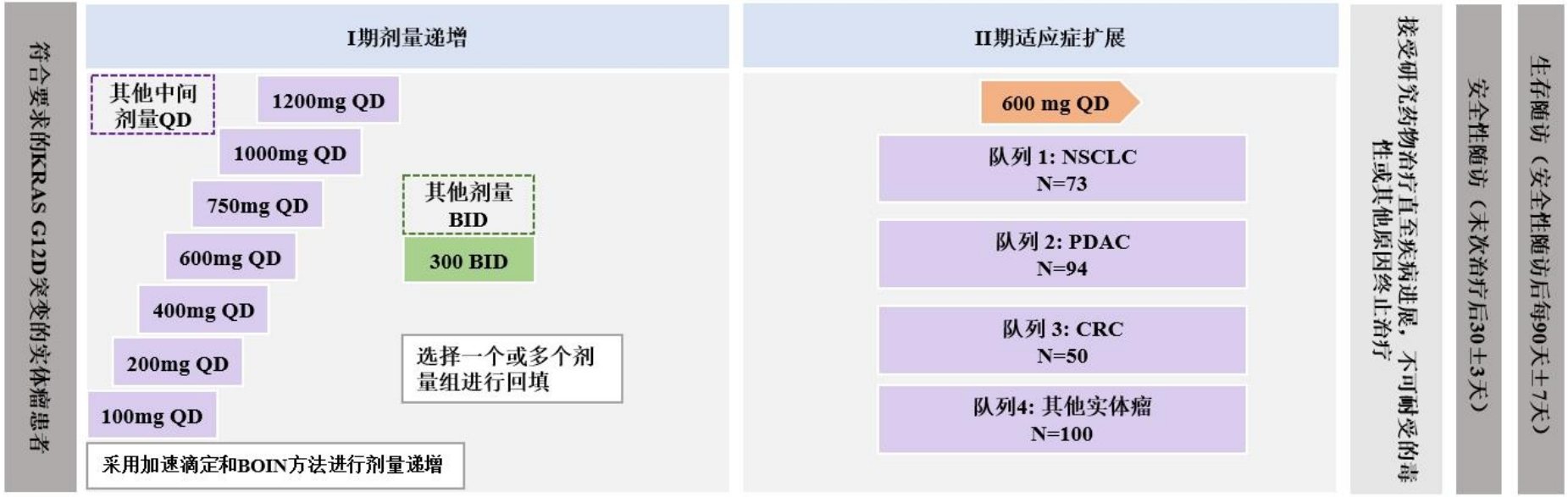

图 1 研究总体设计

缩略语：QD：每日 1 次；BID：每日 2 次； NSCLC：非小细胞肺癌；PDAC：胰腺导管腺癌；CRC：结直肠癌；BOIN：贝叶斯最优区间。

I 期治疗阶段访视流程表

研究阶段	筛选期	治疗期							备注
		第 1 周期				第 2 周期		后续周期	1. 每 21 天/周期：访视窗根据研究首次服药日 C1D1 计算。 2. 除方案规定的访视检查外，研究者还可根据临床指征按需安排检查。
访视日	D-28~D-1	D1	D3	D8	D15	D1	D10	D1	
时间窗（天）	NA	0	0	±3	±3	-1 ~ 3	±3	±3	
知情同意	×								
入选/排除标准	×	×							需在 C1D1 再次审查入选/排除标准。
人口统计学	×								包括性别、年龄、民族等。
身高/体重	×	×				×		×	身高仅在筛选期测量一次。
肿瘤病史	×								包括肿瘤诊断、诊断时间、转移灶等信息。若为晚期 NSCLC，需收集既往 PD-L1 表达水平的检测数据（若有）
其他病史	×								收集所有活动性病况，以及研究者认为有临床意义的任何病况。
既往抗肿瘤治疗史	×								收集所有针对研究疾病的既往抗肿瘤治疗史，包括治疗药物、开始时间、结束时间、最佳总体评估、结束治疗原因等。
其他既往/合并治疗	×								收集首次给药前 30 天至安全性随访结束后的所有既往/合并药物及治疗性操作。
病毒血清学	×								包括乙型肝炎表面抗原 (HBsAg)、乙型肝炎表面抗体 (HBsAb)、乙型肝炎核心抗体 (HBcAb)、HCV 抗体、HIV 抗体以及 HBV-DNA 和 HCV-RNA 检测（如必要）。
妊娠试验	×	×						×	有生育能力的女性受试者需在首次给药前 7 天内进行血妊娠检查，后续每 2 个周期的 D1 进行一次尿妊娠检查。如不能确认尿妊娠结果为阴性，则需要进行血妊娠检查。
体格检查	×	×	×	×		×	×	×	
ECOG PS	×	×				×		×	如首次给药前 72 小时内已进行评估，则无需在 C1D1 重复。
生命体征	×	×	×	×	×	×	×	×	
血常规	×	×	×	×	×	×	×	×	

研究阶段	筛选期	治疗期							备注
		第 1 周期				第 2 周期		后续周期	1. 每 21 天/周期：访视窗根据研究首次服药日 C1D1 计算。 2. 除方案规定的访视检查外，研究者还可根据临床指征按需安排检查。
访视日	**D-28~D-1**	**D1**	**D3**	**D8**	**D15**	**D1**	**D10**	**D1**	
时间窗（天）	**NA**	**0**	**0**	**±3**	**±3**	**-1 ~ 3**	**±3**	**±3**	
血生化	×	×	×	×	×	×	×	×	若首次给药前 7 天内已有实验室检查结果，则无需在 C1D1 重复检测。若受试者的临床状态发生显著变化，则需要在 C1D1 重复实验室检查。
尿常规	×	×			×	×	×	×	
凝血功能	×	×			×	×	×	×	
心电图	×	×	×	×	×	×	×	×	1. 若合并有其他试验流程，需先进行心电图检查以避免试验操作对心电图结果产生影响。 2.心电图检查应在受试者安静休息至少 10 分钟后进行。研究期间每次访视均进行三次心电图，每次间隔至少 5 分钟。 3. 与 PK 采样相匹配的心电图采集，具体要求请参见 PK 采血表。
肿瘤影像学评估	×	×							符合要求的首次给药前 4 周内的检查结果可以作为基线接受，无需重复。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。
GFH375 给药		×							将在指定的访视日为受试者分配 GFH375 片剂，并按计划口服。**接受 QD 给药的受试者应在第一个周期的第 2 天和第 3 天省略给药，接受 BID 给药的受试者无需省略。**
PK 采血		×							参见 PK 采集表
血液 ctDNA	×	×							在基线（如筛选期采集，则无需在 C1D1 重复检测）采集血液样本进行新一代测序（NGS）检测
AE/SAE	×	×							从签署知情同意书开始收集 AE/SAE，直至末次给药后 30 天

缩写：C1D1：第 1 周期第 1 天。ECOG：东部肿瘤协作组织；PS: 体能状况；PK：药代动力学；AE/SAE，不良事件/严重不良事件。

II 期治疗阶段访视流程表

研究阶段	筛选期	治疗期			备注
		第 1 周期		后续周期	1. 每 21 天/周期：访视窗根据研究首次服药日 C1D1 计算。 2. 除方案规定的访视检查外，研究者还可根据临床指征按需安排检查。
访视日	D-28~D-1	D1	D10	D1	
时间窗（天）	NA	0	±3	±3	
知情同意	×				
入选/排除标准	×	×			需要在 C1D1 再次审查入选/排除标准。
人口统计学	×				包括性别、年龄、民族等。
身高/体重	×	×		×	身高仅在筛选期测量一次。
肿瘤组织样本	×				II 期 NSCLC 和 PDAC 受试者需提供存档的福尔马林固定石蜡包埋（FFPE）样本或活检样本。
肿瘤病史	×				包括肿瘤诊断、诊断时间、转移灶等信息。若为晚期 NSCLC 患者，需收集既往 PD-L1 表达水平的检测数据（若有）。
其他病史	×				收集所有活动性病况，以及研究者认为有临床意义的任何病况。
既往/合并治疗	×				收集首次给药前 30 天至安全性随访结束后的所有既往/合并药物及治疗性操作。
NRS 疼痛评分	×	×			仅针对 PDAC 受试者；如首次给药前 72 小时内已进行评估，则无需在 C1D1 重复。
病毒血清学	×				包括乙型肝炎表面抗原 (HBsAg)、乙型肝炎表面抗体 (HBsAb)、乙型肝炎核心抗体 (HBcAb)、HCV 抗体、HIV 抗体以及 HBV-DNA 和 HCV-RNA 检测（如必要）。
妊娠试验	×	×		×	有生育能力的女性受试者需在首次给药前 7 天内进行血妊娠检查，后续每 2 个周期的 D1 进行一次尿妊娠检查。如不能确认尿妊娠结果为阴性，则需要进行血妊娠检查。

研究阶段	筛选期	治疗期			备注
		第 1 周期		后续周期	1. 每 21 天/周期：访视窗根据研究首次服药日 C1D1 计算。 2. 除方案规定的访视检查外，研究者还可根据临床指征按需安排检查。
访视日	**D-28~D-1**	**D1**	**D10**	**D1**	
时间窗（天）	**NA**	**0**	**±3**	**±3**	
体格检查	×	×	×	×	
ECOG PS 评分	×	×		×	如首次给药前 72 小时内已进行评估，则无需在 C1D1 重复。
生命体征	×	×	×	×	
血常规	×	×	×	×	若首次给药前 7 天内已有实验室检查结果，则无需在 C1D1 重复检测。若受试者的临床状态发生显著变化，则需要在 C1D1 重复实验室检查。
血生化	×	×	×	×	
尿常规	×	×	×	×	
凝血功能	×	×	×	×	
心电图	×	×	×	×	1. 若合并有其他试验流程，需先进行心电图检查以避免试验操作对心电图结果产生影响。 2.心电图检查应在受试者安静休息至少 10 分钟后进行。研究期间每次访视均进行三次心电图，每次间隔至少 5 分钟。 3. 与 PK 采样相匹配的心电图采集，具体要求请参见 PK 采血表。
CA19-9	×	×			仅针对 PDAC 的受试者；在基线（如筛选期采集，则无需在 C1D1 重复检测）、治疗期间每 6 周±1 周检测一次。

研究阶段	筛选期	治疗期			备注
		第 1 周期		后续周期	1. 每 21 天/周期：访视窗根据研究首次服药日 C1D1 计算。 2. 除方案规定的访视检查外，研究者还可根据临床指征按需安排检查。
访视日	**D-28~D-1**	**D1**	**D10**	**D1**	
时间窗（天）	**NA**	**0**	**±3**	**±3**	
肿瘤影像学评估	×	×			符合要求的首次给药前 4 周内的检查结果可以作为基线接受，无需重复。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。
GFH375 给药		×			将在指定的访视日为受试者分配 GFH375 片剂，并按计划口服
PK 采血		×			参见 PK 采集表
血液 ctDNA	×	×			在基线（如筛选期采集，则无需在 C1D1 重复检测）采集血液样本进行新一代测序（NGS）检测
AE/SAE	×	×			从签署知情同意书开始收集 AE/SAE，直至末次给药后 30 天

缩写：C1D1：周期 1 第 1 天。ECOG：东部肿瘤协作组；PS：体能状况；PK：药代动力学；AE/SAE，不良事件/严重不良事件。

I 期和 II 期：治疗结束访视和长期随访访视流程表

	治疗结束访视 EOT	安全性随访访视	生存访视	备注
访视	**决定研究治疗结束**	**末次给药后 30 天**	**安全性访视后每 90 天**	
时间窗（天）	**+7**	**±3**	**±7**	
妊娠试验	×	×		进行尿妊娠试验，必要时使用血清试验。
体格检查	×	×		
ECOG PS 评分	×			
生命体征	×	×		
体重	×	×		
血液 ctDNA	×			
血常规	×	×		末次用药后 7 天内进行的检查不需在 EOT 访视重复，但 AE 相关检查应由研究者酌情审查
血生化	×	×		
尿常规	×	×		
凝血功能	×	×		
心电图	×	×		
CA19-9	×			仅针对 II 期 PDAC 受试者；治疗结束访视前 4 周内进行过检测则不需要重复。
影像学评估	×			治疗结束访视前 4 周内进行的影像学检查不需要重复；除疾病进展/因疾病进展以外的原因结束治疗且未开始其他抗肿瘤治疗的受试者，需要按计划接受肿瘤影像学检查，直至疾病进展或开始新的抗肿瘤治疗或退出研究。
合并治疗	×			收集合并用药和治疗性操作

	治疗结束访视 EOT	安全性随访访视	生存访视	备注
访视	**决定研究治疗结束**	**末次给药后 30 天**	**安全性访视后每 90 天**	
时间窗（天）	**+7**	**±3**	**±7**	
AE/SAE	×			从签署知情同意书开始收集 AE/SAE，直至末次给药后 30 天或开始新的抗肿瘤治疗
后续抗肿瘤治疗	×			包括后续抗肿瘤治疗、开始/结束时间、结束原因及 BOR
生存状态	×			

I 期药代动力学（PK）样本和 12 导联心电图采集计划表（QD/BID）

周期	日	计划采样点（h）	时间窗	PK采样[1,2]	12导联心电图[3]
1	1	给药前	-1 h	√	√
1	1	给药后1h	±5min	√	
1	1	给药后2h	±10min	√	√
1	1	给药后4h	±15min	√	√
1	1	给药后6h	±30min	√	√
1	1	给药后8h	±30min	√	
1	**1**[4]	给药后12h	±30min	√	
1	**2**[5]	给药后24h	±1h	√	
1	**3**[5]	给药后48h	±2h	√	
1	**4**[5]	给药后72h （D4给药前采集）	±3h	√	√
1	8	给药前	-1h	√	√
1	15	给药前	-1h	√	√
1	21	给药前	-1h	√	√
1	21	给药后1h	±5min	√	
1	21	给药后2h	±10min	√	√
1	21	给药后4h	±15min	√	√
1	21	给药后6h	±30min	√	√
1	21	给药后8h	±30min	√	
1	**21**[4]	给药后12h	±30min	√	
1	**21**[5]	给药后24h	±1h	√	√
2	10	给药前	-1h	√	√
4	1	给药前	-1h	√	√
5	1	给药前	-1h	√	√
6	1	给药前	-1h	√	√

1. 当患者发生与药物相关的严重不良事件时，在研究者得知发生事件的即刻，可能的情况下，采集当时的一份血样用于 GFH375 血药浓度测定。

2. 如果在计划访视时无法获得 PK 样本，可以推迟到下一次访视进行采集。准确记录给药剂量、给药时间和采样时间即可。

3. 将在有条件的中心收集与 PK 样本匹配的 ECG，建议先进行心电图检查，再进行 PK 采血，如无法在采集血样标本前完成，应在采血后安静休息 10 分钟后进行心电图检查。同时，需要将心电图检查与 PK 采样时间的间隔保持在 30 分钟以内。所有计划的 12-ECG 检查都应该在受试者至少安静休息 5 min 之后进行，每个时间点需测量 3 次，每次间隔在 1-2 min。

4 若为 BID 给药，C1D1 和 C1D21 给药后 12h 的 PK 样本，需在当天第二次给药前采集。

5 仅适用于 QD 给药，需要给药前采集。

II 期药代动力学（PK）样本和 12 导联心电图采集计划表（QD/BID）

周期	日	计划采样点（h）	时间窗	PK采样[1,2]	12导联心电图[3]
1	10	给药前	-1 h	√	√
1	10	给药后	2-4 h	√	√
2	1	给药前	-1 h	√	√
2	1	给药后	1-3 h	√	√
3	1	给药前	-1 h	√	√
3	1	给药后	2-4 h	√	√
4	1	给药前	-1 h	√	√
5	1	给药前	-1 h	√	√
6	1	给药前	-1 h	√	√

1. 当患者发生与药物相关的严重不良事件时，在研究者得知发生事件的即刻，可能的情况下，采集当时的一份血样用于 GFH375 血药浓度测定。
2. 如果在计划访视时无法获得 PK 样本，可以推迟到下一次访视进行采集。准确记录给药剂量、给药时间和采样时间即可。
3. 将在有条件的中心收集与 PK 样本匹配的 ECG，建议先进行心电图检查，再进行 PK 采血，如无法在采集血样标本前完成，应在采血后安静休息 10 分钟后进行心电图检查。同时，需要将心电图检查与 PK 采样时间的间隔保持在 30 分钟以内。所有计划的 12-ECG 检查都应该在受试者至少安静休息 5 min 之后进行，每个时间点需测量 3 次，每次间隔在 1-2 min。

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缩略语表

缩略语	英文全称	中文全称
AE	Adverse Event	不良事件
ALT	Alanine Aminotransferase	谷氨酸丙氨酸氨基转移酶
ANC	Absolute Neutrophil Count	绝对中性粒细胞计数
APTT	Activated Partial Thromboplastin Time	活化部分凝血活酶时间
AST	Aspartate Aminotransferase	谷氨酸天门冬氨酸氨基转移酶
AUC	Area under the curve	曲线下面积
BCRP	Breast Cancer Resistance Protein	乳腺癌耐药蛋白
BICR	Blinded Independent Central Review	盲态独立中心审查委员会
BID, bid	Bis in die	每日二次
BOIN	Bayesian Optimal Interval	贝叶斯最优区间
BOR	Best of Response	最佳反应
C_{max}	Maximal concentration	峰浓度
C_{trough}	Trough concentration	谷浓度
CA19-9	Carbohydrate Antigen 19-9	糖类抗原 19-9
CI	Confidence Interval	置信区间
CL	Clearance	清除率
CL_r	Renal Clearance	肾脏清除率
CNS	Central Nervous System	中枢神经系统
Cr	Creatinine	肌酐
CR	Complete Response	完全缓解
CRC	Colorectal Cancer	结直肠癌
CRO	Contract Research Organization	合同研究组织
CSCO	Chinese Society of Clinical Oncology	中国抗癌协会临床肿瘤学协作专业委员会
CT	Computed Tomography	电子计算机断层扫描
CTCAE	Common Terminology Criteria for Adverse Events	不良事件通用术语评价标准
ctDNA	Circulating tumor DNA	肿瘤循环 DNA

缩略语	英文全称	中文全称
CYP	Cytochrome P450 Proteins	细胞色素 P450 超家族
D	Day	天
DCR	Disease Control Rate	疾病控制率
DDS	Dose Determination Set	剂量确定分析集
DLT	Dose-Limiting Toxicity	剂量限制毒性
DNA	Deoxyribonucleic Acid	脱氧核糖核酸
DoR	Duration of Response	缓解持续时间
DRF	Dose Range Finding	毒性剂量范围探索
ECG	Electrocardiogram	心电图
ECOG	Eastern Cooperative Oncology Group	美国东部肿瘤协作组
EDC	Electronic Data Capture	电子数据采集系统
eCRF	Electronic Case Report Form	电子病例报告表
FAS	Full Analysis Set	全分析集
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography	氟脱氧葡萄糖-正电子发射计算机断层扫描术
G12D	Gly12Asp	第 12 位甘氨酸被天冬氨酸取代
GAP	GTPase-Activating Protein	GTP 酶活化蛋白
GCP	Good Clinical Practice	药物临床研究质量管理规范
GDP	Guanosine Diphosphate	鸟苷二磷酸
GEF	Guanine Nucleotide Exchange Factor	鸟嘌呤核苷酸交换因子
GGT	Gamma-Glutamyl Transpeptidase	谷氨酰转肽酶
GTP	Guanosine Triphosphate	三磷酸鸟苷
GLP	Good Laboratory Practice	药物非临床研究质量管理规范
HBV	Hepatitis B Virus	乙型肝炎病毒
HCV	Hepatitis C Virus	丙型肝炎病毒
HIV	Human Immunodeficiency Virus	人类免疫缺陷病毒
HNSTD	Highest Non-Severely Toxic Dose	最高非严重毒性剂量
HR	Hazard Ratio	风险比

缩略语	英文全称	中文全称
ICH-GCP	International Council for Harmonization	国际人用药品注册技术要求协调会
INR	International Normalized Ratio	国际标准化比值
LLOQ	Lower Limit of Quantification	最低定量限
K^+	Serum Potassium	血钾
KRAS	Kirsten Rat Sarcoma Viral Oncogene	鼠类肉瘤病毒癌基因
MAPK	Mitogen-Activated Protein Kinase	丝裂原活化蛋白激酶
MATE1	Multidrug and toxin extrusion 1	多药及毒性化合物外排转运蛋白 1
MATE2-K	Multidrug and toxin extrusion 2-K	多药及毒性化合物外排转运蛋白 2-K
MedDRA	Medical Dictionary for Regulatory Activities	监管活动医学词典
MRI	Magnetic Resonance Imaging	磁共振成像
MRSD	Maximal Recommended Starting Dose	最大推荐起始剂量
MSI-H	High Microsatellite Instability	微卫星高度不稳定
MTD	Maximum Tolerated Dose	最大耐受剂量
NGS	Next Generation Sequencing	下一代测序
NOAEL	No-Observed-Adverse-Effect Level	未观察到不良反应的剂量水平
NRS	Numerical Rating Scale	数字分级法
NSCLC	Non-Small Cell Lung Cancer	非小细胞肺癌
OATP1B1	Organic anion transporting polypeptide 1b1	有机阴离子转运多肽 1b1
OATP1B3	Organic anion transporting polypeptide 1b3	有机阴离子转运多肽 1b3
OAT1	Organic anion transporter 1	有机阴离子转运体 1
OAT3	Organic anion transporter 3	有机阴离子转运体 3
OCT2	Organic cation transporter 2	有机阳离子转运体 2
ORR	Objective Response Rate	客观缓解率
OS	Overall Survival	总生存期
PD	Progression Disease	疾病进展
PDAC	Pancreatic ductal adenocarcinoma	胰腺导管腺癌
PFS	Progression Free Survival	无进展生存期
P-gp	P-glucoprotein	P-糖蛋白

缩略语	英文全称	中文全称
PLT	Blood Platelet	血小板
PK	Pharmacokinetic	药代动力学
PKS	Pharmacokinetic Set	药代动力学分析集
PO, po, p.o.	Oral Administration	口服
PPoS	Predictive Probability of Success	预测成功概率
PPS	Per Protocol Set	符合方案集
PR	Partial Response	部分缓解
PRO	Protein in Urine	尿蛋白
PS	Physical performance	体能状态
PT	Preferred Term	首选术语
PT	Prothrombin Time	凝血酶原时间
QD, qd	Quaque die	每日一次
RECIST	Response Evaluation Criteria in Solid Tumors	实体瘤疗效评价标准
RP2D	Recommended phase 2 dose	II期推荐剂量
SAE	Serious Adverse Event	严重不良事件
SAP	Statistical Analysis Plan	统计分析计划
SD	Stable Disease	疾病稳定
SOC	System Organ Class	系统器官分类
SS	Safety Set	安全性分析集
STD10	Severely Toxic Dose in 10% of the Animals	10%动物出现严重毒性的剂量
$t_{1/2}$	Elimination half-life	消除半衰期
T_{max}	Time to reach maximum concentration	达峰时间
TEAE	Treatment Emergent Adverse Event	治疗期不良事件
TRAE	Treatment Related Adverse Event	与研究药物相关的治疗期不良事件
T-BIL	Total Bilirubin	总胆红素
TTP	Time to Progression	进展时间
TK	Toxicokinetics	毒代动力学
TTR	Time to Response	至缓解时间

缩略语	英文全称	中文全称
ULN	Upper Limits of Normal	正常值上限
V_d	Volume of distribution	分布容积
V_{dss}	Volume of distribution at steady state	稳态分布容积

1. 介绍

1.1. 疾病背景

1.1.1 KRAS 和 KRAS G12D 突变生物机理

RAS 蛋白属于具有 GTPase 酶活性的鸟嘌呤核苷结合蛋白，其活性因与二磷酸鸟苷 (GDP)，或三磷酸鸟苷 (GTP) 的结合转换而切换，与 GDP 结合时处于失活的状态，与 GTP 结合时则激活。在细胞中，RAS 处于信号通路相对中枢的位置并激活下游多条信号通路。RAS 蛋白通过调节基因转录和蛋白调节过程，负责细胞生长、迁移、存活和分化的细胞间信号通路。RAS 是肿瘤中突变最为广泛的癌基因, 大约 30%的肿瘤中含有 RAS 突变。KRAS、HRAS 和 NRAS 3 种亚型均被发现在肿瘤中存在突变，其中以 KRAS 突变最为常见。KRAS 突变在胰腺癌、非小细胞肺癌 (NSCLC) 和结直肠癌（CRC）中最为常见，特别是在胰腺癌中高达 90%。KRAS 突变主要发生在 12、13 位甘氨酸 (glycine，Gly，G) 和 61 位谷氨酰胺 (glutamine，Gln，Q) 3 个位点，其中 G12 位突变发生率最高。KRAS 的 12 位 Gly 可能产生 10 余种不同形式的突变，其中突变为天冬氨酸 (G12D)、缬氨酸（G12V) 和半胱氨酸的发生频率最高[1-3]。KRAS 在肿瘤中的作用已经得到广泛共识，但因其蛋白结构以及与 GTP 的极强亲和力阻碍针对 KRAS 的靶向药物的研发。近期针对 KRAS 共价抑制策略的突破促使了靶向 KRAS 的创新小分子药物的成功研发并得到临床验证。其中 KRAS G12C 抑制剂（索托拉西布、阿达格拉西布）已被批准用于治疗 KRAS G12C 突变型 NSCLC 患者，并具有确认的疗效和可接受的安全性特征。

1.1.2 KRAS G12D 突变肿瘤

KRAS 突变常见于 CRC（美国约 45%，中国约 49%）、胰腺癌（美国约 90%，中国约 87%）和 NSCLC（腺癌：美国约 35%，中国约 13%）[3]。其中 KRAS G12D 为最常见的突变类型之一，在多种实体瘤中具有高表达，包括 NSCLC、胰腺癌、CRC 和胆管癌等。

晚期 NSCLC

肺癌是第二大常见癌症，也是全球癌症死亡的主要原因。NSCLC 约占肺癌病例的 84%，大多数 NSCLC 患者初诊即为晚期。国际癌症研究机构报告的全球癌症统计数据显示，2020 年中国估计发生 82 万新发肺癌诊断和 71.5 万肺癌相关死亡[4]。KRAS G12D 为 NSCLC 的常见突变之一，一项基于美国癌症研究协会 (AACR)项目 GENIE 数据的研究显示，据估计在美国所有肺腺癌中 G12D 突变占 4.9%[3]。一项回顾性研究分析了肺癌大数据精准治疗协作小组

（LANDSCAPE）项目中 150, 327 例 NSCLC 病例的 NGS 数据， 其中 KRAS G12D 突变频率约为 2.2%[5]。

晚期 NSCLC 的治疗根据是否存在驱动基因突变有所不同。如 EGFR、ALK、ROS 等驱动基因阳性，可选择相应的靶向药物或含铂双药化疗以及化疗联用免疫治疗、抗血管治疗等。由于 KRAS G12D 极少与上述驱动基因同时存在，因此仍以化疗如多西他赛等作为标准系统治疗失败的主要治疗药物，近期报告的 ORR 13.2-16.0%; 中位 PFS: 2.6-4.5 个月[6-8]；既往化疗以及化疗加抗血管药物的 ORR 分别为 8.5-18.3%、8.6%~22.9%；PFS 分别为 2.8~4.2 个月、4.8~5.4 个月；OS 分别在 6~11.4 个月、9.9~12.6 个月[9-13]。考虑到联合治疗的毒性反应可能增加，二线及以上治疗中，双药化疗以及其他联合治疗需要充分评估患者的耐受性。免疫检查点抑制剂治疗 KRAS 突变 NSCLC 患者的数据主要来自大型III期临床研究的亚组分析报告，其中 CheckMate057 和 OAK 研究分别报道相比多西他赛单药，KRAS 突变的患者能够从纳武利尤单抗或阿替利珠单抗治疗中取得更好的总生存期（OS）获益[14,15] ，但由于目前大多数患者在一线治疗时都已经接受了免疫检查点抑制剂，所以二线治疗免疫检查点抑制剂不是主要选择。

KRAS G12C 靶向抑制剂已经在晚期 NSCLC 中单药或联用取得了较好的疗效，预期靶向 KRAS G12D 的药物将进一步为其具有靶向突变的亚组患者人群带来新的治疗选择。

晚期 PDAC

胰腺导管腺癌 (PDAC) 是恶性程度最高的肿瘤之一，治疗疗效差，预计至 2030 年胰腺癌将会成为所有恶性肿瘤导致死亡的第二大原因，其总的 5 年生存率仅为 10%。此外，全球范围内胰腺癌的疾病负担预计会进一步增长[16]。大多数 PDAC 患者在初次就诊时即存在转移性疾病，需要更有效的全身治疗。除携带生殖系乳腺癌易感基因(BRCA) 的患者外，迄今为止发现的 PDAC 可靶向的突变非常少。KRAS 突变是其肿瘤发生过程中的早期基因驱动事件，与其生物学的关键特征如炎症、免疫逃避和代谢改变等密切相关[17]。据估计，37%的胰腺癌携带 KRAS G12D 突变，提示该突变等位基因在人群水平的重要性。一些 PDAC 异种移植模型表明，KRAS G12D 在 PDAC 中作为一致的强致癌驱动因子发挥作用，KRAS G12D 抑制剂在胰腺导管腺癌模型中显示出显著的抗肿瘤活性。

PDAC 的药物治疗手段进展总体上非常有限，尤其是使用靶向药物和免疫治疗的疗效局限。在入组转移性 PDAC（mPDAC）患者的 III 期 NAPOLI-1 研究显示，对于既往以吉西他滨

为基础的化疗方案治疗失败后的 mPDAC 患者，相较于仅接受 5-FU/LV（5-氟尿嘧啶+亚叶酸），患者接受伊立替康脂质体联合 5-FU/LV（5-氟尿嘧啶+亚叶酸）后，疗效得到明显改善：中位总生存期（mOS）为 6.1 月（vs 4.2 月，HR 0.67）中位 PFS 为 3.1 个月 （vs 1.5 月，HR 0.56），ORR 为 16%（vs 1%，p < 0.0001）[18]。三线治疗当前更是缺乏标准或值得推荐的治疗方案，大多数仍是重复使用一线或二线的化疗药物。最近法国发表的队列研究显示，676 例至少接受一次化疗的晚期胰腺癌患者，仅 37%的患者接受了三线化疗，其中位 PFS 仅为 2.03 个月，中位总生存仅 5.5 个月[19,20]。因此临床上急需有效的治疗药物。目前针对 KRAS G12C 靶向抑制剂在经治的 PDAC 中取得了较好的疗效，索托拉西布、阿达格拉西布和格来雷赛单药的 ORR 分别为 21.0%、33.3%和 46.4%，中位 PFS 分别为 4.0 个月、5.4 个月和 5.5 个月[21-23]。预期靶向 KRAS G12D 的药物也能为具有靶向突变的患者人群提供新的治疗选择。

晚期 CRC

结直肠癌 (CRC)目前是排名第 3 的高发生率癌症，据估计全球每年有 1,931,590 例新发病例，CRC 同时也是第二大常见癌症死亡原因，2020 年全球有 935 173 例死亡病例。大约 20%的 CRC 患者在诊断时有转移，而高达 50%的初始局部疾病患者将发生转移[19]。在 CRC 中，KRAS 突变率约为 40%，其中 KRAS G12D 约占 28% [24,25]。携带 KRAS 突变的 CRC 与晚期疾病状态、肿瘤分化差、远处转移和生存率较低相关，可能表明 PFS 和 OS 的预后更差，这也在现实世界临床实践中得到验证[25]。此外，研究表明 KRAS 突变是结直肠癌对西妥昔单抗获得性耐药的常见驱动因素，在经西妥昔（或联合化疗）治疗后的 CRC 转移组织样本中观察到获得性的 KRAS G12D 突变[26,27]。在 CRC 患者中靶向 KRAS 突变有望在这个高度选择的患者群体中潜在地提供更有效的靶向治疗和更好的安全性特征。

晚期 CRC 的治疗同样根据是否存在 RAS、BRAF、HER2 等基因突变有所不同。RAS 或 BRAF 均为野生型时，采用的治疗为单药化疗或多药化疗与西妥昔单抗（左侧病灶）或贝伐单抗（右侧）联用。免疫疗法虽已获批用于 MSI-H 的 CRC 患者治疗，但是 CRC 中 MSI-H 的患者比例较低，仍然存在巨大的未满足临床需求。在三线或三线以后的情况下，为患者提供的治疗选择较少，包括姑息治疗、参加临床试验或批准的药物（瑞戈非尼、曲氟尿苷/替吡嘧啶 +/-贝伐珠单抗和呋喹替尼）。然而，在 CRC 晚期治疗中，目前推荐的标准治疗（瑞戈非尼、曲氟尿苷/替匹嘧啶和呋喹替尼）在经至少 2 线治疗失败的 mCRC 患者中仅提供有限的疗效，ORR 为 1- 4.7%，中位 PFS 为 1.9-3.7 个月，中位 OS 为 6.4-9.3 个月[28-30]。最近，基于一项 III

期研究（SUNLIGHT 研究，NCT01607957），FDA 批准了曲氟尿苷/替匹嘧啶 + 贝伐珠单抗作为三线治疗选择之一。与曲氟尿苷/替匹嘧啶单药治疗相比，使用曲氟尿苷/替匹嘧啶联合贝伐珠单抗提示 OS 和 PFS 改善，但 ORR 仍较低仅为 6.1%[31]。因此，在三线及以上的 mCRC 患者中仍存在大量未满足的医疗需求。在晚期 CRC 患者中，靶向 KRAS G12C 的抑制剂索托拉西布和阿达格拉西布单药治疗已经显示出初步疗效，ORR 分别为 9.7%(95%CI 3.6，19.9) 和 19%(95%CI 8，33)[32,33]。联合抗 EGFR 抗体可进一步提高其疗效。索托拉西布联合帕尼单抗达到的 ORR 为 26.4%-30%，中位 PFS 为 5.6-5.7 个月[34]。阿达格拉西布联合西妥昔单抗的 ORR 为 46% (95%CI 28，66)，中位 PFS 为 6.7 个月[33]。除了 NSCLC、CRC 和 PDAC 外，KRAS G12D 在多种实体瘤中具有较高的突变频率，包括胆管癌、胃癌和食管癌，而针对这类缺乏有效治疗手段的患者，尚未有针对 KRAS 的靶向药物可供选择。

1.1.3 靶向 KRAS G12D 突变的药物研发

目前还没有专门针对 KRAS G12D 突变肿瘤的疗法获批上市。几种 KRAS G12D 选择性抑制剂正在临床开发中，包括 MTRX1133、HRS-4642 及 INCB161734 等。

其中，仅恒瑞研发的 HRS-4642 披露了部分临床数据。HRS-4642 为脂质体制剂，通过静脉注射。FIH 试验中共入组 18 例受试者接受 15mg QW~300 mg QW 进行治疗，总体安全性良好，观察到了初步的有效性 [37]。

1.2. 研究药物: GFH375

1.2.1 GFH375 临床前研究

GFH375 是申办方由劲方自主开发的 KRAS G12D 抑制剂，对其进行了全面的临床前研究，概要总结如下。更多详细信息请参见 GFH375 研究者手册。

1.2.1.1 药理学研究总结

GFH375 在体外研究中表现出高活性和高选择性。体外生化实验研究表明，GFH375 能够有效抑制 KRAS G12D 突变体或野生型蛋白由非活化状态（结合 GDP）转变为活化状态（结合 GDP），半数抑制浓度（IC_{50}）分别为 6 nM 和 9 nM。GFH375 也能够直接阻碍活化状态的 KRAS G12D 或野生型蛋白与其下游效应蛋白 RAF1 的结合，IC_{50} 分别为 2 nM 和 7 nM。GFH375 在多个 KRAS G12D 突变肿瘤细胞系中表现出高活性，对 KRAS 下游通路蛋白 ERK1/2 磷酸化水平的抑制 IC_{50} 为 0.2-0.9 nM, 抗肿瘤细胞增殖 IC_{50} 为 1-10 nM。而在其它 KRAS 突变

类型（KRAS G12C、G12V）的肿瘤细胞株以及 KRAS 野生型、KRAS 功能依赖的肿瘤细胞株中，GFH375 的活性相对较弱，抗肿瘤细胞增殖 IC_{50} 分别为 159-1895 nM 和 17-75 nM。GFH375 在其它 RAS 蛋白突变（NRAS G12D、Q61H，HRAS Q61L）以及 KRAS 非依赖细胞系中只有很弱活性（抗细胞增殖 IC_{50}：1636 nM-7873 nM），说明脱靶非特性细胞毒性很低。

临床前体内研究表明，GFH375 在 KRAS G12D 突变肿瘤动物模型上体现了出色的体内活性和抗肿瘤药效。在人胰腺癌 Panc 04.03 异源移植肿瘤小鼠模型中，单次给药 GFH357 (100 mg/kg)即可对肿瘤内的 ERK/1/2 磷酸化水平产生强烈和持久的抑制。在 Panc 04.03 和另外一个人胰腺癌 AsPC-1 异源移植肿瘤小鼠模型中，GFH375 (10 mg/kg, 30 mg/kg 和 100 mg/kg) 每天 2 次、口服、连续给药 14 天即展现了剂量依赖性的抗肿瘤药效，起效剂量分别为 5 mg/kg 和 10 mg/kg，且在高剂量（100 mg/kg）下使得肿瘤明显消退。

GFH375 针对 KRAS G12D 靶点具有高选择性，脱靶作用的潜在风险低。10 μM 的 GFH375 对 72 个代表性人源激酶无抑制活性，对 44 个包含 G 蛋白偶联受体（GPCR），离子通道和酶的重要安全性相关靶点中的 38 个无抑制活性。而对于 6 个受到影响的靶点，GFH375 的预测 IC_{50} 浓度至少大于 1000 nM, 远高于上面提到的在 KRAS G12D 细胞上的 ERK1/2 磷酸化抑制 IC_{50} 浓度和抗肿瘤细胞增殖 IC_{50} 浓度。

GFH375 安全药理学研究包括体外对 hERG 钾通道电流和体内对大鼠中枢神经、呼吸系统和比格犬心血管系统的影响。

GFH375 在浓度为 3、6、12 和 24 μM 时，对人胚肾细胞（HEK293）上转染表达的 hERG 钾通道电流存在浓度依赖性的抑制作用，其 IC_{50} 值为 9.65 μM。

SD 大鼠单次经口灌胃给予 50、100 和 200 mg/kg 的 GFH375，通过功能观察组合试验（FOB）同时测量前肢握力和体温评价供试品对中枢神经系统的影响。结果显示，GFH375 对中枢神经系统的未见不良反应剂量（NOAEL）为 200 mg/kg。

SD 大鼠单次经口灌胃给予 50、100 或 200 mg/kg 的 GFH375，采用全身体积描记系统评估对呼吸系统的影响。结果表明，本试验 GFH375 对呼吸系统的未见不良反应剂量（No Observed Adverse Effect Level，NOAEL）为 200 mg/kg。

比格犬根据“交叉设计”经口灌胃给予 5、10 和 25 mg/kg 的 GFH375，采用遥测的方法评价对心血管系统的影响。结果显示，GFH375 对 Beagle 犬心血管系统的 NOAEL 为 25 mg/kg/day。

1.2.1.2 药代动力学研究总结

GFH375 在 Caco-2 细胞中表现出低渗透性，有明显的外排转运现象，可口服给药，临床前种属绝对生物利用度为 8.40-16.3%，且系统暴露量均随口服剂量的增加而增加。犬给药后整体没有明显性别差异，大鼠体内有一定雌雄差异；大鼠重复给药后，在 PK 剂量下无蓄积，雌性大鼠在 TK 剂量下有蓄积现象；犬重复给药后有蓄积现象。

GFH375 在小鼠血浆中呈现非常高的结合率，在大鼠和犬血浆中呈高结合，在猴和人血浆中呈中等结合。大鼠和犬的稳态分布容积 Vd_{ss} 范围为 15.7-22.5 L/kg，均呈现高分布。[^{14}C]GFH375 总放射性在大鼠体内广泛分布，C_{max} 由高到低依次为胃壁、肠道壁、肝脏、脾脏、肾脏、肺脏、心脏、卵巢子宫、体脂、骨骼肌、全血和血浆，在全脑和睾丸附睾中放射性水平低，没有明显的红细胞结合。

[^{14}C]GFH375 在大鼠体内主要的代谢途径为葡萄糖醛酸结合，次要代谢途径为单氧化、脱氢、脱氟、半胱氨酸结合、甘氨酸结合和乙酰化。在比格犬血浆中主要代谢途径为氧化、脱氢、脱氟、去烷基、葡萄糖醛酸结合和谷胱甘肽结合水解去谷氨酸。CYP3A 是其主要代谢酶，体内外代谢类型基本一致。

GFH375 在雄性和雌性大鼠血浆中分布呈现中等清除和低清除，在犬血浆中呈现高清除，在大鼠和犬体内半衰期较长，范围为 8.18-14.3 h。[^{14}C]GFH375 总放射性在大鼠体内主要经粪便直接排出或由胆汁经粪便排出，尿液为次要排泄途径。

GFH375 对 CYP1A2 和 CYP2C9 未见抑制作用，对 CYP2B6、CYP2C8、CYP2C19、CYP2D6、CYP3A（以咪达唑仑为底物）和 CYP3A（以睾酮为底物）有抑制作用，其 IC_{50} 值为 42.8、93.2、42.6、26.2、6.40 和 7.95 μM。GFH375 对 CYP3A（分别以咪达唑仑和睾酮为底物）具有显著的时间依赖性抑制。GFH375 不是 CYP1A2 和 CYP2B6 的诱导剂，在基因水平不排除是 CYP3A4 的诱导剂。GFH375 不是乳腺癌耐药蛋白（BCRP）、有机阴离子转运多肽 1b1（OATP1B1）和有机阴离子转运多肽 1b3（OATP1B3）转运体的底物，是 P-糖蛋白（P-gp）的底物。GFH375 对 BCRP、OATP1B1、有机阳离子转运体 2（OCT2）、多药及毒性化合物外排转运蛋白 2-K（MATE2-K）未见抑制作用，对 P-gp、OATP1B3、有机阴离子转运体 1（OAT1）、有机阴离子转运体 3（OAT3）和多药及毒性化合物外排转运蛋白 1（MATE1）有抑制作用，IC_{50} 值分别为 16.9、17.4、2.56、24.4 和 15.6 μM。提示 GFH375 有潜在的药物-药物相互作用。

1.2.1.3 毒理学研究总结

在 SD 大鼠和比格犬中分别进行 14 天重复给药毒性剂量范围探索试验，结果显示，在 SD 大鼠中所得 10%动物的严重毒性反应剂量(STD_{10})大于 150 mg/kg/day。在比格犬中所得动物的最高非严重毒性反应剂量（HNSTD）为 100 mg/kg/day。

在 SD 大鼠 4 周重复给药 GLP 毒性试验中，通过经口灌胃给予剂量为 50、100、200 mg/kg/day 的 GFH375 或空白溶媒[5%（v/v）LABRASOL + 5%（v/v）PEG400 + 90%灭菌注射用水]，每天一次，连续给药 28 天。剂量为 100 mg/kg/day 时，见 1 例雌性动物死亡；剂量为 200 mg/kg/day 时，见 2 例雄性动物和 3 例雌性动物死亡。200 mg/kg/day 剂量组存活动物还见供试品相关的临床症状，血液学和血清生化指标变化以及组织病理学变化。恢复期末，上述改变均恢复。在本试验条件下，供试品的 STD_{10} 为 100 mg/kg/day。

在比格犬 4 周重复给药 GLP 毒性试验中，通过经口灌胃给予剂量为 5、10、25 mg/kg/day 的 GFH375 或空白溶媒[5%（v/v）LABRASOL + 5%（v/v）PEG400 + 90%灭菌注射用水]，每天一次，连续给药 28 天。试验期间未见动物死亡，可见供试品相关的临床症状，血液学和血清生化指标变化以及组织病理学变化。恢复期结束后，变化均可恢复或具有恢复趋势。在本试验条件下，GFH375 对于比格犬的 HNSTD 为 25 mg/kg/day。

通过遗传毒性试验标准组合来评价 GFH375 的遗传毒性，结果显示为阴性。

1.3. 研究设计依据

1.3.1 剂量选择

1.3.1.1 起始剂量选择依据

I 期研究中起始剂量的选择是基于临床前毒理学研究结果，根据 ICH S9 关于最大推荐起始剂量（MRSD）方法的建议计算起始剂量。

在 SD 大鼠和比格犬中开展符合药物非临床研究质量管理规范（GLP）的 4 周毒理学关键研究，大鼠中研究剂量分别为 50、100 和 200 mg/kg/天，犬中研究剂量分别为 5、10 和 25 mg/kg/天。研究结果显示大鼠中 10%的动物出现严重毒性的剂量（STD10）为 100 mg/kg/天，犬中最高非严重毒性剂量（HNSTD）为 25 mg/kg/天。根据 ICH S9，按照啮齿类动物 STD10 的 1/10 或非啮齿类 HNSTD 的 1/6，患者体重 60 kg 计算，分别对应的人体 MRSD 约为 100 mg 和 140 mg/天。

药效学研究显示，在 Panc 04.03 人胰腺癌 CDX 肿瘤小鼠模型进行的体内抗肿瘤药效研究，GFH375 在该模型上起效剂量为 5 mg/kg BID 14 天给药。在 AsPC-1 人胰腺癌 CDX 肿瘤小鼠模型中，GFH375 的起效剂量为 10 mg/kg BID 14 天给药。

综上，从毒理学研究结果提示的安全性，结合 GFH375 片剂规格，选择 100 mg/天剂量水平作为 GFH375 首次人体试验的起始剂量。

1.3.1.2 II期剂量选择依据

完成 I 期剂量递增及回填后，将综合临床前体内外活性、临床 PK、临床安全性、临床有效性数据，确认安全性以及 RP2D 剂量，并以此剂量进行 II 期研究。

1.3.2 风险获益评估

1.3.2.1 潜在风险

目前有少数几款靶向 KRAS G12D 小分子抑制剂处于临床试验阶段，安全性数据和疗效数据披露有限。其中HRS-4642是由恒瑞研发的一款经静脉给药的KRAS G12D小分子，用于治疗KRAS G12D突变的晚期实体瘤患者。在其首次人体I期研究中，共入组18例受试者。总体安全性良好，发生率较高的治疗相关不良事件（>2例）包括血胆固醇升高、输液相关反应、蛋白尿、贫血、高甘油三酯血症、脂肪酶升高、低蛋白血症、血糖升高、丙氨酸氨基转移酶升高、血小板计数减少、高钙血症、低钙血症、发热、乏力、中性粒细胞计数减少、白细胞减少、天门冬氨酸氨基转移酶升高[33]。

GFH375临床前毒理学数据提示其潜在毒性可能包括肝功能损害及胃肠系统不良反应。根据GFH375的临床前研究结果和其它KRAS G12D抑制剂的数据，GFH375的潜在风险如下：

- 肝功能损害
- 胃肠系统不良反应

1.3.2.2 潜在获益

本研究的目标人群为 KRAS G12D 突变阳性的晚期 NSCLC、PDAC、CRC 及其他实体瘤患者。针对此类患者，尚无有效的治疗手段，仍以化疗或化疗联合免疫治疗为主要治疗方案。尚未有靶向这一突变的治疗药物获批上市。

目前已有 KRAS G12D 靶点的药物进入临床研究且有初步临床结果。KRAS G12D 小分子

抑制剂 HRS-4642 的初步疗效数据显示：共入组 18 例晚期实体瘤受试者，7 例受试者靶病灶缩小。其中共 10 例 NSCLC 受试者，5 例受试者靶病灶缩小。

GFH375 的临床前研究显示，在携带 KRAS G12D 突变的人胰腺癌肿瘤动物模型中，单次灌胃给药 GFH375 在肿瘤中观察到对 KRAS 通路下游蛋白 ERK1/2 蛋白磷酸化剂量依赖性的抑制，长期灌胃给药（每天 2 次、连续 14 天）观察到明显的抗肿瘤药效，起效剂量为 5-10 mg/kg, 高剂量下（100 mg/kg)观察到肿瘤消退。

综上，预期 GFH375 值得在这类人群中进一步开展临床研究，以给此类患者提供抗肿瘤治疗的新选择。

1.3.2.3 风险获益评估

根据 KRAS G12D 靶点的生物学特性和 GFH375 的产品特性，以及上述 GFH375 已获得的非临床数据，本方案设计了相应的入排选标准、生活方式要求以及安全性检查和随访流程。通过严密方案设计，研究中心的选择，药物安全信息的收集，药物安全性信息的通报及时更新，尽可能将受试者的风险最小化。基于目前作用机制相同产品的临床数据，预期符合入排选要求的受试者接受 GFH375 单药治疗获益可能性大。总体获益/风险评估支持开展这项研究。

2 研究目的与终点

本研究是一项I/II期研究。研究目的和研究终点分别总结如下。

I期研究部分的目的和终点包括：

研究目的	研究终点
主要目的	**主要终点**
评估 GFH375 在 KRAS G12D 突变的晚期实体瘤患者中的安全性和耐受性	• 不良事件 (AE) 和严重不良事件 (SAE) 的发生率和严重程度；生命体征、心电图 (ECG) 和实验室检查的改变
• 确定 GFH375 的最大耐受剂量 (MTD) 和 II 期推荐剂量(RP2D)	• 剂量限制性毒性 (DLT)事件的发生率
次要目的	**次要终点**
• 评估 GFH375 在 KRAS G12D 突变的晚期实体瘤患者中的药代动力学 (PK)特征	• GFH375 的血浆浓度和 PK 参数，包括但不限于 C_{max}、T_{max}、AUC、$t_{1/2}$、CL/F、V_z/F、C_{trough}
• 评估 GFH375 在 KRAS G12D 突变型晚期实体瘤患者中的初步疗效	• 研究者根据实体瘤疗效评价标准 (RECIST)1.1 评估的客观缓解率 (ORR)、缓解持续时间 (DoR)、疾病控制率 (DCR)、至缓解时间 (TTR)、无进展生存期 (PFS) • 总生存期 (OS)
探索目的	**探索终点**
• 探索与治疗敏感或耐药相关的分子机制	• 基线和治疗结束时血液循环肿瘤 DNA（ctDNA）的突变分析

II期研究部分的目的和终点包括：

研究目的	研究终点
主要目的	**主要终点**
• 评估 GFH375 在 KRAS G12D 突变的晚期非小细胞肺癌（NSCLC）、晚期胰腺癌 (PDAC)、晚期结直肠癌 (CRC) 和其他实体瘤患者中的疗效	• 根据 RECIST 1.1 评估的 ORR
次要目的	**次要终点**
• 使用其他疗效指标评估 GFH375 在 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的疗效	• 根据 RECIST 1.1 评估的最佳总体缓解（BOR）、DoR、DCR、TTR、PFS • OS

• 评估 GFH375 在 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的安全性	• AE、SAE 的发生率和严重程度 • 生命体征、ECG 和实验室检查的改变
• 评估 GFH375 在 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的 PK 特征	• GFH375 的血浆浓度

探索目的	**探索终点**
• 探索与治疗敏感或耐药相关的分子机制	• 基线和治疗结束时血液 ctDNA 的突变分析
• 针对 PDAC 受试者：糖类抗原 19-9（CA19-9）与治疗应答的关系	• 针对 PDAC 受试者：血清CA19-9相对基线的变化

3 研究设计

3.1. 总体设计

本研究是一项评估 GFH375 单药在携带 KRAS G12D 突变的晚期实体瘤患者中的安全性/耐受性、PK 及有效性。I 期研究的主要目的是评估 GFH375 在 携带 KRAS G12D 突变的晚期实体瘤患者中的安全性/耐受性、PK 和初步有效性，并确定 GFH375 的 MTD 和 RP2D。II 期研究的主要目的是评估 GFH375 在携带 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的有效性。

研究期间将设立由研究者及申办方组成的安全监查委员会（SMC），详细信息可参考第 10 章节及本研究的 SMC 章程。

3.1.1 I 期剂量递增部分

I 期将入组 KRAS G12D 阳性的晚期实体瘤患者，研究计划示意图见图 2。

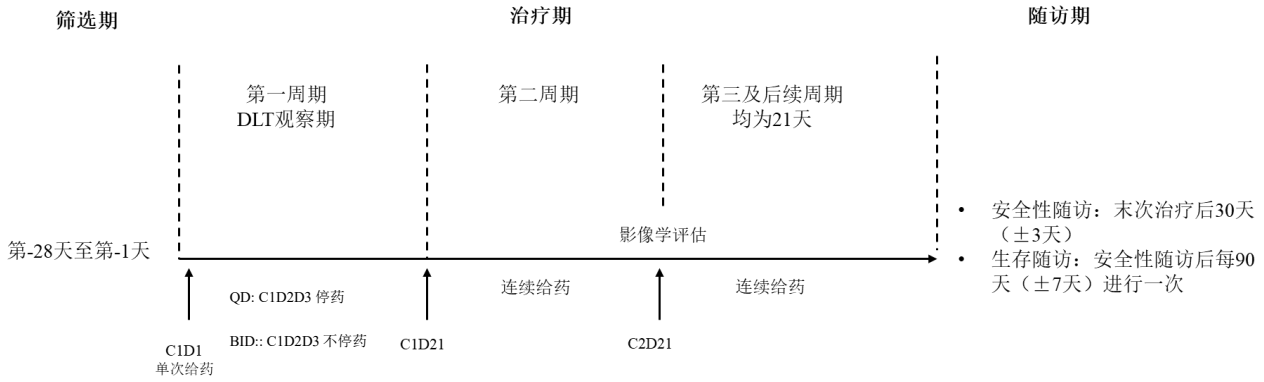

图 2 I 期研究计划示意图

将根据 BOIN 设计，在每个剂量组入组 3-6 例受试者（加速滴定时除外）接受治疗。将根据已获得的安全性/耐受性、PK 及初步有效性数据，可能选择一个或多个剂量组入组额外的受试者作为回填， 接受已确认安全且耐受性良好的、经研究者及申办方评估可能临床获益的 GFH375 单药剂量组进行治疗，以更好的估计 GFH375 单药的 RP2D 以及表征其安全性\耐受性、PK 及有效性。如探索并确认过 750mg QD 剂量组的安全性，亦可进行 700mg QD 剂量组回填。回填的受试者不被纳入 DLT 的评估。回填后，接受 GFH375 每个剂量组治疗的受试者不超过 30 例（包括 BOIN 剂量递增阶段入组的受试者）。

如果需要探索更多的剂量水平或替代给药方案，则可以入组额外的受试者。

受试者入组后将接受 GFH375 口服给药治疗，每 21 天为一个治疗周期。受试者将入组至顺序递增的不同剂量组，起始剂量为 100 mg 每日一次（QD）。预计在剂量递增部分共进行 7 个或更多给药剂量的评估，计划的递增剂量参见表格 1。

剂量递增过程中将综合评估 GFH375 给药方案，必要时将进行给药频率为每日 2 次（BID）的剂量探索，剂量递增可在 QD 和 BID 给药方案上独立并行进行。

首次治疗后的第一个周期将作为剂量限制性毒性（DLT）观察期，DLT 可评估病例需要满足以下两个条件之一：

- 受试者发生 DLT 事件，或
- 受试者未发生 DLT 事件，且在第一周期至少接受了 15 天 GFH375 的计划给药。

如未发生 DLT 事件，受试者将继续接受治疗，并允许在符合本方案准许情况下的剂量调整，直至出现疾病进展、不可耐受的毒性或因其他原因结束研究治疗。若受试者在 DLT 观察期发生 DLT 事件，经研究者与申办方评估继续接受 GFH375 的治疗能够获益，将在相关的不良事件缓解后恢复 GFH375 治疗。恢复给药标准可参考表格 4 和表格 5。

入组 I 期的受试者将进行密集 PK 采样并收集与 PK 采样相匹配的心电图，以评估 GFH375 的药代动力学特征和安全性。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。受试者将在末次研究治疗后 30 (±3) 天返回研究中心完成安全性随访，之后每 90 (±7) 天进行一次生存随访。受试者因疾病进展以外的原因结束研究治疗且尚未开始新的抗肿瘤治疗，需按照之前的影像学评估计划继续进行疾病进展随访，直至疾病进展、撤回 ICF、开始其他抗肿瘤治疗或研究结束。

表格 1 I 期计划/完成递增的 QD 剂量组

	I期计划/完成递增的QD剂量组*
剂量组1	100 mg QD
剂量组2	200 mg QD
剂量组3	400 mg QD
剂量组4	600 mg QD
剂量组5	750 mg QD
剂量组6	1000 mg QD
剂量组7	1200 mg QD

注：可能会在爬坡过程中基于获得的临床数据包括安全性、PK、可能的有效性，进行上述剂量的中间剂量探索，如

150mg、300mg、500mg、800mg、900mg、1100mg QD 等。

基于所获得的数据包括安全性、PK、初步疗效结果，可能会进行 BID 剂量探索。BID 起始剂量将选择下表其中一个剂量组，每日总剂量与正在探索的 QD 剂量一致。

表格 2 I 期可能探索的 BID 剂量组

	I期可能探索的BID剂量组*
剂量组1	100 mg BID
剂量组2	150 mg BID
剂量组3	200 mg BID
剂量组4	300 mg BID
剂量组5	400 mg BID

注：可能会进行上述剂量的中间剂量探索，如 250mg BID 等。

3.1.1.1 DLT 定义

DLT 是指在首次用药后 21 天内出现的、与研究药物 GFH375 相关且符合以下严重程度的不良事件。不良事件的严重程度根据不良事件通用术语评价标准（CTCAE）5.0 版进行分级：

- ≥4级中性粒细胞绝对计数（ANC）降低≥5天；
- ≥3级发热性中性粒细胞减少症（ANC <1.0 × 10^9/L 伴单次体温 > 38.3℃或持续体温≥38℃超过1小时）；
- ≥4级血小板计数降低持续≥5天；
- ≥3级血小板计数降低合并≥2级出血；
- ≥4级贫血；
- 若基线ALT或AST ≤ 1级：≥ 3级血清转氨酶升高（ALT或AST）持续 > 7天被视作DLT；若基线ALT或AST为2级，则 ALT或AST> 10x ULN持续 > 7天被视作DLT；
- 血清胆红素升高≥3级；
- 根据海氏法则，AST或ALT > 3xULN（若基线合并肝转移，则要求 > 3倍基线值），且同时合并总胆红素 > 2xULN（需排除胆道梗阻或其他原因导致的如肝炎、肝内肿瘤进展等病因）；
- ≥3级其他毒性（非肝脏、非血液学），除外以下情况：
  - 3 级的恶心或呕吐、腹泻，在接受/不接受对症支持治疗的情况下持续时间不长于3天；

- 3 级的疲乏，在接受/不接受对症支持治疗的情况下持续时间不长于3天；
- 无症状的3级实验室结果异常，经干预治疗持续时间不长于7天，如胆固醇升高、甘油三酯升高、谷氨酰转肽酶（GGT）升高、碱性磷酸酶（ALP）升高、血淀粉酶升高等。

在 DLT 观察期后出现的符合上述标准的毒性也将被视为评价安全性的重要因素。此外，将在申办方和研究者讨论后确定可能被评估为 DLT 的其他治疗相关毒性。

在第一周期（DLT 观察期）内，对于符合 DLT 标准的 AE，应于获知其发生之后的 24 小时之内报告至申办方。

3.1.1.2 剂量递增规则与 MTD 定义

允许在 QD 给药方案下的前两个剂量采用加速滴定法，即首例受试者将接受第一个剂量水平的治疗。如果前两个剂量组的受试者在 DLT 观察期内均未观察到≥2 级治疗相关 AE，则在下一个较高剂量水平纳入 3~6 例受试者，并使用 BOIN 设计进行本组和后续剂量递增；反之，如果在第一个或第二个剂量组报告任何≥ 2 级治疗相关 AE 或 DLT 事件，则从观察到≥ 2 级治疗相关 AE 或 DLT 事件的最低剂量组开始，直接转为 BOIN 设计。在第一个剂量完成加速滴定的前提下，对于第二个剂量水平是否采用加速滴定，将由 SMC 基于第一个剂量水平的 PK 及安全性数据进行讨论决定。后续剂量水平采用 BOIN 设计确定 MTD，目标毒性概率为 0.3。如需对 BID 给药方案进行剂量探索，则使用 BOIN 设计进行剂量递增，目标毒性概率为 0.3。每个剂量水平将入组 3~6 例受试者接受治疗。如需探索更多剂量水平或给药方案，则可以入组额外的受试者。

BOIN 设计将根据表格 3 所示的剂量升降规则为下一组受试者分配剂量水平。

表格 3 BOIN 设计的剂量递增/递减规则

决策	当前剂量上治疗的受试者总数						
	3	**4**	**5**	**6**	**7**	**8**	**9**
升剂量，若发生 DLT 的受试者例数 ≤	0	0	1	1	1	1	2
降剂量，若发生 DLT 的受试者例数 ≥	2	2	2	3	3	3	4
剔除剂量，若 DLT 受试者例数 ≥	3	3	4	4	5	5	5

具体规则如下：

- 如果根据上表规则得到的决策既非升剂量、降剂量，也非剔除剂量，则继续使用当前剂量治疗下一组受试者。
- 上表中的“剔除剂量”指从试验中剔除当前和更高剂量。
- 如当前剂量被剔除，将自动降低剂量至下一个较低的水平对受试者进行治疗。
- 如果最低剂量水平被剔除，则提前终止试验以确保受试者安全。在此情况下，将无法确定 MTD。
- 如果当前剂量是最低剂量水平且规则提示剂量降低，则仍以当前最低剂量治疗下一组受试者。
- 如果当前剂量是最高剂量水平且规则提示需升高剂量，则仍以最高剂量治疗新入组的受试者。
- 当推荐的下一剂量水平的可评估受试者≥6 例时，剂量递增部分可终止。
- 接受 RP2D 治疗的可评价受试者须达到至少 6 例。

剂量递增阶段结束后，将基于 DDS 采用保序回归分析以确定 MTD。使用 http://www.trialdesign.org 的在线 BOIN 软件进行保序回归分析，得到每个剂量水平毒性概率的保序估计值。最接近目标毒性率 0.3 的剂量水平即为 MTD。如果有 2 个或以上同时满足条件的剂量水平，选择保序估计值<0.3 的最高剂量水平或保序估计值≥0.3 的最低剂量水平。

3.1.1.3 剂量递增阶段受试者回填（Backfill）

将根据已获得的安全性/耐受性、PK 及初步有效性数据，可能选择一个或多个剂量组入组额外的受试者作为回填，接受已确认安全且耐受性良好的、经研究者及申办方评估可能临床获益的 GFH375 单药剂量组进行治疗，以更好的估计 GFH375 单药的 RP2D 以及表征其安全性\耐受性、PK 及有效性。如探索并确认过 750mg QD 剂量组的安全性，亦可进行 700mg QD 剂量组回填。回填的受试者不被纳入 DLT 的评估。回填后，接受 GFH375 每个剂量水平治疗的受试者不超过 30 例（包括 BOIN 剂量递增阶段入组的受试者）。

回填的受试者将根据 I 期的流程访视表及 I 期的 PK 采血表完成相关访视。

3.1.1.4 受试者个体内剂量递增

剂量递增研究期间原则上不进行个体内剂量递增。对于入组 I 期的受试者，经研究者和申办方同意后，允许在本方案的 RP2D 剂量确认后， 进行个体内剂量调整，接受 RP2D 的单药

治疗。

3.1.1.5 推荐 II 期剂量（RP2D）选择依据

截至 2025 年 1 月 17 日，本研究 I 期部分共入组 33 例受试者（包含 22 例剂量递增部分受试者以及 11 例回填受试者），完成了 100 mg、200 mg、400 mg、600 mg、750 mg、900 mg QD 以及 300 mg BID 共 7 个剂量组的 DLT 观察。已入组受试者包含 14 例胰腺癌、11 例 NSCLC、5 例 CRC 以及壶腹癌、子宫内膜癌、胆管癌各 1 例。根据已获得的所有安全性、耐受性、PK 和疗效数据，经申办方和 SMC 主要成员讨论，确定 RP2D 为 600 mg QD。其选择依据如下：

安全性和耐受性：

所有剂量组均未发生 DLT 和 5 级 AE。900 mg 剂量组在已入组的 3 例受试者中有 2 例在第 1 周期因 AE 和耐受不良终止治疗，整体耐受性较差。750 mg 剂量组较重消化道毒性（2/3 级腹泻和呕吐）发生率较高且呕吐持续时间相对较长。750 mg 剂量组 ≥2 级腹泻和 2 级呕吐的发生率均为 50%，其中 1 例 3 级腹泻，750 mg 以下剂量组（QD）均未观察到 3 级腹泻且 2 级腹泻发生率 ≤20.0%。300 mg BID 剂量组 2 级腹泻和呕吐发生率分别为 33.3%和 66.7%，高于 600 mg QD 剂量组。≥ G3 治疗期不良事件（TEAEs）和与研究药物相关的治疗期不良事件（TRAEs）在 400 mg 剂量组发生率高于 600 mg QD 剂量组，SAE 发生率未见明显差异，因 TRAE 暂停给药的发生率 400 mg QD 剂量组亦高于 600 mg 剂量组，600 mg 剂量组仅 1 例受试者因 TRAE 终止给药，无受试者因 TRAE 下调剂量。600 mg 剂量组整体安全性和耐受性与 400 mg 剂量组相似或更好，600 mg 剂量组整体安全可控耐受。

PK：

受试者口服 100-900 mg GFH375 后，在 100-400 mg 范围内，GFH375 的暴露随剂量增加而增加，但在 400-900 mg 范围内，GFH375 的暴露增加不明显。受试者 QD 口服 400 mg-900 mg GFH375 后，中位 T_{max} 为 2-4 h，单次给药半衰期为 18.5-21.6 h，连续 QD 给药蓄积比为 0.859-1.30，未见明显蓄积。当给药剂量高于 400 mg 时，GFH375 的平均谷浓度（34.4-50.2 ng/mL）可持续维持在临床前细胞学 IC_{90}（约 11 ng/mL）之上。如前所述，总体而言，400 mg 组和 600 mg 组的安全性和耐受性优于 750 mg 和 900 mg，但 400 mg 组的个体间变异较大（C_{max} 和 AUC 的几何 CV%为 111%-127%），与 400 mg 相比，600 mg 可使受试者获得较高和较稳定的暴露。

疗效：

400 mg 剂量组开始即可在胰腺癌和 NSCLC 受试者中观察到部分缓解。400 mg 剂量组胰腺癌受试者的 ORR 和 DCR 均为 100%（2/2），NSCLC 受试者的 ORR 为 0，DCR 为 50%（1/2）。600 mg QD 和 300 mg BID 剂量组胰腺癌的 ORR 为 25%（1/4），DCR 为 100%（4/4），NSCLC 的 ORR 为 75%（3/4），DCR 为 100%（4/4）。750 mg 剂量组胰腺癌的 ORR 为 0，DCR 为 100%（2/2），NSCLC 的 ORR 和 DCR 均为 100%（1/1）。NSCLC 受试者中 600 mg 剂量组的疗效优于 400 mg。

综合以上数据，RP2D 定为 600 mg QD。

3.1.2 II 期部分

II 期研究为开放标签、多中心的研究，总体研究计划见图 3。目的是评估 GFH375 治疗携带 KRAS G12D 突变的晚期非小细胞肺癌、晚期胰腺癌、结直肠癌和其他晚期实体瘤患者的有效性、安全性和 PK 特征。II 期研究将入组约 317 例 KRAS G12D 突变的晚期实体瘤受试者，以接受 RP2D 的 GFH375 连续单药治疗，治疗周期为 21 天。该部分入组的所有受试者将根据 II 期 PK 采血表进行稀疏 PK 采样，并收集与 PK 采样相匹配的心电图。

- 晚期NSLCL受试者队列：计划入组约73例携带KRAS G12D 突变的晚期NSCLC受试者。
- 晚期 PDAC受试者队列：计划入组约94例携带KRAS G12D 突变的晚期PDAC受试者。
- 晚期 CRC 受试者队列：计划入组约50例携带KRAS G12D 突变的晚期CRC受试者。
- 其他晚期实体瘤受试者队列：计划入组约携带 100 例 KRAS G12D 突变的晚期实体瘤受试者，如携带 KRAS G12D 突变的胆管癌、阑尾癌等。

筛选合格的受试者将接受 GFH375 单药治疗，直至疾病进展、出现不可耐受的毒性或因其他原因结束研究治疗。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。受试者将在末次研究治疗后 30 (±3) 天返回研究中心完成安全性随访，之后每 90 (±7) 天进行一次生存随访。受试者因疾病进展以外的原因结束研究治疗且尚未开始新的抗肿瘤治疗，需按照之前的影像学评估计划继续进行疾病进展随访，直至疾病进展、撤回 ICF、开始其他抗肿瘤治疗或研究结束。

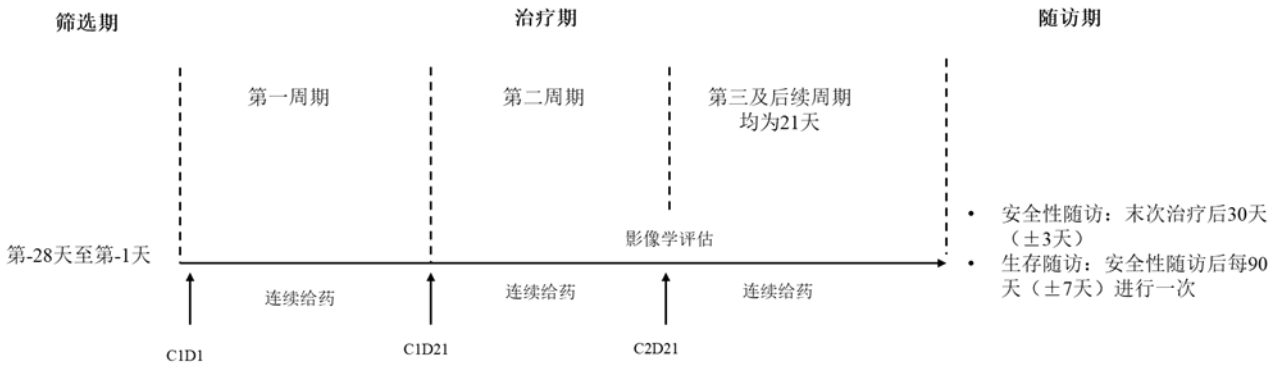

图 3 II 期研究计划示意图

3.2. 研究结束的定义

研究结束定义为末例受试者接受至少 6 个月的研究治疗或提前退出（以先发生者为准）。

3.3. 提前终止研究

由于监管机构的决定、伦理委员会意见，或者是申办方和研究者共同讨论的判断和决定，本研究允许提前终止或暂停。此外，申办方保留停止研发GFH375的权利。

研究提前终止或暂停的原因可能包括：

- 确定对受试者产生非预期的、重大的、或不可接受的风险；
- 已有的疗效结果支持提前终止研究；
- 方案要求的依从性较低。

决定暂停/终止研究的一方将发出书面通知、记录研究终止或暂停的原因给研究者、申办方和监管机构。如果研究被提前终止或暂停，研究者应立即通知伦理委员会和申办者，并且提供相关理由。

一旦上述提到的导致研究药物暂停的安全、方案依从性等问题得到解决并得到申办者、伦理委员会和/或法规监管机构的同意，则研究将继续进行。

4 研究人群

受试者必须符合所有入选标准，且不符合任意一条排除标准。

4.1. 入选标准

参加本研究的受试者需符合所有以下标准：

1. 自愿参加研究并签署知情同意书。
2. 在签署知情同意书时年龄为 18 - 75 周岁的男性或女性。
3. 经组织学或细胞学病理确认的局部晚期或转移性恶性肿瘤受试者，需符合以下标准：

（1） I 期部分：符合以下任意一条标准：1)接受标准治疗后疾病进展，且没有其他标准治疗可用；或 2)已证实标准治疗无效、不耐受或认为不适合。

（2） II 期部分：

a) 晚期 NSCLC：

- ✓ 既往接受过抗 PD-（L）1 治疗和/或以铂类为基础的化疗后进展（除非有使用禁忌或不耐受），且既往治疗线数不超过 3 线；
- ✓ 若既往接受过辅助或新辅助治疗且在治疗期间或治疗停止后 6 个月内出现复发/进展，则可将该治疗计入一个线数的治疗。

b) 晚期 PDAC：既往经过基于吉西他滨的化疗方案或 FOLFIRINOX/mFOLFIRINOX 方案的充分治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗，且既往治疗线数不超过 3 线。存在微卫星高度不稳定（MSI-H）及错配修复基因缺陷型（dMMR）者需既往经过至少一线抗 PD-1 治疗后进展。如果接受过辅助或新辅助治疗且在治疗期间或治疗停止后 6 个月内出现复发/进展，则可将该治疗计入一个线数的治疗。

c) 晚期 CRC：经至少二线标准治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗。受试者须既往在接受氟尿嘧啶、伊立替康和奥沙利铂治疗转移性疾病期间或之后发生疾病进展或复发，除非研究者认为受试者不适合接受以上治疗方案。已知有微卫星高度不稳定（MSI-H）及错配修复基因缺陷型（dMMR）的受试者必须既往接受过免疫检查点抑制剂治疗（如适用）。如果接受过辅助或新辅助治疗且在治疗期间或治疗停止后 6 个月内出现复发/进展，

则可将该治疗计入一个线数的治疗。

d) 其他实体瘤：经标准治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗。

4. 入组本研究的受试者需提供确认 KRAS G12D 突变阳性的书面检测报告。II 期 NSCLC 和 PDAC 受试者需在入组前提供符合要求的存档肿瘤组织样本或在筛选期接受活检。若无法提供肿瘤组织样本亦无法在筛选期接受活检，研究者需与申办方医学沟通，获得申办方医学同意后方可入组。

5. 根据 RECIST 1.1，I 期受试者必须至少有一个可评估病灶， II 期受试者必须至少有一个可测量病灶。

6. 既往抗肿瘤治疗的毒性反应必须缓解至基线水平（不包括脱发）或≤1 级（对于神经系统毒性，≤2 级）。

7. 研究者判断预期生存时间≥ 12 周。

8. 美国东部肿瘤协作组（ECOG）体能状态评分（PS）0~1 分（评分标准参见附录 2）。

9. 具有充分的器官功能，包括：

- 造血功能：中性粒细胞绝对计数 (ANC) ≥ 1.5×10^9/L，血小板计数 ≥ 75×10^9/L，血红蛋白 ≥ 9 g/dL，在血液检查前 14 天内未输血或未接受粒细胞集落刺激因子、血小板生成素或促红细胞生成素治疗。
- 肝功能：
  - AST 和 ALT 均< 2.5×ULN；对于基线存在肝转移的受试者，要求 AST 和 ALT 均< 5×ULN；
  - 总胆红素（TBIL）< 1.5×ULN；Gilbert 综合征受试者：TBIL < 2×ULN。
- 肾功能：肌酐清除率（CrCl）≥ 50 mL/min（Cockcroft-Gault 公式计算，参考附录 3）。
- 凝血功能：凝血酶原时间（PT）或活化部分凝血活酶时间（APTT）< 1.5×ULN，国际标准化比值（INR）< 1.5×ULN 或处于抗凝治疗的目标范围内。
- 白蛋白水平 ≥30 g/L（仅针对 II 期 PDAC 受试者）。

10. 有生育能力的女性（WOCBP）和伴侣为 WOCBP 的男性受试者必须同意从签署知情同意书至末次研究治疗后 30 天内采取有效的避孕方法。WOCBP 在给药前 7 天内的血清妊娠试

验结果必须为阴性。

11. 根据研究者的判断，受试者能够良好沟通、按计划随访并遵守方案的要求。

4.2. 排除标准

符合以下任意一条标准的受试者不能入组本研究：

1. 入组前 3 年内发生进展或需要治疗的其他恶性肿瘤，除外经充分治疗的原位癌、基底细胞癌或皮肤鳞状细胞癌。
2. 研究者判断不稳定的脑转移患者。对于在筛选过程中无意检出的伴脑转移的患者，如果未引起临床症状且不需要治疗干预， 可允许入组；如果研究者判断脑转移控制稳定，激素剂量使用稳定，且强的松剂量≤10mg/d（若使用其他类固醇药物，则为相应等效剂量），可允许入组。
3. II 期部分：
   a) 晚期 NSCLC：排除已知的其他驱动基因突变或融合，如 EGFR、ALK、 BRAF (V600E)、HER2、MET (exon 14)、 ROS1、RET、KRAS G12C 或 NTRK1/2/3
   b) 晚期 CRC：排除已知的其他驱动基因突变、扩增或融合，如 BRAF (V600E)、HER2、NTRK 或 RET
   c) 晚期 PDAC：排除已知的其他驱动基因突变或融合，如 BRAF (V600E)、BRCA、NTRK 或 RET
4. 既往接受过 KRAS G12D 或者泛 KRAS （具有靶向 KRAS G12D 作用）的靶向治疗。
5. 在研究药物给药前 14 天内接受姑息性放疗。
6. 在给药前 28 天内或 5 个半衰期内（以较短者为准）接受过其他抗肿瘤治疗，包括化疗、靶向治疗、内分泌治疗、免疫治疗、具有明确抗肿瘤作用的中成药及其他试验用药物或器械，内分泌维持治疗除外。
7. 合并具有临床意义的严重心血管疾病：
   - 首次研究治疗前 6 个月内发生具有临床意义的严重心血管事件，如心肌梗死、不稳定型心绞痛、症状性充血性心力衰竭（纽约心脏病协会 III 或 IV 级）、需要药物治疗的重度心律失常或接受血管成形术、支架植入术和冠状动脉旁路移植术等。
   - 具有临床意义 QT/QTcF 延长（基于筛选期三次 QTcF 的平均值，QTcF > 470 ms）或合并 QT 间期延长的家族史。
   - 经标准治疗后仍控制不佳的高血压。

8. 入组前 6 个月内发生卒中或其他严重脑血管疾病。
9. 入组前 3 个月内有深静脉血栓或其它任何严重血栓栓塞的病史。
10. 伴随需要反复引流或有明显症状的胸腔积液、腹水或心包积液。
11. 合并上腔静脉综合征。
12. 在研究药物首次给药前 6 个月内有胃肠道穿孔和/或瘘管病史、且经手术治疗未痊愈；当前不稳定或活动性消化道溃疡或合并其他高风险消化道出血疾病；存在胆道或幽门梗阻，或持续性反复呕吐（24 小时内呕吐≥3 次）；因肿瘤侵犯周围重要结构（如大血管、气管等）而存在较高的破裂出血或胃肠道/呼吸道瘘风险；或合并其他可能显著影响 GFH375 吸收的胃肠道功能受损或胃肠道疾病，或无法或不愿意吞咽片剂。
13. 合并具有临床意义并需要治疗的间质性肺病、放射性肺炎或免疫相关性肺炎。
14. 合并重大急性或慢性感染性疾病，包括：
    - 入组前 7 天内需要静脉使用抗生素治疗的活动性感染。
    - 基线时人类免疫缺陷病毒抗体 (HIV-Ab) 阳性。
    - 活动性乙型肝炎病毒感染（HBsAg 阳性伴 HBV-DNA 阳性）。
    - 活动性丙型肝炎病毒感染（HCV-Ab 阳性伴 HCV-RNA 阳性）。
    - 活动性结核病。
15. 合并其他控制不佳的系统性疾病，如糖尿病。
16. 在首次给药前 28 天内接受或计划进行由研究者判断的重大手术（穿刺活检除外）。
17. 既往有器官移植病史或准备接受器官移植。
18. 在研究药物给药前 7 天内或接受研究药物期间需使用抑酸类药物，包括质子泵抑制剂和新型抑酸类药物（如钾离子竞争性酸阻滞剂）。
19. 在研究药物给药前 14 天内或药物的 5 个半衰期内（以较长者为准）接受了 CYP3A 或 P-gp 的强抑制剂或强诱导剂。
20. 在研究药物给药前 14 天内或药物的 5 个半衰期内（以较长者为准）接受过已知敏感的 CYP3A 或 OAT1 底物。除非经研究者和申办方审阅后同意入组。
21. 已知对研究药物或成分过敏。
22. 有严重的精神、心理疾病或有药物滥用史或有严重酗酒史。

23. 妊娠或哺乳期女性。

24. 研究者判断不适合参加研究的其他情况。

25. **II 期 PDAC 受试者：**经过止痛药物规范治疗后疼痛数字分级法（NRS）评分 ≥4 分。

5 研究治疗

5.1 治疗方案

I 期

GFH375 的初始剂量为 100 mg QD, 每 21 天为一个治疗周期。受试者将持续用药直至疾病进展或出现不可耐受的毒性导致治疗终止的情况。

II 期

II 期的受试者将接受 GFH375 RP2D 治疗，每日给药。每 21 天为一个治疗周期。受试者将持续用药直至疾病进展或出现不可耐受的毒性或其他导致治疗终止的情况。

5.2 研究药物

5.2.1 研究药物的描述

研究药物	GFH375 片
活性成分	GFH375
辅料	甘露醇、微晶纤维素、交联羧甲基纤维素钠、羟丙纤维素、胶态二氧化硅、硬脂酸镁、薄膜包衣预混剂（胃溶型）-欧巴代、纯化水
类型	口服固体制剂
剂型	片剂
规格	25mg，100mg
给药途径	口服
储存要求	避光，密封，不超过 25℃保存
有效期	暂定 24 个月
包装及标签	口服固体药用高密度聚乙烯瓶和口服固体药用聚丙烯儿童安全组合瓶盖，内加固体药用高密度聚乙烯非织造（泰维克）袋装干燥剂。每瓶会根据相关法规要求贴上标签。

5.2.2 治疗分配和药物发放

在受试者签署书面的知情同情书时，就会被分配一个受试者编号，该编号会被用于所有的研究文档和病例报告表（CRF）。完成筛选流程后，根据入排选标准判断是否正式入组研究。所有入组的受试者将接受 GFH375 治疗。

研究者或其指定人员必须确保在运输过程中所有用于研究治疗的药物或相关物品保持适宜的温度条件。若出现偏差，则需在进行研究治疗前汇报并解决所出现的问题。

只有入组研究的受试者可以接受研究治疗，且只有经授权的研究中心人员可以提供或管理研究治疗产品。所有研究干预的药物或相关物品必须按照标签上注明的储存条件储存在安全、环境可控、可监测（手动或自动）的区域，并保证仅研究者和经授权的研究中心人员有相关权限接触研究治疗产品。

5.2.3 研究药物给药

GFH375将由研究中心人员在计划的访视发放给受试者，单次发放的药物数量将保证受试者在指定的时期内有足够的药物在院外自行服用。

GFH375 片剂采取口服给药。需告知受试者必须整片吞下，不能嚼碎或掰开。服药前 2h 至服药后 1h 均禁食，并尽可能保证每天的服药时间接近。如当日早晨需要抽取 PK 血样，应在抽血后服药。当每日两次（BID）服药时，建议安排在上午 8:00 和晚上 20:00 左右。

如发生漏服，在计划的服药时间点后 4 小时内补服，并记录实际服药时间，后续服药时间不变。如已超过 4 小时则不用补服，下次服药时间按原计划。如用药后发生呕吐，无需补服。所有的实际服药时间都应记录在受试者日记上，或记录“漏服”等意外情况。

5.3 剂量调整

5.3.1 允许的剂量调整

原则上，入组 I 期的受试者在 DLT 观察期内不允许剂量调整。研究期间应密切监测受试者使用研究药物的安全性，推荐根据所在研究中心实践采用最佳支持治疗处理治疗相关的不良事件。

完成 DLT 观察期的 I 期受试者及入组 II 期的受试者可以根据实际临床需要进行剂量调整。将按照 I 期的剂量组设定进行剂量下调。同一个受试者最多允许 2 次剂量降低。接受 100 mg QD GFH375 治疗的受试者，原则上不允许剂量下降；接受 200 mg QD GFH375 治疗的受试者，原则上只允许下降至 100 mg QD。如有特殊情况，研究者应与申办方进一步讨论达成一致。剂量调整详细原则可参考表格 4 及表格 5。

剂量递增研究期间原则上不进行个体内剂量递增。对于入组 I 期的受试者，经研究者和申办方同意后，允许在本方案的 RP2D 剂量确认后， 进行个体内剂量调整，接受 RP2D 的单药治疗。

5.3.2 暂停给药和永久停药

研究期间受试者如发生与研究治疗有关且符合表格 4、表格 5 的任一永久停药标准，应停止 GFH375 治疗，并随访至事件解决或恢复至基线水平。如该受试者已出现肿瘤治疗响应，研究者判断继续接受治疗有益，可在与申办方充分沟通后，在毒性恢复如下水平后恢复同一剂量或低一剂量研究治疗，同时继续密切监测相关毒性。

表格 4 血液学毒性的剂量调整原则

药物相关不良事件	严重程度	剂量调整
中性粒细胞计数（ANC）减少	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平，恢复原剂量或降低 1 个剂量用药；
	4 级	停药，直至恢复至≤1 级或基线水平，并降低 1 个剂量用药；
	3 级发热性 ANC 减少	停药，直至恢复至≤1 级或基线水平，并降低 1 个剂量用药；
	4 级发热性 ANC 减少	停药，并退出研究治疗；
血小板计数（PLT）减少	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平，恢复原剂量或降低 1 个剂量用药；若伴出血需要临床干预，则降低 1 个剂量用药；
	4 级	停药，直至恢复至≤1 级或基线水平，并降低 1 个剂量用药或停药退出研究治疗；
贫血	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤2 级或基线水平，恢复原剂量或降低 1 个剂量用药；
	4 级	停药，直至恢复至≤2 级或基线水平，并降低 1 个剂量用药或停药退出研究治疗；
其他	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤2 级或基线水平，恢复原剂量或降低 1 个剂量用药；
	4 级	非危及生命且经过治疗可以控制的不良事件，可经停药，不良事件恢复至≤1 级或基线水平后降低剂量用药。危及生命的不良事件，则终止用药。

表格 5 非血液学毒性的剂量调整原则

药物相关不良事件	严重程度	剂量调整
ALT/AST 升高	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平，恢复原剂量或降低 1 个剂量用药；若 ALT/ AST>5×ULN 超过 2 周，或 ALT/ AST > 8×ULN，需停药并退出研究治疗；
	4 级/符合海氏法则	停药，退出研究治疗；
血胆红素升高	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平；无合并转氨酶或碱性磷酸酶升高，可恢复原剂量或降低 1 个剂量用药；
	4 级	停药，退出研究治疗；
血淀粉酶/脂肪酶升高	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平；若无症状可恢复原剂量或降低 1 个剂量用药；若有症状则降低 1 个剂量用药；
	4 级	停药，直至恢复至≤1 级或基线水平并降低 1 个剂量用药或停药并退出研究治疗；
胰腺炎	2 级	停药，直至淀粉酶及影像学正常或无临床意义； 降低 1 个剂量用药；
	3/4 级	停药，退出研究治疗；
恶心/呕吐/腹泻	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平，恢复原剂量或降低 1 个剂量用药；若经对症支持治疗超过 3 天仍无好转，则降低 1 个剂量用药；
	4 级	停药，退出研究治疗；
乏力	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤2 级或基线水平； 若恢复时间 ≤ 1 周，建议采用原剂量用药治疗；若>1 周，建议降低 1 个剂量用药
其他系统不良事件	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平； 若恢复时间 ≤ 1 周，建议采用原剂量用药治疗；若恢复时间 >1 周，建议降低 1 个剂量用药
	4 级	非危及生命且经过治疗可以控制的不良事件，可经停药，不良事件恢复至≤1 级或基线水平后降低剂 量用药。 危及生命的不良事件，则终止用药。

发生上述血液学毒性时，建议在 3 天内复查血常规，之后继续密切监测恢复情况。如恢复至如下标准可考虑恢复治疗：非血液学毒性恢复至≤1 级或基线水平；血液学毒性恢复至

ANC≥1.0×10^9/L，PLT ≥ 75×10^9/L，Hb≥8g/dL。

如治疗相关的不良事件在 4 周内仍无法恢复到可用药的水平，或在恢复用药后再次发生同一需要暂停治疗的毒性，应考虑永久停止治疗。永久停药的后续研究流程请参见方案 6.4.2 章节。

5.4 既往和伴随治疗

5.4.1 既往治疗

受试者参加本研究前禁止的既往/合并治疗请参见方案第四章节。

受试者签署知情同意书后，将收集其既往治疗研究疾病（晚期实体瘤）的各线用药情况，以及在本研究首次用药前 30 天的其他既往用药/治疗。

5.4.2 伴随治疗

受试者从首次接受研究治疗开始至安全性随访访视期间，将记录接受的所有伴随治疗、血制品、非药物干预（如穿刺）。

5.4.2.1 允许/慎用的伴随治疗

研究过程中研究者需遵从以下原则并谨慎使用合并药物，最大限度的保障受试者的安全。

研究期间允许进行针对疾病症状的姑息治疗和最佳支持治疗，但 DLT 观察期间的伴随治疗应避免影响对 DLT 的判断。对疾病相关症状的姑息性和支持性治疗将取决于研究者的判断及相关的指南（如《美国临床肿瘤学会指南》）。例如，允许以缓解症状为目的的姑息性局部放疗治疗痛性骨病灶，前提是已知这些病灶在入组时即存在，且并非唯一靶病灶。进行放疗前研究者应判断并记录放疗的使用是否与疾病进展相关。

研究期间如受试者合并其他疾病，研究者应判断是否需要使用药物治疗，应尽可能避免对研究结果的判断影响较大的药物，以免影响对受试者安全性和耐受性的判断。如发生严重不良反应或严重不良事件、或原病情恶化或并发其他严重疾病，研究者应及时给予伴随治疗和积极治疗。如达到受试者退出研究标准，应妥善安排受试者退出。

- 如果研究者不能确定伴随治疗是否会影响受试者安全，或用药后是否会影响对受试者安全性和耐受性的判断，或用药后是否会影响受试者入组合格性以及数据的可评估性，应在使用伴随治疗前与申办方进行讨论并达成一致意见。

研究期间受试者谨慎合并使用已知的 H2 受体阻抗剂和抗酸药，包括但不限于西咪替丁、

法莫替丁、尼扎替丁、罗沙替丁。抗酸药包括铝碳酸镁咀嚼片、磷酸铝凝胶、氢氧化铝、氢氧化镁、碳酸钙等。如必须使用上述药物，需在上述药物治疗前或治疗后至少 2 小时以后使用 GFH375。

5.4.2.2 禁用的伴随治疗

研究期间，受试者不应接受下列治疗：

1) 除本研究治疗外的其他任何抗肿瘤治疗（化疗、免疫治疗、生物制品、广泛的放疗、激素治疗、靶向治疗、手术、具有已批准抗肿瘤适应症的中药），包括研究性治疗或已获批的治疗。服用拮抗促性腺激素释放激素（GnRH）治疗前列腺癌，口服避孕药，或进行激素替代治疗的受试者可以继续用药。

2) 首次用药前 7 天内禁止使用中药（包括中成药），研究最终 PK 采集完成之前不建议使用中药（包括中成药）。如处理不良事件或疾病需要使用中药，使用前须经申办方审阅和批准。

3) 使用粒细胞集落刺激因子类药物作为预防用药。此类药物仅可在研究者的判断下，用于不良事件的治疗。

4) 除本研究治疗外的任何其他正在进行临床研究的药物。

5) 在首次用药前 14 天内或 5 个半衰期内（以较长者为准）至末次给药后两周期间，禁止使用已知的 CYP3A 和 P-gp 的强效抑制剂和诱导剂（见附录 4）。

6) 研究药物首次用药前 14 天内或药物 5 个半衰期内（以较长者为准）至末次给药后两周期间，禁止使用已知 CYP3A 或 OAT1 的敏感底物（见附录 4）。除非该药物在筛选期经过研究者和申办方医学负责人审阅和批准。

7) 研究药物首次用药前 7 天内或药物 5 个半衰期内（以较长者为准）至末次给药后一周内，禁止使用已知的质子泵抑制剂和新型抑酸药物（如钾离子竞争性酸阻滞剂），包括但不限于奥美拉唑、兰索拉唑、泮托拉唑、雷贝拉唑、艾斯奥美拉唑、艾普拉唑、伏诺拉生。

5.5 治疗依从性

受试者将遵循研究者的指导，在指定访视日返还前一周期所有未服用的 GFH375 片剂和包装，并交还已完成的受试者日志。受试者返还的数量将会被清点、记录和存档，并根据实际用药情况计算用药依从性。

5.6 药品管理

5.6.1 研究药物接收和清点

申办方将根据研究中心预期的入组计划提供 GFH375。GFH375 将通过第三方的有运输资质的物流公司运送至研究中心。研究中心授权工作人员将会在发货单上进行签字，以确认其收到药物。

GFH375 只能用于本研究，而且只能由研究者授权的专人进行管理。为完全控制 GFH375 的发放与使用，在每次访视时均需进行数量登记。

5.6.2 研究药物的储存和管理

研究者或授权的其他研究中心工作人员（如药剂师），将确保所有的研究药品存放在符合方案 5.2.1 章节所述存放条件的、出入受控的安全区域，并且其存放符合适用的法规要求。受试者领取 GFH375 片剂后，将遵循研究者或授权人员的指导，进行正确的贮存。如果发现不符合要求的储存情况，研究者应联系申办方获取指导。

5.6.3 研究药物回收和销毁

未使用的研究药物及包装将由申办方清点后回收和销毁，或授权研究中心销毁。申办方或其授权人员将提供给研究中心如何销毁未使用的研究药物的指导。如果被授权在研究中心进行销毁，研究者需确保所有的回收和销毁依据相应法规、指导原则和规章制度进行并记录。

5.6.4 研究药物的记录

研究中心指定人员需根据相关法规和指南，本试验的操作流程的要求及时做好研究药物的接收、分发、使用、库存、销毁、回收、损毁等相关记录。

5.7 投诉处理

为了确保受试者的安全性和监测质量，并协助流程和药品的改进，申办方将收集临床试验使用的研究药物相关的产品投诉。对于合并药物相关的投诉，将根据产品说明直接报告给生产商。研究者或其指定人员负责按照本研究的相关规定，完成下列产品投诉流程：

- 采用研究专用的投诉表，记录所报告的产品投诉和相关的完整描述。
- 将填写完成的产品投诉表在 24 小时内传真或邮件至申办者或其指定人员。

如果要求研究者返还产品以便进行调查，研究者应将产品投诉表复印件连同产品一起返还。

6 研究流程

在开始进行本方案所要求的任何研究步骤前，受试者必须阅读并且签署经伦理委员会批准的知情同意书。

所有步骤应在要求的时间窗内进行，如特殊情况下无法按时或按要求完成研究步骤，研究者应采取一切必要的措施来保障受试者的安全和利益，并记录原因和采取的措施。另外研究者需及时通知研究团队所发生的意外状况。

6.1 筛选期

筛选期：首次研究给药前第-28 天至第-1 天。受试者签署知情同意书后，根据方案要求提供相关信息并进行相关检查。基线定义为用药前最后一次检查结果。需根据访视流程表完成所有筛选期的检查和确认。II 期 NSCLC 和 PDAC 受试者需在入组前提供符合要求的存档肿瘤组织样本或在筛选期接受活检。若无法提供肿瘤组织样本亦无法在筛选期接受活检，研究者需与申办方医学沟通，获得申办方医学同意后方可入组。

因任何原因最终未开始首次研究给药为筛选失败。对于筛选失败的受试者可以进行重新筛选。如果考虑对受试者进行重新筛选，则研究者必须联系申办方医学负责人。再次筛选时须取得申办方医学负责人同意。进行重新筛选时，受试者必须重新签署知情同意书，而且将被重新分配一个识别号。初始筛选期间进行的评估结果如果仍然在研究规定的时间范围内，并且结果符合入排标准，则仍然可以接受，而无需重复检测。

必须严格遵守入排标准。如果发现入组了不符合入排标准的受试者，申办方医学负责人和研究者需讨论确定是否让受试者继续参与本研究，使用或不使用研究药物。如果研究者认为让受试者继续参与本研究从医疗角度来看对该受试者是适当的，而且申办方医学负责人同意研究者的此决定，则受试者可以继续参与本研究并接受研究药物的治疗。如果研究者认为受试者继续参与本研究在医学上是适当的，但申办方医学负责人不同意研究者的此决定，则受试者不得继续参与本研究（无论接受或不接受研究药物治疗）。研究者只有在收到申办方书面批准后才能够允许意外入组本研究的受试者继续参与本研究。

6.2 治疗期

符合条件的受试者将接受研究治疗，直至发生疾病进展（除外由研究者判断继续治疗仍可获益的受试者）、不可耐受的毒性、撤回知情同意、研究结束或提前终止、开始了新的抗肿

瘤治疗或死亡，以先发生者为准。治疗期从研究药物给药第 1 天开始，每个治疗周期均为 21 天。在研究期间，受试者将按计划定期完成访视。将在方案中指定的时间点收集药代动力学样本。疗效将由研究者根据 RECIST 1.1 进行评估。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。

6.3 疾病进展后继续用药

疾病进展后，如研究者判断受试者将继续获益，在受试者充分知情并同意的情况下，允许继续使用 GFH375 治疗，直至符合治疗终止标准（参见方案 6.4 章节）。

疾病进展后继续用药，需要按照研究设计的访视继续收集数据。

6.4 受试者终止治疗和退出研究

6.4.1 受试者终止治疗

终止研究治疗不代表退出研究。终止研究治疗的受试者应按方案要求完成治疗结束访视（EOT 访视）和后续随访访视。终止研究治疗的可能原因包括：

1) 受试者发生需停止治疗的疾病进展，如研究者判断受试者继续用药仍然获益，可与申办方讨论后继续给予研究治疗；
2) 不良事件；
3) 受试者开始其他抗肿瘤治疗；
4) 受试者严重不遵从研究方案的要求；
5) 受试者妊娠；
6) 受试者失访；
7) 受试者死亡；
8) 受试者要求终止治疗，但接受后续随访；
9) 受试者撤回知情；
10) 研究者认为终止研究治疗符合受试者的最大利益；
11) 整个临床研究结束或中止。

发生上述情况时，应在、决定结束研究治疗的 7 天内完成治疗结束访视（EOT 访视）。EOT 访视前 7 天内进行过的检查无需重复，但 AE 相关的检查应根据研究者判断进行复查。

6.4.2 受试者退出研究

受试者可以在任何时候自愿退出研究。退出研究的原因可能包括：

1) 受试者撤回知情，拒绝进行研究步骤、拒绝未来被联系并提供信息；
2) 受试者死亡；
3) 受试者失访；
4) 整个研究结束或中止。

如果受试者未按约定返回中心进行随访，应尽一切努力及时联系受试者，并尽快重新安排遗漏的访视。研究者应询问退出原因，要求受试者尽可能返回中心完成访视，并随访未结束的不良事件。在任何情况下，如有可能，应尽力记录受试者的结局。

如果受试者拒绝到研究中心进行进一步的访视，仍应继续追踪收集其疾病和生存情况，除非受试者撤回知情（即拒绝被继续联系）。在这种情况下，不应再进行任何的研究评价，也不应再收集任何资料。

6.5 失访

如果受试者连续 3 次未能返回研究中心进行计划内的访视，并且研究中心工作人员无法与之取得联系，将被视为失访。

如果受试者没有返回研究中心进行规定的研究访视，必须采取下列行动：

- 研究中心尝试与受试者联系，重新安排错过的访视，向受试者说明遵守访视日程表的重要性，并确认受试者是否愿意和/或应该继续参与研究。
- 在受试者被认定为失访之前，研究者或指定人员将尽力重新与受试者取得联系（应尝试打至少两次电话，如果仍无法取得联系，应给受试者最近更新的联系地址发一封信）。这些联系受试者的尝试应记录在受试者的病历或研究文件中。在本研究结束之前，研究者仍需尽量与受试者取得联系。

如果仍然联系不上受试者，将被认为失访。所有进行联系的尝试应在原始文件上进行记录。

6.6 计划外访视

如研究者判断由于安全性评估或不良事件随访的需要，或出现提示疾病进展的临床症状，研究者可以安排进行相应的访视，以进一步检查和评估。

6.7 随访期

6.7.1 安全性随访

在治疗结束访视之后（包括完成治疗结束/退出研究访视的受试者），进入随访期。末次研究给药后 30 天（±3 天），无论受试者是否开始新的抗肿瘤治疗，受试者需要返回研究中心进行安全性随访。

安全随访访视后，不再主动收集不良事件，但所有治疗相关不良事件都必须随访至解决、恢复至基线，或研究者判断为稳定且不可逆状况。

6.7.2 疾病进展随访

受试者因疾病进展以外的原因结束研究治疗且尚未开始新的抗肿瘤治疗，需按照之前的影像学评估计划继续进行疾病进展随访，直至疾病进展、撤回 ICF、开始其他抗肿瘤治疗或研究结束。

6.7.3 生存随访

安全性随访结束后，受试者将进入生存随访。受试者将每 90 天（±7 天）接受一次生存随访。研究者将通过电话或电子邮件等方式，获取受试者的生存状态、疾病状态及后续的抗肿瘤治疗。

7 研究评估

7.1 安全性评估

将从筛选/基线期开始对受试者进行安全性终点数据集的记录并评估。安全性终点评估指标包括不良事件的发生率、严重程度和类型、受试者的体格检查结果、生命体征测量值和临床实验室检查结果，评估时间点根据访视计划。不良反应将根据 CTCAE v5.0 进行分级。关于 AE 收集和报告的详细信息，请参见第 8.0 章安全性报告和不良事件管理。

7.1.1 实验室检查

血常规、尿常规、血生化、凝血功能以及妊娠检测将按研究流程表进行。筛选期还需要进行病毒血清学检查以评估入组合格性。具体请参见表格 6实验室检查。

如受试者在研究中心以外进行了实验室检查并报告了相关AE，该实验室检查结果也应收集并录入eCRF。

表格 6 实验室检查

检查项目	观察指标
血常规	红细胞计数（RBC）、血红蛋白浓度（HGB）、红细胞比容（HCT）、平均红细胞体积（MCV）、平均红细胞血红蛋白含量（MCH）、平均红细胞血红蛋白浓度（MCHC）、白细胞计数（WBC）、血小板计数（PLT）、中性粒细胞计数（ANC）、淋巴细胞（LY）计数、单核细胞（MO）计数、嗜酸性粒细胞（EO）计数、嗜碱性粒细胞（BA）计数、中性粒细胞百分比、淋巴细胞百分比、单核细胞百分比、嗜酸性粒细胞百分比、嗜碱性粒细胞百分比
尿常规	尿白细胞（LEU）、尿亚硝酸盐（NIT）、尿 pH 值、尿比重（SG）、尿蛋白（PRO）、尿葡萄糖（GLU）、尿酮体（KET）、尿胆原（UBG）、尿胆红素（BIL）、尿潜血（BLD）；24 小时尿蛋白（尿蛋白≥2+时，需进行此项检查）
凝血功能	凝血酶原时间（PT）、活化部分凝血活酶时间（APTT）、国际标准化比率（INR）
血生化	天冬氨酸氨基转移酶（AST）、丙氨酸氨基转移酶（ALT）、碱性磷酸酶（ALP）、乳酸脱氢酶（LDH）、谷氨酰转肽酶（GGT）、尿素（UREA）/尿素氮、血肌酐（CREA）、总蛋白（TP）、白蛋白（ALB）、总胆红素（TBIL）、直接胆红素（DBIL）、肌酸激酶（CK）、胰淀粉酶（AMY）、空腹血糖（FPG）、总胆固醇（TCHO）、低密度脂蛋白胆固醇（LDL-C）、高密度脂蛋白胆固醇（HDL-C）、甘油三酯（TG）、钙、钠、氯、钾
病毒血清学	乙肝表面抗原（HBsAg）、乙肝表面抗体（HBsAb）、乙肝核心抗体（HBcAb）、HBV-DNA（必要时）、丙型肝炎病毒抗体（HCV 抗体）、HCV-RNA（必要时）、HIV 抗体
妊娠检测	有生育能力的女性受试者基线行血清 β-HCG 妊娠检测，其余访视行尿妊娠检测

7.1.2 体格检查

将根据对应的访视流程表中规定的时间点进行体格检查。

完整的体格检查包括一般情况、皮肤、颈部（甲状腺）、眼、耳、鼻、喉、胸部（包括肺）、心脏、腹部、背部、淋巴结、四肢、血管神经系统；如有临床指征，将进行乳房、盆腔、直肠、外生殖器检查。筛选期将进行全面的体格检查。

在 GFH375 首次给药前和方案规定的时间点，根据临床指征进行简要的体格检查。研究者也可根据需要相应增加体格检查的频率。

7.1.3 生命体征

将记录受试者生命体征（呼吸、脉搏、血压和体温）。

7.1.4 体能状态

体能状态评估将在筛选期、首次给药前、每个周期的 D1、EOT 和末次治疗后 30 天时进行。如首次给药前 72 小时内已进行评估，则无需在 C1D1 重复。体能状态将根据美国东部肿瘤协作组（ECOG）身体状况评分标准（见附录 2）进行评分。

7.1.5 身高与体重

身高仅在筛选期测量一次。筛选期、C1D1、C2D1、后续每个周期的 D1、EOT 和末次治疗后 30 天时测量体重。根据医院标准测量身高[厘米（cm）]和体重[千克（kg），四舍五入到小数点后一位，穿着室内衣服、不穿鞋测量]。

7.1.6 12 导联心电图

12 导联心电图将依据研究流程表规定的日期和时间要求完成。

心电图检查应在受试者安静休息至少 10 分钟后进行。筛选期及研究期间检查 3 次心电图检查，要求每次间隔至少 5 分钟。若合并有其他试验流程，需先进行心电图检查以避免试验操作对心电图结果产生影响。

应评估并收集心率（HR）、PR 间期、QRS 间期、QT 间期和 QTcF（Frederica 公式）间期。

I 期剂量递增部分 12-ECG 采集

受试者将在 C1D1（给药前、给药后 2 小时、给药后 4 小时、给药后 6 小时）、C1D4（给药前，仅适用于 QD 给药）、C1D8（给药前）、C1D15（给药前）、C1D21（给药前，给药后 2

小时，给药后 4 小时、给药后 6 小时、给药后 24 小时[仅适用于 QD 给药]）、C2D10（给药前）、C4D1（给药前）、C5D1（给药前）和 C6D1（给药前）进行心电图检查。

II 期 12-ECG 采集

受试者将在 C1D10（给药前、给药后 2-4 小时）、C2D1（给药前、给药后 1-3 小时），C3D1（给药前、给药后 2-4 小时）、C4D1（给药前）、C5D1（给药前）和 C6D1（给药前）进行心电图检查。

将在有条件的中心收集与 PK 样本匹配的 ECG，建议先进行心电图检查，再进行 PK 采血。如无法在采集血样标本前完成，应在采血后安静休息 10 分钟后进行心电图检查。同时，需要将心电图检查与 PK 采样时间的间隔保持在 30 分钟以内。所有计划的 12-ECG 检查都应该在受试者至少安静休息 10 分钟之后进行，每个时间点需测量 3 次，每次间隔在 1-2 分钟。

7.1.7 不良事件与伴随治疗

不良事件的评估包括事件名称、严重程度（分级依照第 5.0 版 CTCAE）、开始和结束时间、是否为严重不良事件、与研究治疗的相关性、对研究治疗采取的措施以及转归。

签署知情同意书后直到完成研究安全随访访视，期间发生的 AE，将被记录在原始病历中并收集至 eCRF。接受研究治疗期间受试者使用过的其他药物或治疗，作为伴随治疗记录在原始病历中并收集至 eCRF。

7.2 药代动力学评价

7.2.1 血样采集

I期研究剂量递增部分

将在 C1D1（单次给药）、C1D21（稳态）、C2D1、C2D10、C4D1、C5D1 和 C6D1 采集系列药代动力学样本，具体时间点见 **I 期药代动力学（PK）样本和 12 导联心电图采集计划表**，评估 GFH375 的药代动力学。

II 期研究部分

入组受试者于 C1D10、C2D1、C3D1、C4D1、C5D1 和 C6D1 给药前采集 PK 样本，详见 **II 期药代动力学（PK）样本和 12 导联心电图采集计划表**。

- **非计划 PK 采血**

当受试者发生与药物相关的严重不良事件时，在研究者得知发生事件的即刻，可能的情

况下，采集当时的一份血样用于 GFH375 血药浓度测定。

- **胃肠道 AE（呕吐和腹泻）与 PK 采样**

研究过程中发现受试者服用 GFH375 后，胃肠道 AE 发生率较高，可能会影响到受试者的 PK 结果。将在 CRF 中收集呕吐和腹泻的发生时间及次数，以便进行后续分析。

7.2.2 样本分析

将使用验证过的液相色谱串联质谱法（LC-MS/MS）测定 GFH375 的浓度。低于定量下限（LLOQ）的浓度将被标记为 LLOQ，如有缺失样本将相应标记。样本检测由上海观合医药科技股份有限公司负责。关于分析的详细信息将记录在生物分析报告中。

生物样本的采集、处理方法详见实验室操作手册。

7.3 疗效评价

对肿瘤缓解的评价将包括所有已知或可疑的发病部位。成像包括胸、腹或盆腔的计算机断层扫描（CT）或磁共振成像（MRI）扫描；脑部 CT 或 MRI 用于受试者已知或可疑的脑转移；骨扫描和/或骨 X 射线用于受试者已知或可疑的骨转移。

应在首次治疗前 28 天内进行基线 CT/MRI 扫描。研究期间，疗效将由盲态独立中心审查委员会（BICR）或研究者根据 RECIST 1.1 标准进行评估（所有受试者的疗效均需研究者评估，II 期 PDAC 和 NSCLC 受试者还需 BICR 评估），前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。在后续肿瘤评价中对相同类型的病灶应采用与在筛选期相同的影像学手段，并尽可能在同一影像设备上进行检查。基线头颅影像及骨扫描未发现相应病灶的受试者，治疗期间如有临床指征，研究者可决定增加相应检查。

疾病缓解评价将由 BICR 或研究者根据 RECIST 1.1（附录 1）进行。所有受试者放射影像检查必须符合 RECIST 1.1 标准，所有资料应妥善存留并能接受来源验证和同行评议。

如果受试者终止研究治疗的原因不是疾病进展，且未开始后续其他抗肿瘤治疗，将继续进行影像学检查，直至发生疾病进展，或开始后续抗肿瘤治疗，或因其他原因退出研究。

7.4 生物标志物和耐药机制探索

II 期 NSCLC 和 PDAC 受试者需在入组前提供符合要求的存档肿瘤组织样本或在筛选期接

受活检，在本研究指定的中心实验室（燃石医学）检测确认基线基因突变状态。

I 期和 II 期会在基线（如筛选期采集，则无需在 C1D1 重复检测）和治疗结束访视时采集受试者的血液样本并运送至中心实验室分离 ctDNA 后进行测序。测序结果将和疗效进行关联分析，探索治疗敏感或者耐药相关生物标志物。

II 期 PDAC 受试者会在基线（如筛选期采集，则无需在 C1D1 重复检测）、治疗期间每 6 周±1 周以及治疗结束时（治疗结束访视前 4 周内进行检测则不需要重复）采集血液样本进行 CA19-9 检测，探索其变化与治疗应答的相关性。

7.5 生物样品的储存和销毁

将对剩余样本进行处置或销毁，并进行匿名化及合并处理。

样本重现性分析（如果进行）将与试验样本的生物分析同步进行。这些评估结果将不在 CSR 中报告，而是在一份生物分析报告中另行给出。

8. 安全性报告和不良事件管理

8.1 不良事件的定义和记录

8.1.1 不良事件的定义

AE 定义为受试者签署知情同意书后出现的（或加重的）不良体征、症状、异常实验室值或检查结果、医疗状况，无论该事件是否被认为与研究药物有关。TEAE 定义为在治疗前未出现，在治疗期间（定义为从研究药物首次给药到末次给药后 30±3 天） 出现或相对于治疗前状态加重的事件。

在知情同意后开始或加重的不良事件应记录在不良事件 eCRF 中。知情同意时已经存在的情况应记录在受试者 eCRF 的病史页上。不良事件监测应在末次给药治疗后持续 30 天±3 天，或直到开始新的抗肿瘤治疗，详情见 8.2.3 节。不良事件（包括构成 AE 的实验室异常） 应尽可能使用诊断来描述，而不是单个的潜在体征和症状。当不能明确诊断时，每个体征或症状都应作为一个单独的不良事件报告。

8.1.2 不良事件的严重程度判断标准

不良事件将使用 NCI-CTCAE 5.0 版进行评估。如果在 CTCAE v5.0 中没有对应的 AE，请参考以下标准（从 CTCAE v5.0 中的分级标准总结而来）。

表格 7 不良事件严重程度判断标准

等级	严重程度的临床描述
1	轻度；无临床症状或有轻微临床症状；仅为临床或诊断所见；无需治疗
2	中度；需要较小的、局部的或非侵入性的治疗；与年龄相符的使用工具性日常生活活动受限，使用工具性日常生活活动指做饭、购物、打电话、理财等
3	严重或者具重要医学意义但不会立即危及生命；导致住院或住院时间延长；导致残疾；自理性日常生活活动受限。自理性日常生活活动指：洗澡、穿衣、脱衣、吃饭、盥洗、服药等，并未卧床不起
4	危及生命；需要紧急治疗
5	导致死亡的不良事件

8.1.3 不良事件的记录和处理

应尽可能评估每个不良事件，以确定:

- 不良事件的名称
- 严重程度等级
- 持续时间（开始和结束日期）
- 与研究治疗的关系
- 对研究药物采取的措施（无、剂量减少、暂停用药、永久停药、未知、不适用）
- 是否给予药物或治疗（无伴随药物/非药物治疗，伴随药物/非药物治疗）
- 结局（未好转，痊愈，好转，痊愈伴有后遗症，致命，未知）
- 是否为严重不良事件，如第 **8.2 节**中定义的 SAE

所有不良事件都应得到适当处理。如果同时给予药物或非药物治疗，应记录在不良事件 eCRF 上。一旦发现不良事件，应随访其直至其消退或稳定或判断为永久性，并应在每次就诊时（必要时，可更频繁地）评估严重程度的变化、与研究治疗的相关性、治疗 AE 所需的干预措施以及结果。

8.2 严重不良事件

8.2.1 定义

SAE 定义为在任何临床研究期间发生的符合以下一个或多个标准的不良事件:

- 导致死亡；
- 危及生命，指严重病人即刻存在死亡的风险，并非是指假设将来发展严重时可能出现死亡；
- 导致住院或住院时间延长；
- 永久或显著的功能丧失；
- 致畸、致出生缺陷；
- 其他重要医学事件：必须运用医学和科学的判断决定是否对其他的情况加速报告，如重要医学事件可能不会立即危及生命、死亡或住院，但如需要采取医学措施来预防如上情形之一的发生，也通常被视为是严重的。

因以下原因住院不应报告为 SAE：

- 所研究适应症的常规治疗或监测，与任何病情恶化无关
- 选择性或预先计划的治疗，用于与所研究适应症无关的已有疾病，且自签署知情同意书以来没有恶化
- 社会原因和在患者一般情况没有任何恶化的情况下的临时护理

急诊门诊治疗不导致住院，且涉及不符合上述 SAE 定义的事件，不属于 SAE。

8.2.2 恶性肿瘤进展及死亡

恶性肿瘤进展导致的临床症状，如果不能完全排他性地确定为是由于研究疾病进展导致，或者和研究疾病进展的症状特点不相符时，可记录为 AE。如果与研究疾病的怀疑进展明确一致，则不记录为 AE。恶性肿瘤进展本身不作为 AE 报告。

恶性肿瘤进展导致的临床症状，如果满足 SAE 标准，且不能完全排除与研究药物的相关性时，需要报告为 SAE。如果事件满足 SAE 标准（死亡事件除外），且与研究疾病的怀疑进展明确一致，则不报告为 SAE。SAE 报告收集的时间为从受试者签署知情同意书开始至末次给药后 30 天。

临床试验中，如受试者在安全随访期内死亡，都必须作为 SAE 报告，无论研究者是否评估其可能是与疾病进展有关。“死亡”一词不应作为 SAE 术语，而应作为事件的结果。将引起或导致死亡的医学状况/疾病（含症状和体征的恶化）作为 SAE 术语记录在 eCRF 中，并按

SAE 报告。如果在报告时无法确定死亡原因，则 SAE 术语记录为“不明原因死亡”。死亡结局的 SAE 报告收集的时间为从受试者签署知情同意书开始至末次给药后 30 天。

8.2.3 新的抗肿瘤治疗

如果受试者在安全随访期间开始新的抗肿瘤治疗，此后将不再收集不相关的 AE 和 SAE。如果死亡事件发生在安全随访期间，则必须作为 SAE 报告，无论是否有任何干预治疗，无论事件与研究治疗的因果关系。

8.2.4 SAE 的报告

SAE 收集将在签署 ICF 时开始，无论受试者是否筛查失败。SAE 的随访将持续到症状缓解或临床改善或稳定为止。

为确保受试者安全，在受试者签署知情同意书后和受试者停止研究治疗后 30 天内发生的任何 SAE，无论疑似因果关系如何，都必须在获悉其发生后 24 小时内报告给主办方。在受试者接受末次治疗 30 天后，则只报告怀疑与研究治疗有关的 SAE。

任何 SAE 的附加信息，包括并发症、初始 SAE 的进展和反复发作，必须在研究者收到随访信息后 24 小时内作为原始发作的随访报告。在不同的时间间隔内发生的 SAE 或被认为与以前报告的 SAE 完全无关的 SAE 应作为新的事件单独进行报告。

在安全随访期后发生的任何 SAE 仅当研究者怀疑与研究治疗存在因果关系时才应报告给申办方。

收集所有 SAE 的信息并记录在 SAE 报告表上；为了提供一份完整的临床报告，必须填写表格中所有适用的部分。研究人员必须评估并记录各 SAE 与研究治疗的关系，填写由研究人员签名的 SAE 报告表，并在 24 小时内将报告表发送给主办方和指定 CRO 药品安全部门，并根据当地要求及时向相关部门报告。

- **申办方药物警戒邮箱**：drugsafety@genfleet.com
- **泰格药物警戒邮箱:** PV@TigermedGrp.com

随访信息的提交方式与原始 SAE 报告表相同，使用新的 SAE 报告表，说明这是先前报告 SAE 的随访报告，并给出原始报告的日期。随访信息应描述事件是否已经缓解或持续，如何治疗，以及受试者是否继续参加研究或退出研究。

8.3 不良事件的因果关系判断

AE 与研究治疗的因果关系判断是指通过综合评估确定研究治疗对引起或促成 AE 是否存在合理的可能性。研究者应考虑的因素包括 AE 的发生是否与研究治疗给药存在合理时间顺序、研究治疗的特性、研究治疗的毒理学和药理学作用、合并用药的使用、受试者的基础疾病、病史、家族史、去激发（研究停药或减量后，症状/体征是否减轻或好转）、再激发（再次用药后，症状/体征是否复现或加重）等。通常应当提供判定因果关系的事实和依据。

请研究者根据以下列出的标准判断 AE/SAE 与研究药物的相关性：

表格 8 不良事件相关性判断结果分类及判断依据

相关性	判断依据
有关	• 有合理的时间关系 • 符合已知的药物作用机制、特性或已知的不良反应 • 去激发阳性 • 无其他合理的原因解释 • 再激发阳性
很可能有关	• 有合理的时间关系 • 符合已知的药物作用机制、特性或已知的不良反应 • 去激发阳性 • 无其他合理的原因解释 • 缺乏再激发阳性证据
可能有关	• 有合理的时间关系 • 缺乏再激发阳性证据 • 表现为以下任何一种情况： 1) 符合已知的药物作用机制、特性或已知的不良反应，去激发阳性，但也可用其他合理的原因解释； 2) 符合已知的药物作用机制、特性或已知的不良反应，缺乏去激发阳性证据，且无其他合理的原因解释； 3) 不符合已知的药物作用机制、特性或已知的不良反应，去激发阳性，无其他合理的原因来解释； 4) 不符合已知的作用机制、特性或已知的不良反应，缺乏去激发阳性证据，也无其他合理的原因解释。
可能无关	• 时间关系不能排除 • 缺乏去激发阳性证据 • 缺乏再激发阳性证据 • 表现为以下任何一种情况： 1) 不符合已知的作用机制、特性或已知的不良反应，且可用其他合理的原因解释； 2) 符合已知的作用机制、特性或已知的不良反应，但可用其他更加合理的原

	因解释；
无关	• 无合理的时间关系 • 不符合已知的药物作用机制、特性或已知的不良反应 • 缺乏去激发阳性证据 • 缺乏再激发阳性证据 • 可用其他合理的原因解释

注：在进行不良事件判断时，如果与表格中的判定依据无法完全对应时，请参考该表中对不良事件与药物相关性的专业判断逻辑，作出尽可能合理的判定结果。

表格 9 不良事件相关性判断简表

判断结果 / 判断依据	有关	很可能有关	可能有关				可能无关		无关
是否有合理的时间关系	+	+	+				±		-
是否符合已知的药物作用机制、特性或已知的不良反应	+	+	+		-		+	-	-
去激发结果	+	+	+	-/?	+	-/?	-/?		-/?
再激发结果	+	-/?	-/?				-/?		-/?
是否可用其他合理的原因解释	-	-	+	-	-	-	++	+	+

注：+表示肯定，或阳性结果；-表示否定，或阴性结果，或暂未获得结果的情况；±表示时间关系不能排除；++表示可用其他“更加”合理的原因解释；-/？表示去激发/再激发结果为阴性，或尚未进行去激发/再激发，或不适用去激发/再激发。

符合有关、很可能有关、可能有关的，将视为“相关”；符合无关、可能无关的，将视为“不相关”。如果研究人员对因果关系“未知”，或无法做出相关性判断，则应视为与药物有关的事件。研究人员应进一步收集的不良事件信息，并根据后续信息提供因果关系评估。

8.4 妊娠报告

临床研究期间女性受试者妊娠，则受试者必须终止研究治疗，并退出研究；临床研究期间男性受试者的伴侣妊娠，受试者可继续临床研究。研究者应在获知妊娠事件后的 24 小时内填写《临床研究妊娠报告/随访表》报告给申办方和指定的 CRO 药品安全部门。

研究者需对妊娠事件进行追踪至最终结果（包括任何的提前终止妊娠或分娩），分娩需随访至母亲生产后 1 个月，妊娠结果需报告申办方。如果妊娠结果符合 SAE 的标准（如宫外孕、自发性流产、胎儿宫内死亡、新生儿死亡或先天异常等），需要遵循 SAE 程序进行上报。

如果受试者在妊娠期间同时发生 SAE，则还须遵循 SAE 报告程序进行上报。

8.5 符合海氏法则事件的报告

若 AST 和/或 ALT 水平异常并发总胆红素水平异常升高，同时满足以下（1）（2）（3）条件且没有导致异常的其他原因，应始终将此类情况作为 SAE 进行上报，遵循 SAE 报告流程进行上报。

表格 10 海氏法则事件的判断标准

满足条件	判断标准
(1) ALT 或 AST 异常	1) 基线正常：治疗期 ALT 或 AST > 3×ULN 基线异常：治疗期 ALT 或 AST > 3×基线水平
(2) TBIL 异常	2) 基线正常：治疗期 TBIL > 2×ULN 基线异常：治疗期 TBIL > 2×基线水平
(3) 碱性磷酸酶 < 2×ULN（或未获得信息）	

缩略语：ALT=丙氨酸氨基转移酶，AST=天门冬氨酸氨基转移酶，TBIL=总胆红素，ULN=正常范围上限。

如果受试者在治疗期或者随访期间 AST 和/或 ALT 水平异常并发总胆红素水平异常升高，应尽可能在得知异常结果之后尽快返回研究中心进行检查和评估。应该包括相关肝功能实验室检查、详细询问病史和体格检查，并应考虑肝脏肿瘤（原发性或继发性）的可能性。

如发生满足上述标准的肝损事件，应遵循 5.3.1 和 5.3.2 进行相应的剂量调整或停止治疗。

8.6 药物过量的报告

药物过量的定义是任何意外或故意地超过计划剂量。如果药物过量导致了 AE，则必须在 eCRF 上记录 AE。如果药物过量与任何 SAE 相关，请参阅 **8.2.4 SAE 报告**部分。

8.7 AE/SAE/妊娠的报告时限

表格 11 AE/SAE/妊娠事件的报告时限

期限	收集要求
从受试者签署知情同意书开始，直至末次给药治疗后30天±3天，或直到开始新的抗肿瘤治疗	所有AE/SAE/妊娠事件 妊娠事件：研究治疗首次给药后开始收集
上述期限之后	与研究治疗有关的 SAE

缩略语：AE=不良事件，SAE=严重不良事件。

9. 统计分析

将在统计分析计划（SAP）中描述详细的统计分析方法，并将在临床数据库锁定前完成SAP 的定稿。

9.1. 样本量

9.1.1. I 期：剂量递增部分

将根据 BOIN 设计，在每个剂量组入组 3-6 例受试者（加速滴定时除外）接受治疗。将根据已获得的安全性/耐受性、PK 及初步有效性数据，可能选择一个或多个剂量组入组额外的受试者作为回填， 接受已确认安全且耐受性良好的、经研究者及申办方评估可能临床获益的GFH375 单药剂量进行治疗，以更好的估计 GFH375 单药的 RP2D 以及表征其安全性\耐受性、PK 及有效性。回填的受试者不被纳入 DLT 的评估。回填后，接受 GFH375 每个剂量组治疗的受试者不超过 30 例（包括 BOIN 剂量递增阶段入组的受试者）。

如果需要探索更多的剂量组或替代给药方案，则可以入组额外的受试者。

9.1.2. II 期

总共预计入组约 317 例受试者，其中约 73 例晚期 NSCLC 受试者、94 例晚期 PDAC 受试者、50 例晚期 CRC 受试者、100 例晚期其他实体瘤受试者。

肿瘤类型	历史对照 ORR	预期 ORR	样本量
NSCLC	23%	40%	73
PDAC	15%	30%	94
CRC	10%	30%	50
其他			100
合计			317

对于晚期二线 NSCLC，ORR 的历史对照值为 23%，预计本研究 ORR 可达到 40%。若观测到的 ORR 的 95% CI 下限不低于历史对照 23%，则视为成功。单侧 α = 0.025，要达到 89%把握度，则需要 73 例受试者。当 73 例受试者中有至少 25 例 CR/PR 时，ORR 观测值的 exact 95% CI 下限高于历史对照 23%。25 例 CR/PR 时，ORR＝34.2%，其 95% CI 为 23.5%, 46.3%。

对于晚期二线 PDAC，ORR 的历史对照值设定值为 15%，预计 GFH375 治疗下 ORR 可达到 30%，若采用 GFH375 治疗后 ORR 的 95%CI 下限大于 15%，则认为 GFH375 的疗效具有统计学显著意义。当单侧 α ＝0.025，94 例受试者可获得 95%的把握度以保证试验数据获得 ORR 的 95%CI 下限大于 15%。计划入组 PDAC 受试者约 94 例。当 94 例受试者中观察到 22 例获得

缓解（PR/CR）时， ORR 观测值的 exact 95% 为（15.29%，33.26%）。因此 94 例受试者中观察到≥22 例缓解时，则认为 GFH375 的疗效具有统计学意义。

对于三线 CRC，ORR 的历史对照值为 10%，预计本研究 ORR 可以达到 30%。若观测到的 ORR 的 95% CI 下限不低于历史对照 10%，则视为成功。计划入组 50 例受试者，在单侧 α = 0.025 的情况下，把握度可达到 96%。当 50 例受试者中有至少 10 例 CR/PR 时，ORR 观测值的 exact 95% CI 下限高于历史对照 10%。10 例 CR/PR 时，ORR = 20.0%，其 95% CI 为 (10.0%, 33.7%)。

对于其他实体瘤：计划入组约 100 例 KRAS G12D 突变的晚期实体瘤受试者，如携带 KRAS G12D 突变的胆管癌、阑尾癌等。

以上样本量和 ORR（及其 95% exact CI） 的计算使用了 R 语言。其中，样本量计算使用了“gsDesign”package 中的“nBinomial1Sample”function（option：conservative = TRUE）；ORR 及其 95% exact CI 使用了“epitools”package 中的“binom.exact”function（default options）。

9.2. 分析集

- 全分析集 (FAS)：至少接受 1 次 GFH375 给药的所有受试者。
- 安全性分析集 (SS)：至少接受 1 次 GFH375 给药且至少有 1 次有效的基线后安全性评估的所有受试者。
- 剂量确定分析集 (DDS)： I 期 SS 中在 DLT 观察期间至少累计 15 天接受未减量的 GFH375 的所有受试者、有充分的安全性评估，或在 DLT 观察期间发生 DLT。DDS 不包含回填（backfill）的受试者。
- 符合方案集 (PPS)： FAS 中符合方案的所有 II 期受试者。研究团队将在最终数据库锁定前对所有方案偏离进行审查，据此将发生影响疗效评价的重大方案偏离的受试者从 PPS 中排除。
- 药代动力学分析集 (PKAS)：至少接受 1 次 GFH375 给药且至少有 1 份血样提供可评价 PK 数据的所有受试者。

9.3. 统计分析方法

将对 I 期、 II 期的数据分别单独进行分析汇总。其中，I 期的数据将按照不同剂量水平和给药方案进行分析汇总；II 期的数据将按照肿瘤类型分别进行分析汇总。

9.4. 安全性分析

按系统器官分类、首选术语、严重程度汇总 AE、治疗相关 AE 、 SAE 的发生率。对于 I 期部分，基于 DDS 汇总各类 DLT 的发生率，并对 DLT 进行列表。对实验室检查、生命体征、ECG 进行描述性汇总。

9.5. 有效性分析

计算最佳总体缓解 (BOR)、ORR、DCR 的相应人群占比，并采用 Clopper-Pearson 方法估计 ORR 和 DCR 的双侧 95%置信区间 (CI)。采用 Kaplan-Meier 方法估计 DoR、PFS、 OS 的中位数及其 95% Brookmeyer-Crowley CI。对 TTR 进行描述性汇总。

对于 I 期阶段，当分析组的样本量小于 10 例时，将按受试者单独列出 DoR、TTR、PFS、OS，不采用 Kaplan-Meier 方法进行分析。

对于 II 期阶段，设置**主要估计目标**如下：

研究人群	KRAS G12D 突变型晚期实体瘤受试者（按瘤种）
治疗	GFH375
终点	根据 RECIST 1.1 标准评估达到 CR 或 PR 的受试者百分比。若受试者基线后无任何评价结果，则认为该受试者未缓解。 **注：**对于 NSCLC 和 PDAC，将基于 BICR 评估的确认的 CR 或 PR 的受试者百分比。
伴发事件	开始新的抗肿瘤治疗（处理策略：在治策略，开始新的抗肿瘤治疗后的评估结果不纳入分析。）
群体层面汇总	ORR

9.6. 药代动力学分析

将对血浆中GFH375的浓度数据按照方案规定的采样时间进行列表和描述性统计汇总，汇总将按照研究分期、剂量组和给药频率呈现。将使用线性和半对数坐标，按研究分期、剂量组和给药频率绘制个体受试者的血浆中GFH375浓度-时间曲线和相应的汇总曲线（平均值 + 标准差）。使用计划PK采样时间计算汇总统计量及绘制汇总曲线（平均值 + 标准差）；将使用实际PK采样时间，绘制个体受试者曲线。

将使用Phoenix WinNonlin软件（v8.2版或以上版本, Certara USA, Inc., New Jersey, US）采用非房室模型分析（NCA），按实际采血时间点计算GFH375的PK参数。对I期剂量递增阶段受试者单次和多次给药后GFH375的PK参数进行描述性统计汇总，汇总按照剂量组和给药频

率呈现。

9.7 生物标志物评估

在I和II期收集基线和治疗结束时的血液样本分离ctDNA进行NGS检测，探索与治疗敏感或耐药相关的肿瘤基因变异。

II期PDAC受试者会在基线、治疗期间以及治疗结束时检测CA19-9，以探索其变化与治疗应答的相关性。

9.8 期中分析

将分别对NSCLC、PDAC、CRC进行无效性中期分析。对于单个瘤种，计划在约35例受试者（包括I期接受RP2D治疗的受试者和II期受试者）至少有一次基线后影像学肿瘤评估或提前退出研究时进行。考虑实际临床操作的原因，允许中期分析时的受试者例数与计划例数有所差别。期中分析过程中，项目不停止入组。

期中分析时，将分别针对 NSCLC、PDAC、CRC 的 ORR，采用贝叶斯预测概率的方法进行无效性分析。允许（但不强制）因缺乏有效性证据而提前终止对相应瘤种的研究。

基于观察到的获得缓解（CR/PR）的 II 期受试者例数计算预测成功概率（PPoS），如果 PPoS < 0.2，则允许（但不强制）因为缺少有效性证据而提前终止入组。PPoS < 0.2 的对应的终止标准见下表：

瘤种	受试者例数*	建议终止试验，当缓解受试者例数 ≤
NSCLC	20 ~ 21	3
	22 ~ 25	4
	26 ~ 29	5
	30 ~ 33	6
	34 ~ 37	7
	38 ~ 41	8
	42 ~ 45	9
PDAC	25 ~ 26	2
	27 ~ 33	3
	34 ~ 39	4

瘤种	受试者例数*	建议终止试验，当缓解受试者例数 ≤
	40 ~ 45	5
CRC	20 ~ 23	1
	24 ~ 30	2
	31 ~ 37	3
	38 ~ 43	4
	44 ~ 48	5

*受试者例数：至少有一次基线后影像学肿瘤评估或提前退出研究（至少满足其一）的I期接受 RP2D 治疗的受试者和 II 期受试者数之和。

上述计划的中期分析不强制进行，在达到中期分析计划的时间点前，如果有足够的安全性和有效性综合数据支持，可以省略该中期无效性分析。

10. 安全监查

本研究将成立由研究者及申办方组成的安全性监查委员会（SMC）。SMC 将从第一位受试者首次给药开始持续审查安全性数据，直至研究结束。在剂量递增及扩展阶段，SMC 成员将审阅安全性数据、PK 数据等，以决定下一个剂量的入组或者探索潜在的其他剂量组，并推荐合适的 RP2D。

研究期间，若研究者及申办方均认为受试者存在安全性风险或已达到耐受限度，剂量递增或研究治疗将立即停止。

详细信息请参阅 SMC 章程。

11 研究质量保证和质量控制

根据药物临床试验质量管理规范（GCP）的指导原则，申办方有责任根据相应标准操作流程实施和维护质量保证和质量控制系统，以确保临床试验的实施及数据的真实，收集、记录和汇报遵循方案、GCP和相应的法规要求。

11.1 临床监查

申办方或申办方授权的合同研究组织（CRO）对此研究进行临床监查。临床监查员应按照申办方或CRO的标准操作流程进行监查，并具有与申办方监查员相同的权利和责任。监查员应与研究者，及试验授权人员和申办方保持定期交流。

在研究开始前，监查员将评估各研究中心的胜任能力，并将设施、技术装备，或医务人员的相关问题报告给申办方。在研究过程中，监查员将负责监查研究者是否已获得所有受试者的书面知情同意书，以及数据记录是否正确、完整。同时，监查员也将对输入到eCRF的数据与原始数据进行比较，并告知研究者出现的错误或遗漏。监查员还将控制研究中心的方案和试验流程的依从性，安排供应研究用药，并确保药物保存在适当的条件。

监查访视将按照相关法律法规的要求进行。从受试者入组开始，每个中心将接受定期监查访视。每次对研究者进行访视后，监查员应向申办方提交书面报告。

11.2 质量保证稽查

研究过程中，申办方或申办方授权的代表可能对研究中心、研究数据库和相关研究文件进行质量保证的稽查，同时，相应监管机构也可自行决定对研究中心、研究数据库和相关研究文件进行视察。当研究者收到监管机构视察通知后，需立即告知申办方。

申办方的质量保证部门对临床试验机构进行稽查。稽查包括：药物的供给、所要求的试验文件、知情同意过程的记录、以及病历报告表与原始文件的一致性等。也可根据情况增加稽查内容和范围。在进行合理的通知后，研究者应允许申办方委托的稽查人员进行试验相关的稽查和管理当局进行的视察。稽查或视察的主要目的是证实参加试验的受试者的权利或健康得到保护，知情同意的签署及试验过程的实施正确进行，所有与研究药物评价有关的数据的处理和汇报与预先计划安排、方案、设施、伦理的标准操作规程、GCP 和适用的法规要求一致。研究者应使其能直接接触到所有试验文件、原始记录和原始数据。

12 伦理学

12.1 伦理委员会

申办方或其申办方授权的代表将准备需提交给研究中心的EC的相关文件，包括试验方案、知情同意书、研究者手册、受试者招募材料或广告及其它法规要求的文件都要提交给相应的EC进行审批。在开始本研究之前，必须获得研究中心EC的书面批准，并提供给申办方。EC的批件上必须确切说明研究方案的名称、编号、版本号及其它文件的版本号（例知情同意书）和批准日期。研究者需将EC关于延迟、暂停、重新批准的书面意见通知申办方。

研究中心必须遵循本中心EC的要求。可能包括方案修订、知情同意书修订、受试者招募材料修订时需提交EC进行审批，当地的安全性报告要求，按照EC规定进行定期报告和更新，提交终版报告。以上所有文件及EC批件均须提供给申办方或其指定人员。

12.2 伦理学执行

研究过程及知情同意的获取应遵守赫尔辛基宣言、相关GCP要求及中国的药品和数据保护相关的法律法规。

GCP为有人类受试者参加的临床研究的设计、实施、记录和报告提供了符合伦理要求的、科学的全球性质量标准。此研究将按照GCP和相关国家法规进行，并遵守赫尔辛基宣言中相关的伦理原则，以保护受试者的权利、安全和健康。

研究者需遵守本试验方案规定的流程，不得未经申办方允许更改。任何的方案偏离将向EC、申办方、或监管机构报告。

12.3 受试者信息和知情同意

在任何研究流程开始前，使用ICF向可能参加的受试者解释本研究可能带来的风险和受益，知情同意语言应简单易懂。ICF声明中应明确，知情同意为自愿签署，并明确参加本研究可能带来的风险和受益，且受试者可随时退出研究。研究者只有在充分解释研究的详细内容，受试者的问题得到满意答复，并给予足够时间考虑后，获得受试者或其监护人的书面同意后，方可入组受试者。所有签署过的知情同意书必须在研究者文档中或受试者文件夹中。

研究者负责向受试者解释知情同意内容，并在研究开始前获得受试者或其监护人签署并注明日期的知情同意书。在签署后，研究者应当发给受试者一份签署完毕的知情同意书副本。研究者需将知情同意的过程记录在试验原始文件中。

初始知情同意书、任何后续修订的书面知情同意书以及提供给受试者的任何书面信息在使用前应获得IRB/IEC的意见。如果获得了可能与受试者继续参与试验意愿相关的新信息，应及时告知受试者或其监护人。将通过修订的知情同意书或原始知情同意书附录（获取受试者注明日期的签名或受试者的法监护人注明日期的签名）提供并记录该信息的沟通。

12.4 数据保护

ICF中将包含（或在某些情况下，连同使用独立的文件）数据保护和隐私保护的相关信息。

采取预防措施保证文件的机密性，防止判断出受试者身份。然而，在特殊情况下，某些人员可能会看到某受试者的遗传数据和个人识别码。例如，在出现医疗急救的情况下，申办方、其代表医生或研究者知悉受试者识别码，并具有该受试者基因数据的访问权。此外，相关监管机构要求访问相关文件。

12.5 方案偏离

方案偏离是指任何不依从临床试验方案、国际协调会议药物临床试验管理规范（ICH GCP）或操作手册要求的情况。不依从情况可能来自于受试者、研究者或试验机构工作人员。针对违背情况，应采取纠正措施并及时完成。

13 研究管理

13.1 数据处理和记录保存

临床试验中的文件（方案和方案修订，完成的 eCRF，签署的 ICF 等）需按照 GCP 的要求进行保存和管理。研究中心应将这些文件保存到研究结束后 5 年。

研究文件应合理保存，以便日后访问或数据溯源。保存文件时应考虑安全及环境风险问题。

未经申办方及研究者的书面许可，不得销毁任何研究文件。只有在通知申办方并得到其书面同意后，研究者/研究中心方可将研究文件转交给遵守文件保存要求的其他方或转移到满足要求的其他地点保存。

13.2 原始数据/文件访问权限

研究者同意申办方、CRO及相关授权监管部门直接访问所有研究相关文件，包括受试者病历。

13.3 方案修订

在研究进行过程中对方案进行的所有修订均需申办方与研究者沟通并得到同意。申办方应确保及时向管理部门提交方案修订。

方案的所有修订均应作为方案增补件保存。对方案的任何修改，都需提交伦理委员会，根据伦理委员会的规定进行批准或备案。如需要，也应提交给监管部门进行审批，并经 EC 和监管部门（若需要）批准后方可执行（为消除对试验受试者的直接危害而对方案进行的变更除外）。

13.4 研究者职责

研究者将遵循方案、赫尔辛基宣言的伦理原则、ICH GCP 及相应的法规要求开展本研究。

相关研究者的详细职责在中国 GCP（2020 年第 57 号）第 5 章中列出。

13.5 出版政策

本研究产生的所有数据均为申办方的保密信息，申办方有权公布研究结果。关于申办方与研究者出版政策方面的信息将在临床试验协议中描述。

所有有关本次试验的信息（不限于以下文件：方案和研究者手册）都必须严格保密。研究者必须认识到由这次试验所得出的科学或医学结论可能对申办方具有商业价值。研究者应

该对与本试验相关的信息和数据予以保密，若要公开发表与本次试验有关的数据或从试验中所得出的结论，需提前与申办方协商并征得申办方书面同意。为了保护自身权益，申办方可以要求研究者在本试验产品获得上市批准前不发表相关的试验数据。

申办方有权发表或出版与本试验相关的信息或数据，或将之呈报给药品管理部门。申办方如需在发表、出版或广告内容中出现研究者的姓名，应征得研究者的同意。

13.6 财务和保险

申办方将根据当地法规和最低要求为参加本研究的受试者购买保险。保险相关条款将保存在研究文件夹中。

14 数据管理

14.1 数据保密性

将根据适用的法律法规对研究受试者相关信息进行保密和管理。

数据采集系统的访问将通过一系列单独分配的用户名和密码来控制，这些账户和密码仅提供给已完成必要培训的授权人员使用。

14.2 数据采集

本研究的数据采集使用 EDC 系统完成。

研究者或指定的研究人员将根据方案向 eCRF 中输入数据。研究中心工作人员只有在接受培训之后方可进入 EDC 系统。系统将由自动化核查流程检查 eCRF 中的数据不一致情况，允许对中心工作人员输入的数据进行修改或核查。

在 EDC 中进行数据修改时，需按照系统提示，填写数据修改的原因。修改履历和修改原因会被记录在 EDC 系统的稽查轨迹中。研究者或其授权的人员需要对 eCRF 数据的真实性、完整性和及时性进行确认，并在 EDC 系统中进行电子签名。

14.3 数据管理

申办方或指定的 CRO 人员将审核研究人员输入数据的完整性和准确性。对于任何不一致或缺失的数据，需要发送数据质疑给研究中心。要求指定的研究中心人员及时解答质疑，并对数据做出必要的变更。

本项目将使用世界卫生组织药物词典(WHODrug)对录入到数据库中的合并治疗和既往用药进行编码。将使用 MedDRA 术语对病史/当前疾病和不良事件编码。

数据库锁定之前研究团队需要完成数据清理，并汇总研究进行中出现的所有方案偏离的事件，并召开数据审核会议确定分析人群。数据审核会议中所作的决定都需用文件记录。数据审核会议通过后，经研究团队确认对 EDC 系统中的研究数据库进行锁定。如需对锁定后的数据进行任何变更，需要经项目组讨论后授权解锁数据库。

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16 附录

附录 1：实体瘤疗效评价标准 1.1 版（RECIST V1.1）

注：此翻译版本仅供参考，最终版本以英文版为准。

1. 肿瘤在基线水平的可测量性

1.1 定义

在基线水平上，肿瘤病灶/淋巴结将按以下定义分为可测量和不可测量两种：

可测量病灶

肿瘤病灶：至少有一条可以精确测量的径线（记录为最大径），其最小长度如下：

- CT 扫描 10 mm（CT 扫描层厚不大于 5 mm）
- 临床常规检查仪器 10 mm（肿瘤病灶不能用测径仪器准确测量的应记录为不可测量）
- 胸部 X-射线 20 mm
- 恶性淋巴结：病理学增大且可测量，单个淋巴结 CT 扫描短径须≥15mm（CT 扫描层厚推荐不超过 5 mm）。基线和随访中，仅测量和随访短径。

不可测量病灶

所有其他病灶，包括小病灶（最长径＜10 mm 或者病理淋巴结短径≥10 mm 至＜15 mm）和无法测量的病灶。无法测量的病灶包括：脑膜疾病、腹水、胸膜或者心包积液、炎性乳腺癌、皮肤/肺的癌性淋巴管炎、影像学不能确诊和随诊的腹部包块，以及囊性病变。

关于病灶测量的特殊考虑

骨病灶、囊性病灶和先前接受过局部治疗的病灶需要特别注明：

骨病灶：

- 骨扫描、PET 扫描或者平片不适合于测量骨病灶，但是可用于确认骨病灶的存在或者消失；
- 溶骨性病灶或者混合性溶骨/成骨病灶有确定的软组织成分，且软组织成分符

合上述可测量性定义时，如果这些病灶可用断层影像技术如 CT 或者 MRI 进行评价，那么这些病灶可以作为可测量病灶；

- 成骨病灶属不可测量病灶。
- 囊性病灶：
- 符合放射影像学单纯囊肿定义标准的病灶，不应因其为定义上的单纯性囊肿，而认为是恶性病灶，既不属于可测量病灶，也不属于不可测量病灶；
- 若为囊性转移病灶，且符合上述可测量性定义的，可以作为是可测量病灶。但如果在同一病人中存在非囊性病灶，应优先选择非囊性病灶作为靶病灶。

局部治疗过的病灶；

- 位于曾放疗过或经其他局部区域性治疗的部位的病灶，一般作为不可测量病灶，除非该病灶出现明确进展。研究方案应详细描述这些病灶属于可测量病灶的条件。

1.2 测量方法说明

病灶测量

临床评价时，所有肿瘤测量都要以公制米制记录。所有关于肿瘤病灶大小的基线评定都应尽量在接近治疗开始前完成，且必须在治疗开始前的 28 天内（4 周）完成。

评价方法

对病灶基线评估和后续测量应采用同样的技术和方法。除了不能用影像学检查，而仅能用临床检查来评价的病灶之外，所有病灶必须使用影像学检查进行评价。

临床病灶：临床病灶只有位于浅表且测量时直径≥10mm 时才能认为是可测量病灶（如皮肤结节等）。对于有皮肤病灶的患者，建议用含有标尺测量病灶大小的彩色照片作为存档。当病灶同时使用影像学和临床检查评价时，由于影像学更客观且研究结束时可重复审阅，应尽可能选用影像学评价。

胸部 X 片：当肿瘤进展作为重要研究终点时，应优先使用胸部 CT，因为 CT 比 X 线更敏感，尤其对于新发病灶。胸部 X 片检测仅当被测量病灶边界清晰且肺

部通气良好时适用。

CT、MRI：CT 是目前用于疗效评价最好的可用可重复的方法。本指导原则对可测量性的定义建立在CT扫描层厚≤5 mm的基础上。如果CT层厚大于5 mm，可测量病灶最小应为层厚的2倍。建议采用增强CT进行疗效评估（除非有造影剂禁忌）。MRI在部分情况下也可接受（如全身扫描）。

超声：超声不应作为一种测量方法用于测量病灶大小。超声检查因其操作依赖性，在测量结束后不具备可重复性，不能保证不同测量间技术和测量的同一性。如果在研究期间使用超声发现新病灶，应使用 CT 或者 MRI 进行确认。如果考虑到 CT 的放射线暴露，可以使用 MRI 代替。

内窥镜，腹腔镜检查：不建议使用这些技术用于肿瘤客观评价，但这种方法在取得的活检标本时可以用于确认 CR，也可在研究终点为 CR 后复发或手术切除的研究中，用于确认复发。

肿瘤标志物：肿瘤标志物不能单独用来评价肿瘤客观缓解。但如果标志物水平在基线时超过正常值上限，用于评价完全缓解时必须回到正常水平。因为肿瘤标志物因病而异，在将测量标准写入方案中时需考虑到这个因素。有关 CA-125 缓解（复发性卵巢癌）及 PSA（复发性前列腺癌）缓解的特定标准已经发表。且国际妇科癌症组织已制定了 CA-125 进展标准，即将被加入到卵巢癌一线治疗方案的肿瘤客观评价标准中。

细胞学/组织学技术：在方案规定的特定情况下，这些技术可用于鉴定 PR 和 CR（如生殖细胞肿瘤的病灶中常存在残留的良性肿瘤组织）。当渗出可能是某种疗法潜在的副反应（如使用紫杉烷化合物或血管生成抑制剂的治疗），且可测量肿瘤符合缓解或疾病稳定标准时，在治疗过程中肿瘤相关的渗出出现或加重，可通过细胞学技术来确诊，以区分缓解（或疾病稳定）和疾病进展。

2. 肿瘤缓解的评估

2.1 靶病灶评估

完全缓解（CR）：所有靶病灶消失，全部病理淋巴结（包括靶结节和非靶结节）短直径必须减少至＜10 mm。

部分缓解（PR）：靶病灶直径之和比基线水平减少至少 30%。

疾病进展（PD）：以整个实验研究过程中所有测量的靶病灶直径之和的最小值为参照，直径和相对增加至少 20%（如果基线测量值最小就以基线值为参照）；除此之外，必须满足直径和的绝对值增加至少 5 mm（出现一个或多个新病灶也视为疾病进展）。

疾病稳定（SD）：靶病灶减小的程度没达到 PR，增加的程度也没达到 PD 水平，介于两者之间，研究时可以直径之和的最小值作为参考。

2.2 靶病灶评估的注意事项

淋巴结：即使鉴定为靶病灶的淋巴结减小至 10 mm 以内，每次测量时仍需记录与基线对应的实际短直径的值（与基线测量时的解剖平面一致）。这意味着如果淋巴结属于靶病灶，即使达到完全缓解的标准，也不能说病灶已全部消失，因为正常淋巴结的短直径就定义为＜10 mm。在 CRF 表或其他的记录方式中需在特定位置专门记录靶淋巴节病灶：对于 CR，所有淋巴节短直径必须＜10 mm；对于 PR、SD 和 PD，靶淋巴节短直径实际测量值将被包含在靶病灶直径的和之中。

小到无法测量的靶病灶：临床研究中，基线记录过的所有病灶（结节或非结节）在后面的评估中都应再次记录实际测量值，即使病灶非常小（如 2 mm）。但有时候可能太小导致 CT 扫描出的图像十分模糊，放射科医生也很难定义出确切的数值，就可能报告为“太小而测量不到”。出现这种情况时，在 CRF 表上记录上一个数值是十分重要的。如果放射科医生认为病灶可能消失了，那也应该记录为 0 mm。如果病灶确实存在但比较模糊，无法给出精确的测量值时，可默认为 5 mm。（注：淋巴结出现这种情况的可能性不大，因其正常情况下一般都具有可测量的尺寸，或者像在腹膜后腔中一样常常为脂肪组织所包绕；但是如果也出现这种无法给出测量值的情况，也默认为 5 mm）。5 mm 的默认值源于 CT 扫描的切割厚度（这个值不因 CT 不同的切割厚度值而改变）。由于同一测量值重复出现的几率不大，提供这个默认值将降低错误评估的风险。但需要重申的是，如果放射医生能给出病灶大小的确切数值，即使病灶直径小于 5 mm，也必须记录实际值。

分离或结合的病灶：当非结节性病灶分裂成碎片状时，将各分离部分的最长

径加起来计算病灶的直径之和。同样，对于结合型病灶，通过各结合部分间的平面可将其区分开来，然后计算各自的最大直径。但如果结合得密不可分，最长径应取融合病灶整体的最长径。

2.3 非靶病灶的评估

这部分对非靶病灶肿瘤的缓解标准进行了定义。虽然一些非靶病灶实际可测量，但无需测量，只需在方案规定的时间点进行定性评估即可。

完全缓解（CR）：所有非靶病灶消失，且肿瘤标记物恢复至正常水平。所有淋巴结为非病理尺寸（短径＜10 mm）。

非完全缓解/非疾病进展：存在一个或多个非靶病灶和/或持续存在肿瘤标记物水平超出正常水平。

疾病进展：已存在的非靶病灶出现明确进展。注：出现一个或多个新病灶也被视为疾病进展。

2.4 关于非靶病灶进展评估的特别注意事项

关于非靶病灶进展的定义补充解释如下：当患者存在可测量非靶病灶时，即使靶病灶评估为稳定或部分缓解，要在非靶病灶的基础上作出明确进展的定义，必须满足非靶病灶整体的恶化程度已达到必须终止治疗的程度。而一个或多个非靶病灶尺寸的一般性增大往往不足以达到进展标准，因此，在靶病灶为稳定或部分缓解时，仅依靠非靶病灶的改变就能定义整体肿瘤进展的情况几乎是十分稀少的。

当患者的非靶病灶均不可测量时：在一些III期研究中，当入选标准中没有规定必须存在可测量病灶时，就会出现这种情况。整体评估还是参照上文标准，但因为这种情况下没有病灶的可测量数据。非靶病灶的恶化不容易评估（根据定义：必须所有非靶病灶都确实无法测量），因此当非靶病灶改变导致整体疾病负荷增加的程度相当于靶病灶出现疾病进展时，依据非靶病灶作出明确进展的定义，需要建立一种有效的检测方法来进行评估。如描述为肿瘤负荷增加相当于体积额外增加 73%（相当于可测量病灶直径增加 20%）。又比如腹膜渗出从“微量”到“大量”；淋巴管病变从“局部”到“广泛播散”；或在方案中描述为“足够至改变治疗方法”。例子包括胸膜渗出液从痕量到大量，淋巴受累从原发部位向远处扩散，或者在方

案中可能被描述为“有必要进行治疗方面的改变”。如果发现有明确的进展，该患者应该在那个时点总体上视为疾病进展。最好具有客观标准可适用于不可测量的病灶的评估，注意，增加的标准必须是可靠的。

2.5 新病灶

新的恶性病灶的出现预示着疾病的进展；因此针对新病变的一些评价是非常重要的。目前没有针对影像学检测病灶的具体标准，然而一种新的病灶的发现应该是明确的。比如说，进展不能归因于影像学技术的不同，成像形态的改变，或者肿瘤以外的其它病变（如：一些所谓新的骨病灶仅仅是原病灶的治愈，或原病灶的复发）。当病人的基线病灶出现部分或完全反应时，这一点非常重要的，例如：一例肝脏病灶的坏死可能在 CT 报告上定为新的囊性病变，而其实不是。

在随访中已检测到的而在基线检查中未发现的病灶将视为新的病灶，并提示疾病进展。例如一个在基线检查中发现有内脏病灶的患者，当他做 CT 或 MRI 的头颅检查时发现有转移灶，该患者的颅内转移病灶将被视为疾病进展的依据，即使他在基线检查时并未做头颅检查。

如果一个新的病灶是不明确的，比如因其形态小所致，则需要进一步的治疗和随访评价以确认其是否是一个新的病灶。如果重复的检查证实其是一个新的病灶，那么疾病进展的时间应从其最初的发现的时间算起。

病灶进行 FDG-PET 评估一般需要额外的检测进行补充确认，FDG-PET 检查和补充 CT 检查结果相结合评价进展情况是合理的（尤其是新的可疑疾病）。新的病灶可通过 FDG-PET 检查予明确的，依据以下程序执行：

基线 FDG-PET 检查结果是阴性的，接下来随访的 FDG-PET 检查是阳性的，表明疾病的进展。

没有进行基线的 FDG-PET 检查，后续的 FDG-PET 检查结果是阳性的：

如果随访的 FDG-PET 阳性检查结果发现的新的病变灶与经 CT 检查结果相符，证明是疾病进展。

如果随访的 FDG-PET 的阳性检查结果发现的新的病变灶未能得到 CT 检查结果的确认，需再行 CT 检查予以确认（如果得到确认，疾病进展时间从前期 FDG-

PET 检查发现异常算起）。

如果随访的 FDG-PET 的阳性检查结果与经 CT 检查已存在的病灶相符，而该病灶在影像学检测上无进展，则疾病无进展。

2.6 评估缺失和不可评价说明

如果在某个特定时间点上无法进行病灶成像或测量，则该患者在该时间点上无法评价。如果在一个评价中只能对部分病灶进行评价，通常这种情况视为在那个时间点无法评价，除非有证据证实缺失的病灶不会影响指定时间点的疗效反应评价。

2.7 疗效评估的特别提示

当结节性病灶被包括在总的靶病灶评估中，同时该结节大小缩小到“正常”大小时（＜10 mm），它们依然会有一个病灶大小扫描报告。为了避免过高评估基于结节大小增加所反映的情况，即便是结节正常，测量结果也将被记录。正如前面已经提及的，这就意味着疗效为完全缓解的受试者，CRF 表上也不会记录为 0。

若研究过程中需要进行疗效确认，重复的“不可测量”时间点将使最佳疗效评估变得复杂。研究的分析计划必须说明，在确定疗效时，这些缺失的数据/评估可以被解释清楚。比如，在大部分研究中，可以将某受试者 PR-NE-PR 的反应作为得到了疗效确认。

当受试者出现健康情况整体恶化要求停止给药治疗，但是没有客观证据证明时，应该被报道为症状性进展。即便在治疗终止后也应该尽量去评估客观进展的情况。症状性恶化不是客观反应的评估描述，它是停止治疗的原因。那样的受试者的客观反应情况将通过附表 1～3 所示的目标和非目标病灶情况进行评估。

定义为早期进展、早期死亡和不可评估的情况是研究特例，且应该在每个方案中进行明确的描述（取决于治疗间期和治疗周期）。

在一些情况下，从正常组织中辨别局部病灶比较困难。当完全缓解的评估基于这样的定义时，我们推荐在进行局部病灶完全缓解的疗效评估前进行活检。当一些受试者局部病灶影像学检测结果异常被认为是代表了病灶纤维化或者疤痕形成时，FDG-PET 被当作与活检相似的评估标准，用来对完全缓解进行疗效确认。

在此种情况下，应该在方案中对 FDG-PET 的应用进行前瞻性描述，同时以针对此情况专科医学文献的报告作为支持。但是必须意识到的是由于 FDG-PET 和活检本身的限制性（包括二者的分辨率和敏感性高低），将会导致完全缓解评估时的假阳性结果。

附表 1. 时间点反应-有靶病灶的受试者（包括或者不包括非靶病灶）

目标病灶	非目标病灶	新病灶	总缓解
CR	CR	无	CR
CR	非 CR/非 PD	无	PR
CR	不能评估	无	PR
PR	非进展或者不能完全评估	无	PR
SD	非进展或者不能完全评估	无	SD
不能完全评估	非进展	无	NE
PD	任何情况	是或否	PD
任何情况	PD	是或否	PD
任何情况	任何情况	是	PD

注：CR=完全缓解，PR=部分缓解，SD=疾病稳定，PD=疾病进展，NE=不能评估。

附表 2. 时间点反应-仅有非目标病灶的受试者

非目标病灶	新病灶	总缓解
CR	无	CR
非 CR 或者非 PD	无	非 CR 或非 PD
不能完全评估	无	不能评估
不能明确的 PD	是或否	PD
任何情况	是	PD

注：对于非目标病灶，“非 CR/非 PD”是指优于 SD 的疗效。由于 SD 越来越多作为评价疗效的终点指标，因而制定非 CR/非 PD 的疗效，以针对未规定无病灶可测量的情况。

对于不明确的进展发现（如非常小的不确定的新病灶；原有病灶的囊性变或坏死病变）治疗可以持续到下一次评估。如果在下一次评估中，证实了疾病进展，进展日期应该是先前出现疑似进展的日期。

附表 3. CR 和 PR 疗效需要确认的最佳总缓解

第一个时间点总缓解	随后时间点总缓解	最佳总缓解
CR	CR	CR
CR	PR	SD，PD 或 PRa
CR	SD	如果 SD 持续足够时间则为 SD，否则应为 PD
CR	PD	如果 SD 持续足够时间则为 SD，否则应为 PD
CR	NE	如果 SD 持续足够时间则为 SD，否则应为 NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	如果 SD 持续足够时间则为 SD，否则应为 PD
PR	NE	如果 SD 持续足够时间则为 SD，否则应为 NE
NE	NE	NE

注：CR 即是完全缓解，PR 是部分缓解，SD 是疾病稳定，PD 是疾病进展，NE 即不可评价。上标“a”：如果在第一个时间点 CR 真正出现，在随后的时间点出现的任何疾病，那么即便相对于基线该受试者疗效达到 PR 标准，其疗效评价在之后的时间点仍然为 PD（因为在 CR 之后疾病将再次出现）。最佳缓解取决于是否在最短的治疗间隔内出现 SD。然而有时第 1 次评价为 CR，但随后的时间点扫描提示小病灶似乎依然出现，因而实际上受试者疗效在第一个时间点应该是 PR 而不是 CR。在这种情况下，首次 CR 判断应该被修改为 PR，同时最好的反应是 PR。

2.8 疗效评估/缓解期的确认

疗效确认

对于以肿瘤缓解疗效为主要研究终点的非随机临床研究，必须对 PR 和 CR 的疗效进行确认，以保证疗效不是评价失误的结果。以疾病稳定或者疾病进展为主要研究终点的研究中，不再需要疗效确认，因为这对于研究结果的解释没有价值。SD 的情况下，在研究开始后的最短时间间隔内（一般不少于 6～8 周），至少有一次测量符合方案中规定的 SD 标准。

总缓解期

总缓解期是从测量首次符合 CR 或 PR（无论哪个先测量到）标准的时间到首次真实记录疾病复发或进展的时间（把研究中记录的最小测量值作为疾病进展的参考）。总完全缓解时间是从测量首次符合 CR 标准的时间到首次真实记录疾病复发

或进展的时间。

疾病稳定期

从治疗开始到疾病进展的时间（在随机化研究中，从随机分组的时间开始），以研究中最小的总和作为参考（如果基线总和最小，则作为 PD 计算的参考）。疾病稳定期的临床相关性因不同研究和不同疾病而不同。如果在某一特定的研究中，以维持最短时间稳定期的病人比例作为研究终点，方案应特别说明 SD 定义中两个测量间的最短时间间隔。

注意：缓解期、稳定期以及 PFS 受基线评价后随访频率的影响。定义标准随访频率不属于本指导原则范围。随访频率应考虑许多因素，如疾病类型和分期、治疗周期及标准规范等。但若需进行研究间的比较，应考虑这些测量终点准确度的限制。

2.9 PFS/TTP

晚期肿瘤许多研究以 PFS 或者 TTP 作为主要研究终点。如果方案要求所有患者都有可测量病灶，进展评价就相对简单。越来越多的研究允许有可测量病灶和无可测量病灶的患者都可以进入研究。在这种情况下，必须对无可测量病灶患者疾病进展的临床发现进行详细明确的描述。因为进展日期常有确定偏差，各研究组的观测时间点安排应该相同。

附录 2：体力状况评分标准（ECOG PS）

评分	标准
0	活动能力完全正常，与起病前活动能力无任何差异
1	能自由走动及从事轻体力活动，包括一般家务或办公室工作，但不能从事较重的体力活动
2	能自由走动及生活自理，但已丧失工作能力，日间不少于一半时间可以起床活动
3	生活仅能部分自理，日间一半以上时间卧床或坐轮椅
4	卧床不起，生活不能自理
5	死亡

附录 3：Cockcroft-Gault 公式

血清肌酐浓度单位为（mg/dL）的计算公式:

$$\text{男性肌酐清除率（mL/min）} = \frac{\text{（140－年龄）×（体重）}^{a}}{\text{72×血清肌酐}}$$

$$\text{女性肌酐清除率（mL/min）} = \frac{\text{0.85×（140－年龄）×（体重）}^{a}}{\text{72×血清肌酐}}$$

血清肌酐浓度单位为（μmol/L）的计算公式:

$$\text{男性肌酐清除率（mL/min）} = \frac{\text{（140－年龄）×（体重）}^{a}}{\text{0.818×血清肌酐}}$$

$$\text{女性肌酐清除率（mL/min）} = \frac{\text{0.85×（140－年龄）×（体重）}^{a}}{\text{0.818×血清肌酐}}$$

a：年龄单位为岁，体重单位为 kg。

附录 4：禁用药物列表

相互作用机制	药物名称
CYP3A 和 P-gp 强效诱导剂	阿帕鲁胺、卡马西平、恩杂鲁胺、艾伏尼布、鲁马卡托/依伐卡托、米托坦、苯妥英、利福平、圣约翰草
CYP3A 和 P-gp 强效抑制剂	色瑞替尼、克拉霉素、可比司他、埃替拉韦和利托那韦、艾代拉利司、茚地那韦和利托那韦、伊曲康唑、酮康唑、洛匹那韦/利托那韦片、奈法唑酮、胺碘酮、环孢菌素、决奈达隆、红霉素、拉帕替尼、普拉帕酮、奎尼丁、雷诺嗪、维拉帕米
CYP3A4 敏感底物	阿芬太尼、阿伐那非、布地奈德、丁螺环酮、考尼伐坦、达非那新、达芦那韦、达沙替尼、决奈达隆、依来曲普坦、依普利酮、依维莫司、非洛地平、依鲁替尼、茚地那韦、艾沙康唑、伊伐布雷定、莱博雷生、洛美他派、洛伐他汀、鲁拉西酮、马拉韦罗、咪达唑仑、莫博替尼、纳洛昔醇、尼索地平、奎硫平、沙奎那韦、西地那非、辛伐他汀、西罗莫司、他克莫司、替格瑞洛、替拉那韦、托伐普坦、三唑仑、伐地那非、维奈托克
OAT1 敏感底物	阿德福韦、环丙沙星、呋喃苯胺酸、替诺福韦

表格中列出的是常见的 CYP3A4 和 P-gp 的强效抑制剂和诱导剂，OAT1 和 CYP3A4 敏感底物。如对于其他可能的合并用药有疑问，研究者可与申办方进行沟通。药物相互作用可在 FDA 的官网上进行查询，网址如下：https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems。

附录 5：BOIN 设计的详细参数与模拟性能

使用从 http://www.trialdesign.org 获取的 Shiny app “BOIN”，并考虑以下两种情形：

1. 前两个剂量水平采用加速滴定

BOIN 设计的具体参数如下：

参数	值
剂量组数	5
起始剂量	1
每次入组例数	3
入组次数	10
如果分配到某个剂量组的受试者数达到 m 例且接下来仍将分配受试者到该剂量组，则研究终止。m =	6
目标毒性概率	0.3
使用默认的剂量升降边界值（推荐）	True
使用加速滴定	Yes
加速滴定最高剂量	2
当 3 例受试者中观察到 1 例 DLT 时，将决策由降低剂量改为保持当前剂量	Yes
消除剂量阈值 p_K	0.95
每个情形的重复次数	1000
随机数生成器种子	12345

注：最大样本量 = 每次入组例数 * 入组次数 = 3 * 10 = 30.

该 BOIN 设计的模拟性能如下：

	剂量 1	剂量 2	剂量 3	剂量 4	剂量 5	患者数	提前终止%
情形 1							
真实 DLT 率	0.3	0.46	0.5	0.54	0.58		
选择%	56.6	22.4	11.7	1.6	0		7.7

接受治疗的患者%	44.1	35.1	17.6	2.9	0.3	12.1	
情形 2							
真实 DLT 率	0.16	0.3	0.47	0.54	0.6		
选择%	24.8	47.5	23.8	2.9	0.1		0.9
接受治疗的患者%	26.7	39.7	28.1	5.1	0.4	14.4	
情形 3							
真实 DLT 率	0.04	0.15	0.3	0.48	0.68		
选择%	1.6	22.9	56.7	18	0.8		0
接受治疗的患者%	9.8	23.3	43.4	20.7	2.8	15.3	
情形 4							
真实 DLT 率	0.02	0.07	0.12	0.3	0.45		
选择%	0.2	3.3	23.8	51.2	21.4		0.1
接受治疗的患者%	6.8	9.7	31.8	35.7	15.9	17	
情形 5							
真实 DLT 率	0.02	0.06	0.1	0.13	0.3		
选择%	0.3	2.2	11.1	22.7	63.7		0
接受治疗的患者%	7	9.2	24.3	29.5	30	16.4	

2. 仅考虑后三个剂量水平的 BOIN 设计

BOIN 设计的具体参数如下：

参数	**值**
剂量组数	5
起始剂量	1
每次入组例数	3
入组次数	10
如果分配到某个剂量组的受试者数达到 m 例且接下来仍将分配受试者到该剂量	6

组，则研究终止。m =	
目标毒性概率	0.3
使用默认的剂量升降边界值（推荐）	True
使用加速滴定	No
当 3 例受试者中观察到 1 例 DLT 时，将决策由降低剂量改为保持当前剂量	Yes
消除剂量阈值 p_K	0.95
每个情形的重复次数	1000
随机数生成器种子	12345

该 BOIN 设计的模拟性能如下：

	剂量 1	剂量 2	剂量 3	患者数	提前终止%
情形 1					
真实 DLT 率	0.3	0.48	0.67		
选择%	70.6	20.4	0.9		8.1
接受治疗的患者%	63.7	32	4.3	10.4	
情形 2					
真实 DLT 率	0.13	0.3	0.44		
选择%	27.7	50.1	21.7		0.5
接受治疗的患者%	39.3	41.7	19	13.9	
情形 3					
真实 DLT 率	0.05	0.13	0.3		
选择%	3.6	26.2	70.1		0.1
接受治疗的患者%	25.1	37.4	37.5	14.7	

根据上述模拟性能结果，本设计可大概率选择准确的 MTD（如果有 MTD），并将更多的患者分配到 DLT 发生率最接近目标概率为 0.3 的剂量水平组。

附录 6：期中分析统计学方法

中期分析采用了贝叶斯预测概率（predictive probability，PP）的方法计算成功率，为早期的无效性判断提供依据。基于中期分析时观察到的有效性数据，对达到最大计划样本量时成功的概率（即认为研究药物有效）进行计算。基于已观察到的数据，高 PP 表示在试验结束时很有可能得到研究治疗有效的结论，与之相反，低 PP 则表示研究治疗或许并没有足够的疗效。

下表展示了通过在线软件（https://www.trialdesign.org/one-page-shell.html#BEMPR）设定的相关参数值和计算结果：

Input Parameter	**Input Value**		
	NSCLC	**CRC**	**PDAC**
Reference response rate (θ_0)	0.23	0.10	0.15
Threshold for declaring efficacy at the end of the trial (p_T)	0.7		
Early Stopping for Futility	TRUE		
Probability confidence threshold for futility stopping (p_L)	0.2		
Early Stopping for Efficacy	FALSE		
Prior distribution for θ: Beta(a_0,b_0) a_0	0.5		
Prior distribution for θ: Beta(a_0,b_0) b_0	0.5		
Input Cohort Manually	FALSE		
Maximum number of patients in the trial	73	50	94
Minimum number of patients before early stopping rule applies	20		
Cohort size	1		

附录 7：中心实验室信息和样本销毁公司信息

中心实验室一：药代动力学检测

名称：上海观合医药科技股份有限公司

统一社会信用代码：91310110MA1G83F27K

地址：上海市杨浦区翔殷路 128 号 12 号楼三楼 C 座 101-110 室

中心实验室二： ctDNA 测序

名称：广州燃石医学检验所有限公司

统一社会信用代码：91440116094098415C

地址：广州市黄埔区广州国际生物岛星岛环北路 5 号

样本销毁公司一：药代动力学样本销毁单位

名称：上海市固体废物处置有限公司

统一社会信用代码：913101147294906145

地址：上海市嘉定区嘉朱公路 2491 号

样本销毁公司二： ctDNA 测序样本销毁单位

名称：广州环保投资集团有限公司

统一社会信用代码：91440101671815024A

地址：广州市越秀区流花路 121 号（南塔）1218 房

临床研究方案

研究标题：	一项评估 GFH375 治疗 KRAS G12D 突变型晚期实体瘤患者的安全性、耐受性、药代动力学和疗效的开放标签、I/II 期临床研究
方案编号：	GFH375X1101
版本号及版本日期：	1.0 版/2024 年 03 月 15 日
产品名称：	GFH375
研究分期：	I/II 期
申办方：	劲方医药科技（上海）有限公司
申办方联系人：	朱华强，医学科学副总裁 电话：15601727272 Email：hqzhu@genfleet.com

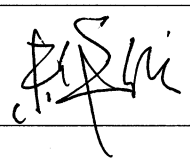
保密声明

本临床试验方案所含信息均属机密，并为劲方医药科技（上海）有限公司所有。未经事先书面许可不得向任何第三方（团体或个人）公开。若事先未获得授权而持有本方案，请及时与劲方医药科技（上海）有限公司联系，并将方案和副本交还该公司。

申办方签字页

研究标题：一项评估 GFH375 治疗 KRAS G12D 突变型晚期实体瘤患者的安全性、耐受性、药代动力学和疗效的开放标签、I/II 期临床研究

方案编号：GFH375X1101

职位	姓名	签名（正楷）	日期
医学科学副总裁	朱华强		2026-3-15

研究者签字页

研究标题：一项评估 GFH375 治疗 KRAS G12D 突变型晚期实体瘤患者的安全性、耐受性、药代动力学和疗效的开放标签、I/II 期临床研究

方案编号：GFH375X1101

通过签署此方案签字页，研究者确认并同意：

我已阅读了上述研究方案及其附件。我已与申办方劲方医药科技（上海）有限公司充分讨论了该方案的内容。我同意按照此研究方案开展研究，以及国际人用药品注册技术要求协调会-药物临床研究质量管理规范（ICH-GCP）、当地法规和其他适用的法规履行相关的职责。我同意将确保所有参与本研究的工作人员了解他们在履行上述承诺方面的义务。

本文件包含机密信息，未经申办方书面授权，除直接参与研究执行或伦理/法规审查的人员外，不予披露。

我已阅读本研究方案的全部内容并保证按要求开展本研究：

研究者签名：_____ 日期：_____

打印体姓名：_____

研究者职称：_____

联系电话：_____

中心名称/地址：_____

_____

_____

方案摘要

<table>
<tr><td>方案编号：</td><td>GFH375X1101</td></tr>
<tr><td>申办方</td><td>劲方医药科技（上海）有限公司</td></tr>
<tr><td>试验药物</td><td>代码：GFH375</td></tr>
<tr><td>研究标题</td><td>一项评估 GFH375 治疗 KRAS G12D 突变型晚期实体瘤患者的安全性、耐受性、药代动力学和疗效的开放标签、I/II 期临床研究</td></tr>
<tr><td>简要标题</td><td>一项评估 GFH375治疗KRAS G12D 突变实体瘤患者的 I/II 期研究</td></tr>
<tr><td>分期</td><td>I/II 期</td></tr>
<tr><td>版本号/日期</td><td>V 1.0/2024年3月15日</td></tr>
<tr><td>研究时间</td><td>预计48个月</td></tr>
<tr><td>研究目的与终点</td><td>本研究是一项 I/II 期研究。其中 I 期研究部分包括 Ia 期剂量递增部分和 Ib 期剂量扩展部分。
Ia 期（剂量递增部分）的目的和终点包括：
<table>
<tr><th>研究目的</th><th>研究终点</th></tr>
<tr><td>主要目的</td><td>主要终点</td></tr>
<tr><td>评估 GFH375 在 KRAS G12D 突变的晚期实体瘤患者中的安全性和耐受性</td><td>• 不良事件 (AE) 和严重不良事件 (SAE) 的发生率和严重程度；生命体征、心电图 (ECG) 和实验室检查的改变</td></tr>
<tr><td>• 确定 GFH375 的最大耐受剂量 (MTD) 和/或推荐的扩展剂量 (RDE)</td><td>• 剂量限制性毒性 (DLT)事件的发生率</td></tr>
<tr><td>次要目的</td><td>次要终点</td></tr>
<tr><td>• 评估 GFH375 在 KRAS G12D 突变的晚期实体瘤患者中的药代动力学 (PK)特征</td><td>• GFH375 的血浆浓度和 PK 参数，包括但不限于C_{max}、T_{max}、AUC、$t_{1/2}$、CL/F、V_z/F、C_{trough}</td></tr>
<tr><td>• 评估 GFH375 在 KRAS G12D 突变型晚期实体瘤患者中的初步疗效</td><td>• 根据实体瘤疗效评价标准 (RECIST) 1.1 评估的客观缓解率 (ORR)、缓解持续时间 (DoR)、疾病控制率 (DCR)、</td></tr>
</table></td></tr>
</table>

	至缓解时间 (TTR)、无进展生存期 (PFS) 和总生存期 (OS)

Ib 期（剂量扩展部分）的目的和终点：

研究目的	研究终点
主要目的	**主要终点**
确认 GFH375 在 KRAS G12D 突变的晚期实体瘤患者中的安全性和耐受性；以及 GFH375 的 II 期推荐剂量（RP2D）	• 不良事件 (AE) 和严重不良事件 (SAE) 的发生率和严重程度；生命体征、心电图 (ECG) 和实验室检查的改变
次要目的	**次要终点**
• 评估 GFH375 在 KRAS G12D 突变的晚期实体瘤患者中的药代动力学 (PK) 特征	• GFH375 的血浆浓度
• 评估 GFH375 在 KRAS G12D 突变型晚期实体瘤患者中的初步疗效	• 根据实体瘤疗效评价标准 (RECIST)1.1 评估的客观缓解率 (ORR)、缓解持续时间 (DoR)、疾病控制率 (DCR)、至缓解时间 (TTR)、无进展生存期 (PFS) 和总生存期 (OS)
探索目的	**探索终点**
• 探索与治疗敏感或耐药相关的分子机制	• 基线和治疗结束时血液循环肿瘤 DNA（ctDNA)的突变分析

II 期部分的研究目的和终点：

研究目的	研究终点
主要目的	**主要终点**
• 评估 GFH375 在 KRAS G12D 突变的晚期非小细胞肺癌（NSCLC）、晚期胰腺导管腺癌 (PDAC)、晚期结直肠癌 (CRC)和其他实体瘤患者中的疗效	• 研究者根据 RECIST 1.1 评估的 ORR
次要目的	**次要终点**

	• 使用其他疗效指标评估 GFH375 在 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的疗效	• 研究者根据 RECIST 1.1 评估的 DoR、DCR、TTR、PFS • OS
	• 评估 GFH375 在 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的安全性	• AE、SAE 的发生率和严重程度；生命体征、ECG 和实验室检查的改变
	• 评估 GFH375 在 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的 PK 特征	• GFH375 的血浆浓度
	探索目的	**探索终点**
	• 探索与治疗敏感或耐药相关的分子机制	• 基线和治疗结束时血液循环肿瘤 DNA（ctDNA）的突变分析
研究背景	RAS 家族负责调节细胞的生长、迁移、存活和分化相关的信号通路。RAS 蛋白通常在 GTP 和 GDP 结合构象之间进行切换，分别对应激酶的“开启”和“关闭”状态。在各种恶性肿瘤中，RAS 的致癌突变导致 GTP 水解被抑制，使激酶处于变构激活状态，从而导致细胞恶性增殖和生物行为学的改变。 KRAS 是 RAS 家族中最常见的突变类型，约占胰腺导管腺癌的 90%、结直肠癌的 50%和肺腺癌的 30%。因此，KRAS 被认为是许多恶性肿瘤发生和肿瘤转移的驱动癌基因。KRAS G12D 为 KRAS 最常见的突变类型之一，据估计在肺腺癌中美国的数据显示 G12D 突变占 4.9%，而国内 NSCLC 患者的大样本量分析显示 KRAS G12D 突变频率约为 2.2%。在胰腺癌中，约 37%的患者携带 KRAS G12D 突变，提示该突变等位基因在胰腺癌患者人群水平的重要性。临床前研究中已在多个 PDAC 异种移植模型中证实，KRAS G12D 在 PDAC 中作为一种持续发挥作用的致癌驱动基因，KRAS G12D 抑制剂在 PDAC 模型中显示出显著的抗肿瘤活性。在结直肠癌中，KRAS 突变率约为 40%，其中 KRAS G12D 约占 28%。此外，研究表明 KRAS 突变是结直肠癌对西妥昔单抗获得性耐药的常见因素，在经西妥昔单抗（或联合化疗）治疗后的 CRC 转移组织样本中观察到获得性的 KRAS G12D 突变。目前，已有数款 KRAS G12D 选择性的抑制剂（如 MTRX1133 和 HRS-4642	

	等）进入临床开发中，分别通过口服或静脉给药，尚未有特异性靶向 KRAS G12D 突变肿瘤的疗法获批。 晚期 NSCLC、 PDAC 、CRC 以及其他携带 KRAS G12D 突变的实体瘤患者通常首选接受化疗、免疫治疗或抗血管生成药物联合治疗，在标准治疗失败后，均缺乏有效的治疗手段。如晚期 NSCLC 虽然 EGFR、ALK 等驱动基因阳性的患者可以选用针对性的靶向治疗，获得较好的疗效，但由于 KRAS G12D 极少与上述驱动基因同时存在，因此仍以化疗如多西他赛等作为标准系统治疗失败的主要治疗药物，近期报告的 ORR：7.1-16.0%; 中位 PFS: 2.6-4.5 个月。在入组转移性 PDAC（mPDAC）患者的 III 期 NAPOLI-1 研究显示，对于既往以吉西他滨为基础的化疗方案治疗失败后的 mPDAC 患者，相较于仅接受 5-FU/LV（5-氟尿嘧啶+亚叶酸），患者接受伊立替康脂质体联合 5-FU/LV（5-氟尿嘧啶+亚叶酸）后，疗效得到明显改善：中位总生存期（mOS）为 6.1 月（vs 4.2 月，HR 0.67）中位 PFS 为 3.1 个月 （vs 1.5 月，HR 0.56），ORR 为 16%（vs 1%，$p < 0.0001$） 。在接受≥1 线治疗后的 mPDAC 受试者中开展的其他 II 期研究中（多数受试者接受过≥ 2 线治疗），报告的 ORR 为 0%-10.7%。在 CRC 受试者中，TAS-102+/-贝伐珠单抗、瑞戈非尼和呋喹替尼等通常作为三线治疗的选择，ORR 仅为 1 - 4%。因此，标准治疗失败的 NSCLC、PDAC 和 CRC 目前均缺乏有效的治疗方法，有巨大的未被满足的临床需求。 KRAS G12C 抑制剂（索托拉西布、阿达格拉西布）获批 NSCLC 的适应症，在此类患者中证实了良好的疗效和安全性。而与其他 KRAS 突变肺癌相比，KRAS G12D 突变阳性的肿瘤具有不同的临床、基因组和免疫学特征，如在 NSCLC 中，KRAS G12D 突变阳性状态可能与低肿瘤突变负荷和低 PD-(L)1 表达相关，多为“immune cold”，从而促进肿瘤细胞对免疫抑制剂治疗耐药，临床上需要针对这些人群单独开展研究，KRAS G12D 抑制剂提供了很好的研究机会，可能为这些患者带来潜在获益。 GFH375 是一种靶向 KRAS G12D 突变的高选择性、口服、非共价小分子抑制剂。GFH375 在临床前体外研究中显示出对 KRAS 依赖性的信号转导和癌细胞活力的强效抑制作用，并在 KRAS G12D 突变肿瘤动物模型上体现了显著的抗肿瘤药效。上述结果支持在携带 KRAS G12D 突变的晚期实体瘤患者中进一步评估 GFH375 的安全性和疗效。
研究设计	本研究是一项评估 GFH375 单药在携带 KRAS G12D 突变的晚期实体瘤患者中的安全性/耐受性、PK 及有效性。I 期研究的主要目的是评估 GFH375

在携带 KRAS G12D 突变的晚期实体瘤患者中的安全性/耐受性、PK 和初步有效性，并确定 GFH375 的 MTD 和/或 RP2D。II 期研究的主要目的是评估 GFH375 在携带 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的有效性。

研究期间将设立由研究者及申办方组成的安全监查委员会（SMC），详细信息可参考第 10 章节及本研究的 SMC 章程。

Ia 期：剂量递增部分

将根据 BOIN 设计，在每个剂量水平入组 3-6 例受试者（加速滴定时除外）接受治疗。Ia 期将入组约 30 例受试者并接受治疗。如果需要探索更多的剂量水平或替代给药方案，则可以入组额外的受试者。

受试者入组后将接受 GFH375 每日一次（QD）口服给药治疗，每 21 天为一个治疗周期。受试者将入组至顺序递增的不同剂量组，起始剂量为 100 mg QD。预计在剂量递增部分共进行 5 个给药剂量的评估，计划的递增剂量参见**下表**。研究者和申办方将根据所有已获得的数据讨论并决定是否探索更高的剂量水平，或其他给药方案，如每日两次给药方案（BID）。

首次治疗后的第一个周期将作为剂量限制性毒性（DLT）观察期，DLT 可评估病例需要满足以下两个条件之一：

- 受试者发生 DLT 事件，或
- 受试者未发生 DLT 事件，且在第一周期至少接受了 15 天 GFH375 的计划给药。

DLT 不可评估病例将进行受试者替代，替代后的受试者将接受相同剂量水平 GFH375 的单药治疗。

如未发生 DLT 事件，受试者将继续接受治疗，并允许在符合本方案准许情况下的剂量调整，直至出现疾病进展、不可耐受的毒性或因其他原因结束研究治疗。若受试者在 DLT 观察期发生 DLT 事件，经研究者与申办方评估继续接受 GFH375 的治疗能够获益，将在相关的不良事件缓解后恢复 GFH375 治疗。恢复给药标准可参考正文相应章节。

入组 Ia 期的受试者将进行密集 PK 采样并收集与 PK 采样相匹配的心电图，以评估 GFH375 的药代动力学特征和安全性。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。受试者将在末次研究治疗后 30 (±3) 天返回研究中心完成安全性随访，之后每 90 (±7) 天进行一次生存随访。受试者因

疾病进展以外的原因结束研究治疗且尚未开始新的抗肿瘤治疗，需按照之前的影像学评估计划继续进行疾病进展随访，直至疾病进展、撤回 ICF、开始其他抗肿瘤治疗或研究结束。

	Ia期计划进行递增的剂量组*
剂量组1	100 mg QD
剂量组2	200 mg QD
剂量组3	400 mg QD
剂量组4	600 mg QD
剂量组5	900 mg QD

注：可能会在爬坡过程中基于获得的临床数据包括安全性、PK、可能的有效性进行目前设定的剂量中间剂量的探索，如 150mg, 300mg, 500mg,750mg 等。

DLT 定义

DLT 是指在首次用药后 21 天内出现的、与研究药物 GFH375 相关且符合以下严重程度的不良事件。不良事件的严重程度根据不良事件通用术语评价标准（CTCAE）5.0 版进行分级：

- ≥4级中性粒细胞绝对计数（ANC）降低≥5天；
- ≥ 3级发热性中性粒细胞减少症（ANC <1.0 × 10^9/L 伴体温 > 38.3℃）；
- ≥4级血小板计数降低持续≥5天；
- ≥3级血小板计数降低合并≥2级出血；
- ≥4级贫血；
- 若基线ALT或AST ≤ 1级：≥ 3级血清转氨酶升高（ALT或AST）持续＞7天被视作DLT；若基线ALT或AST为2级，则 ALT或AST> 10x ULN持续＞7天被视作DLT；
- 血清胆红素升高≥3级；
- 根据海氏法则，AST或ALT ＞ 3xULN（若基线合并肝转移，则要求 ＞ 3倍基线值），且同时合并总胆红素 ＞ 2xULN（需排除胆道梗阻或其他原因导致的如肝炎、肝内肿瘤进展等病因）；
- ≥3级其他毒性（非肝脏、非血液学），除外以下情况：
  - 3 级的恶心或呕吐、腹泻，在接受/不接受对症支持治疗的情况下持续时间不长于3天；
  - 3 级的疲乏，在接受/不接受对症支持治疗的情况下持续时间

不长于3天；

- 无症状的3级实验室结果异常，研究者判断无临床意义。

在 DLT 观察期后出现的符合上述标准的毒性也将被视为评价安全性的重要因素。此外，将在申办方和研究者讨论后确定可能被评估为 DLT 的其他治疗相关毒性。

在第一周期（DLT 观察期）内，对于符合 DLT 标准的 AE，应于获知其发生之后的 24 小时之内报告至申办方（报告方法请参见 8.2.4 严重不良事件（SAE）的报告）。

剂量递增规则与 MTD 定义

允许在前两个剂量采用加速滴定法，即首例受试者将接受第一个剂量水平的治疗。如果前两个剂量组的受试者在 DLT 观察期内均未观察到≥2 级治疗相关 AE，则在下一个较高剂量水平纳入 3~6 例受试者，并使用 BOIN 设计进行本组和后续剂量递增；反之，如果在第一个或第二个剂量组报告任何≥ 2 级治疗相关 AE 或 DLT 事件，则从观察到≥ 2 级治疗相关 AE 或 DLT 事件的最低剂量组开始，直接转为 BOIN 设计。在第一个剂量完成加速滴定的前提下，对于第二个剂量水平是否采用加速滴定，将由 SMC 基于第一个剂量水平的 PK 及安全性数据进行讨论决定。后续剂量水平采用 BOIN 设计确定 MTD，目标毒性概率为 0.3。每个剂量水平将入组 3~6 例受试者接受治疗，Ia 期入组约 30 例受试者。

BOIN 设计将根据下表所示的剂量升降规则，为下一组受试者分配剂量水平。

决策	当前剂量上治疗的受试者总数						
	3	**4**	**5**	**6**	**7**	**8**	**9**
升剂量，若发生 DLT 的受试者例数 ≤	0	0	1	1	1	1	2
降剂量，若发生 DLT 的受试者例数 ≥	2	2	2	3	3	3	4
剔除剂量，若 DLT受试者例数 ≥	3	3	4	4	5	5	5

具体规则请见正文章节 3.1.1.2。

剂量递增阶段结束后，将基于剂量确定分析集（DDS）采用保序回归分析以确定 MTD。使用 http://www.trialdesign.org 的在线 BOIN 软件进行保

序回归分析，得到每个剂量水平毒性概率的保序估计值。最接近目标毒性率 0.3 的剂量水平即为 MTD。如果有 2 个或以上同时满足条件的剂量水平，选择保序估计值<0.3 的最高剂量水平或保序估计值≥0.3 的最低剂量水平。

剂量递增阶段受试者回填

将根据已获得的安全性/耐受性、PK 及初步有效性数据，可能选择一个或多个剂量水平入组额外的受试者作为回填，接受已确认安全且耐受性良好的、经研究者及申办方评估可能临床获益的 GFH375 单药剂量进行治疗，以更好的估计 GFH375 单药的 RDE/RP2D 以及表征其安全性\耐受性、PK 及有效性。回填的受试者不被纳入 DLT 的评估。回填后，接受 GFH375 每个剂量水平治疗的受试者不超过 9 例（包括 BOIN 剂量递增阶段入组的受试者）。

回填的受试者将根据 Ia 期的流程访视表及 Ia 期的 PK 采血表完成相关访视。

受试者个体内剂量递增

剂量递增研究期间原则上不进行个体内剂量递增。对于入组 Ia 期的受试者，经研究者和申办方同意后，允许在本方案的 RP2D 剂量确认后，进行个体内剂量调整，接受 RP2D 的单药治疗。

Ib 期：剂量扩展部分

完成剂量递增部分后，将综合本产品临床前及临床数据，选择 1 个或多个 RDE 进行剂量扩展研究，预计每个 RDE 剂量组纳入不超过 30 例受试者，以确认安全性及 RP2D 剂量。

筛选合格的受试者将接受 GFH375 单药治疗，每 21 天为一个治疗周期，直至疾病进展、出现不可耐受的毒性或因其他原因结束研究。纳入 Ib 期研究剂量扩展部分的受试者将进行稀疏 PK 采样，并收集与 PK 采样相匹配的心电图。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。受试者将在末次研究治疗后 30 (±3) 天返回研究中心完成安全性随访，之后每 90 (±7) 天进行一次生存随访。受试者因疾病进展以外的原因结束研究治疗且尚未开始新的抗肿瘤治疗，需按照之前的影像学评估计划继续进行疾病进展随访，直至疾病进展、撤回 ICF、开始其他抗肿瘤治疗或研究结束。

若入组 Ib 期的受试者接受的治疗剂量，经研究者和申办方同意后，允许在本方案的 RP2D 剂量确认后，进行个体内剂量递增，接受 RP2D 的单药

	治疗。 **II 期部分** II 期研究为开放标签、多中心的研究，总体研究计划见正文图 3。目的是评估 GFH375 治疗携带 KRAS G12D 突变的晚期非小细胞肺癌、晚期胰腺癌、结直肠癌和其他晚期实体瘤患者的有效性、安全性和 PK 特征。II 期研究将入组约 213 例 KRAS G12D 突变的晚期实体瘤受试者，以接受 RP2D 的 GFH375 连续单药治疗，治疗周期为 21 天。该部分入组的受试者将根据 II 期 PK 采血表进行稀疏 PK 采样，并收集与 PK 采样相匹配的心电图。 • 晚期NSLCL受试者队列：计划入组约 73 例携带KRAS G12D 突变的晚期NSCLC受试者。 • 晚期 PDAC受试者队列：计划入组约 50 例携带KRAS G12D 突变的晚期PDAC受试者。 • 晚期 CRC 受试者队列：计划入组约 50 例携带KRAS G12D 突变的晚期CRC受试者。 • 其他晚期实体瘤受试者队列：计划入组约 40 例携带 KRAS G12D 突变的晚期实体瘤受试者，如携带 KRAS G12D 突变的胆管癌、阑尾癌等。 筛选合格的受试者将接受 GFH375 单药治疗，直至疾病进展、出现不可耐受的毒性或因其他原因结束研究治疗。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。受试者将在末次研究治疗后 30 (±3) 天返回研究中心完成安全性随访，之后每 90 (±7) 天进行一次生存随访。受试者因疾病进展以外的原因结束研究治疗且尚未开始新的抗肿瘤治疗，需按照之前的影像学评估计划继续进行疾病进展随访，直至疾病进展、撤回 ICF、开始其他抗肿瘤治疗或研究结束。
入选标准	**参加本研究的受试者需符合所有以下标准：** 1. 自愿参加研究并签署知情同意书。 2. 在签署知情同意书时年龄为 18 - 75 周岁的男性或女性。 3. 经组织学或细胞学病理确认的局部晚期或转移性恶性肿瘤受试者，需符合以下标准： （1） I 期部分：经标准治疗后进展，或由于不可耐受的毒性等原因

不适合标准治疗，或拒绝标准治疗。

（2） II 期部分：

a) 晚期 NSCLC：

- ✓ 既往接受过抗 PD-（L）1 治疗和/或以铂类为基础的化疗后进展（除非有使用禁忌或不耐受）；
- ✓ 若既往接受过辅助或新辅助治疗且在治疗期间或治疗停止后 6 个月内出现复发/进展，则可将该治疗计入一个线数的治疗。

b) 晚期 PDAC：既往经过基于吉西他滨的化疗方案或 FOLFIRINOX/mFOLFIRINOX 方案的充分治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗，或拒绝标准治疗。存在微卫星高度不稳定（MSI-H）及错配修复基因缺陷型（dMMR）者需既往经过至少一线抗 PD-1 治疗后进展。如果接受过辅助或新辅助治疗且在治疗期间或治疗停止后 6 个月内出现复发/进展，则可将该治疗计入一个线数的治疗。

c) 晚期 CRC：经至少二线标准治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗，或拒绝标准治疗。受试者须既往在接受氟尿嘧啶、伊立替康和奥沙利铂治疗转移性疾病期间或之后发生疾病进展或复发，除非研究者认为受试者不适合接受以上治疗方案。已知有微卫星高度不稳定（MSI-H）及错配修复基因缺陷型（dMMR）的受试者必须既往接受过免疫检查点抑制剂治疗（如适用）。如果接受过辅助或新辅助治疗且在治疗期间或治疗停止后 6 个月内出现复发/进展，则可将该治疗计入一个线数的治疗。

d) 其他实体瘤：经标准治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗，或拒绝标准治疗。

4. 入组本研究的受试者需提供确认 KRAS G12D 突变阳性的书面检测报告。
5. 根据 RECIST 1.1，Ia 期受试者必须至少有一个可评估病灶，Ib 期、II 期受试者必须至少有一个可测量病灶。

	6. 既往抗肿瘤治疗的毒性反应必须缓解至基线水平（不包括脱发）或≤1 级（对于神经系统毒性，≤2 级）。 7. 研究者判断预期生存时间≥ 12 周。 8. 美国东部肿瘤协作组（ECOG）体能状态评分（PS）0~1 分（评分标准参见附录 2）。 9. 具有充分的器官功能，包括： • 造血功能：中性粒细胞绝对计数 (ANC) ≥ 1.5 × 10^9/L，血小板计数 ≥ 75 × 10^9/L，血红蛋白 ≥ 9 g/dL，在血液检查前 14 天内未输血或未接受粒细胞集落刺激因子、血小板生成素或促红细胞生成素治疗。 • 肝功能： ➢ AST 和 ALT 均< 2.5×ULN；对于基线存在肝转移的受试者，要求 AST 和 ALT 均< 5×ULN； ➢ 总胆红素（TBIL）< 1.5×ULN；Gilbert 综合征受试者：TBIL < 2×ULN。 • 肾功能：肌酐清除率（CrCl）≥ 50 mL/min（Cockcroft-Gault 公式计算，参考附录 3）。 • 凝血功能：凝血酶原时间（PT）或活化部分凝血活酶时间（APTT）< 1.5×ULN，国际标准化比值（INR） < 1.5×ULN 或处于抗凝治疗的目标范围内。 10. 有生育能力的女性（WOCBP）和伴侣为 WOCBP 的男性受试者必须同意从签署知情同意书至末次研究治疗后 30 天内采取有效的避孕方法。WOCBP 在给药前 7 天内的血清妊娠试验结果必须为阴性。 11. 根据研究者的判断，受试者能够良好沟通、按计划随访并遵守方案的要求。
排除标准	**符合以下任意一条标准的受试者不能入组本研究：** 1. 入组前 3 年内发生进展或需要治疗的其他恶性肿瘤，除外经充分治疗的原位癌、基底细胞癌或皮肤鳞状细胞癌。 2. 研究者判断不稳定的脑转移患者。对于在筛选过程中无意检出的伴脑转移的患者，如果未引起临床症状且不需要治疗干预， 可允许入组；如果研究者判断脑转移控制稳定，激素剂量使用稳定，且强的松剂量≤10mg/d（若使用其他类固醇药物，则为相应等效剂量），可允许入

	组。 3. II 期部分： a) 晚期 NSCLC：排除已知的其他驱动基因突变或融合，如 EGFR、ALK、 BRAF (V600E)、HER2、MET (exon 14)、 ROS1、RET 或 NTRK1/2/3 b) 晚期 CRC：排除已知的其他驱动基因突变、扩增或融合，如 BRAF (V600E)、HER2、NTRK 或 RET c) 晚期 PDAC：排除已知的其他驱动基因突变或融合，如 BRAF (V600E)、BRCA、NTRK 或 RET 4. 既往接受过 KRAS G12D 或者泛 KRAS （具有主要靶向 KRAS G12D 作用）的靶向治疗。 5. 在研究药物给药前 14 天内接受姑息性放疗。 6. 在给药前 28 天内或 5 个半衰期内（以较短者为准）接受过其他抗肿瘤治疗，包括化疗、靶向治疗、内分泌治疗、免疫治疗、具有明确抗肿瘤作用的中成药及其他试验用药物或器械，内分泌维持治疗除外。 7. 合并具有临床意义的严重心血管疾病： • 首次研究治疗前 6 个月内发生具有临床意义的严重心血管事件，如心肌梗死、不稳定型心绞痛、症状性充血性心力衰竭（纽约心脏病协会 III 或 IV 级）、需要药物治疗的重度心律失常或接受血管成形术、支架植入术和冠状动脉旁路移植术等。 • 具有临床意义 QT/QTcF 延长（基于筛选期三次 QTcF 的平均值，QTcF > 470 ms）或合并 QT 间期延长的家族史。 • 经标准治疗后仍控制不佳的高血压。 8. 入组前 6 个月内发生卒中或其他严重脑血管疾病。 9. 入组前 3 个月内有深静脉血栓或其它任何严重血栓栓塞的病史。 10. 伴随需要反复引流或有明显症状的胸腔积液、腹水或心包积液。 11. 合并上腔静脉综合征。 12. 合并可能显著影响 GFH375 吸收的胃肠道功能受损或胃肠道疾病，或无法或不愿意吞咽片剂。 13. 合并具有临床意义并需要治疗的间质性肺病、放射性肺炎或免疫相关性肺炎。

	14. 合并重大急性或慢性感染性疾病，包括： • 入组前 7 天内需要静脉使用抗生素治疗的活动性感染。 • 基线时人类免疫缺陷病毒抗体 (HIV-Ab) 阳性。 • 活动性乙型肝炎病毒感染（HBsAg 阳性伴 HBV-DNA 阳性）。 • 活动性丙型肝炎病毒感染（HCV-Ab 阳性伴 HCV-RNA 阳性）。 • 活动性结核病。 15. 合并其他控制不佳的系统性疾病，如糖尿病。 16. 在首次给药前 28 天内接受或计划进行由研究者判断的重大手术（穿刺活检除外）。 17. 既往有器官移植病史或准备接受器官移植。 18. 在研究药物给药前 7 天内或接受研究药物期间需使用抑酸类药物，包括质子泵抑制剂和新型抑酸类药物（如钾离子竞争性酸阻滞剂）。 19. 在研究药物给药前 14 天内或药物的 5 个半衰期内（以较长者为准）接受了 CYP3A 或 P-gp 的强抑制剂或强诱导剂。 20. 在研究药物给药前 14 天内或药物的 5 个半衰期内（以较长者为准）接受过已知敏感的 CYP3A 或 OAT1 底物。除非经研究者和申办方审阅后同意入组。 21. 已知对研究药物或成分过敏。 22. 有严重的精神、心理疾病或有药物滥用史或有严重酗酒史。 23. 妊娠或哺乳期女性。 24. 研究者判断不适合参加研究的其他情况。
统计分析	**分析集** • 全分析集（FAS）：至少接受过 1 次 GFH375 给药的所有受试者。 • 安全性分析集（SS）：至少接受过 1 次 GFH375 给药且至少有 1 次治疗后安全性评估的所有受试者。 • 剂量确定分析集（DDS）：Ia 期在 DLT 观察期间至少累计 15 天接受未减量 的 GFH375、有充分的安全性评估的所有受试者，或在 DLT 观察期间发生 DLT。DDS 不包含回填（backfill）的受试者。 • 符合方案集（PPS）：FAS 中符合方案的所有 II 期受试者。研究团队将在最终数据库锁定前对所有方案偏离进行审查，据此将发生影响疗效评价的重大方案偏离的受试者从 PPS 中排除。

- 药代动力学分析集 (PKAS)：至少接受过 1 次 GFH375 给药且至少有 1 份血样提供可评价 PK 数据的所有受试者。

统计分析方法

将对 Ia 期、Ib 期、 II 期的数据分别单独进行分析汇总。其中，I 期阶段的数据将按照不同剂量水平和给药方案进行分析汇总；II 期阶段的数据将按照肿瘤类型分别进行分析汇总。

安全性分析

按系统器官分类、首选术语、严重程度汇总 AE、治疗相关 AE 、 SAE 的发生率。对于 I a 期部分，基于 DDS 汇总各类 DLT 的发生率，并对 DLT 进行列表。对实验室检查、生命体征、 ECG 进行描述性汇总。

有效性分析

计算最佳总体缓解（BOR）、ORR、DCR，并采用 Clopper-Pearson 方法估计 ORR 和 DCR 的双侧 95%置信区间（CI）。采用 Kaplan-Meier 方法估计 DoR、PFS、OS 的中位数及其 95% Brookmeyer-Crowley CI。对 TTR 进行描述性汇总。

对于 I 期阶段，当分析组的样本量小于 10 例时，将按受试者单独列出 DoR、TTR、PFS、OS，不采用 Kaplan-Meier 方法进行分析。

对于 II 期阶段，设置主要估计目标如下：

研究人群	KRAS G12D 突变型晚期实体瘤受试者
治疗	GFH375
终点	根据 RECIST 1.1 标准评估达到 CR 或 PR 的受试者百分比。若受试者基线后无任何评价结果，则认为该受试者未缓解。
伴发事件	开始新的抗肿瘤治疗（处理策略：在治策略，开始新的抗肿瘤治疗后的评估结果不纳入分析。）
群体层面汇总	ORR

药代动力学分析

将对血浆中 GFH375 的浓度数据按照方案规定的采样时间进行列表和描述性统计汇总，汇总将按照研究分期和剂量组呈现。将使用线性和半对数坐标，按研究分期和剂量组绘制个体受试者的血浆中 GFH375 浓度-时间曲

	线和相应的汇总曲线（平均值 + 标准差）。使用计划 PK 采样时间计算汇总统计量及绘制汇总曲线（平均值 + 标准差）；将使用实际 PK 采样时间，绘制个体受试者曲线。 将使用 Phoenix WinNonlin 软件（v8.2 版或以上版本, Certara USA, Inc., New Jersey, US）采用非房室模型分析（NCA），按实际采血时间点计算 GFH375 的 PK 参数。对 Ia 期剂量递增阶段受试者单次和多次给药后 GFH375 的 PK 参数进行描述性统计汇总，汇总按照剂量组呈现。
样本量计算	**Ia 期** Ia 期共预计入组约 30 例患者。 将根据 BOIN 设计，在每个剂量水平入组 3-6 例患者（加速滴定时除外）接受治疗。将根据已获得的安全性/耐受性、PK 及初步有效性数据，可能选择一个或多个剂量水平入组额外的受试者作为回填， 接受已确认安全且耐受性良好的、经研究者及申办方评估可能临床获益的 GFH375 单药剂量进行治疗，以更好的估计 GFH375 单药的 RDE/RP2D 以及表征其安全性\耐受性、PK 及有效性。回填的受试者不被纳入 DLT 的评估。回填后，接受 GFH375 每个剂量水平治疗的受试者不超过 9 例（包括 BOIN 剂量递增阶段入组的受试者）。 如果需要探索更多的剂量水平或替代给药方案，则可以入组额外的患者。 **Ib 期** 对于一个或多个 RDE 水平，计划每个 RDE 剂量组纳入不超过 30 例受试者。 **II 期** 总共预计入组约 213 例受试者，其中约 73 例晚期 NSCLC 患者、约 50 例晚期 PDAC 患者、约 50 例晚期 CRC 患者、约 40 例晚期其他实体瘤患者。

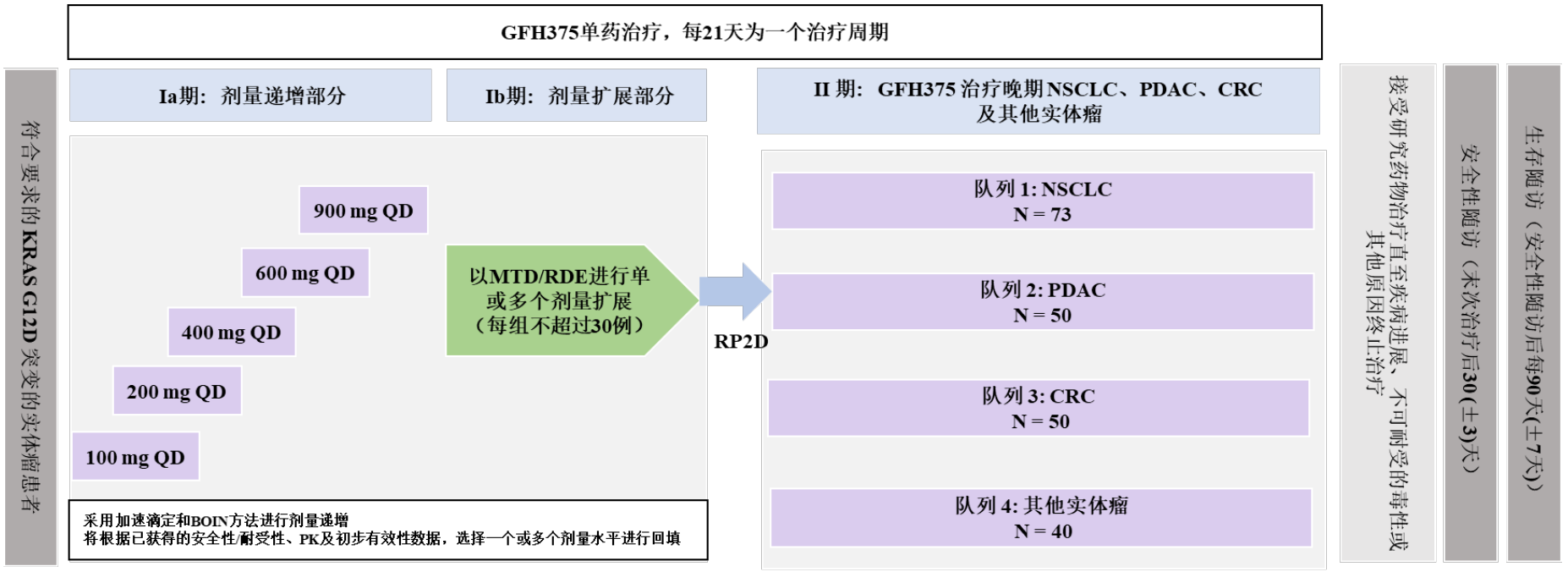
肿瘤类型	历史对照 ORR	预期 ORR	样本量
NSCLC	23%	40%	73
PDAC	10%	30%	50
CRC	10%	30%	50
其他			40

	<table><tr><td>合计</td><td></td><td></td><td>213</td></tr></table> 对于晚期 NSCLC，ORR 的历史对照值为 23%，预计本研究 ORR 可达到 40%。若观测到的 ORR 的 95% CI 下限不低于历史对照 23%，则视为成功。单侧 α = 0.025，要达到 85%把握度，则需要 73 例受试者。当 73 例受试者中有至少 25 例 CR/PR 时，ORR 观测值的 exact 95% CI 下限高于历史对照 23%。25 例 CR/PR 时，ORR = 34.2% ，其 95% CI 为(23.5%, 46.3%)。 对于晚期 PDAC 和 CRC，ORR 的历史对照值同为 10%，预计本研究 ORR 都可以达到 30%。若观测到的 ORR 的 95% CI 下限不低于历史对照 10%，则视为成功。计划入组 50 例受试者，在单侧 α = 0.025 的情况下，把握度可达到 94%。当 50 例受试者中有至少 10 例 CR/PR 时，ORR 观测值的 exact 95% CI 下限高于历史对照 10%。10 例 CR/PR 时，ORR = 20.0% ，其 95% CI 为 (10.0%, 33.7%)。 对于其他实体瘤：计划入组约 40 例 KRAS G12D 突变的晚期实体瘤受试者，如携带 KRAS G12D 突变的胆管癌、阑尾癌等。
期中分析	II期研究中，将分别对NSCLC、PDAC、CRC进行有效性中期分析。对于单个瘤种，计划在约25例受试者至少有一次基线后影像学肿瘤评估或提前退出研究时进行。考虑实际临床操作的原因，允许中期分析时的受试者例数与计划例数有所差别。期中分析过程中，项目不停止入组。 期中分析时，将分别针对 NSCLC、PDAC、CRC 的 ORR，采用贝叶斯预测概率的方法进行无效性分析。允许（但不强制）因缺乏有效性证据而提前终止对相应瘤种的研究。 基于观察到的获得缓解（CR/PR）的 II 期受试者例数计算预测成功概率（PPoS），如果 PPoS < 0.2，则允许（但不强制）因为缺少有效性证据而提前终止入组。PPoS < 0.2 的对应的终止标准见下表： <table><tr><th>瘤种</th><th>受试者例数*</th><th>建议终止试验，当缓解受试者例数 ≤</th></tr><tr><td rowspan="4">NSCLC</td><td>20 ~ 21</td><td>3</td></tr><tr><td>22 ~ 25</td><td>4</td></tr><tr><td>26 ~ 29</td><td>5</td></tr><tr><td>30</td><td>6</td></tr><tr><td>PDAC</td><td>20 ~ 23</td><td>1</td></tr></table>

CRC	24～30	2

*受试者例数：至少有一次基线后影像学肿瘤评估或提前退出研究（至少满足其一）的 II 期受试者数。

上述计划的中期分析不强制进行，在达到中期分析计划的时间点前，如果有足够的安全性和有效性综合数据支持，可以省略该中期无效性分析。



剂量递增过程中将根据累积的安全性及PK数据，对探索的剂量水平和给药方案进行调整。

图 1 研究总体设计

缩略语：DL：剂量水平；QD：每日 1 次；MTD:最大耐受剂量；RDE:推荐的扩展剂量；RP2D：推荐的 II 期剂量；晚期 PDAC：局部晚期/转移性胰腺导管腺癌；CRC：结直肠癌；BOIN：贝叶斯最佳间期；N: 例数。

Ia 期剂量递增阶段访视流程表

研究阶段	筛选期	治疗期								备注
		第 1 周期					第 2 周期		后续周期	1. 每 21 天/周期：访视窗根据研究首次服药日 C1D1 计算。 2. 除方案规定的访视检查外，研究者还可根据临床指征按需安排检查。
访视日	D-28~D-1	D1	D2	D3	D8	D15	D1	D10	D1	
时间窗（天）	NA	0	0	0	±3	±3	-1 ~ +3	±3	±3	
知情同意	×									
入选/排除标准	×	×								需在 C1D1 再次审查入选/排除标准。
人口统计学	×									包括性别、年龄、民族等。
身高/体重	×	×					×		×	身高仅在筛选期测量一次。
肿瘤病史	×									包括肿瘤诊断、诊断时间、转移灶等信息。若为晚期 NSCLC，需收集既往 PD-L1 表达水平的检测数据（若有）
其他病史	×									收集所有活动性病况，以及研究者认为有临床意义的任何病况。
既往抗肿瘤治疗史	×									收集所有针对研究疾病的既往抗肿瘤治疗史，包括治疗药物、开始时间、结束时间、最佳总体评估、结束治疗原因等。
其他既往/合并治疗	×									收集首次给药前 30 天至安全性随访结束后的所有既往/合并药物及治疗性操作。
病毒血清学	×									包括乙型肝炎表面抗原 (HBsAg)、乙型肝炎表面抗体 (HBsAb)、乙型肝炎核心抗体 (HBcAb)、HCV 抗体、HIV 抗体以及 HBV-DNA 和 HCV-RNA 检测（如必要）。
妊娠试验	×	×							×	有生育能力的女性受试者需在首次给药前 7 天内进行血妊娠检查，后续每 2 个周期的 D1 进行一次尿妊娠检查。如不能确认尿妊娠结果为阴性，则需要进行血妊娠检查。
体格检查	×	×		×	×		×	×	×	
ECOG PS	×	×					×		×	如首次给药前 72 小时内已进行评估，则无需在 C1D1 重复。

研究阶段	筛选期	治疗期							备注
		第 1 周期					第 2 周期	后续周期	1. 每 21 天/周期：访视窗根据研究首次服药日 C1D1 计算。 2. 除方案规定的访视检查外，研究者还可根据临床指征按需安排检查。
访视日	**D-28~D-1**	**D1**	**D2**	**D3**	**D8**	**D15**	**D1**	**D10**	**D1**
时间窗（天）	**NA**	**0**	**0**	**0**	**±3**	**±3**	**-1 ~ +3**	**±3**	**±3**
生命体征	×	×		×	×	×	×	×	×	
血常规	×	×		×	×	×	×	×	×	若首次给药前 7 天内已有实验室检查结果，则无需在 C1D1 重复检测。若受试者的临床状态发生显著变化，则需要在 C1D1 重复实验室检查。
血生化	×	×		×	×	×	×	×	×	
尿常规	×	×				×	×	×	×	
凝血功能	×	×				×	×	×	×	
心电图	×	×	×	×	×	×	×	×	×	1. 若合并有其他试验流程，需先进行心电图检查以避免试验操作对心电图结果产生影响。 2.心电图检查应在受试者安静休息至少 10 分钟后进行。研究期间每次访视均进行三次心电图，每次间隔至少 5 分钟。 3. 与 PK 采样相匹配的心电图采集，具体要求请参见 PK 采血表。
肿瘤影像学评估	×	×								符合要求的首次给药前 4 周内的检查结果可以作为基线接受，无需重复。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。
GFH375 给药		×								将在指定的访视日为受试者分配 GFH375 片剂，并按计划口服。**受试者应在第一个周期的第 2 天和第 3 天省略给药。**
PK 采血		×								参见 PK 采集表
AE/SAE	×	×								从签署知情同意书开始收集 AE/SAE，直至末次给药后 30 天

缩写：C1D1：第 1 周期第 1 天。ECOG：东部肿瘤协作组织；PS: 体能状况；PK：药代动力学；AE/SAE，不良事件/严重不良事件。

Ib 期剂量扩展阶段访视流程表

研究阶段	筛选期	治疗期					备注
		第 1 周期		第 2 周期		后续周期	1. 每 21 天/周期：访视窗根据研究首次服药日 C1D1 计算。 2. 除方案规定的访视检查外，研究者还可根据临床指征按需安排检查。
访视日	D-28~D-1	D1	D10	D1	D10	D1	
时间窗（天）	NA	0	±3	±3	±3	±3	
知情同意	×						
入选/排除标准	×	×					需要在 C1D1 再次审查入选/排除标准。
人口统计学	×						包括性别、年龄、民族等。
身高/体重	×	×		×		×	身高仅在筛选期测量一次。
肿瘤病史	×						包括肿瘤诊断、诊断时间、转移灶等信息。若为晚期 NSCLC 患者，需收集既往 PD-L1 表达水平的检测数据（若有）。
其他病史	×						收集所有活动性病况，以及研究者认为有临床意义的任何病况。
既往抗肿瘤治疗史	×						收集所有针对研究疾病的既往抗肿瘤治疗史，包括治疗药物、开始时间、结束时间、最佳总体评估、结束治疗原因等。
既往/合并治疗	×						收集首次给药前 30 天至安全性随访结束后的所有既往/合并药物及治疗性操作。
病毒血清学	×						包括乙型肝炎表面抗原 (HBsAg)、乙型肝炎表面抗体 (HBsAb)、乙型肝炎核心抗体 (HBcAb)、HCV 抗体、HIV 抗体以及 HBV-DNA 和 HCV-RNA 检测（如必要）。
妊娠试验	×	×				×	有生育能力的女性受试者需在首次给药前 7 天内进行血妊娠检查，后续每两个周期的 D1 进行一次尿妊娠检查。如不能确认尿妊娠结果为阴性，则需要进行血妊娠检查。
体格检查	×	×	×	×	×	×	
ECOG PS 评分	×	×		×		×	如首次给药前 72 小时内已进行评估，则无需在 C1D1 重复。

研究阶段	筛选期	治疗期					备注
		第 1 周期		第 2 周期		后续周期	1. 每 21 天/周期：访视窗根据研究首次服药日 C1D1 计算。 2. 除方案规定的访视检查外，研究者还可根据临床指征按需安排检查。
访视日	**D-28~D-1**	**D1**	**D10**	**D1**	**D10**	**D1**	
时间窗（天）	**NA**	**0**	**±3**	**±3**	**±3**	**±3**	
生命体征	×	×	×	×	×	×	
血常规	×	×	×	×	×	×	若首次给药前 7 天内已有实验室检查结果，则无需在 C1D1 重复检测。若受试者的临床状态发生显著变化，则需要在 C1D1 重复实验室检查。
血生化	×	×	×	×	×	×	
尿常规	×	×	×	×	×	×	
凝血功能	×	×	×	×	×	×	
心电图	×	×	×	×	×	×	1. 若合并有其他试验流程，需先进行心电图检查以避免试验操作对心电图结果产生影响。 2.心电图检查应在受试者安静休息至少 10 分钟后进行。研究期间每次访视均进行三次心电图，每次间隔至少 5 分钟。 3. 与 PK 采样相匹配的心电图采集，具体要求请参见 PK 采血表。
肿瘤影像学评估	×	×					符合要求的首次给药前 4 周内的检查结果可以作为基线接受，无需重复。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。
GFH375 给药		×					将在指定的访视日为受试者分配 GFH375 片剂，并按计划口服
PK 采血		×					参见 PK 采集表
血液 ctDNA		×					在基线（C1D1 给药前）采集血液样本进行二代测序（NGS）检测
AE/SAE	×	×					从签署知情同意书开始收集 AE/SAE，直至末次给药后 30 天

缩写：C1D1：第 1 周期第 1 天。ECOG：东部肿瘤协作组；PS：体能状况；PK：药代动力学；AE/SAE，不良事件/严重不良事件。

II 期治疗阶段访视流程表

研究阶段	筛选期	治疗期			备注
		第 1 周期		后续周期	1. 每 21 天/周期：访视窗根据研究首次服药日 C1D1 计算。 2. 除方案规定的访视检查外，研究者还可根据临床指征按需安排检查。
访视日	D-28~D-1	D1	D10	D1	
时间窗（天）	NA	0	±3	±3	
知情同意	×				
入选/排除标准	×	×			需要在 C1D1 再次审查入选/排除标准。
人口统计学	×				包括性别、年龄、民族等。
身高/体重	×	×		×	身高仅在筛选期测量一次。
肿瘤病史	×				包括肿瘤诊断、诊断时间、转移灶等信息。若为晚期 NSCLC 患者，需收集既往 PD-L1 表达水平的检测数据（若有）。
其他病史	×				收集所有活动性病况，以及研究者认为有临床意义的任何病况。
既往/合并治疗	×				收集首次给药前 30 天至安全性随访结束后的所有既往/合并药物及治疗性操作。
病毒血清学	×				包括乙型肝炎表面抗原 (HBsAg)、乙型肝炎表面抗体 (HBsAb)、乙型肝炎核心抗体 (HBcAb)、HCV 抗体、HIV 抗体以及 HBV-DNA 和 HCV-RNA 检测（如必要）。
妊娠试验	×	×		×	有生育能力的女性受试者需在首次给药前 7 天内进行血妊娠检查，后续每 2 个周期的 D1 进行一次尿妊娠检查。如不能确认尿妊娠结果为阴性，则需要进行血妊娠检查。
体格检查	×	×	×	×	
ECOG PS 评分	×	×		×	如首次给药前 72 小时内已进行评估，则无需在 C1D1 重复。
生命体征	×	×	×	×	
血常规	×	×	×	×	若首次给药前 7 天内已有实验室检查结果，则无需在 C1D1 重复检测。若受试者的临床状态发生显著变化，则需要在 C1D1 重复实验室检查。
血生化	×	×	×	×	
尿常规	×	×	×	×	

研究阶段	筛选期	治疗期			备注
		第 1 周期		后续周期	1. 每 21 天/周期：访视窗根据研究首次服药日 C1D1 计算。 2. 除方案规定的访视检查外，研究者还可根据临床指征按需安排检查。
访视日	**D-28~D-1**	**D1**	**D10**	**D1**	
时间窗（天）	**NA**	**0**	**±3**	**±3**	
凝血功能	×	×	×	×	
心电图	×	×	×	×	1. 若合并有其他试验流程，需先进行心电图检查以避免试验操作对心电图结果产生影响。 2.心电图检查应在受试者安静休息至少 10 分钟后进行。研究期间每次访视均进行三次心电图，每次间隔至少 5 分钟。 3. 与 PK 采样相匹配的心电图采集，具体要求请参见 PK 采血表。
肿瘤影像学评估	×	×			符合要求的首次给药前 4 周内的检查结果可以作为基线接受，无需重复。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。
GFH375 给药		×			将在指定的访视日为受试者分配 GFH375 片剂，并按计划口服
PK 采血		×			参见 PK 采集表
血液 ctDNA		×			在基线（C1D1 给药前）采集血液样本进行下一代测序（NGS）检测
AE/SAE	×	×			从签署知情同意书开始收集 AE/SAE，直至末次给药后 30 天

缩写：C1D1：周期 1 第 1 天。ECOG：东部肿瘤协作组；PS：体能状况；PK：药代动力学；AE/SAE，不良事件/严重不良事件。

I 期和 II 期：治疗结束访视和长期随访访视流程表

	治疗结束访视 EOT	安全性随访访视	生存访视	备注
访视	**决定研究治疗结束**	**末次给药后 30 天**	**安全性访视后每 90 天**	
时间窗（天）	**+7**	**±3**	**±7**	
妊娠试验	×	×		进行尿妊娠试验，必要时使用血清试验。
体格检查	×	×		
ECOG PS 评分	×			
生命体征	×	×		
血液 ctDNA	×			入组 Ib 期和 II 期的受试者，需采集血液样本进行 NGS 检测
血常规	×	×		末次用药后 7 天内进行的检查不需在 EOT 访视重复，但 AE 相关检查应由研究者酌情审查
血生化	×	×		
尿常规	×	×		
凝血功能	×	×		
心电图	×	×		
影像学评估	×			治疗结束访视前 4 周内进行的影像学检查不需要重复；除疾病进展/因疾病进展以外的原因结束治疗且未开始其他抗肿瘤治疗的受试者，需要按计划接受肿瘤影像学检查，直至疾病进展或开始新的抗肿瘤治疗或退出研究。
合并治疗	×			收集合并用药和治疗性操作
AE/SAE	×			从签署知情同意书开始收集 AE/SAE，直至末次给药后 30 天或开始新的抗肿瘤治疗
后续抗肿瘤治疗	×			包括后续抗肿瘤治疗、开始/结束时间、结束原因及 BOR
生存状态	×			

Ia 期药代动力学（PK）样本和 12 导联心电图采集计划表

周期	日	计划采样点（h）	时间窗	PK采样[1,2]	12导联心电图[3]
1	1	给药前	-1 h	√	√
1	1	给药后0.5h	±5min	√	
1	1	给药后1h	±5min	√	
1	1	给药后2h	±10min	√	√
1	1	给药后4h	±15min	√	√
1	1	给药后8h	±30min	√	
1	1	给药后12h	±30min	√	
1	2	给药后24h	±1h	√	
1	3	给药后48h	±2h	√	
1	4	给药后72h （D4给药前采集）	±3h	√	√
1	8	给药前	-1h	√	√
1	15	给药前	-1h	√	√
1	21	给药前	-1h	√	√
1	21	给药后0.5h	±5min	√	
1	21	给药后1h	±5min	√	
1	21	给药后2h	±10min	√	√
1	21	给药后4h	±15min	√	√
1	21	给药后8h	±30min	√	
1	21	给药后12h	±30min	√	
2	1	给药前	-1h	√	√
2	10	给药前	-1h	√	√
4	1	给药前	-1h	√	√

1. 当患者发生与药物相关的严重不良事件时，在研究者得知发生事件的即刻，可能的情况下，采集当时的一份血样用于 GFH375 血药浓度测定。

2. 如果在计划访视时无法获得 PK 样本，可以推迟到下一次访视进行采集。准确记录给药剂量、给药时间和采样时间即可。

3. 将在有条件的中心收集与 PK 样本匹配的 ECG，建议先进行心电图检查，再进行 PK 采血，如无法在采集血样标本前完成，应在采血后安静休息 10 分钟后进行心电图检查。同时，需要将心电图检查与 PK 采样时间的间隔保持在至少 30 分钟以内。所有计划的 12-ECG 检查都应该在受试者至少安静休息 5 min 之后进行，每个时间点需测量 3 次，每次间隔在 1-2 min。

Ib 期和 II 期药代动力学（PK）样本和 12 导联心电图采集计划表

周期	日	计划采样点（h）	时间窗	PK采样[1,2]	12导联心电图[3]
1	10	给药前	-1 h	√	√
1	10	给药后	2-4 h	√	√
2	1	给药前	-1 h	√	√
2	1	给药后	1-3 h	√	√
3	1	给药前	-1 h	√	√
3	1	给药后	2-4 h	√	√
4	1	给药前	-1 h	√	√

1. 当患者发生与药物相关的严重不良事件时，在研究者得知发生事件的即刻，可能的情况下，采集当时的一份血样用于 GFH375 血药浓度测定。
2. 如果在计划访视时无法获得 PK 样本，可以推迟到下一次访视进行采集。准确记录给药剂量、给药时间和采样时间即可。
3. 将在有条件的中心收集与 PK 样本匹配的 ECG，建议先进行心电图检查，再进行 PK 采血，如无法在采集血样标本前完成，应在采血后安静休息 10 分钟后进行心电图检查。同时，需要将心电图检查与 PK 采样时间的间隔保持在至少 30 分钟以内。所有计划的 12-ECG 检查都应该在受试者至少安静休息 5 min 之后进行，每个时间点需测量 3 次，每次间隔在 1-2 min。

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缩略语表

缩略语	英文全称	中文全称
AE	Adverse Event	不良事件
ALT	Alanine Aminotransferase	谷氨酸丙氨酸氨基转移酶
ANC	Absolute Neutrophil Count	绝对中性粒细胞计数
APTT	Activated Partial Thromboplastin Time	活化部分凝血活酶时间
AST	Aspartate Aminotransferase	谷氨酸天门冬氨酸氨基转移酶
AUC	Area under the curve	曲线下面积
BCRP	Breast Cancer Resistance Protein	乳腺癌耐药蛋白
BID, bid	Bis in die	每日二次
BOIN	Bayesian Optimal Interval	贝叶斯最优区间
BOR	Best of Response	最佳反应
C_{max}	Maximal concentration	峰浓度
C_{trough}	Trough concentration	谷浓度
CI	Confidence Interval	置信区间
CL	Clearance	清除率
CL_r	Renal Clearance	肾脏清除率
CNS	Central Nervous System	中枢神经系统
Cr	Creatinine	肌酐
CR	Complete Response	完全缓解
CRC	Colorectal Cancer	结直肠癌
CRO	Contract Research Organization	合同研究组织
CSCO	Chinese Society of Clinical Oncology	中国抗癌协会临床肿瘤学协作专业委员会
CT	Computed Tomography	电子计算机断层扫描
CTCAE	Common Terminology Criteria for Adverse Events	不良事件通用术语评价标准
ctDNA	Circulating tumor DNA	肿瘤循环 DNA
CYP	Cytochrome P450 Proteins	细胞色素 P450 超家族
D	Day	天

缩略语	英文全称	中文全称
DCR	Disease Control Rate	疾病控制率
DDS	Dose Determination Set	剂量确定分析集
DLT	Dose-Limiting Toxicity	剂量限制毒性
DNA	Deoxyribonucleic Acid	脱氧核糖核酸
DoR	Duration of Response	缓解持续时间
DRF	Dose Range Finding	毒性剂量范围探索
ECG	Electrocardiogram	心电图
ECOG	Eastern Cooperative Oncology Group	美国东部肿瘤协作组
EDC	Electronic Data Capture	电子数据采集系统
eCRF	Electronic Case Report Form	电子病例报告表
FAS	Full Analysis Set	全分析集
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography	氟脱氧葡萄糖-正电子发射计算机断层扫描术
G12D	Gly12Asp	第 12 位甘氨酸被天冬氨酸取代
GAP	GTPase-Activating Protein	GTP 酶活化蛋白
GCP	Good Clinical Practice	药物临床研究质量管理规范
GDP	Guanosine Diphosphate	鸟苷二磷酸
GEF	Guanine Nucleotide Exchange Factor	鸟嘌呤核苷酸交换因子
GGT	Gamma-Glutamyl Transpeptidase	谷氨酰转肽酶
GTP	Guanosine Triphosphate	三磷酸鸟苷
GLP	Good Laboratory Practice	药物非临床研究质量管理规范
HBV	Hepatitis B Virus	乙型肝炎病毒
HCV	Hepatitis C Virus	丙型肝炎病毒
HIV	Human Immunodeficiency Virus	人类免疫缺陷病毒
HNSTD	Highest Non-Severely Toxic Dose	最高非严重毒性剂量
HR	Hazard Ratio	风险比
ICH-GCP	International Council for Harmonization	国际人用药品注册技术要求协调会
INR	International Normalized Ratio	国际标准化比值

缩略语	英文全称	中文全称
LLOQ	Lower Limit of Quantification	最低定量限
K^+	Serum Potassium	血钾
KRAS	Kirsten Rat Sarcoma Viral Oncogene	鼠类肉瘤病毒癌基因
MAPK	Mitogen-Activated Protein Kinase	丝裂原活化蛋白激酶
MATE1	Multidrug and toxin extrusion 1	多药及毒性化合物外排转运蛋白 1
MATE2-K	Multidrug and toxin extrusion 2-K	多药及毒性化合物外排转运蛋白 2-K
MedDRA	Medical Dictionary for Regulatory Activities	监管活动医学词典
MRI	Magnetic Resonance Imaging	磁共振成像
MRSD	Maximal Recommended Starting Dose	最大推荐起始剂量
MSI-H	High Microsatellite Instability	微卫星高度不稳定
MTD	Maximum Tolerated Dose	最大耐受剂量
NGS	Next Generation Sequencing	下一代测序
NOAEL	No-Observed-Adverse-Effect Level	未观察到不良反应的剂量水平
NSCLC	Non-Small Cell Lung Cancer	非小细胞肺癌
OATP1B1	Organic anion transporting polypeptide 1b1	有机阴离子转运多肽 1b1
OATP1B3	Organic anion transporting polypeptide 1b3	有机阴离子转运多肽 1b3
OAT1	Organic anion transporter 1	有机阴离子转运体 1
OAT3	Organic anion transporter 3	有机阴离子转运体 3
OCT2	Organic cation transporter 2	有机阳离子转运体 2
ORR	Objective Response Rate	客观缓解率
OS	Overall Survival	总生存期
PD	Progression Disease	疾病进展
PDAC	Pancreatic ductal adenocarcinoma	胰腺导管腺癌
PFS	Progression Free Survival	无进展生存期
P-gp	P-glucoprotein	P-糖蛋白
PLT	Blood Platelet	血小板
PK	Pharmacokinetic	药代动力学
PKS	Pharmacokinetic Set	药代动力学分析集

缩略语	英文全称	中文全称
PO, po, p.o.	Oral Administration	口服
PPoS	Predictive Probability of Success	预测成功概率
PPS	Per Protocol Set	符合方案集
PR	Partial Response	部分缓解
PRO	Protein in Urine	尿蛋白
PS	Physical performance	体能状态
PT	Preferred Term	首选术语
PT	Prothrombin Time	凝血酶原时间
QD, qd	Quaque die	每日一次
RDE	Recommended Dose for Expansion	推荐的扩展剂量
RECIST	Response Evaluation Criteria in Solid Tumors	实体瘤疗效评价标准
RP2D	Recommended phase 2 dose	II期推荐剂量
SAE	Serious Adverse Event	严重不良事件
SAP	Statistical Analysis Plan	统计分析计划
SD	Stable Disease	疾病稳定
SOC	System Organ Class	系统器官分类
SS	Safety Set	安全性分析集
STD10	Severely Toxic Dose in 10% of the Animals	10%动物出现严重毒性的剂量
$t_{1/2}$	Elimination half-life	消除半衰期
T_{max}	Time to reach maximum concentration	达峰时间
TEAE	Treatment Emergent Adverse Event	治疗期不良事件
TRAE	Treatment Related Adverse Event	与研究药物相关的治疗期不良事件
T-BIL	Total Bilirubin	总胆红素
TTP	Time to Progression	进展时间
TK	Toxicokinetics	毒代动力学
TTR	Time to Response	至缓解时间
ULN	Upper Limits of Normal	正常值上限
V_d	Volume of distribution	分布容积

缩略语	英文全称	中文全称
V_{dss}	Volume of distribution at steady state	稳态分布容积

1. 介绍

1.1. 疾病背景

1.1.1 KRAS 和 KRAS G12D 突变生物机理

RAS 蛋白属于具有 GTPase 酶活性的鸟嘌呤核苷结合蛋白，其活性因与二磷酸鸟苷 (GDP)，或三磷酸鸟苷 (GTP) 的结合转换而切换，与 GDP 结合时处于失活的状态，与 GTP 结合时则激活。在细胞中，RAS 处于信号通路相对中枢的位置并激活下游多条信号通路。RAS 蛋白通过调节基因转录和蛋白调节过程，负责细胞生长、迁移、存活和分化的细胞间信号通路。RAS 是肿瘤中突变最为广泛的癌基因, 大约 30%的肿瘤中含有 RAS 突变。KRAS、HRAS 和 NRAS 3 种亚型均被发现在肿瘤中存在突变，其中以 KRAS 突变最为常见。KRAS 突变在胰腺癌、非小细胞肺癌 (NSCLC) 和结直肠癌（CRC）中最为常见，特别是在胰腺癌中高达 90%。KRAS 突变主要发生在 12、13 位甘氨酸 (glycine，Gly，G) 和 61 位谷氨酰胺 (glutamine，Gln，Q) 3 个位点，其中 G12 位突变发生率最高。KRAS 的 12 位 Gly 可能产生 10 余种不同形式的突变，其中突变为天冬氨酸 (G12D)、缬氨酸（G12V) 和半胱氨酸的发生频率最高[1-3]。KRAS 在肿瘤中的作用已经得到广泛共识，但因其蛋白结构以及与 GTP 的极强亲和力阻碍针对 KRAS 的靶向药物的研发。近期针对 KRAS 共价抑制策略的突破促使了靶向 KRAS 的创新小分子药物的成功研发并得到临床验证。其中 KRAS G12C 抑制剂（索托拉西布、阿达格拉西布）已被批准用于治疗 KRAS G12C 突变型 NSCLC 患者，并具有确认的疗效和可接受的安全性特征。

1.1.2 KRAS G12D 突变肿瘤

KRAS 突变常见于 CRC（美国约 45%，中国约 49%）、胰腺癌（美国约 90%，中国约 87%）和 NSCLC（腺癌：美国约 35%，中国约 13%）[3]。其中 KRAS G12D 为最常见的突变类型之一，在多种实体瘤中具有高表达，包括 NSCLC、胰腺癌、CRC 和胆管癌等。

晚期 NSCLC

肺癌是第二大常见癌症，也是全球癌症死亡的主要原因。NSCLC 约占肺癌病例的 84%，大多数 NSCLC 患者初诊即为晚期。国际癌症研究机构报告的全球癌症统计数据显示，2020 年中国估计发生 82 万新发肺癌诊断和 71.5 万肺癌相关死亡[4]。KRAS G12D 为 NSCLC 的常见突变之一，一项基于美国癌症研究协会 (AACR)项目 GENIE 数据的研究显示，据估计在美国所有肺腺癌中 G12D 突变占 4.9%[3]。一项回顾性研究分析了肺癌大数据精准治疗协作小组

（LANDSCAPE）项目中 150, 327 例 NSCLC 病例的 NGS 数据， 其中 KRAS G12D 突变频率约为 2.2%[5]。

晚期 NSCLC 的治疗根据是否存在驱动基因突变有所不同。如 EGFR、ALK、ROS 等驱动基因阳性，可选择相应的靶向药物或含铂双药化疗以及化疗联用免疫治疗、抗血管治疗等。由于 KRAS G12D 极少与上述驱动基因同时存在，因此仍以化疗如多西他赛等作为标准系统治疗失败的主要治疗药物，近期报告的 ORR 13.2-16.0%; 中位 PFS: 2.6-4.5 个月[6-8]；既往化疗以及化疗加抗血管药物的 ORR 分别为 8.5-18.3%、8.6%~22.9%；PFS 分别为 2.8~4.2 个月、4.8~5.4 个月；OS 分别在 6~11.4 个月、9.9~12.6 个月[9-13]。考虑到联合治疗的毒性反应可能增加，二线及以上治疗中，双药化疗以及其他联合治疗需要充分评估患者的耐受性。免疫检查点抑制剂治疗 KRAS 突变 NSCLC 患者的数据主要来自大型III期临床研究的亚组分析报告，其中 CheckMate057 和 OAK 研究分别报道相比多西他赛单药，KRAS 突变的患者能够从纳武利尤单抗或阿替利珠单抗治疗中取得更好的总生存期（OS）获益[14,15] ，但由于目前大多数患者在一线治疗时都已经接受了免疫检查点抑制剂，所以二线治疗免疫检查点抑制剂不是主要选择。

KRAS G12C 靶向抑制剂已经在晚期 NSCLC 中单药或联用取得了较好的疗效，预期靶向 KRAS G12D 的药物将进一步为其具有靶向突变的亚组患者人群带来新的治疗选择。

晚期 PDAC

胰腺导管腺癌 (PDAC) 是恶性程度最高的肿瘤之一，治疗疗效差，预计至 2030 年胰腺癌将会成为所有恶性肿瘤导致死亡的第二大原因，其总的 5 年生存率仅为 10%。此外，全球范围内胰腺癌的疾病负担预计会进一步增长[16]。大多数 PDAC 患者在初次就诊时即存在转移性疾病，需要更有效的全身治疗。除携带生殖系乳腺癌易感基因(BRCA) 的患者外，迄今为止发现的 PDAC 可靶向的突变非常少。KRAS 突变是其肿瘤发生过程中的早期基因驱动事件，与其生物学的关键特征如炎症、免疫逃避和代谢改变等密切相关[17]。据估计，37%的胰腺癌携带 KRAS G12D 突变，提示该突变等位基因在人群水平的重要性。一些 PDAC 异种移植模型表明，KRAS G12D 在 PDAC 中作为一致的强致癌驱动因子发挥作用，KRAS G12D 抑制剂在胰腺导管腺癌模型中显示出显著的抗肿瘤活性。

PDAC 的药物治疗手段进展总体上非常有限，尤其是使用靶向药物和免疫治疗的疗效局限。在入组转移性 PDAC（mPDAC）患者的 III 期 NAPOLI-1 研究显示，对于既往以吉西他滨

为基础的化疗方案治疗失败后的 mPDAC 患者，相较于仅接受 5-FU/LV（5-氟尿嘧啶+亚叶酸），患者接受伊立替康脂质体联合 5-FU/LV（5-氟尿嘧啶+亚叶酸）后，疗效得到明显改善：中位总生存期（mOS）为 6.1 月（vs 4.2 月，HR 0.67）中位 PFS 为 3.1 个月 （vs 1.5 月，HR 0.56），ORR 为 16%（vs 1%，p < 0.0001）[18]。三线治疗当前更是缺乏标准或值得推荐的治疗方案，大多数仍是重复使用一线或二线的化疗药物。最近法国发表的队列研究显示，676 例至少接受一次化疗的晚期胰腺癌患者，仅 37%的患者接受了三线化疗，其中位 PFS 仅为 2.03 个月，中位总生存仅 5.5 个月[19,20]。因此临床上急需有效的治疗药物。目前针对 KRAS G12C 靶向抑制剂在经治的 PDAC 中取得了较好的疗效，索托拉西布、阿达格拉西布和格来雷赛单药的 ORR 分别为 21.0%、33.3%和 46.4%，中位 PFS 分别为 4.0 个月、5.4 个月和 5.5 个月[21-23]。预期靶向 KRAS G12D 的药物也能为具有靶向突变的患者人群提供新的治疗选择。

晚期 CRC

结直肠癌 (CRC)目前是排名第 3 的高发生率癌症，据估计全球每年有 1,931,590 例新发病例，CRC 同时也是第二大常见癌症死亡原因，2020 年全球有 935 173 例死亡病例。大约 20%的 CRC 患者在诊断时有转移，而高达 50%的初始局部疾病患者将发生转移[19]。在 CRC 中，KRAS 突变率约为 40%，其中 KRAS G12D 约占 28% [24,25]。携带 KRAS 突变的 CRC 与晚期疾病状态、肿瘤分化差、远处转移和生存率较低相关，可能表明 PFS 和 OS 的预后更差，这也在现实世界临床实践中得到验证[25]。此外，研究表明 KRAS 突变是结直肠癌对西妥昔单抗获得性耐药的常见驱动因素，在经西妥昔（或联合化疗）治疗后的 CRC 转移组织样本中观察到获得性的 KRAS G12D 突变[26,27]。在 CRC 患者中靶向 KRAS 突变有望在这个高度选择的患者群体中潜在地提供更有效的靶向治疗和更好的安全性特征。

晚期 CRC 的治疗同样根据是否存在 RAS、BRAF、HER2 等基因突变有所不同。RAS 或 BRAF 均为野生型时，采用的治疗为单药化疗或多药化疗与西妥昔单抗（左侧病灶）或贝伐单抗（右侧）联用。免疫疗法虽已获批用于 MSI-H 的 CRC 患者治疗，但是 CRC 中 MSI-H 的患者比例较低，仍然存在巨大的未满足临床需求。在三线或三线以后的情况下，为患者提供的治疗选择较少，包括姑息治疗、参加临床试验或批准的药物（瑞戈非尼、曲氟尿苷/替吡嘧啶 +/-贝伐珠单抗和呋喹替尼）。然而，在 CRC 晚期治疗中，目前推荐的标准治疗（瑞戈非尼、曲氟尿苷/替匹嘧啶和呋喹替尼）在经至少 2 线治疗失败的 mCRC 患者中仅提供有限的疗效，ORR 为 1- 4.7%，中位 PFS 为 1.9-3.7 个月，中位 OS 为 6.4-9.3 个月[28-30]。最近，基于一项 III

期研究（SUNLIGHT 研究，NCT01607957），FDA 批准了曲氟尿苷/替匹嘧啶 + 贝伐珠单抗作为三线治疗选择之一。与曲氟尿苷/替匹嘧啶单药治疗相比，使用曲氟尿苷/替匹嘧啶联合贝伐珠单抗提示 OS 和 PFS 改善，但 ORR 仍较低仅为 6.1%[31]。因此，在三线及以上的 mCRC 患者中仍存在大量未满足的医疗需求。在晚期 CRC 患者中，靶向 KRAS G12C 的抑制剂索托拉西布和阿达格拉西布单药治疗已经显示出初步疗效，ORR 分别为 9.7%(95%CI 3.6，19.9) 和 19%(95%CI 8，33)[32,33]。联合抗 EGFR 抗体可进一步提高其疗效。索托拉西布联合帕尼单抗达到的 ORR 为 26.4%-30%，中位 PFS 为 5.6-5.7 个月[34]。阿达格拉西布联合西妥昔单抗的 ORR 为 46% (95%CI 28，66)，中位 PFS 为 6.7 个月[33]。除了 NSCLC、CRC 和 PDAC 外，KRAS G12D 在多种实体瘤中具有较高的突变频率，包括胆管癌、胃癌和食管癌，而针对这类缺乏有效治疗手段的患者，尚未有针对 KRAS 的靶向药物可供选择。

1.1.3 靶向 KRAS G12D 突变的药物研发

目前还没有专门针对 KRAS G12D 突变肿瘤的疗法获批上市。几种 KRAS G12D 选择性抑制剂正在临床开发中，包括 MTRX1133、HRS-4642 及 INCB161734 等。

其中，仅恒瑞研发的 HRS-4642 披露了部分临床数据。HRS-4642 为脂质体制剂，通过静脉注射。FIH 试验中共入组 18 例受试者接受 15mg QW~300 mg QW 进行治疗，总体安全性良好，观察到了初步的有效性 [37]。

1.2. 研究药物: GFH375

1.2.1 GFH375 临床前研究

GFH375 是申办方由劲方自主开发的 KRAS G12D 抑制剂，对其进行了全面的临床前研究，概要总结如下。更多详细信息请参见 GFH375 研究者手册。

1.2.1.1 药理学研究总结

GFH375 在体外研究中表现出高活性和高选择性。体外生化实验研究表明，GFH375 能够有效抑制 KRAS G12D 突变体或野生型蛋白由非活化状态（结合 GDP）转变为活化状态（结合 GDP），半数抑制浓度（IC_{50}）分别为 6 nM 和 9 nM。GFH375 也能够直接阻碍活化状态的 KRAS G12D 或野生型蛋白与其下游效应蛋白 RAF1 的结合，IC_{50} 分别为 2 nM 和 7 nM。GFH375 在多个 KRAS G12D 突变肿瘤细胞系中表现出高活性，对 KRAS 下游通路蛋白 ERK1/2 磷酸化水平的抑制 IC_{50} 为 0.2-0.9 nM, 抗肿瘤细胞增殖 IC_{50} 为 1-10 nM。而在其它 KRAS 突变

类型（KRAS G12C、G12V）的肿瘤细胞株以及 KRAS 野生型、KRAS 功能依赖的肿瘤细胞株中，GFH375 的活性相对较弱，抗肿瘤细胞增殖 IC_{50} 分别为 159-1895 nM 和 17-75 nM。GFH375 在其它 RAS 蛋白突变（NRAS G12D、Q61H，HRAS Q61L）以及 KRAS 非依赖细胞系中只有很弱活性（抗细胞增殖 IC_{50}：1636 nM-7873 nM），说明脱靶非特性细胞毒性很低。

临床前体内研究表明，GFH375 在 KRAS G12D 突变肿瘤动物模型上体现了出色的体内活性和抗肿瘤药效。在人胰腺癌 Panc 04.03 异源移植肿瘤小鼠模型中，单次给药 GFH357 (100 mg/kg)即可对肿瘤内的 ERK/1/2 磷酸化水平产生强烈和持久的抑制。在 Panc 04.03 和另外一个人胰腺癌 AsPC-1 异源移植肿瘤小鼠模型中，GFH375 (10 mg/kg, 30 mg/kg 和 100 mg/kg) 每天 2 次、口服、连续给药 14 天即展现了剂量依赖性的抗肿瘤药效，起效剂量分别为 5 mg/kg 和 10 mg/kg，且在高剂量（100 mg/kg）下使得肿瘤明显消退。

GFH375 针对 KRAS G12D 靶点具有高选择性，脱靶作用的潜在风险低。10 μM 的 GFH375 对 72 个代表性人源激酶无抑制活性，对 44 个包含 G 蛋白偶联受体（GPCR），离子通道和酶的重要安全性相关靶点中的 38 个无抑制活性。而对于 6 个受到影响的靶点，GFH375 的预测 IC_{50} 浓度至少大于 1000 nM, 远高于上面提到的在 KRAS G12D 细胞上的 ERK1/2 磷酸化抑制 IC_{50} 浓度和抗肿瘤细胞增殖 IC_{50} 浓度。

GFH375 安全药理学研究包括体外对 hERG 钾通道电流和体内对大鼠中枢神经、呼吸系统和比格犬心血管系统的影响。

GFH375 在浓度为 3、6、12 和 24 μM 时，对人胚肾细胞（HEK293）上转染表达的 hERG 钾通道电流存在浓度依赖性的抑制作用，其 IC_{50} 值为 9.65 μM。

SD 大鼠单次经口灌胃给予 50、100 和 200 mg/kg 的 GFH375，通过功能观察组合试验（FOB）同时测量前肢握力和体温评价供试品对中枢神经系统的影响。结果显示，GFH375 对中枢神经系统的未见不良反应剂量（NOAEL）为 200 mg/kg。

SD 大鼠单次经口灌胃给予 50、100 或 200 mg/kg 的 GFH375，采用全身体积描记系统评估对呼吸系统的影响。结果表明，本试验 GFH375 对呼吸系统的未见不良反应剂量（No Observed Adverse Effect Level，NOAEL）为 200 mg/kg。

比格犬根据“交叉设计”经口灌胃给予 5、10 和 25 mg/kg 的 GFH375，采用遥测的方法评价对心血管系统的影响。结果显示，GFH375 对 Beagle 犬心血管系统的 NOAEL 为 25 mg/kg/day。

1.2.1.2 药代动力学研究总结

GFH375 在 Caco-2 细胞中表现出低渗透性，有明显的外排转运现象，可口服给药，临床前种属绝对生物利用度为 8.40-16.3%，且系统暴露量均随口服剂量的增加而增加。犬给药后整体没有明显性别差异，大鼠体内有一定雌雄差异；大鼠重复给药后，在 PK 剂量下无蓄积，雌性大鼠在 TK 剂量下有蓄积现象；犬重复给药后有蓄积现象。

GFH375 在小鼠血浆中呈现非常高的结合率，在大鼠和犬血浆中呈高结合，在猴和人血浆中呈中等结合。大鼠和犬的稳态分布容积 Vd_{ss} 范围为 15.7-22.5 L/kg，均呈现高分布。[^{14}C]GFH375 总放射性在大鼠体内广泛分布，C_{max} 由高到低依次为胃壁、肠道壁、肝脏、脾脏、肾脏、肺脏、心脏、卵巢子宫、体脂、骨骼肌、全血和血浆，在全脑和睾丸附睾中放射性水平低，没有明显的红细胞结合。

[^{14}C]GFH375 在大鼠体内主要的代谢途径为葡萄糖醛酸结合，次要代谢途径为单氧化、脱氢、脱氟、半胱氨酸结合、甘氨酸结合和乙酰化。在比格犬血浆中主要代谢途径为氧化、脱氢、脱氟、去烷基、葡萄糖醛酸结合和谷胱甘肽结合水解去谷氨酸。CYP3A 是其主要代谢酶，体内外代谢类型基本一致。

GFH375 在雄性和雌性大鼠血浆中分布呈现中等清除和低清除，在犬血浆中呈现高清除，在大鼠和犬体内半衰期较长，范围为 8.18-14.3 h。[^{14}C]GFH375 总放射性在大鼠体内主要经粪便直接排出或由胆汁经粪便排出，尿液为次要排泄途径。

GFH375 对 CYP1A2 和 CYP2C9 未见抑制作用，对 CYP2B6、CYP2C8、CYP2C19、CYP2D6、CYP3A（以咪达唑仑为底物）和 CYP3A（以睾酮为底物）有抑制作用，其 IC_{50} 值为 42.8、93.2、42.6、26.2、6.40 和 7.95 μM。GFH375 对 CYP3A（分别以咪达唑仑和睾酮为底物）具有显著的时间依赖性抑制。GFH375 不是 CYP1A2 和 CYP2B6 的诱导剂，在基因水平不排除是 CYP3A4 的诱导剂。GFH375 不是乳腺癌耐药蛋白（BCRP）、有机阴离子转运多肽 1b1（OATP1B1）和有机阴离子转运多肽 1b3（OATP1B3）转运体的底物，是 P-糖蛋白（P-gp）的底物。GFH375 对 BCRP、OATP1B1、有机阳离子转运体 2（OCT2）、多药及毒性化合物外排转运蛋白 2-K（MATE2-K）未见抑制作用，对 P-gp、OATP1B3、有机阴离子转运体 1（OAT1）、有机阴离子转运体 3（OAT3）和多药及毒性化合物外排转运蛋白 1（MATE1）有抑制作用，IC_{50} 值分别为 16.9、17.4、2.56、24.4 和 15.6 μM。提示 GFH375 有潜在的药物-药物相互作用。

1.2.1.3 毒理学研究总结

在 SD 大鼠和比格犬中分别进行 14 天重复给药毒性剂量范围探索试验，结果显示，在 SD 大鼠中所得 10%动物的严重毒性反应剂量(STD_{10})大于 150 mg/kg/day。在比格犬中所得动物的最高非严重毒性反应剂量（HNSTD）为 100 mg/kg/day。

在 SD 大鼠 4 周重复给药 GLP 毒性试验中，通过经口灌胃给予剂量为 50、100、200 mg/kg/day 的 GFH375 或空白溶媒[5%（v/v）LABRASOL + 5%（v/v）PEG400 + 90%灭菌注射用水]，每天一次，连续给药 28 天。剂量为 100 mg/kg/day 时，见 1 例雌性动物死亡；剂量为 200 mg/kg/day 时，见 2 例雄性动物和 3 例雌性动物死亡。200 mg/kg/day 剂量组存活动物还见供试品相关的临床症状，血液学和血清生化指标变化以及组织病理学变化。恢复期末，上述改变均恢复。在本试验条件下，供试品的 STD_{10} 为 100 mg/kg/day。

在比格犬 4 周重复给药 GLP 毒性试验中，通过经口灌胃给予剂量为 5、10、25 mg/kg/day 的 GFH375 或空白溶媒[5%（v/v）LABRASOL + 5%（v/v）PEG400 + 90%灭菌注射用水]，每天一次，连续给药 28 天。试验期间未见动物死亡，可见供试品相关的临床症状，血液学和血清生化指标变化以及组织病理学变化。恢复期结束后，变化均可恢复或具有恢复趋势。在本试验条件下，GFH375 对于比格犬的 HNSTD 为 25 mg/kg/day。

通过遗传毒性试验标准组合来评价 GFH375 的遗传毒性，结果显示为阴性。

1.3. 研究设计依据

1.3.1 剂量选择

1.3.1.1 起始剂量选择依据

Ia 期研究中起始剂量的选择是基于临床前毒理学研究结果，根据 ICH S9 关于最大推荐起始剂量（MRSD）方法的建议计算起始剂量。

在 SD 大鼠和比格犬中开展符合药物非临床研究质量管理规范（GLP）的 4 周毒理学关键研究，大鼠中研究剂量分别为 50、100 和 200 mg/kg/天，犬中研究剂量分别为 5、10 和 25 mg/kg/天。研究结果显示大鼠中 10%的动物出现严重毒性的剂量（STD10）为 100 mg/kg/天，犬中最高非严重毒性剂量（HNSTD）为 25 mg/kg/天。根据 ICH S9，按照啮齿类动物 STD10 的 1/10 或非啮齿类 HNSTD 的 1/6，患者体重 60 kg 计算，分别对应的人体 MRSD 约为 100 mg 和 140 mg/天。

药效学研究显示，在 Panc 04.03 人胰腺癌 CDX 肿瘤小鼠模型进行的体内抗肿瘤药效研究，GFH375 在该模型上起效剂量为 5 mg/kg QD 14 天给药。在 AsPC-1 人胰腺癌 CDX 肿瘤小鼠模型中，GFH375 的起效剂量为 10 mg/kg QD 14 天给药。

综上，从毒理学研究结果提示的安全性，结合 GFH375 片剂规格，选择 100 mg/天剂量水平作为 GFH375 首次人体试验的起始剂量。

1.3.1.2 Ib 期和II期剂量选择依据

完成剂量递增部分后，将综合临床前体内外活性、临床 PK、临床安全性、临床有效性数据，选择 1 个或多个推荐的扩展剂展（RDE）进行剂量扩展研究，预计每个 RDE 剂量组纳入不超过 30 例受试者，以确认安全性以及 RP2D 剂量。

1.3.2 风险获益评估

1.3.2.1 潜在风险

目前有少数几款靶向 KRAS G12D 小分子抑制剂处于临床试验阶段，安全性数据和疗效数据披露有限。其中HRS-4642是由恒瑞研发的一款经静脉给药的KRAS G12D小分子，用于治疗KRAS G12D突变的晚期实体瘤患者。在其首次人体I期研究中，共入组18例受试者。总体安全性良好，发生率较高的治疗相关不良事件（>2例）包括血胆固醇升高、输液相关反应、蛋白尿、贫血、高甘油三酯血症、脂肪酶升高、低蛋白血症、血糖升高、丙氨酸氨基转移酶升高、血小板计数减少、高钙血症、低钙血症、发热、乏力、中性粒细胞计数减少、白细胞减少、天门冬氨酸氨基转移酶升高[33]。

GFH375尚未进行人体内研究。GFH375临床前毒理学数据提示其潜在毒性可能包括肝功能损害及胃肠系统不良反应。

根据 GFH375 的临床前研究结果和其它 KRAS G12D 抑制剂的数据，GFH375 的潜在风险如下：

- 肝功能损害
- 胃肠系统不良反应

1.3.2.2 潜在获益

本研究的目标人群为 KRAS G12D 突变阳性的晚期 NSCLC、PDAC、CRC 及其他实体瘤

患者。针对此类患者，尚无有效的治疗手段，仍以化疗或化疗联合免疫治疗为主要治疗方案。尚未有靶向这一突变的治疗药物获批上市。

目前已有 KRAS G12D 靶点的药物进入临床研究且有初步临床结果。KRAS G12D 小分子抑制剂 HRS-4642 的初步疗效数据显示：共入组 18 例晚期实体瘤受试者，7 例受试者靶病灶缩小。其中共 10 例 NSCLC 受试者，5 例受试者靶病灶缩小。

GFH375 的临床前研究显示，在携带 KRAS G12D 突变的人胰腺癌肿瘤动物模型中，单次灌胃给药 GFH375 在肿瘤中观察到对 KRAS 通路下游蛋白 ERK1/2 蛋白磷酸化剂量依赖性的抑制，长期灌胃给药（每天 2 次、连续 14 天）观察到明显的抗肿瘤药效，起效剂量为 5-10 mg/kg, 高剂量下（100 mg/kg)观察到肿瘤消退。

综上，预期 GFH375 值得在这类人群中进一步开展临床研究，以给此类患者提供抗肿瘤治疗的新选择。

1.3.2.3 风险获益评估

根据 KRAS G12D 靶点的生物学特性和 GFH375 的产品特性，以及上述 GFH375 已获得的非临床数据，本方案设计了相应的入排选标准、生活方式要求以及安全性检查和随访流程。通过严密方案设计，研究中心的选择，药物安全信息的收集，药物安全性信息的通报及时更新，尽可能将受试者的风险最小化。基于目前作用机制相同产品的临床数据，预期符合入排选要求的受试者接受 GFH375 单药治疗获益可能性大。总体获益/风险评估支持开展这项研究。

2 研究目的与终点

本研究是一项I/II期研究。其中 I 期研究部分包括 Ia 期剂量递增部分和 Ib 期剂量扩展部分。研究目的和研究终点分别总结如下。

Ia 期研究部分的目的和终点包括：

研究目的	研究终点
主要目的	**主要终点**
评估 GFH375 在 KRAS G12D 突变的晚期实体瘤患者中的安全性和耐受性	• 不良事件 (AE) 和严重不良事件 (SAE) 的发生率和严重程度；生命体征、心电图 (ECG) 和实验室检查的改变
• 确定 GFH375 的最大耐受剂量 (MTD) 和/或推荐的扩展剂量 (RDE)	• 剂量限制性毒性 (DLT)事件的发生率
次要目的	**次要终点**
• 评估 GFH375 在 KRAS G12D 突变的晚期实体瘤患者中的药代动力学 (PK)特征	• GFH375 的血浆浓度和 PK 参数，包括但不限于 C_{max}、T_{max}、AUC、$t_{1/2}$、CL/F、V_z/F、C_{trough}
• 评估 GFH375 在 KRAS G12D 突变型晚期实体瘤患者中的初步疗效	• 研究者根据实体瘤疗效评价标准 (RECIST)1.1 评估的客观缓解率 (ORR)、缓解持续时间 (DoR)、疾病控制率 (DCR)、至缓解时间 (TTR)、无进展生存期 (PFS) • 总生存期 (OS)

Ib 期研究部分的目的和终点包括：

研究目的	研究终点
主要目的	**主要终点**
• 确认 GFH375 在 KRAS G12D 突变的晚期实体瘤患者中的安全性和耐受性，以及 GFH375 的 II 期推荐剂量（RP2D）	• 不良事件 (AE) 和严重不良事件 (SAE) 的发生率和严重程度 • 生命体征、心电图 (ECG) 和实验室检查的改变
次要目的	**次要终点**
• 评估 GFH375 在 KRAS G12D 突变的晚期实体瘤患者中的 PK 特征	• GFH375 的血浆浓度
• 评估 GFH375 在 KRAS G12D 突变型晚期实体瘤患者中的初步疗效	• 研究者根据 RECIST 1.1 评估的 ORR、DoR、DCR、TTR、PFS • OS

探索目的	探索终点
• 探索与治疗敏感或耐药相关的分子机制	• 基线和治疗结束时血液循环肿瘤 DNA（ctDNA)的突变分析

II期研究部分的目的和终点包括：

研究目的	研究终点
主要目的	**主要终点**
• 评估 GFH375 在 KRAS G12D 突变的晚期非小细胞肺癌（NSCLC）、晚期胰腺癌 (PDAC)、晚期结直肠癌 (CRC) 和其他实体瘤患者中的疗效	• 研究者根据 RECIST 1.1 评估的 ORR
次要目的	**次要终点**
• 使用其他疗效指标评估 GFH375 在 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的疗效	• 研究者根据 RECIST 1.1 评估的 DoR、DCR、TTR、PFS • OS
• 评估 GFH375 在 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的安全性	• AE、SAE 的发生率和严重程度 • 生命体征、ECG 和实验室检查的改变
• 评估 GFH375 在 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的 PK 特征	• GFH375 的血浆浓度
探索目的	**探索终点**
• 探索与治疗敏感或耐药相关的分子机制	• 基线和治疗结束时血液 ctDNA 的突变分析

3 研究设计

3.1. 总体设计

本研究是一项评估 GFH375 单药在携带 KRAS G12D 突变的晚期实体瘤患者中的安全性/耐受性、PK 及有效性。I 期研究的主要目的是评估 GFH375 在 携带 KRAS G12D 突变的晚期实体瘤患者中的安全性/耐受性、PK 和初步有效性，并确定 GFH375 的 MTD 和/或 RDE 剂量。II 期研究的主要目的是评估 GFH375 在携带 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的有效性。

研究期间将设立由研究者及申办方组成的安全监查委员会（SMC），详细信息可参考第 10 章节及本研究的 SMC 章程。

3.1.1 Ia 期：剂量递增部分

Ia 期将入组 KRAS G12D 阳性的晚期实体瘤患者，研究计划示意图见图 2。

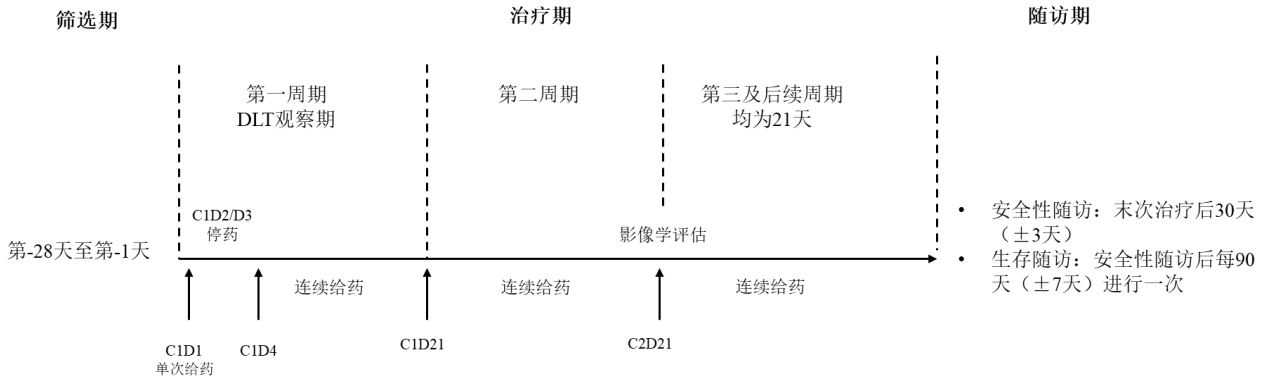

图 2 Ia 期研究计划示意图

Ia 期共入组约 30 例受试者。

将根据 BOIN 设计，在每个剂量水平入组 3-6 例受试者（加速滴定时除外）接受治疗。将根据已获得的安全性/耐受性、PK 及初步有效性数据，可能选择一个或多个剂量水平入组额外的受试者作为回填， 接受已确认安全且耐受性良好的、经研究者及申办方评估可能临床获益的 GFH375 单药剂量进行治疗，以更好的估计 GFH375 单药的 RDE/RP2D 以及表征其安全性\耐受性、PK 及有效性。回填的受试者不被纳入 DLT 的评估。回填后，接受 GFH375 每个剂量水平治疗的受试者不超过 9 例（包括 BOIN 剂量递增阶段入组的受试者）。

如果需要探索更多的剂量水平或替代给药方案，则可以入组额外的受试者。

受试者入组后将接受 GFH375 每日一次（QD）口服给药治疗，每 21 天为一个治疗周期。受试者将入组至顺序递增的不同剂量组，起始剂量为 100 mg QD。预计在剂量递增部分共进行 5 个给药剂量的评估，计划的递增剂量参见表格 1。研究者和申办方将根据所有已获得的数据讨论并决定是否探索更高的剂量水平，或其他给药方案，如每日两次给药方案（BID）。

首次治疗后的第一个周期将作为剂量限制性毒性（DLT）观察期，DLT 可评估病例需要满足以下两个条件之一：

- 受试者发生 DLT 事件，或
- 受试者未发生 DLT 事件，且在第一周期至少接受了 15 天 GFH375 的计划给药。

DLT 不可评估病例将进行受试者替代，替代后的受试者将接受相同剂量水平 GFH375 的单药治疗。

如未发生 DLT 事件，受试者将继续接受治疗，并允许在符合本方案准许情况下的剂量调整，直至出现疾病进展、不可耐受的毒性或因其他原因结束研究治疗。若受试者在 DLT 观察期发生 DLT 事件，经研究者与申办方评估继续接受 GFH375 的治疗能够获益，将在相关的不良事件缓解后恢复 GFH375 治疗。恢复给药标准可参考表格 3 和表格 4。

入组 Ia 期的受试者将进行密集 PK 采样并收集与 PK 采样相匹配的心电图，以评估 GFH375 的药代动力学特征和安全性。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。受试者将在末次研究治疗后 30 (±3) 天返回研究中心完成安全性随访，之后每 90 (±7) 天进行一次生存随访。受试者因疾病进展以外的原因结束研究治疗且尚未开始新的抗肿瘤治疗，需按照之前的影像学评估计划继续进行疾病进展随访，直至疾病进展、撤回 ICF、开始其他抗肿瘤治疗或研究结束。

表格 1 剂量递增表格

	Ia期计划进行递增的剂量组*
剂量组1	100 mg QD
剂量组2	200 mg QD
剂量组3	400 mg QD
剂量组4	600 mg QD
剂量组5	900 mg QD

注：可能会在爬坡过程中基于获得的临床数据包括安全性、PK、可能的有效性进行目前设定的剂量中间剂量的探索，如

150mg, 300mg, 500mg,750mg 等。

3.1.1.1 DLT 定义

DLT 是指在首次用药后 21 天内出现的、与研究药物 GFH375 相关且符合以下严重程度的不良事件。不良事件的严重程度根据不良事件通用术语评价标准（CTCAE）5.0 版进行分级：

- ≥4级中性粒细胞绝对计数（ANC）降低≥5天；
- ≥3级发热性中性粒细胞减少症（ANC <1.0 × 10^9/L 伴体温 > 38.3℃）；
- ≥4级血小板计数降低持续≥5天；
- ≥3级血小板计数降低合并≥2级出血；
- ≥4级贫血；
- 若基线ALT或AST ≤ 1级：≥ 3级血清转氨酶升高（ALT或AST）持续 > 7天被视作DLT；若基线ALT或AST为2级，则 ALT或AST> 10x ULN持续 > 7天被视作DLT；
- 血清胆红素升高≥3级；
- 根据海氏法则，AST或ALT > 3xULN（若基线合并肝转移，则要求 > 3倍基线值），且同时合并总胆红素 > 2xULN（需排除胆道梗阻或其他原因导致的如肝炎、肝内肿瘤进展等病因）；
- ≥3级其他毒性（非肝脏、非血液学），除外以下情况：
  - 3 级的恶心或呕吐、腹泻，在接受/不接受对症支持治疗的情况下持续时间不长于3天；
  - 3 级的疲乏，在接受/不接受对症支持治疗的情况下持续时间不长于3天；
  - 无症状的3级实验室结果异常，研究者判断无临床意义。

在 DLT 观察期后出现的符合上述标准的毒性也将被视为评价安全性的重要因素。此外，将在申办方和研究者讨论后确定可能被评估为 DLT 的其他治疗相关毒性。

在第一周期（DLT 观察期）内，对于符合 DLT 标准的 AE，应于获知其发生之后的 24 小时之内报告至申办方（报告方法请参见 8.2.4 严重不良事件（SAE）的报告）。

3.1.1.2 剂量递增规则与 MTD 定义

允许在前两个剂量采用加速滴定法，即首例受试者将接受第一个剂量水平的治疗。如果前两个剂量组的受试者在 DLT 观察期内均未观察到≥2 级治疗相关 AE，则在下一个较高剂量

水平纳入 3~6 例受试者，并使用 BOIN 设计进行本组和后续剂量递增；反之，如果在第一个或第二个剂量组报告任何≥ 2 级治疗相关 AE 或 DLT 事件，则从观察到≥ 2 级治疗相关 AE 或 DLT 事件的最低剂量组开始，直接转为 BOIN 设计。在第一个剂量完成加速滴定的前提下，对于第二个剂量水平是否采用加速滴定，将由 SMC 基于第一个剂量水平的 PK 及安全性数据进行讨论决定。后续剂量水平采用 BOIN 设计确定 MTD，目标毒性概率为 0.3。每个剂量水平将入组 3~6 例受试者接受治疗，Ia 期入组约 30 例受试者。

BOIN 设计将根据表格 2 所示的剂量升降规则为下一组受试者分配剂量水平。

表格 2 BOIN 设计的剂量递增/递减规则

决策	当前剂量上治疗的受试者总数						
	3	**4**	**5**	**6**	**7**	**8**	**9**
升剂量，若发生 DLT 的受试者例数 ≤	0	0	1	1	1	1	2
降剂量，若发生 DLT 的受试者例数 ≥	2	2	2	3	3	3	4
剔除剂量，若 DLT 受试者例数 ≥	3	3	4	4	5	5	5

具体规则如下：

- 如果根据上表规则得到的决策既非升剂量、降剂量，也非剔除剂量，则继续使用当前剂量治疗下一组受试者。
- 上表中的“剔除剂量”指从试验中剔除当前和更高剂量。
- 如当前剂量被剔除，将自动降低剂量至下一个较低的水平对受试者进行治疗。
- 如果最低剂量水平被剔除，则提前终止试验以确保受试者安全。在此情况下，将无法确定 MTD。
- 如果当前剂量是最低剂量水平且规则提示剂量降低，则仍以当前最低剂量治疗下一组受试者。
- 如果当前剂量是最高剂量水平且规则提示需升高剂量，则仍以最高剂量治疗新入组的受试者。
- 当推荐的下一剂量水平的可评估受试者≥6 例时，剂量递增部分可终止。
- 接受最高的推荐剂量水平（RDE）治疗的可评价受试者须达到至少 6 例。

剂量递增阶段结束后，将基于 DDS 采用保序回归分析以确定 MTD。使用 http://www.trialdesign.org 的在线 BOIN 软件进行保序回归分析，得到每个剂量水平毒性概率的保序估计值。最接近目标毒性率 0.3 的剂量水平即为 MTD。如果有 2 个或以上同时满足条件的剂量水平，选择保序估计值<0.3 的最高剂量水平或保序估计值≥0.3 的最低剂量水平。

3.1.1.3 剂量递增阶段受试者回填（Backfill）

将根据已获得的安全性/耐受性、PK 及初步有效性数据，可能选择一个或多个剂量水平入组额外的受试者作为回填，接受已确认安全且耐受性良好的、经研究者及申办方评估可能临床获益的 GFH375 单药剂量进行治疗，以更好的估计 GFH375 单药的 RDE/RP2D 以及表征其安全性\耐受性、PK 及有效性。回填的受试者不被纳入 DLT 的评估。回填后，接受 GFH375 每个剂量水平治疗的受试者不超过 9 例（包括 BOIN 剂量递增阶段入组的受试者）。

回填的受试者将根据 Ia 期的流程访视表及 Ia 期的 PK 采血表完成相关访视。

3.1.1.4 受试者个体内剂量递增

剂量递增研究期间原则上不进行个体内剂量递增。对于入组 Ia 期的受试者，经研究者和申办方同意后，允许在本方案的 RP2D 剂量确认后， 进行个体内剂量调整，接受 RP2D 的单药治疗。

3.1.2 Ib 期：剂量扩展部分

Ib 期的研究计划示意图见图 3。

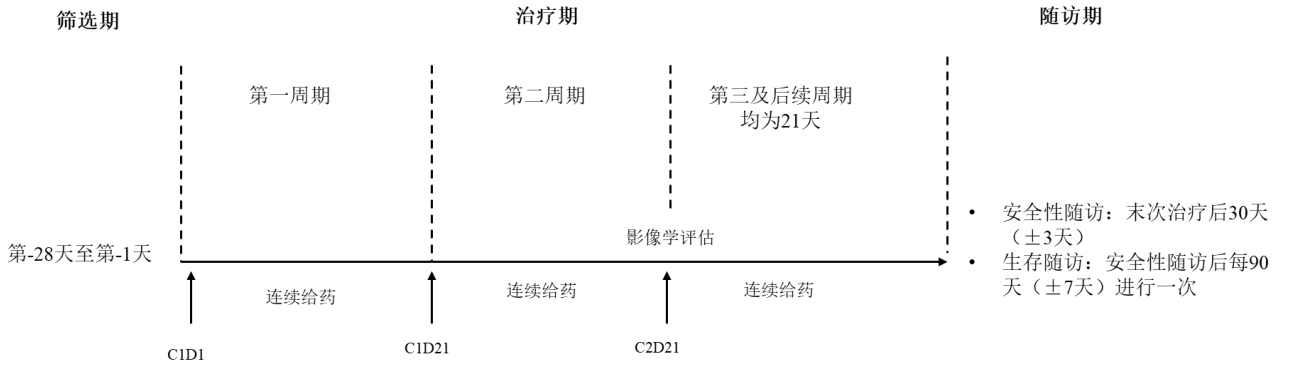

图 3 Ib 及 II 期研究计划示意图

完成剂量递增部分后，将综合本产品临床前及临床数据，选择 1 个或多个 RDE 进行剂量扩展研究，预计每个 RDE 剂量组纳入不超过 30 例受试者，以确认安全性及 RP2D 剂量。

筛选合格的受试者将接受 GFH375 单药治疗，每 21 天为一个治疗周期，直至疾病进展、

出现不可耐受的毒性或因其他原因结束研究。纳入 Ib 期研究剂量扩展部分的受试者将进行稀疏 PK 采样该部分入组的受试者将根据 Ib 和 II 期 PK 采血表进行稀疏 PK 采样，并收集与 PK 采样相匹配的心电图。治疗期间，受试者在前 48 周每 6 周 ± 1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。受试者将在末次研究治疗后 30 (±3) 天返回研究中心完成安全性随访，之后每 90 (±7) 天进行一次生存随访。受试者因疾病进展以外的原因结束研究治疗且尚未开始新的抗肿瘤治疗，需按照之前的影像学评估计划继续进行疾病进展随访，直至疾病进展、撤回 ICF、开始其他抗肿瘤治疗或研究结束。

剂量递增研究期间原则上不进行个体内剂量递增。对于入组 Ib 期的受试者，经研究者和申办方同意后，允许在本方案的 RP2D 剂量确认后， 进行个体内剂量调整，接受 RP2D 的单药治疗。

3.1.3 II 期部分

II 期研究为开放标签、多中心的研究，总体研究计划见**图 3**。目的是评估 GFH375 治疗携带 KRAS G12D 突变的晚期非小细胞肺癌、晚期胰腺癌、结直肠癌和其他晚期实体瘤患者的有效性、安全性和 PK 特征。II 期研究将入组约 213 例 KRAS G12D 突变的晚期实体瘤受试者，以接受 RP2D 的 GFH375 连续单药治疗，治疗周期为 21 天。该部分入组的所有受试者将根据 Ib 和 II 期 PK 采血表进行稀疏 PK 采样，并收集与 PK 采样相匹配的心电图。

- 晚期NSLCL受试者队列：计划入组约73例携带KRAS G12D 突变的晚期NSCLC受试者。
- 晚期 PDAC受试者队列：计划入组约50例携带KRAS G12D 突变的晚期PDAC受试者。
- 晚期 CRC 受试者队列：计划入组约50例携带KRAS G12D 突变的晚期CRC受试者。
- 其他晚期实体瘤受试者队列：计划入组约携带 40 例 KRAS G12D 突变的晚期实体瘤受试者，如携带 KRAS G12D 突变的胆管癌、阑尾癌等。

筛选合格的受试者将接受 GFH375 单药治疗，直至疾病进展、出现不可耐受的毒性或因其他原因结束研究治疗。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。受试者将在末次研究治疗后 30 (±3) 天返回研究中心完成安全性随访，之后每 90 (±7) 天进行一次生存随访。受试者因疾病进展以外的原因结束研究治疗且尚未开始新的抗肿瘤治疗，需按照之前的影像学评估计划继续进行疾病进展随访，直至疾病进展、撤回 ICF、开始其他抗肿瘤治疗或研究结束。

3.2. 研究结束的定义

研究结束定义为末例受试者接受至少 6 个月的研究治疗或提前退出（以先发生者为准）。

3.3. 提前终止研究

由于监管机构的决定、伦理委员会意见，或者是申办方和研究者共同讨论的判断和决定，本研究允许提前终止或暂停。此外，申办方保留停止研发GFH375的权利。

研究提前终止或暂停的原因可能包括：

- 确定对受试者产生非预期的、重大的、或不可接受的风险；
- 已有的疗效结果支持提前终止研究；
- 方案要求的依从性较低。

决定暂停/终止研究的一方将发出书面通知、记录研究终止或暂停的原因给研究者、申办方和监管机构。如果研究被提前终止或暂停，研究者应立即通知伦理委员会和申办者，并且提供相关理由。

一旦上述提到的导致研究药物暂停的安全、方案依从性等问题得到解决并得到申办者、伦理委员会和/或法规监管机构的同意，则研究将继续进行。

4 研究人群

受试者必须符合所有入选标准，且不符合任意一条排除标准。

4.1. 入选标准

参加本研究的受试者需符合所有以下标准：

1. 自愿参加研究并签署知情同意书。
2. 在签署知情同意书时年龄为 18 - 75 周岁的男性或女性。
3. 经组织学或细胞学病理确认的局部晚期或转移性恶性肿瘤受试者，需符合以下标准：

（1） I 期部分：经标准治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗，或拒绝标准治疗。

（2） II 期部分：

a) 晚期 NSCLC：

- ✓ 既往接受过抗 PD-（L）1 治疗和/或以铂类为基础的化疗后进展（除非有使用禁忌或不耐受）；
- ✓ 若既往接受过辅助或新辅助治疗且在治疗期间或治疗停止后 6 个月内出现复发/进展，则可将该治疗计入一个线数的治疗。

b) 晚期 PDAC：既往经过基于吉西他滨的化疗方案或 FOLFIRINOX/mFOLFIRINOX 方案的充分治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗，或拒绝标准治疗。存在微卫星高度不稳定（MSI-H）及错配修复基因缺陷型（dMMR）者需既往经过至少一线抗 PD-1 治疗后进展。如果接受过辅助或新辅助治疗且在治疗期间或治疗停止后 6 个月内出现复发/进展，则可将该治疗计入一个线数的治疗。

c) 晚期 CRC：经至少二线标准治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗，或拒绝标准治疗。受试者须既往在接受氟尿嘧啶、伊立替康和奥沙利铂治疗转移性疾病期间或之后发生疾病进展或复发，除非研究者认为受试者不适合接受以上治疗方案。已知有微卫星高度不稳定（MSI-H）及错配修复基因缺陷型（dMMR）的受试者必须既往接受过免疫检查点抑制剂治疗（如适用）。如果接受过辅助或新辅助治疗且在治疗期间或治疗停止后 6 个

月内出现复发/进展，则可将该治疗计入一个线数的治疗。

d) 其他实体瘤：经标准治疗后进展，或由于不可耐受的毒性等原因不适合标准治疗，或拒绝标准治疗。

4. 入组本研究的受试者需提供确认 KRAS G12D 突变阳性的书面检测报告。

5. 根据 RECIST 1.1，Ia 期受试者必须至少有一个可评估病灶，Ib 期、II 期受试者必须至少有一个可测量病灶。

6. 既往抗肿瘤治疗的毒性反应必须缓解至基线水平（不包括脱发）或≤1 级（对于神经系统毒性，≤2 级）。

7. 研究者判断预期生存时间≥ 12 周。

8. 美国东部肿瘤协作组（ECOG）体能状态评分（PS）0~1 分（评分标准参见附录 2）。

9. 具有充分的器官功能，包括：

4 造血功能：中性粒细胞绝对计数 (ANC) ≥ 1.5 × 10^9/L，血小板计数 ≥ 75 × 10^9/L，血红蛋白 ≥ 9 g/dL，在血液检查前 14 天内未输血或未接受粒细胞集落刺激因子、血小板生成素或促红细胞生成素治疗。

5 肝功能：

- AST 和 ALT 均< 2.5×ULN；对于基线存在肝转移的受试者，要求 AST 和 ALT 均< 5×ULN；
- 总胆红素（TBIL）< 1.5×ULN；Gilbert 综合征受试者：TBIL < 2×ULN。

6 肾功能：肌酐清除率（CrCl）≥ 50 mL/min（Cockcroft-Gault 公式计算，参考附录 3）。

7 凝血功能：凝血酶原时间（PT）或活化部分凝血活酶时间（APTT）< 1.5×ULN，国际标准化比值（INR）< 1.5×ULN 或处于抗凝治疗的目标范围内。

10. 有生育能力的女性（WOCBP）和伴侣为 WOCBP 的男性受试者必须同意从签署知情同意书至末次研究治疗后 30 天内采取有效的避孕方法。WOCBP 在给药前 7 天内的血清妊娠试验结果必须为阴性。

11. 根据研究者的判断，受试者能够良好沟通、按计划随访并遵守方案的要求。

4.2. 排除标准

符合以下任意一条标准的受试者不能入组本研究：

1. 入组前 3 年内发生进展或需要治疗的其他恶性肿瘤，除外经充分治疗的原位癌、基底细胞癌或皮肤鳞状细胞癌。
2. 研究者判断不稳定的脑转移患者。对于在筛选过程中无意检出的伴脑转移的患者，如果未引起临床症状且不需要治疗干预， 可允许入组；如果研究者判断脑转移控制稳定，激素剂量使用稳定，且强的松剂量≤10mg/d（若使用其他类固醇药物，则为相应等效剂量），可允许入组。
3. II 期部分：
   a) 晚期 NSCLC：排除已知的其他驱动基因突变或融合，如 EGFR、ALK、 BRAF (V600E)、HER2、MET (exon 14)、 ROS1、RET 或 NTRK1/2/3
   b) 晚期 CRC：排除已知的其他驱动基因突变、扩增或融合，如 BRAF (V600E)、HER2、NTRK 或 RET
   c) 晚期 PDAC：排除已知的其他驱动基因突变或融合，如 BRAF (V600E)、BRCA、NTRK 或 RET
4. 既往接受过 KRAS G12D 或者泛 KRAS （具有靶向 KRAS G12D 作用）的靶向治疗。
5. 在研究药物给药前 14 天内接受姑息性放疗。
6. 在给药前 28 天内或 5 个半衰期内（以较短者为准）接受过其他抗肿瘤治疗，包括化疗、靶向治疗、内分泌治疗、免疫治疗、具有明确抗肿瘤作用的中成药及其他试验用药物或器械，内分泌维持治疗除外。
7. 合并具有临床意义的严重心血管疾病：
   - 首次研究治疗前 6 个月内发生具有临床意义的严重心血管事件，如心肌梗死、不稳定型心绞痛、症状性充血性心力衰竭（纽约心脏病协会 III 或 IV 级）、需要药物治疗的重度心律失常或接受血管成形术、支架植入术和冠状动脉旁路移植术等。
   - 具有临床意义 QT/QTcF 延长（基于筛选期三次 QTcF 的平均值，QTcF > 470 ms）或合并 QT 间期延长的家族史。
   - 经标准治疗后仍控制不佳的高血压。

8. 入组前 6 个月内发生卒中或其他严重脑血管疾病。
9. 入组前 3 个月内有深静脉血栓或其它任何严重血栓栓塞的病史。
10. 伴随需要反复引流或有明显症状的胸腔积液、腹水或心包积液。
11. 合并上腔静脉综合征。
12. 合并可能显著影响 GFH375 吸收的胃肠道功能受损或胃肠道疾病，或无法或不愿意吞咽片剂。
13. 合并具有临床意义并需要治疗的间质性肺病、放射性肺炎或免疫相关性肺炎。
14. 合并重大急性或慢性感染性疾病，包括：
    - 入组前 7 天内需要静脉使用抗生素治疗的活动性感染。
    - 基线时人类免疫缺陷病毒抗体 (HIV-Ab) 阳性。
    - 活动性乙型肝炎病毒感染（HBsAg 阳性伴 HBV-DNA 阳性）。
    - 活动性丙型肝炎病毒感染（HCV-Ab 阳性伴 HCV-RNA 阳性）。
    - 活动性结核病。
15. 合并其他控制不佳的系统性疾病，如糖尿病。
16. 在首次给药前 28 天内接受或计划进行由研究者判断的重大手术（穿刺活检除外）。
17. 既往有器官移植病史或准备接受器官移植。
18. 在研究药物给药前 7 天内或接受研究药物期间需使用抑酸类药物，包括质子泵抑制剂和新型抑酸类药物（如钾离子竞争性酸阻滞剂）。
19. 在研究药物给药前 14 天内或药物的 5 个半衰期内（以较长者为准）接受了 CYP3A 或 P-gp 的强抑制剂或强诱导剂。
20. 在研究药物给药前 14 天内或药物的 5 个半衰期内（以较长者为准）接受过已知敏感的 CYP3A 或 OAT1 底物。除非经研究者和申办方审阅后同意入组。
21. 已知对研究药物或成分过敏。
22. 有严重的精神、心理疾病或有药物滥用史或有严重酗酒史。
23. 妊娠或哺乳期女性。
24. 研究者判断不适合参加研究的其他情况。

5 研究治疗

5.1 治疗方案

Ia 期

GFH375 的初始剂量为 100 mg QD, 每 21 天为一个治疗周期。受试者将持续用药直至疾病进展或出现不可耐受的毒性导致治疗终止的情况。

Ib 期和 II 期

Ib 期的受试者将接受 GFH375 MTD/RDE 治疗，II 期的受试者将接受 GFH375 RP2D 治疗，每日给药。每 21 天为一个治疗周期。受试者将持续用药直至疾病进展或出现不可耐受的毒性或其他导致治疗终止的情况。

5.2 研究药物

5.2.1 研究药物的描述

研究药物	GFH375 片
活性成分	GFH375
辅料	甘露醇、微晶纤维素、交联羧甲基纤维素钠、羟丙纤维素、胶态二氧化硅、硬脂酸镁、薄膜包衣预混剂（胃溶型）-欧巴代、纯化水
类型	口服固体制剂
剂型	片剂
规格	25mg，100mg
给药途径	口服
储存要求	避光，密封，不超过 25℃保存
有效期	暂定 24 个月
包装及标签	口服固体药用高密度聚乙烯瓶和口服固体药用聚丙烯儿童安全组合瓶盖，内加固体药用高密度聚乙烯非织造（泰维克）袋装干燥剂。每瓶会根据相关法规要求贴上标签。

5.2.2 治疗分配和药物发放

在受试者签署书面的知情同情书时，就会被分配一个受试者编号，该编号会被用于所有的研究文档和病例报告表（CRF）。完成筛选流程后，根据入排选标准判断是否正式入组研究。所有入组的受试者将接受 GFH375 治疗。

研究者或其指定人员必须确保在运输过程中所有用于研究治疗的药物或相关物品保持适宜的温度条件。若出现偏差，则需在进行研究治疗前汇报并解决所出现的问题。

只有入组研究的受试者可以接受研究治疗，且只有经授权的研究中心人员可以提供或管理研究治疗产品。所有研究干预的药物或相关物品必须按照标签上注明的储存条件储存在安全、环境可控、可监测（手动或自动）的区域，并保证仅研究者和经授权的研究中心人员有相关权限接触研究治疗产品。

5.2.3 研究药物给药

GFH375将由研究中心人员在计划的访视发放给受试者，单次发放的药物数量将保证受试者在指定的时期内有足够的药物在院外自行服用。

GFH375 片剂采取口服给药。需告知受试者必须整片吞下，不能嚼碎或掰开。服药前 2h 至服药后 1h 均禁食，并尽可能保证每天的服药时间接近。如当日早晨需要抽取 PK 血样，应在抽血后服药。

如发生漏服，对于接受 QD 给药的受试者，需在计划的服药时间点后 12 小时内补服，并记录实际服药时间，后续服药时间不变。如已超过 12 小时则不用补服，下次服药时间按原计划。如用药后发生呕吐，无需补服。所有的实际服药时间都应记录在受试者日记上，或记录“漏服”等意外情况。

5.3 剂量调整

5.3.1 允许的剂量调整

原则上，入组 Ia 期的受试者在 DLT 观察期内不允许剂量调整。研究期间应密切监测受试者使用研究药物的安全性，推荐根据所在研究中心实践采用最佳支持治疗处理治疗相关的不良事件。

完成 DLT 观察期的 Ia 期受试者及入组 Ib 期或 II 期的受试者可以根据实际临床需要进行剂量调整。将按照 Ia 期的剂量设定进行剂量下调。同一个受试者最多允许 2 次剂量降低。接受 100 mg QD GFH375 治疗的受试者，原则上不允许剂量下降；接受 200 mg QD GFH375 治疗的受试者，原则上只允许下降至 100 mg QD。如有特殊情况，研究者应与申办方进一步讨论达成一致。剂量调整详细原则可参考表格 3 及表格 4。

剂量递增研究期间原则上不进行个体内剂量递增。对于入组 Ia 期的受试者，经研究者和申办方同意后，允许在本方案的 RP2D 剂量确认后， 进行个体内剂量调整，接受 RP2D 的单药治疗。

5.3.2 暂停给药和永久停药

研究期间受试者如发生与研究治疗有关且符合表格 3、表格 4 的任一永久停药标准，应停止 GFH375 治疗，并随访至事件解决或恢复至基线水平。如该受试者已出现肿瘤治疗响应，研究者判断继续接受治疗有益，可在与申办方充分沟通后，在毒性恢复如下水平后恢复同一剂量或低一剂量研究治疗，同时继续密切监测相关毒性。

表格 3 血液学毒性的剂量调整原则

药物相关不良事件	严重程度	剂量调整
中性粒细胞计数（ANC）减少	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平，恢复原剂量或降低 1 个剂量用药；
	4 级	停药，直至恢复至≤1 级或基线水平，并降低 1 个剂量用药；
	3 级发热性 ANC 减少	停药，直至恢复至≤1 级或基线水平，并降低 1 个剂量用药；
	4 级发热性 ANC 减少	停药，并退出研究治疗；
血小板计数（PLT）减少	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平，恢复原剂量或降低 1 个剂量用药；若伴出血需要临床干预，则降低 1 个剂量用药；
	4 级	停药，直至恢复至≤1 级或基线水平，并降低 1 个剂量用药或停药退出研究治疗；
贫血	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤2 级或基线水平，恢复原剂量或降低 1 个剂量用药；
	4 级	停药，直至恢复至≤2 级或基线水平，并降低 1 个剂量用药或停药退出研究治疗；
其他	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤2 级或基线水平，恢复原剂量或降低 1 个剂量用药；
	4 级	非危及生命且经过治疗可以控制的不良事件，可经停药，不良事件恢复至≤1 级或基线水平后降低剂量用药。危及生命的不良事件，则终止用药。

表格 4 非血液学毒性的剂量调整原则

药物相关不良事件	严重程度	剂量调整
ALT/AST 升高	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平，恢复原剂量或降低 1 个剂量用药；若 ALT/ AST>5×ULN 超过 2 周，或 ALT/ AST > 8×ULN，需停药并退出研究治疗；
	4 级/符合海氏法则	停药，退出研究治疗；
血胆红素升高	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平；无合并转氨酶或碱性磷酸酶升高，可恢复原剂量或降低 1 个剂量用药；
	4 级	停药，退出研究治疗；
血淀粉酶/脂肪酶升高	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平；若无症状可恢复原剂量或降低 1 个剂量用药；若有症状则降低 1 个剂量用药；
	4 级	停药，直至恢复至≤1 级或基线水平并降低 1 个剂量用药或停药并退出研究治疗；
胰腺炎	2 级	停药，直至淀粉酶及影像学正常或无临床意义； 降低 1 个剂量用药；
	3/4 级	停药，退出研究治疗；
恶心/呕吐/腹泻	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平，恢复原剂量或降低 1 个剂量用药；若经对症支持治疗超过 3 天仍无好转，则降低 1 个剂量用药；
	4 级	停药，退出研究治疗；
乏力	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤2 级或基线水平； 若恢复时间 ≤ 1 周，建议采用原剂量用药治疗；若>1 周，建议降低 1 个剂量用药
其他系统不良事件	1/2 级	维持原剂量用药；
	3 级	停药，直至恢复至≤1 级或基线水平； 若恢复时间 ≤ 1 周，建议采用原剂量用药治疗；若恢复时间 >1 周，建议降低 1 个剂量用药
	4 级	非危及生命且经过治疗可以控制的不良事件，可经停药，不良事件恢复至≤1 级或基线水平后降低剂 量用药。 危及生命的不良事件，则终止用药。

发生上述血液学毒性时，建议在 3 天内复查血常规，之后继续密切监测恢复情况。如恢复至如下标准可考虑恢复治疗：非血液学毒性恢复至≤1 级或基线水平；血液学毒性恢复至

ANC≥1.0×10^9/L，PLT≥75×10^9/L，Hb≥8g/dL。

如治疗相关的不良事件在 4 周内仍无法恢复到可用药的水平，或在恢复用药后再次发生同一需要暂停治疗的毒性，应考虑永久停止治疗。永久停药的后续研究流程请参见方案 6.4.2 章节。

5.4 既往和伴随治疗

5.4.1 既往治疗

受试者参加本研究前禁止的既往/合并治疗请参见方案第四章节。

受试者签署知情同意书后，将收集其既往治疗研究疾病（晚期实体瘤）的各线用药情况，以及在本研究首次用药前 30 天的其他既往用药/治疗。

5.4.2 伴随治疗

受试者从首次接受研究治疗开始至安全性随访访视期间，将记录接受的所有伴随治疗、血制品、非药物干预（如穿刺）。

5.4.2.1 允许/慎用的伴随治疗

研究过程中研究者需遵从以下原则并谨慎使用合并药物，最大限度的保障受试者的安全。

研究期间允许进行针对疾病症状的姑息治疗和最佳支持治疗，但 DLT 观察期间的伴随治疗应避免影响对 DLT 的判断。对疾病相关症状的姑息性和支持性治疗将取决于研究者的判断及相关的指南（如《美国临床肿瘤学会指南》）。例如，允许以缓解症状为目的的姑息性局部放疗治疗痛性骨病灶，前提是已知这些病灶在入组时即存在，且并非唯一靶病灶。进行放疗前研究者应判断并记录放疗的使用是否与疾病进展相关。

研究期间如受试者合并其他疾病，研究者应判断是否需要使用药物治疗，应尽可能避免对研究结果的判断影响较大的药物，以免影响对受试者安全性和耐受性的判断。如发生严重不良反应或严重不良事件、或原病情恶化或并发其他严重疾病，研究者应及时给予伴随治疗和积极治疗。如达到受试者退出研究标准，应妥善安排受试者退出。

- 如果研究者不能确定伴随治疗是否会影响受试者安全，或用药后是否会影响对受试者安全性和耐受性的判断，或用药后是否会影响受试者入组合格性以及数据的可评估性，应在使用伴随治疗前与申办方进行讨论并达成一致意见。

研究期间受试者谨慎合并使用已知的 H2 受体阻抗剂，包括但不限于西咪替丁、法莫替丁、

尼扎替丁、罗沙替丁。抗酸药包括铝碳酸镁咀嚼片、磷酸铝凝胶、氢氧化铝、氢氧化镁、碳酸钙等。如必须使用上述药物，需在上述药物治疗前或治疗后至少 2 小时以后使用 GFH375。

5.4.2.2 禁用的伴随治疗

研究期间，受试者不应接受下列治疗：

1) 除本研究治疗外的其他任何抗肿瘤治疗（化疗、免疫治疗、生物制品、广泛的放疗、激素治疗、靶向治疗、手术、具有已批准抗肿瘤适应症的中药），包括研究性治疗或已获批的治疗。服用拮抗促性腺激素释放激素（GnRH）治疗前列腺癌，口服避孕药，或进行激素替代治疗的受试者可以继续用药。
2) 首次用药前 7 天内禁止使用中药，研究最终 PK 采集完成之前不建议使用中药。如处理不良事件或疾病需要使用中药，使用前须经申办方审阅和批准。
3) 使用粒细胞集落刺激因子类药物作为预防用药。此类药物仅可在研究者的判断下，用于不良事件的治疗。
4) 除本研究治疗外的任何其他正在进行临床研究的药物。
5) 在首次用药前 14 天内或 5 个半衰期内（以较长者为准）至末次给药后两周期间，禁止使用已知的 CYP3A 和 P-gp 的强效抑制剂和诱导剂（见附录 4）。
6) 研究药物首次用药前 14 天内或药物 5 个半衰期内（以较长者为准）至末次给药后两周期间，禁止使用已知 CYP3A 或 OAT1 的敏感底物（见附录 4）。除非该药物在筛选期经过研究者和申办方医学负责人审阅和批准。
7) 研究药物首次用药前 7 天内或药物 5 个半衰期内（以较长者为准）至末次给药后一周内，禁止使用已知的质子泵抑制剂和新型抑酸药物（如钾离子竞争性酸阻滞剂），包括但不限于奥美拉唑、兰索拉唑、泮托拉唑、雷贝拉唑、艾斯奥美拉唑、艾普拉唑、伏诺拉生。

5.5 治疗依从性

受试者将遵循研究者的指导，在指定访视日返还前一周期所有未服用的 GFH375 片剂和包装，并交还已完成的受试者日志。受试者返还的数量将会被清点、记录和存档，并根据实际用药情况计算用药依从性。

5.6 药品管理

5.6.1 研究药物接收和清点

申办方将根据研究中心预期的入组计划提供 GFH375。GFH375 将通过第三方的有运输资质的物流公司运送至研究中心。研究中心授权工作人员将会在发货单上进行签字，以确认其收到药物。

GFH375 只能用于本研究，而且只能由研究者授权的专人进行管理。为完全控制 GFH375 的发放与使用，在每次访视时均需进行数量登记。

5.6.2 研究药物的储存和管理

研究者或授权的其他研究中心工作人员（如药剂师），将确保所有的研究药品存放在符合方案 5.2.1 章节所述存放条件的、出入受控的安全区域，并且其存放符合适用的法规要求。受试者领取 GFH375 片剂后，将遵循研究者或授权人员的指导，进行正确的贮存。如果发现不符合要求的储存情况，研究者应联系申办方获取指导。

5.6.3 研究药物回收和销毁

未使用的研究药物及包装将由申办方清点后回收和销毁，或授权研究中心销毁。申办方或其授权人员将提供给研究中心如何销毁未使用的研究药物的指导。如果被授权在研究中心进行销毁，研究者需确保所有的回收和销毁依据相应法规、指导原则和规章制度进行并记录。

5.6.4 研究药物的记录

研究中心指定人员需根据相关法规和指南，本试验的操作流程的要求及时做好研究药物的接收、分发、使用、库存、销毁、回收、损毁等相关记录。

5.7 投诉处理

为了确保受试者的安全性和监测质量，并协助流程和药品的改进，申办方将收集临床试验使用的研究药物相关的产品投诉。对于合并药物相关的投诉，将根据产品说明直接报告给生产商。研究者或其指定人员负责按照本研究的相关规定，完成下列产品投诉流程：

- 采用研究专用的投诉表，记录所报告的产品投诉和相关的完整描述。
- 将填写完成的产品投诉表在 24 小时内传真或邮件至申办者或其指定人员。

如果要求研究者返还产品以便进行调查，研究者应将产品投诉表复印件连同产品一起返还。

6 研究流程

在开始进行本方案所要求的任何研究步骤前，受试者必须阅读并且签署经伦理委员会批准的知情同意书。

所有步骤应在要求的时间窗内进行，如特殊情况下无法按时或按要求完成研究步骤，研究者应采取一切必要的措施来保障受试者的安全和利益，并记录原因和采取的措施。另外研究者需及时通知研究团队所发生的意外状况。

6.1 筛选期

筛选期：首次研究给药前第-28 天至第-1 天。受试者签署知情同意书后，根据方案要求提供相关信息并进行相关检查。基线定义为用药前最后一次检查结果。需根据访视流程表完成所有筛选期的检查和确认。

因任何原因最终未开始首次研究给药为筛选失败。对于筛选失败的受试者可以进行重新筛选。如果考虑对受试者进行重新筛选，则研究者必须联系申办方医学负责人。再次筛选时须取得申办方医学负责人同意。进行重新筛选时，受试者必须重新签署知情同意书，而且将被重新分配一个识别号。初始筛选期间进行的评估结果如果仍然在研究规定的时间范围内，并且结果符合入排标准，则仍然可以接受，而无需重复检测。

必须严格遵守入排标准。如果发现入组了不符合入排标准的受试者，申办方医学负责人和研究者需讨论确定是否让受试者继续参与本研究，使用或不使用研究药物。如果研究者认为让受试者继续参与本研究从医疗角度来看对该受试者是适当的，而且申办方医学负责人同意研究者的此决定，则受试者可以继续参与本研究并接受研究药物的治疗。如果研究者认为受试者继续参与本研究在医学上是适当的，但申办方医学负责人不同意研究者的此决定，则受试者不得继续参与本研究（无论接受或不接受研究药物治疗）。研究者只有在收到申办方书面批准后才能够允许意外入组本研究的受试者继续参与本研究。

6.2 治疗期

符合条件的受试者将接受研究治疗，直至发生疾病进展（除外由研究者判断继续治疗仍可获益的受试者）、不可耐受的毒性、撤回知情同意、研究结束或提前终止、开始了新的抗肿瘤治疗或死亡，以先发生者为准。治疗期从研究药物给药第 1 天开始，每个治疗周期均为 21 天。在研究期间，受试者将按计划定期完成访视。将在方案中指定的时间点收集药代动力学

样本。疗效将由研究者根据 RECIST 1.1 进行评估（附件 2）。治疗期间，受试者在前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。

6.3 疾病进展后继续用药

疾病进展后，如研究者判断受试者将继续获益，在受试者充分知情并同意的情况下，允许继续使用 GFH375 治疗，直至符合治疗终止标准（参见方案 6.4 章节）。

疾病进展后继续用药，需要按照研究设计的访视继续收集数据。

6.4 受试者终止治疗和退出研究

6.4.1 受试者终止治疗

终止研究治疗不代表退出研究。终止研究治疗的受试者应按方案要求完成治疗结束访视（EOT 访视）和后续随访访视。终止研究治疗的可能原因包括：

1) 受试者发生需停止治疗的疾病进展，如研究者判断受试者继续用药仍然获益，可与申办方讨论后继续给予研究治疗；
2) 受试者出现不可耐受的毒性；
3) 受试者开始其他抗肿瘤治疗；
4) 受试者严重不遵从研究方案的要求；
5) 受试者妊娠；
6) 受试者失访；
7) 受试者死亡；
8) 受试者要求终止治疗，但接受后续随访；
9) 受试者撤回知情；
10) 研究者认为终止研究治疗符合受试者的最大利益；
11) 整个临床研究结束或中止。

发生上述情况时，应在、决定结束研究治疗的 7 天内完成治疗结束访视（EOT 访视）。EOT 访视前 7 天内进行过的检查无需重复，但 AE 相关的检查应根据研究者判断进行复查。

6.4.2 受试者退出研究

受试者可以在任何时候自愿退出研究。退出研究的原因可能包括：

1) 受试者撤回知情，拒绝进行研究步骤、拒绝未来被联系并提供信息；
2) 受试者死亡；
3) 受试者失访；
4) 整个研究结束或中止。

如果受试者未按约定返回中心进行随访，应尽一切努力及时联系受试者，并尽快重新安排遗漏的访视。研究者应询问退出原因，要求受试者尽可能返回中心完成访视，并随访未结束的不良事件。在任何情况下，如有可能，应尽力记录受试者的结局。

如果受试者拒绝到研究中心进行进一步的访视，仍应继续追踪收集其疾病和生存情况，除非受试者撤回知情（即拒绝被继续联系）。在这种情况下，不应再进行任何的研究评价，也不应再收集任何资料。

6.5 失访

如果受试者连续 3 次未能返回研究中心进行计划内的访视，并且研究中心工作人员无法与之取得联系，将被视为失访。

如果受试者没有返回研究中心进行规定的研究访视，必须采取下列行动：

- 研究中心尝试与受试者联系，重新安排错过的访视，向受试者说明遵守访视日程表的重要性，并确认受试者是否愿意和/或应该继续参与研究。
- 在受试者被认定为失访之前，研究者或指定人员将尽力重新与受试者取得联系（应尝试打至少两次电话，如果仍无法取得联系，应给受试者最近更新的联系地址发一封信）。这些联系受试者的尝试应记录在受试者的病历或研究文件中。在本研究结束之前，研究者仍需尽量与受试者取得联系。

如果仍然联系不上受试者，将被认为失访。所有进行联系的尝试应在原始文件上进行记录。

6.6 计划外访视

如研究者判断由于安全性评估或不良事件随访的需要，或出现提示疾病进展的临床症状，研究者可以安排进行相应的访视，以进一步检查和评估。

6.7 随访期

6.7.1 安全性随访

在治疗结束访视之后（包括完成治疗结束/退出研究访视的受试者），进入随访期。末次研究给药后 30 天（±3 天），无论受试者是否开始新的抗肿瘤治疗，受试者需要返回研究中心进行安全性随访。

安全随访访视后，不再主动收集不良事件，但所有治疗相关不良事件都必须随访至解决、恢复至基线，或研究者判断为稳定且不可逆状况。

6.7.2 疾病进展随访

受试者因疾病进展以外的原因结束研究治疗且尚未开始新的抗肿瘤治疗，需按照之前的影像学评估计划继续进行疾病进展随访，直至疾病进展、撤回 ICF、开始其他抗肿瘤治疗或研究结束。

6.7.3 生存随访

安全性随访结束后，受试者将进入生存随访。受试者将每 90 天（±7 天）接受一次生存随访。研究者将通过电话或电子邮件等方式，获取受试者的生存状态、疾病状态及后续的抗肿瘤治疗。

7 研究评估

7.1 安全性评估

将从筛选/基线期开始对受试者进行安全性终点数据集的记录并评估。安全性终点评估指标包括不良事件的发生率、严重程度和类型、受试者的体格检查结果、生命体征测量值和临床实验室检查结果，评估时间点根据访视计划（表 1-3）。不良反应将根据 CTCAE v5.0 进行分级。关于 AE 收集和报告的详细信息，请参见第 8.0 章安全性报告和不良事件管理。

7.1.1 实验室检查

血常规、尿常规、血生化、凝血功能以及妊娠检测将按研究流程表进行。筛选期还需要进行病毒血清学检查以评估入组合格性。具体请参见表格 5实验室检查。

如受试者在研究中心以外进行了实验室检查并报告了相关AE，该实验室检查结果也应收集并录入eCRF。

表格 5 实验室检查

检查项目	观察指标
血常规	红细胞计数（RBC）、血红蛋白浓度（HGB）、红细胞比容（HCT）、平均红细胞体积（MCV）、平均红细胞血红蛋白含量（MCH）、平均红细胞血红蛋白浓度（MCHC）、白细胞计数（WBC）、血小板计数（PLT）、中性粒细胞计数（ANC）、淋巴细胞（LY）计数、单核细胞（MO）计数、嗜酸性粒细胞（EO）计数、嗜碱性粒细胞（BA）计数、中性粒细胞百分比、淋巴细胞百分比、单核细胞百分比、嗜酸性粒细胞百分比、嗜碱性粒细胞百分比
尿常规	尿白细胞（LEU）、尿亚硝酸盐（NIT）、尿 pH 值、尿比重（SG）、尿蛋白（PRO）、尿葡萄糖（GLU）、尿酮体（KET）、尿胆原（UBG）、尿胆红素（BIL）、尿潜血（BLD）；24 小时尿蛋白（尿蛋白≥2+时，需进行此项检查）
凝血功能	凝血酶原时间（PT）、活化部分凝血活酶时间（APTT）、国际标准化比率（INR）
血生化	天冬氨酸氨基转移酶（AST）、丙氨酸氨基转移酶（ALT）、碱性磷酸酶（ALP）、乳酸脱氢酶（LDH）、谷氨酰转肽酶（GGT）、尿素（UREA）/尿素氮、血肌酐（CREA）、总蛋白（TP）、白蛋白（ALB）、总胆红素（TBIL）、直接胆红素（DBIL）、肌酸激酶（CK）、胰淀粉酶（AMY）、空腹血糖（FPG）、总胆固醇（TCHO）、低密度脂蛋白胆固醇（LDL-C）、高密度脂蛋白胆固醇（HDL-C）、甘油三酯（TG）、钙、钠、氯、钾
病毒血清学	乙肝表面抗原（HBsAg）、乙肝表面抗体（HBsAb）、乙肝核心抗体（HBcAb）、HBV 表面抗原、HBV-DNA（必要时）、丙型肝炎病毒抗体（HCV 抗体）、HCV-RNA（必要时）、HIV 抗体
妊娠检测	有生育能力的女性受试者基线行血清 β-HCG 妊娠检测，其余访视行尿妊娠检测

7.1.2 体格检查

将根据对应的访视流程表中规定的时间点进行体格检查。

完整的体格检查包括一般情况、皮肤、颈部（甲状腺）、眼、耳、鼻、喉、胸部（包括肺）、心脏、腹部、背部、淋巴结、四肢、血管神经系统；如有临床指征，将进行乳房、盆腔、直肠、外生殖器检查。筛选期将进行全面的体格检查。

在 GFH375 首次给药前和方案规定的时间点，根据临床指征进行简要的体格检查。研究者也可根据需要相应增加体格检查的频率

7.1.3 生命体征

将记录受试者生命体征（呼吸、脉搏、血压和体温）。如果计划的生命体征与抽血在同一时间，则先进行抽血。

7.1.4 体能状态

体能状态评估将在筛选期、首次给药前、每个周期的 D1、EOT 和末次治疗后 30 天时进行。如首次给药前 72 小时内已进行评估，则无需在 C1D1 重复。体能状态将根据美国东部肿瘤协作组（ECOG）身体状况评分标准（见附录 2）进行评分。

7.1.5 身高与体重

身高仅在筛选期测量一次。筛选期、C1D1、C1D21、后续每个周期的 D1、EOT 和末次治疗后 30 天时测量体重。根据医院标准测量身高[厘米（cm）]和体重[千克（kg），四舍五入到小数点后一位，穿着室内衣服、不穿鞋测量]。

7.1.6 12 导联心电图

12 导联心电图将依据研究流程表规定的日期和时间要求完成。

心电图检查应在受试者安静休息至少 10 分钟后进行。筛选期及研究期间检查 3 次心电图检查，要求每次间隔至少 5 分钟。若合并有其他试验流程，需先进行心电图检查以避免试验操作对心电图结果产生影响。

应评估并收集心率（HR）、PR 间期、QRS 间期、QT 间期和 QTcF（Frederica 公式）间期。

Ia 期剂量递增部分 12-ECG 采集

受试者将在 C1D1（给药前、给药后 2 小时、给药后 4 小时）、C1D4（给药前）、C1D8

（给药前）、C1D15（给药前）、C1D21（给药前，给药后 2 小时，给药后 4 小时）、C2D1（给药前）、C2D10（给药前）和 C4D1（给药前）进行心电图检查。

Ib 期剂量扩展部分和 II 期 12-ECG 采集

受试者将在 C1D10（给药前、给药后 2-4 小时）、C2D1（给药前、给药后 1-3 小时），C3D1（给药前、给药后 2-4 小时）和 C4D1（给药前）进行心电图检查。

将在有条件的中心收集与 PK 样本匹配的 ECG，建议先进行心电图检查，再进行 PK 采血。如无法在采集血样标本前完成，应在采血后安静休息 10 分钟后进行心电图检查。同时，需要将心电图检查与 PK 采样时间的间隔保持在 30 分钟以内。所有计划的 12-ECG 检查都应该在受试者至少安静休息 10 分钟之后进行，每个时间点需测量 3 次，每次间隔在 1-2 分钟。

7.1.5 不良事件与伴随治疗

不良事件的评估包括事件名称、严重程度（分级依照第 5.0 版 CTCAE）、开始和结束时间、是否为严重不良事件、与研究治疗的相关性、对研究治疗采取的措施以及转归。

签署知情同意书后直到完成研究安全随访访视，期间发生的 AE，将被记录在原始病历中并收集至 eCRF。接受研究治疗期间受试者使用过的其他药物或治疗，作为伴随治疗记录在原始病历中并收集至 eCRF。

7.2 药代动力学评价

7.2.1 血样采集

Ia 期研究剂量递增部分

将在 C1D1（单次给药）、C1D21（稳态）、C2D1、C2D10 和 C4D1 采集系列药代动力学样本，具体时间点见 **Ia 期药代动力学（PK）样本和 12 导联心电图采集计划表**，评估 GFH375 的药代动力学。

Ib 期研究剂量扩展部分和 II 期研究部分

入组受试者于 C1D10、C2D1、C3D1 和 C4D1 给药前采集 PK 样本，详见 **Ib 期和 II 期药代动力学（PK）样本和 12 导联心电图采集计划表**。

- **非计划 PK 采血**

当受试者发生与药物相关的严重不良事件时，在研究者得知发生事件的即刻，可能的情况下，采集当时的一份血样用于 GFH375 血药浓度测定。

7.2.2 样本分析

将使用验证过的液相色谱串联质谱法（LC-MS/MS）测定 GFH375 的浓度。低于定量下限（LLOQ）的浓度将被标记为 LLOQ，如有缺失样本将相应标记。样本检测由上海观合医药科技股份有限公司负责。关于分析的详细信息将记录在生物分析报告中。

生物样本的采集、处理方法详见实验室操作手册。

7.3 疗效评价

对肿瘤缓解的评价将包括所有已知或可疑的发病部位。成像包括胸、腹或盆腔的计算机断层扫描（CT）或磁共振成像（MRI）扫描；脑部 CT 或 MRI 用于受试者已知或可疑的脑转移；骨扫描和/或骨 X 射线用于受试者已知或可疑的骨转移。

应在首次治疗前 28 天内进行基线 CT/MRI 扫描。研究期间，疗效将由研究者根据 RECIST 1.1 标准进行评估，前 48 周每 6 周±1 周进行一次影像学检查和肿瘤评估（首次在研究治疗满 6 周后进行），48 周以后每 12 ± 1 周。在后续肿瘤评价中对相同类型的病灶应采用与在筛选期相同的影像学手段，并尽可能在同一影像设备上进行检查。基线头颅影像及骨扫描未发现相应病灶的受试者，治疗期间如有临床指征，研究者可决定增加相应检查。

疾病缓解评价将由研究者根据 RECIST 1.1（附录 1）进行。所有受试者放射影像检查必须符合 RECIST 1.1 标准，所有资料应妥善存留并能接受来源验证和同行评议。

如果受试者终止研究治疗的原因不是疾病进展，且未开始后续其他抗肿瘤治疗，将继续进行影像学检查，直至发生疾病进展，或开始后续抗肿瘤治疗，或因其他原因退出研究。

7.4 生物标志物和耐药机制探索

Ib 期和 II 期会在基线和治疗结束访视时采集受试者的血液样本并运送至中心实验室分离 ctDNA 后进行测序。测序结果将和疗效进行关联分析，探索治疗敏感或者耐药相关生物标志物。

7.5 生物样品的储存和销毁

将对剩余样本进行处置或销毁，并进行匿名化及合并处理。

样本重现性分析（如果进行）将与试验样本的生物分析同步进行。这些评估结果将不在 CSR 中报告，而是在一份生物分析报告中另行给出。

8. 安全性报告和不良事件管理

8.1 不良事件的定义和记录

8.1.1 不良事件的定义

AE 定义为受试者签署知情同意书后出现的（或加重的）不良体征、症状、异常实验室值或检查结果、医疗状况，无论该事件是否被认为与研究药物有关。TEAE 定义为在治疗前未出现，在治疗期间（定义为从研究药物首次给药到末次给药后 30±3 天） 出现或相对于治疗前状态加重的事件。

在知情同意后开始或加重的不良事件应记录在不良事件 eCRF 中。知情同意时已经存在的情况应记录在受试者 eCRF 的病史页上。不良事件监测应在末次给药治疗后持续 30 天±3 天，或直到开始新的抗肿瘤治疗，详情见 8.2.3 节。不良事件（包括构成 AE 的实验室异常） 应尽可能使用诊断来描述，而不是单个的潜在体征和症状。当不能明确诊断时，每个体征或症状都应作为一个单独的不良事件报告。

8.1.2 不良事件的严重程度判断标准

不良事件将使用 NCI-CTCAE 5.0 版进行评估。如果在 CTCAE v5.0 中没有对应的 AE，请参考以下标准（从 CTCAE v5.0 中的分级标准总结而来）。

表格 6 不良事件严重程度判断标准

等级	严重程度的临床描述
1	轻度；无临床症状或有轻微临床症状；仅为临床或诊断所见；无需治疗
2	中度；需要较小的、局部的或非侵入性的治疗；与年龄相符的使用工具性日常生活活动受限，使用工具性日常生活活动指做饭、购物、打电话、理财等
3	严重或者具重要医学意义但不会立即危及生命；导致住院或住院时间延长；导致残疾；自理性日常生活活动受限。自理性日常生活活动指：洗澡、穿衣、脱衣、吃饭、盥洗、服药等，并未卧床不起
4	危及生命；需要紧急治疗
5	导致死亡的不良事件

8.1.3 不良事件的记录和处理

应尽可能评估每个不良事件，以确定:

- 不良事件的名称
- 严重程度等级
- 持续时间（开始和结束日期）
- 与研究治疗的关系
- 对研究药物采取的措施（无、剂量减少、暂停用药、永久停药、未知、不适用）
- 是否给予药物或治疗（无伴随药物/非药物治疗，伴随药物/非药物治疗）
- 结局（未好转，痊愈，好转，痊愈伴有后遗症，致命，未知）
- 是否为严重不良事件，如第 **8.2 节**中定义的 SAE

所有不良事件都应得到适当处理。如果同时给予药物或非药物治疗，应记录在不良事件 eCRF 上。一旦发现不良事件，应随访其直至其消退或稳定或判断为永久性，并应在每次就诊时（必要时，可更频繁地）评估严重程度的变化、与研究治疗的相关性、治疗 AE 所需的干预措施以及结果。

8.2 严重不良事件

8.2.1 定义

SAE 定义为在任何临床研究期间发生的符合以下一个或多个标准的不良事件:

- 导致死亡；
- 危及生命，指严重病人即刻存在死亡的风险，并非是指假设将来发展严重时可能出现死亡；
- 导致住院或住院时间延长；
- 永久或显著的功能丧失；
- 致畸、致出生缺陷；
- 其他重要医学事件：必须运用医学和科学的判断决定是否对其他的情况加速报告，如重要医学事件可能不会立即危及生命、死亡或住院，但如需要采取医学措施来预防如上情形之一的发生，也通常被视为是严重的。

因以下原因住院不应报告为 SAE：

- 所研究适应症的常规治疗或监测，与任何病情恶化无关

- 选择性或预先计划的治疗，用于与所研究适应症无关的已有疾病，且自签署知情同意书以来没有恶化
- 社会原因和在患者一般情况没有任何恶化的情况下的临时护理

急诊门诊治疗不导致住院，且涉及不符合上述 SAE 定义的事件，不属于 SAE。

8.2.2 恶性肿瘤进展及死亡

恶性肿瘤进展导致的临床症状，如果不能完全排他性地确定为是由于研究疾病进展导致，或者和研究疾病进展的症状特点不相符时，可记录为 AE。如果与研究疾病的怀疑进展明确一致，则不记录为 AE。恶性肿瘤进展本身不作为 AE 报告。

恶性肿瘤进展导致的临床症状，如果满足 SAE 标准，且不能完全排除与研究药物的相关性时，需要报告为 SAE。如果事件满足 SAE 标准（死亡事件除外），且与研究疾病的怀疑进展明确一致，则不报告为 SAE。SAE 报告收集的时间为从受试者签署知情同意书开始至末次给药后 30 天。

临床试验中，如受试者在安全随访期内死亡，都必须作为 SAE 报告，无论研究者是否评估其可能是与疾病进展有关。“死亡”一词不应作为 SAE 术语，而应作为事件的结果。将引起或导致死亡的医学状况/疾病（含症状和体征的恶化）作为 SAE 术语记录在 eCRF 中，并按 SAE 报告。如果在报告时无法确定死亡原因，则 SAE 术语记录为“不明原因死亡”。死亡结局的 SAE 报告收集的时间为从受试者签署知情同意书开始至末次给药后 30 天。

8.2.3 新的抗肿瘤治疗

如果受试者在安全随访期间开始新的抗肿瘤治疗，此后将不再收集不相关的 AE 和 SAE。如果死亡事件发生在安全随访期间，则必须作为 SAE 报告，无论是否有任何干预治疗，无论事件与研究治疗的因果关系。

8.2.4 SAE 的报告

SAE 收集将在签署 ICF 时开始，无论受试者是否筛查失败。SAE 的随访将持续到症状缓解或临床改善或稳定为止。

为确保受试者安全，在受试者签署知情同意书后和受试者停止研究治疗后 30 天内发生的任何 SAE，无论疑似因果关系如何，都必须在获悉其发生后 24 小时内报告给主办方。在受试者接受末次治疗 30 天后，则只报告怀疑与研究治疗有关的 SAE。

任何 SAE 的附加信息，包括并发症、初始 SAE 的进展和反复发作，必须在研究者收到随访信息后 24 小时内作为原始发作的随访报告。在不同的时间间隔内发生的 SAE 或被认为与以前报告的 SAE 完全无关的 SAE 应作为新的事件单独进行报告。

在安全随访期后发生的任何 SAE 仅当研究者怀疑与研究治疗存在因果关系时才应报告给申办方。

收集所有 SAE 的信息并记录在 SAE 报告表上；为了提供一份完整的临床报告，必须填写表格中所有适用的部分。研究人员必须评估并记录各 SAE 与研究治疗的关系，填写由研究人员签名的 SAE 报告表，并在 24 小时内将报告表发送给主办方和指定 CRO 药品安全部门，并根据当地要求及时向相关部门报告。

- **申办方药物警戒邮箱**：drugsafety@genfleet.com
- **泰格药物警戒邮箱:** PV@TigermedGrp.com

随访信息的提交方式与原始 SAE 报告表相同，使用新的 SAE 报告表，说明这是先前报告 SAE 的随访报告，并给出原始报告的日期。随访信息应描述事件是否已经缓解或持续，如何治疗，以及受试者是否继续参加研究或退出研究。

8.3 不良事件的因果关系判断

AE 与研究治疗的因果关系判断是指通过综合评估确定研究治疗对引起或促成 AE 是否存在合理的可能性。研究者应考虑的因素包括 AE 的发生是否与研究治疗给药存在合理时间顺序、研究治疗的特性、研究治疗的毒理学和药理学作用、合并用药的使用、受试者的基础疾病、病史、家族史、去激发（研究停药或减量后，症状/体征是否减轻或好转）、再激发（再次用药后，症状/体征是否复现或加重）等。通常应当提供判定因果关系的事实和依据。

请研究者根据以下列出的标准判断 AE/SAE 与研究药物的相关性：

表格 7 不良事件相关性判断结果分类及判断依据

相关性	判断依据
有关	• 有合理的时间关系 • 符合已知的药物作用机制、特性或已知的不良反应 • 去激发阳性 • 无其他合理的原因解释 • 再激发阳性
很可能有关	• 有合理的时间关系 • 符合已知的药物作用机制、特性或已知的不良反应

	• 去激发阳性 • 无其他合理的原因解释 • 缺乏再激发阳性证据
可能有关	• 有合理的时间关系 • 缺乏再激发阳性证据 • 表现为以下任何一种情况： 1) 符合已知的药物作用机制、特性或已知的不良反应，去激发阳性，但也可用其他合理的原因解释； 2) 符合已知的药物作用机制、特性或已知的不良反应，缺乏去激发阳性证据，且无其他合理的原因解释； 3) 不符合已知的药物作用机制、特性或已知的不良反应，去激发阳性，无其他合理的原因来解释； 4) 不符合已知的药物作用机制、特性或已知的不良反应，去激发阳性，也有其他合理的原因解释； 5) 不符合已知的作用机制、特性或已知的不良反应，缺乏去激发阳性证据，也无其他合理的原因解释。
可能无关	• 有合理的时间关系 • 缺乏去激发阳性证据 • 缺乏再激发阳性证据 • 表现为以下任何一种情况： 1) 不符合已知的作用机制、特性或已知的不良反应，且可用其他合理的原因解释； 2) 符合已知的作用机制、特性或已知的不良反应，但可用其他更加合理的原因解释；
无关	• （医学上认为）无合理的时间关系 • 不符合已知的药物作用机制、特性或已知的不良反应 • 缺乏去激发阳性证据 • 缺乏再激发阳性证据 • 可用其他合理的原因解释

注：在进行不良事件判断时，如果与表格中的判定依据无法完全对应时，请参考该表中对不良事件与药物相关性的专业判断逻辑，作出尽可能合理的判定结果。

表格 8 不良事件相关性判断简表

判断结果 / 判断依据	有关	很可能有关	可能有关		可能无关		无关
是否有合理的时间关系	+	+	+		+		-
是否符合已知的药物作用机制、特性或已知的不	+	+	+	-	+	-	-

良反应								
去激发结果	+	+	+	-	+	-	-	-
再激发结果	+	-	-				-	-
是否可用其他合理的原因解释	-	-	+	-	-/+	-	++	+	+

注：+表示肯定，或阳性结果；-表示否定，或阴性结果，或暂未获得结果的情况；++表示可用其他“更加”合理的原因解释。

符合有关、很可能有关、可能有关的，将视为“相关”；符合无关、可能无关的，将视为“不相关”。如果研究人员对因果关系“未知”，或无法做出相关性判断，则应视为与药物有关的事件。研究人员应进一步收集的不良事件信息，并根据后续信息提供因果关系评估。

8.4 妊娠报告

临床研究期间女性受试者妊娠，则受试者必须终止研究治疗，并退出研究；临床研究期间男性受试者的伴侣妊娠，受试者可继续临床研究。研究者应在获知妊娠事件后的 24 小时内填写《临床研究妊娠报告/随访表》报告给申办方和指定的 CRO 药品安全部门。

研究者需对妊娠事件进行追踪至最终结果（包括任何的提前终止妊娠或分娩），分娩需随访至母亲生产后 1 个月，妊娠结果需报告申办方。如果妊娠结果符合 SAE 的标准（如宫外孕、自发性流产、胎儿宫内死亡、新生儿死亡或先天异常等），需要遵循 SAE 程序进行上报。

如果受试者在妊娠期间同时发生 SAE，则还须遵循 SAE 报告程序进行上报。

8.5 符合海氏法则事件的报告

若 AST 和/或 ALT 水平异常并发总胆红素水平异常升高，同时满足以下（1）（2）（3）条件且没有导致异常的其他原因，应始终将此类情况作为 SAE 进行上报，遵循 SAE 报告流程进行上报。

表格 9 海氏法则事件的判断标准

满足条件	判断标准
(1) ALT 或 AST 异常	1) 基线正常：治疗期 ALT 或 AST > 3×ULN 基线异常：治疗期 ALT 或 AST > 3×基线水平
(2) TBIL 异常	2) 基线正常：治疗期 TBIL > 2×ULN 基线异常：治疗期 TBIL > 2×基线水平
(3) 碱性磷酸酶 < 2×ULN（或未获得信息）	

缩略语：ALT=丙氨酸氨基转移酶，AST=天门冬氨酸氨基转移酶，TBIL=总胆红素，ULN=正常范围上限。

如果受试者在治疗期或者随访期间 AST 和/或 ALT 水平异常并发总胆红素水平异常升高，应尽可能在得知异常结果之后尽快返回研究中心进行检查和评估。应该包括相关肝功能实验室检查、详细询问病史和体格检查，并应考虑肝脏肿瘤（原发性或继发性）的可能性。

如发生满足上述标准的肝损事件，应遵循 5.3.1 和 5.3.2 进行相应的剂量调整或停止治疗。

8.6 药物过量的报告

药物过量的定义是任何意外或故意地超过计划剂量。如果药物过量导致了 AE，则必须在 eCRF 上记录 AE。如果药物过量与任何 SAE 相关，请参阅 **8.2.4 SAE 报告**部分。

8.7 AE/SAE/妊娠的报告时限

表格 10 AE/SAE/妊娠事件的报告时限

期限	收集要求
从受试者签署知情同意书开始，直至末次给药治疗后30天±3天，或直到开始新的抗肿瘤治疗	所有AE/SAE/妊娠事件 妊娠事件：研究治疗首次给药后开始收集
上述期限之后	与研究治疗有关的 SAE

缩略语：AE=不良事件，SAE=严重不良事件。

9. 统计分析

9.1. 样本量

9.1.1. Ia 期：剂量递增部分

Ia 期共入组约 30 例受试者。

将根据 BOIN 设计，在每个剂量水平入组 3-6 例受试者（加速滴定时除外）接受治疗。将根据已获得的安全性/耐受性、PK 及初步有效性数据，可能选择一个或多个剂量水平 入组额外的受试者作为回填， 接受已确认安全且耐受性良好的、经研究者及申办方评估可能临床获益的 GFH375 单药剂量进行治疗，以更好的估计 GFH375 单药的 RDE/RP2D 以及表征其安全性\耐受性、PK 及有效性。回填的受试者不被纳入 DLT 的评估。回填后，接受 GFH375 每个剂量水平治疗的受试者不超过 9 例（包括 BOIN 剂量递增阶段入组的受试者）。

如果需要探索更多的剂量水平或替代给药方案，则可以入组额外的受试者。

9.1.2. Ib 期：剂量扩展部分

对于一个或多个 RDE 水平，每个 RDE 剂量水平将入组不超过 30 例受试者接受治疗。

9.1.3. II 期

总共预计入组约 213 例受试者，其中约 73 例晚期 NSCLC 受试者、50 例晚期 PDAC 受试者、50 例晚期 CRC 受试者、40 例晚期其他实体瘤受试者。

肿瘤类型	历史对照 ORR	预期 ORR	样本量
NSCLC	23%	40%	73
PDAC	10%	30%	50
CRC	10%	30%	50
其他			40
合计			213

对于晚期 NSCLC，ORR 的历史对照值为 23%，预计本研究 ORR 可达到 40%。若观测到的 ORR 的 95% CI 下限不低于历史对照 23%，则视为成功。单侧 $\alpha = 0.025$，要达到 85%把握度，则需要 73 例受试者。当 73 例受试者中有至少 25 例 CR/PR 时，ORR 观测值的 exact 95% CI 下限高于历史对照 23%。25 例 CR/PR 时，ORR = 34.2% ，其 95% CI 为 23.5%, 46.3%。

对于晚期 PDAC 和 CRC，ORR 的历史对照值同为 10%，预计本研究 ORR 都可以达到 30%。若观测到的 ORR 的 95% CI 下限不低于历史对照 15%，则视为成功。计划入组 50 例受

试者，在单侧 α = 0.025 的情况下，把握度可达到 94%。当 50 例受试者中有至少 10 例 CR/PR 时，ORR 观测值的 exact 95% CI 下限高于历史对照 10%。10 例 CR/PR 时，ORR = 20.0%，其 95% CI 为 (10.0%, 33.7%)。

对于其他实体瘤：计划入组约 40 例 KRAS G12D 突变的晚期实体瘤受试者，如携带 KRAS G12D 突变的胆管癌、阑尾癌等。

以上样本量和 ORR（及其 95% exact CI） 的计算使用了 R 语言。其中，样本量计算使用了“gsDesign”package 中的“nBinomial1Sample”function（option：conservative = TRUE）；ORR 及其 95% exact CI 使用了“epitools”package 中的“binom.exact”function（default options）。

9.2. 分析集

- 全分析集 (FAS)：至少接受 1 次 GFH375 给药的所有受试者。
- 安全性分析集 (SS)：至少接受 1 次 GFH375 给药且至少有 1 次有效的基线后安全性评估的所有受试者。
- 剂量确定分析集 (DDS)： Ia 期 SS 中在 DLT 观察期间至少累计 15 天接受未减量的 GFH375 的所有受试者、有充分的安全性评估，或在 DLT 观察期间发生 DLT。DDS 不包含回填（backfill）的受试者。
- 符合方案集 (PPS)： FAS 中符合方案的所有 II 期受试者。研究团队将在最终数据库锁定前对所有方案偏离进行审查，据此将发生影响疗效评价的重大方案偏离的受试者从 PPS 中排除。
- 药代动力学分析集 (PKAS)：至少接受 1 次 GFH375 给药且至少有 1 份血样提供可评价 PK 数据的所有受试者。

9.3. 统计分析方法

将对 I a 期、Ib 期、 II 期的数据分别单独进行分析汇总。其中，I 期的数据将按照不同剂量水平和给药方案进行分析汇总；II 期的数据将按照肿瘤类型分别进行分析汇总。

9.4. 安全性分析

按系统器官分类、首选术语、严重程度汇总 AE、治疗相关 AE 、 SAE 的发生率。对于 I a 期部分，基于 DDS 汇总各类 DLT 的发生率，并对 DLT 进行列表。对实验室检查、生命体征、ECG 进行描述性汇总。

9.5. 有效性分析

计算最佳总体缓解 (BOR)、ORR、DCR 的相应人群占比，并采用 Clopper-Pearson 方法估计 ORR 和 DCR 的双侧 95%置信区间 (CI)。采用 Kaplan-Meier 方法估计 DoR、PFS、 OS 的中位数及其 95% Brookmeyer-Crowley CI。对 TTR 进行描述性汇总。

对于 I 期阶段，当分析组的样本量小于 10 例时，将按受试者单独列出 DoR、TTR、PFS、OS，不采用 Kaplan-Meier 方法进行分析。

对于 II 期阶段，设置**主要估计目标**如下：

研究人群	KRAS G12D 突变型晚期实体瘤受试者（按瘤种）
治疗	GFH375
终点	根据 RECIST 1.1 标准评估达到 CR 或 PR 的受试者百分比。若受试者基线后无任何评价结果，则认为该受试者未缓解。
伴发事件	开始新的抗肿瘤治疗（处理策略：在治策略，开始新的抗肿瘤治疗后的评估结果不纳入分析。）
群体层面汇总	ORR

9.6. 药代动力学分析

将对血浆中GFH375的浓度数据按照方案规定的采样时间进行列表和描述性统计汇总，汇总将按照研究分期和剂量组呈现。将使用线性和半对数坐标，按研究分期和剂量组绘制个体受试者的血浆中GFH375浓度-时间曲线和相应的汇总曲线（平均值 + 标准差）。使用计划PK采样时间计算汇总统计量及绘制汇总曲线（平均值 + 标准差）；将使用实际PK采样时间，绘制个体受试者曲线。

将使用Phoenix WinNonlin软件（v8.2版或以上版本, Certara USA, Inc., New Jersey, US）采用非房室模型分析（NCA），按实际采血时间点计算GFH375的PK参数。对Ia期剂量递增阶段受试者单次和多次给药后GFH375的PK参数进行描述性统计汇总，汇总按照剂量组呈现。

9.7 生物标志物评估

在Ib和II期收集基线和治疗结束时的血液样本分离ctDNA进行NGS检测，探索与治疗敏感或耐药相关的肿瘤基因变异。

9.8 期中分析

II期研究中，将分别期中分析预计在对NSCLC、PDAC、CRC进行有效性中期分析。对于

单个瘤种，计划在约25例受试者至少有一次基线后影像学肿瘤评估或提前退出研究时进行。考虑实际临床操作的原因，允许中期分析时的受试者例数与计划例数有所差别。期中分析过程中，项目不停止入组。

期中分析时，将分别针对 NSCLC、PDAC、CRC 的 ORR，采用贝叶斯预测概率的方法进行无效性分析。允许（但不强制）因缺乏有效性证据而提前终止对相应瘤种的研究。

基于观察到的获得缓解（CR/PR）的 II 期受试者例数计算预测成功概率（PPoS），如果 PPoS < 0.2，则允许（但不强制）因为缺少有效性证据而提前终止入组。PPoS < 0.2 的对应的终止标准见下表：

瘤种	**受试者例数***	**建议终止试验，当缓解受试者例数 ≤**
NSCLC	20 ~ 21	3
	22 ~ 25	4
	26 ~ 29	5
	30	6
PDAC CRC	20 ~ 23	1
	24 ~ 30	2

*受试者例数：至少有一次基线后影像学肿瘤评估或提前退出研究（至少满足其一）的 II 期受试者数。

上述计划的中期分析不强制进行，在达到中期分析计划的时间点前，如果有足够的安全性和有效性综合数据支持，可以省略该中期无效性分析。

10. 安全监查

本研究将成立由研究者及申办方组成的安全性监查委员会（SMC）。SMC 将从第一位受试者首次给药开始持续审查安全性数据，直至研究结束。在剂量递增及扩展阶段，SMC 成员将审阅安全性数据、PK 数据等，以决定下一个剂量的入组或者探索潜在的其他剂量组，并推荐合适的 RDE 及 RP2D。

研究期间，若研究者及申办方均认为受试者存在安全性风险或已达到耐受限度，剂量递增或研究治疗将立即停止。

详细信息请参阅 SMC 章程。

11 研究质量保证和质量控制

根据药物临床试验质量管理规范（GCP）的指导原则，申办方有责任根据相应标准操作流程实施和维护质量保证和质量控制系统，以确保临床试验的实施及数据的真实，收集、记录和汇报遵循方案、GCP和相应的法规要求。

11.1 临床监查

申办方或申办方授权的合同研究组织（CRO）对此研究进行临床监查。临床监查员应按照申办方或CRO的标准操作流程进行监查，并具有与申办方监查员相同的权利和责任。监查员应与研究者，及试验授权人员和申办方保持定期交流。

在研究开始前，监查员将评估各研究中心的胜任能力，并将设施、技术装备，或医务人员的相关问题报告给申办方。在研究过程中，监查员将负责监查研究者是否已获得所有受试者的书面知情同意书，以及数据记录是否正确、完整。同时，监查员也将对输入到eCRF的数据与原始数据进行比较，并告知研究者出现的错误或遗漏。监查员还将控制研究中心的方案和试验流程的依从性，安排供应研究用药，并确保药物保存在适当的条件。

监查访视将按照相关法律法规的要求进行。从受试者入组开始，每个中心将接受定期监查访视。每次对研究者进行访视后，监查员应向申办方提交书面报告。

11.2 质量保证稽查

研究过程中，申办方或申办方授权的代表可能对研究中心、研究数据库和相关研究文件进行质量保证的稽查，同时，相应监管机构也可自行决定对研究中心、研究数据库和相关研究文件进行视察。当研究者收到监管机构视察通知后，需立即告知申办方。

申办方的质量保证部门对临床试验机构进行稽查。稽查包括：药物的供给、所要求的试验文件、知情同意过程的记录、以及病历报告表与原始文件的一致性等。也可根据情况增加稽查内容和范围。在进行合理的通知后，研究者应允许申办方委托的稽查人员进行试验相关的稽查和管理当局进行的视察。稽查或视察的主要目的是证实参加试验的受试者的权利或健康得到保护，知情同意的签署及试验过程的实施正确进行，所有与研究药物评价有关的数据的处理和汇报与预先计划安排、方案、设施、伦理的标准操作规程、GCP 和适用的法规要求一致。研究者应使其能直接接触到所有试验文件、原始记录和原始数据。

12 伦理学

12.1 伦理委员会

申办方或其申办方授权的代表将准备需提交给研究中心的EC的相关文件，包括试验方案、知情同意书、研究者手册、受试者招募材料或广告及其它法规要求的文件都要提交给相应的EC进行审批。在开始本研究之前，必须获得研究中心EC的书面批准，并提供给申办方。EC的批件上必须确切说明研究方案的名称、编号、版本号及其它文件的版本号（例知情同意书）和批准日期。研究者需将EC关于延迟、暂停、重新批准的书面意见通知申办方。

研究中心必须遵循本中心EC的要求。可能包括方案修订、知情同意书修订、受试者招募材料修订时需提交EC进行审批，当地的安全性报告要求，按照EC规定进行定期报告和更新，提交终版报告。以上所有文件及EC批件均须提供给申办方或其指定人员。

12.2 伦理学执行

研究过程及知情同意的获取应遵守赫尔辛基宣言、相关GCP要求及中国的药品和数据保护相关的法律法规。

GCP为有人类受试者参加的临床研究的设计、实施、记录和报告提供了符合伦理要求的、科学的全球性质量标准。此研究将按照GCP和相关国家法规进行，并遵守赫尔辛基宣言中相关的伦理原则，以保护受试者的权利、安全和健康。

研究者需遵守本试验方案规定的流程，不得未经申办方允许更改。任何的方案偏离将向EC、申办方、或监管机构报告。

12.3 受试者信息和知情同意

在任何研究流程开始前，使用ICF向可能参加的受试者解释本研究可能带来的风险和受益，知情同意语言应简单易懂。ICF声明中应明确，知情同意为自愿签署，并明确参加本研究可能带来的风险和受益，且受试者可随时退出研究。研究者只有在充分解释研究的详细内容，受试者的问题得到满意答复，并给予足够时间考虑后，获得受试者或其监护人的书面同意后，方可入组受试者。所有签署过的知情同意书必须在研究者文档中或受试者文件夹中。

研究者负责向受试者解释知情同意内容，并在研究开始前获得受试者或其监护人签署并注明日期的知情同意书。在签署后，研究者应当发给受试者一份签署完毕的知情同意书副本。研究者需将知情同意的过程记录在试验原始文件中。

初始知情同意书、任何后续修订的书面知情同意书以及提供给受试者的任何书面信息在使用前应获得IRB/IEC的意见。如果获得了可能与受试者继续参与试验意愿相关的新信息，应及时告知受试者或其监护人。将通过修订的知情同意书或原始知情同意书附录（获取受试者注明日期的签名或受试者的法监护人注明日期的签名）提供并记录该信息的沟通。

12.4 数据保护

ICF中将包含（或在某些情况下，连同使用独立的文件）数据保护和隐私保护的相关信息。

采取预防措施保证文件的机密性，防止判断出受试者身份。然而，在特殊情况下，某些人员可能会看到某受试者的遗传数据和个人识别码。例如，在出现医疗急救的情况下，申办方、其代表医生或研究者知悉受试者识别码，并具有该受试者基因数据的访问权。此外，相关监管机构要求访问相关文件。

12.5 方案偏离

方案偏离是指任何不依从临床试验方案、国际协调会议药物临床试验管理规范（ICH GCP）或操作手册要求的情况。不依从情况可能来自于受试者、研究者或试验机构工作人员。针对违背情况，应采取纠正措施并及时完成。

13 研究管理

13.1 数据处理和记录保存

临床试验中的文件（方案和方案修订，完成的 eCRF，签署的 ICF 等）需按照 GCP 的要求进行保存和管理。研究中心应将这些文件保存到研究结束后 5 年。

研究文件应合理保存，以便日后访问或数据溯源。保存文件时应考虑安全及环境风险问题。

未经申办方及研究者的书面许可，不得销毁任何研究文件。只有在通知申办方并得到其书面同意后，研究者/研究中心方可将研究文件转交给遵守文件保存要求的其他方或转移到满足要求的其他地点保存。

13.2 原始数据/文件访问权限

研究者同意申办方、CRO及相关授权监管部门直接访问所有研究相关文件，包括受试者病历。

13.3 方案修订

在研究进行过程中对方案进行的所有修订均需申办方与研究者沟通并得到同意。申办方应确保及时向管理部门提交方案修订。

方案的所有修订均应作为方案增补件保存。对方案的任何修改，都需提交伦理委员会，根据伦理委员会的规定进行批准或备案。如需要，也应提交给监管部门进行审批，并经 EC 和监管部门（若需要）批准后方可执行（为消除对试验受试者的直接危害而对方案进行的变更除外）。

13.4 研究者职责

研究者将遵循方案、赫尔辛基宣言的伦理原则、ICH GCP 及相应的法规要求开展本研究。

相关研究者的详细职责在中国 GCP（2020 年第 57 号）第 5 章中列出。

13.5 出版政策

本研究产生的所有数据均为申办方的保密信息，申办方有权公布研究结果。关于申办方与研究者出版政策方面的信息将在临床试验协议中描述。

所有有关本次试验的信息（不限于以下文件：方案和研究者手册）都必须严格保密。研究者必须认识到由这次试验所得出的科学或医学结论可能对申办方具有商业价值。研究者应

该对与本试验相关的信息和数据予以保密，若要公开发表与本次试验有关的数据或从试验中所得出的结论，需提前与申办方协商并征得申办方书面同意。为了保护自身权益，申办方可以要求研究者在本试验产品获得上市批准前不发表相关的试验数据。

申办方有权发表或出版与本试验相关的信息或数据，或将之呈报给药品管理部门。申办方如需在发表、出版或广告内容中出现研究者的姓名，应征得研究者的同意。

13.6 财务和保险

申办方将根据当地法规和最低要求为参加本研究的受试者购买保险。保险相关条款将保存在研究文件夹中。

14 数据管理

14.1 数据保密性

将根据适用的法律法规对研究受试者相关信息进行保密和管理。

数据采集系统的访问将通过一系列单独分配的用户名和密码来控制，这些账户和密码仅提供给已完成必要培训的授权人员使用。

14.2 数据采集

本研究的数据采集使用 EDC 系统完成。

研究者或指定的研究人员将根据方案向 eCRF 中输入数据。研究中心工作人员只有在接受培训之后方可进入 EDC 系统。系统将由自动化核查流程检查 eCRF 中的数据不一致情况，允许对中心工作人员输入的数据进行修改或核查。

在 EDC 中进行数据修改时，需按照系统提示，填写数据修改的原因。修改履历和修改原因会被记录在 EDC 系统的稽查轨迹中。研究者或其授权的人员需要对 eCRF 数据的真实性、完整性和及时性进行确认，并在 EDC 系统中进行电子签名。

14.3 数据管理

申办方或指定的 CRO 人员将审核研究人员输入数据的完整性和准确性。对于任何不一致或缺失的数据，需要发送数据质疑给研究中心。要求指定的研究中心人员及时解答质疑，并对数据做出必要的变更。

本项目将使用世界卫生组织药物词典(WHODrug)对录入到数据库中的合并治疗和既往用药进行编码。将使用 MedDRA 术语对病史/当前疾病和不良事件编码。

数据库锁定之前研究团队需要完成数据清理，并汇总研究进行中出现的所有方案偏离的事件，并召开数据审核会议确定分析人群。数据审核会议中所作的决定都需用文件记录。数据审核会议通过后，经研究团队确认对 EDC 系统中的研究数据库进行锁定。如需对锁定后的数据进行任何变更，需要经项目组讨论后授权解锁数据库。

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16 附录

附录 1：实体瘤疗效评价标准 1.1 版（RECIST V1.1）

注：此翻译版本仅供参考，最终版本以英文版为准。

1. 肿瘤在基线水平的可测量性

1.1 定义

在基线水平上，肿瘤病灶/淋巴结将按以下定义分为可测量和不可测量两种：

可测量病灶

肿瘤病灶：至少有一条可以精确测量的径线（记录为最大径），其最小长度如下：

- CT 扫描 10 mm（CT 扫描层厚不大于 5 mm）
- 临床常规检查仪器 10 mm（肿瘤病灶不能用测径仪器准确测量的应记录为不可测量）
- 胸部 X-射线 20 mm
- 恶性淋巴结：病理学增大且可测量，单个淋巴结 CT 扫描短径须≥15mm（CT 扫描层厚推荐不超过 5 mm）。基线和随访中，仅测量和随访短径。

不可测量病灶

所有其他病灶，包括小病灶（最长径＜10 mm 或者病理淋巴结短径≥10 mm 至＜15 mm）和无法测量的病灶。无法测量的病灶包括：脑膜疾病、腹水、胸膜或者心包积液、炎性乳腺癌、皮肤/肺的癌性淋巴管炎、影像学不能确诊和随诊的腹部包块，以及囊性病变。

关于病灶测量的特殊考虑

骨病灶、囊性病灶和先前接受过局部治疗的病灶需要特别注明：

骨病灶：

- 骨扫描、PET 扫描或者平片不适合于测量骨病灶，但是可用于确认骨病灶的存在或者消失；
- 溶骨性病灶或者混合性溶骨/成骨病灶有确定的软组织成分，且软组织成分符

合上述可测量性定义时，如果这些病灶可用断层影像技术如 CT 或者 MRI 进行评价，那么这些病灶可以作为可测量病灶；

- 成骨病灶属不可测量病灶。
- 囊性病灶：
- 符合放射影像学单纯囊肿定义标准的病灶，不应因其为定义上的单纯性囊肿，而认为是恶性病灶，既不属于可测量病灶，也不属于不可测量病灶；
- 若为囊性转移病灶，且符合上述可测量性定义的，可以作为是可测量病灶。但如果在同一病人中存在非囊性病灶，应优先选择非囊性病灶作为靶病灶。

局部治疗过的病灶；

- 位于曾放疗过或经其他局部区域性治疗的部位的病灶，一般作为不可测量病灶，除非该病灶出现明确进展。研究方案应详细描述这些病灶属于可测量病灶的条件。

1.2 测量方法说明

病灶测量

临床评价时，所有肿瘤测量都要以公制米制记录。所有关于肿瘤病灶大小的基线评定都应尽量在接近治疗开始前完成，且必须在治疗开始前的 28 天内（4 周）完成。

评价方法

对病灶基线评估和后续测量应采用同样的技术和方法。除了不能用影像学检查，而仅能用临床检查来评价的病灶之外，所有病灶必须使用影像学检查进行评价。

临床病灶：临床病灶只有位于浅表且测量时直径≥10mm 时才能认为是可测量病灶（如皮肤结节等）。对于有皮肤病灶的患者，建议用含有标尺测量病灶大小的彩色照片作为存档。当病灶同时使用影像学和临床检查评价时，由于影像学更客观且研究结束时可重复审阅，应尽可能选用影像学评价。

胸部 X 片：当肿瘤进展作为重要研究终点时，应优先使用胸部 CT，因为 CT

比 X 线更敏感，尤其对于新发病灶。胸部 X 片检测仅当被测量病灶边界清晰且肺部通气良好时适用。

CT、MRI：CT 是目前用于疗效评价最好的可用可重复的方法。本指导原则对可测量性的定义建立在CT扫描层厚≤5 mm的基础上。如果CT层厚大于5 mm，可测量病灶最小应为层厚的2倍。建议采用增强CT进行疗效评估（除非有造影剂禁忌）。MRI在部分情况下也可接受（如全身扫描）。

超声：超声不应作为一种测量方法用于测量病灶大小。超声检查因其操作依赖性，在测量结束后不具备可重复性，不能保证不同测量间技术和测量的同一性。如果在研究期间使用超声发现新病灶，应使用 CT 或者 MRI 进行确认。如果考虑到 CT 的放射线暴露，可以使用 MRI 代替。

内窥镜，腹腔镜检查：不建议使用这些技术用于肿瘤客观评价，但这种方法在取得的活检标本时可以用于确认 CR，也可在研究终点为 CR 后复发或手术切除的研究中，用于确认复发。

肿瘤标志物：肿瘤标志物不能单独用来评价肿瘤客观缓解。但如果标志物水平在基线时超过正常值上限，用于评价完全缓解时必须回到正常水平。因为肿瘤标志物因病而异，在将测量标准写入方案中时需考虑到这个因素。有关 CA-125 缓解（复发性卵巢癌）及 PSA（复发性前列腺癌）缓解的特定标准已经发表。且国际妇科癌症组织已制定了 CA-125 进展标准，即将被加入到卵巢癌一线治疗方案的肿瘤客观评价标准中。

细胞学/组织学技术：在方案规定的特定情况下，这些技术可用于鉴定 PR 和 CR（如生殖细胞肿瘤的病灶中常存在残留的良性肿瘤组织）。当渗出可能是某种疗法潜在的副反应（如使用紫杉烷化合物或血管生成抑制剂的治疗），且可测量肿瘤符合缓解或疾病稳定标准时，在治疗过程中肿瘤相关的渗出出现或加重，可通过细胞学技术来确诊，以区分缓解（或疾病稳定）和疾病进展。

2. 肿瘤缓解的评估

2.1 靶病灶评估

完全缓解（CR）：所有靶病灶消失，全部病理淋巴结（包括靶结节和非靶结

节）短直径必须减少至＜10 mm。

部分缓解（PR）：靶病灶直径之和比基线水平减少至少 30%。

疾病进展（PD）：以整个实验研究过程中所有测量的靶病灶直径之和的最小值为参照，直径和相对增加至少 20%（如果基线测量值最小就以基线值为参照）；除此之外，必须满足直径和的绝对值增加至少 5 mm（出现一个或多个新病灶也视为疾病进展）。

疾病稳定（SD）：靶病灶减小的程度没达到 PR，增加的程度也没达到 PD 水平，介于两者之间，研究时可以直径之和的最小值作为参考。

2.2 靶病灶评估的注意事项

淋巴结：即使鉴定为靶病灶的淋巴结减小至 10 mm 以内，每次测量时仍需记录与基线对应的实际短直径的值（与基线测量时的解剖平面一致）。这意味着如果淋巴结属于靶病灶，即使达到完全缓解的标准，也不能说病灶已全部消失，因为正常淋巴结的短直径就定义为＜10 mm。在 CRF 表或其他的记录方式中需在特定位置专门记录靶淋巴节病灶：对于 CR，所有淋巴节短直径必须＜10 mm；对于 PR、SD 和 PD，靶淋巴节短直径实际测量值将被包含在靶病灶直径的和之中。

小到无法测量的靶病灶：临床研究中，基线记录过的所有病灶（结节或非结节）在后面的评估中都应再次记录实际测量值，即使病灶非常小（如 2 mm）。但有时候可能太小导致 CT 扫描出的图像十分模糊，放射科医生也很难定义出确切的数值，就可能报告为“太小而测量不到”。出现这种情况时，在 CRF 表上记录上一个数值是十分重要的。如果放射科医生认为病灶可能消失了，那也应该记录为 0 mm。如果病灶确实存在但比较模糊，无法给出精确的测量值时，可默认为 5 mm。（注：淋巴结出现这种情况的可能性不大，因其正常情况下一般都具有可测量的尺寸，或者像在腹膜后腔中一样常常为脂肪组织所包绕；但是如果也出现这种无法给出测量值的情况，也默认为 5 mm）。5 mm 的默认值源于 CT 扫描的切割厚度（这个值不因 CT 不同的切割厚度值而改变）。由于同一测量值重复出现的几率不大，提供这个默认值将降低错误评估的风险。但需要重申的是，如果放射医生能给出病灶大小的确切数值，即使病灶直径小于 5 mm，也必须记录实际值。

分离或结合的病灶：当非结节性病灶分裂成碎片状时，将各分离部分的最长径加起来计算病灶的直径之和。同样，对于结合型病灶，通过各结合部分间的平面可将其区分开来，然后计算各自的最大直径。但如果结合得密不可分，最长径应取融合病灶整体的最长径。

2.3 非靶病灶的评估

这部分对非靶病灶肿瘤的缓解标准进行了定义。虽然一些非靶病灶实际可测量，但无需测量，只需在方案规定的时间点进行定性评估即可。

完全缓解（CR）：所有非靶病灶消失，且肿瘤标记物恢复至正常水平。所有淋巴结为非病理尺寸（短径＜10 mm）。

非完全缓解/非疾病进展：存在一个或多个非靶病灶和/或持续存在肿瘤标记物水平超出正常水平。

疾病进展：已存在的非靶病灶出现明确进展。注：出现一个或多个新病灶也被视为疾病进展。

2.4 关于非靶病灶进展评估的特别注意事项

关于非靶病灶进展的定义补充解释如下：当患者存在可测量非靶病灶时，即使靶病灶评估为稳定或部分缓解，要在非靶病灶的基础上作出明确进展的定义，必须满足非靶病灶整体的恶化程度已达到必须终止治疗的程度。而一个或多个非靶病灶尺寸的一般性增大往往不足以达到进展标准，因此，在靶病灶为稳定或部分缓解时，仅依靠非靶病灶的改变就能定义整体肿瘤进展的情况几乎是十分稀少的。

当患者的非靶病灶均不可测量时：在一些III期研究中，当入选标准中没有规定必须存在可测量病灶时，就会出现这种情况。整体评估还是参照上文标准，但因为这种情况下没有病灶的可测量数据。非靶病灶的恶化不容易评估（根据定义：必须所有非靶病灶都确实无法测量），因此当非靶病灶改变导致整体疾病负荷增加的程度相当于靶病灶出现疾病进展时，依据非靶病灶作出明确进展的定义，需要建立一种有效的检测方法来进行评估。如描述为肿瘤负荷增加相当于体积额外增加 73%（相当于可测量病灶直径增加 20%）。又比如腹膜渗出从“微量”到“大量”；

淋巴管病变从“局部”到“广泛播散”；或在方案中描述为“足够至改变治疗方法”。例子包括胸膜渗出液从痕量到大量，淋巴受累从原发部位向远处扩散，或者在方案中可能被描述为“有必要进行治疗方面的改变”。如果发现有明确的进展，该患者应该在那个时点总体上视为疾病进展。最好具有客观标准可适用于不可测量的病灶的评估，注意，增加的标准必须是可靠的。

2.5 新病灶

新的恶性病灶的出现预示着疾病的进展；因此针对新病变的一些评价是非常重要的。目前没有针对影像学检测病灶的具体标准，然而一种新的病灶的发现应该是明确的。比如说，进展不能归因于影像学技术的不同，成像形态的改变，或者肿瘤以外的其它病变（如：一些所谓新的骨病灶仅仅是原病灶的治愈，或原病灶的复发）。当病人的基线病灶出现部分或完全反应时，这一点非常重要的，例如：一例肝脏病灶的坏死可能在 CT 报告上定为新的囊性病变，而其实不是。

在随访中已检测到的而在基线检查中未发现的病灶将视为新的病灶，并提示疾病进展。例如一个在基线检查中发现有内脏病灶的患者，当他做 CT 或 MRI 的头颅检查时发现有转移灶，该患者的颅内转移病灶将被视为疾病进展的依据，即使他在基线检查时并未做头颅检查。

如果一个新的病灶是不明确的，比如因其形态小所致，则需要进一步的治疗和随访评价以确认其是否是一个新的病灶。如果重复的检查证实其是一个新的病灶，那么疾病进展的时间应从其最初的发现的时间算起。

病灶进行 FDG-PET 评估一般需要额外的检测进行补充确认，FDG-PET 检查和补充 CT 检查结果相结合评价进展情况是合理的（尤其是新的可疑疾病）。新的病灶可通过 FDG-PET 检查予明确的，依据以下程序执行：

基线 FDG-PET 检查结果是阴性的，接下来随访的 FDG-PET 检查是阳性的，表明疾病的进展。

没有进行基线的 FDG-PET 检查，后续的 FDG-PET 检查结果是阳性的：

如果随访的 FDG-PET 阳性检查结果发现的新的病变灶与经 CT 检查结果相符，证明是疾病进展。

如果随访的 FDG-PET 的阳性检查结果发现的新的病变灶未能得到 CT 检查结果的确认，需再行 CT 检查予以确认（如果得到确认，疾病进展时间从前期 FDG-PET 检查发现异常算起）。

如果随访的 FDG-PET 的阳性检查结果与经 CT 检查已存在的病灶相符，而该病灶在影像学检测上无进展，则疾病无进展。

2.6 评估缺失和不可评价说明

如果在某个特定时间点上无法进行病灶成像或测量，则该患者在该时间点上无法评价。如果在一个评价中只能对部分病灶进行评价，通常这种情况视为在那个时间点无法评价，除非有证据证实缺失的病灶不会影响指定时间点的疗效反应评价。

2.7 疗效评估的特别提示

当结节性病灶被包括在总的靶病灶评估中，同时该结节大小缩小到“正常”大小时（＜10 mm），它们依然会有一个病灶大小扫描报告。为了避免过高评估基于结节大小增加所反映的情况，即便是结节正常，测量结果也将被记录。正如前面已经提及的，这就意味着疗效为完全缓解的受试者，CRF 表上也不会记录为 0。

若研究过程中需要进行疗效确认，重复的“不可测量”时间点将使最佳疗效评估变得复杂。研究的分析计划必须说明，在确定疗效时，这些缺失的数据/评估可以被解释清楚。比如，在大部分研究中，可以将某受试者 PR-NE-PR 的反应作为得到了疗效确认。

当受试者出现健康情况整体恶化要求停止给药治疗，但是没有客观证据证明时，应该被报道为症状性进展。即便在治疗终止后也应该尽量去评估客观进展的情况。症状性恶化不是客观反应的评估描述，它是停止治疗的原因。那样的受试者的客观反应情况将通过附表 1～3 所示的目标和非目标病灶情况进行评估。

定义为早期进展、早期死亡和不可评估的情况是研究特例，且应该在每个方案中进行明确的描述（取决于治疗间期和治疗周期）。

在一些情况下，从正常组织中辨别局部病灶比较困难。当完全缓解的评估基于这样的定义时，我们推荐在进行局部病灶完全缓解的疗效评估前进行活检。当

一些受试者局部病灶影像学检测结果异常被认为是代表了病灶纤维化或者疤痕形成时，FDG-PET 被当作与活检相似的评估标准，用来对完全缓解进行疗效确认。在此种情况下，应该在方案中对 FDG-PET 的应用进行前瞻性描述，同时以针对此情况专科医学文献的报告作为支持。但是必须意识到的是由于 FDG-PET 和活检本身的限制性（包括二者的分辨率和敏感性高低），将会导致完全缓解评估时的假阳性结果。

附表 1. 时间点反应-有靶病灶的受试者（包括或者不包括非靶病灶）

目标病灶	非目标病灶	新病灶	总缓解
CR	CR	无	CR
CR	非 CR/非 PD	无	PR
CR	不能评估	无	PR
PR	非进展或者不能完全评估	无	PR
SD	非进展或者不能完全评估	无	SD
不能完全评估	非进展	无	NE
PD	任何情况	是或否	PD
任何情况	PD	是或否	PD
任何情况	任何情况	是	PD

注：CR=完全缓解，PR=部分缓解，SD=疾病稳定，PD=疾病进展，NE=不能评估。

附表 2. 时间点反应-仅有非目标病灶的受试者

非目标病灶	新病灶	总缓解
CR	无	CR
非 CR 或者非 PD	无	非 CR 或非 PD
不能完全评估	无	不能评估
不能明确的 PD	是或否	PD
任何情况	是	PD

注：对于非目标病灶，“非 CR/非 PD”是指优于 SD 的疗效。由于 SD 越来越多作为评价疗效的终点指标，因而制定非 CR/非 PD 的疗效，以针对未规定无病灶可测量的情况。

对于不明确的进展发现（如非常小的不确定的新病灶；原有病灶的囊性变或坏死病变）治疗可以持续到下一次评估。如果在下一次评估中，证实了疾病进展，

进展日期应该是先前出现疑似进展的日期。

附表 3. CR 和 PR 疗效需要确认的最佳总缓解

第一个时间点总缓解	随后时间点总缓解	最佳总缓解
CR	CR	CR
CR	PR	SD，PD 或 PRa
CR	SD	如果 SD 持续足够时间则为 SD，否则应为 PD
CR	PD	如果 SD 持续足够时间则为 SD，否则应为 PD
CR	NE	如果 SD 持续足够时间则为 SD，否则应为 NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	如果 SD 持续足够时间则为 SD，否则应为 PD
PR	NE	如果 SD 持续足够时间则为 SD，否则应为 NE
NE	NE	NE

注：CR 即是完全缓解，PR 是部分缓解，SD 是疾病稳定，PD 是疾病进展，NE 即不可评价。上标“a”：如果在第一个时间点 CR 真正出现，在随后的时间点出现的任何疾病，那么即便相对于基线该受试者疗效达到 PR 标准，其疗效评价在之后的时间点仍然为 PD（因为在 CR 之后疾病将再次出现）。最佳缓解取决于是否在最短的治疗间隔内出现 SD。然而有时第 1 次评价为 CR，但随后的时间点扫描提示小病灶似乎依然出现，因而实际上受试者疗效在第一个时间点应该是 PR 而不是 CR。在这种情况下，首次 CR 判断应该被修改为 PR，同时最好的反应是 PR。

2.8 疗效评估/缓解期的确认

疗效确认

对于以肿瘤缓解疗效为主要研究终点的非随机临床研究，必须对 PR 和 CR 的疗效进行确认，以保证疗效不是评价失误的结果。以疾病稳定或者疾病进展为主要研究终点的研究中，不再需要疗效确认，因为这对于研究结果的解释没有价值。SD 的情况下，在研究开始后的最短时间间隔内（一般不少于 6～8 周），至少有一次测量符合方案中规定的 SD 标准。

总缓解期

总缓解期是从测量首次符合 CR 或 PR（无论哪个先测量到）标准的时间到首次

真实记录疾病复发或进展的时间（把研究中记录的最小测量值作为疾病进展的参考）。总完全缓解时间是从测量首次符合 CR 标准的时间到首次真实记录疾病复发或进展的时间。

疾病稳定期

从治疗开始到疾病进展的时间（在随机化研究中，从随机分组的时间开始），以研究中最小的总和作为参考（如果基线总和最小，则作为 PD 计算的参考）。疾病稳定期的临床相关性因不同研究和不同疾病而不同。如果在某一特定的研究中，以维持最短时间稳定期的病人比例作为研究终点，方案应特别说明 SD 定义中两个测量间的最短时间间隔。

注意：缓解期、稳定期以及 PFS 受基线评价后随访频率的影响。定义标准随访频率不属于本指导原则范围。随访频率应考虑许多因素，如疾病类型和分期、治疗周期及标准规范等。但若需进行研究间的比较，应考虑这些测量终点准确度的限制。

2.9 PFS/TTP

晚期肿瘤许多研究以 PFS 或者 TTP 作为主要研究终点。如果方案要求所有患者都有可测量病灶，进展评价就相对简单。越来越多的研究允许有可测量病灶和无可测量病灶的患者都可以进入研究。在这种情况下，必须对无可测量病灶患者疾病进展的临床发现进行详细明确的描述。因为进展日期常有确定偏差，各研究组的观测时间点安排应该相同。

附录 2：体力状况评分标准（ECOG PS）

评分	标准
0	活动能力完全正常，与起病前活动能力无任何差异
1	能自由走动及从事轻体力活动，包括一般家务或办公室工作，但不能从事较重的体力活动
2	能自由走动及生活自理，但已丧失工作能力，日间不少于一半时间可以起床活动
3	生活仅能部分自理，日间一半以上时间卧床或坐轮椅
4	卧床不起，生活不能自理
5	死亡

附录 3：Cockcroft-Gault 公式

血清肌酐浓度单位为（mg/dL）的计算公式:

$$\text{男性肌酐清除率（mL/min）} = \frac{\text{（140－年龄）×（体重）}^{a}}{72\times\text{血清肌酐}}$$

$$\text{女性肌酐清除率（mL/min）} = \frac{0.85\times\text{（140－年龄）×（体重）}^{a}}{72\times\text{血清肌酐}}$$

血清肌酐浓度单位为（mmol/L）的计算公式:

$$\text{男性肌酐清除率（mL/min）} = \frac{\text{（140－年龄）×（体重）}^{a}}{0.818\times\text{血清肌酐}}$$

$$\text{女性肌酐清除率（mL/min）} = \frac{0.85\times\text{（140－年龄）×（体重）}^{a}}{0.818\times\text{血清肌酐}}$$

a：年龄单位为岁，体重单位为 kg。

附录 4：禁用药物列表

相互作用机制	药物名称
CYP3A 和 P-gp 强效诱导剂	卡马西平、苯妥英、利福平、圣约翰草、恩杂鲁胺、阿帕鲁胺、米托坦
CYP3A 和 P-gp 强效抑制剂	博赛泼维、克拉霉素、可比司他、葡萄柚汁（>1L/天，高浓度）、茚地那韦、伊曲康唑、酮康唑、洛匹那韦和利托那韦、奈法唑酮、奈非那韦、泊沙康唑、奎奴普丁、利托那韦、沙奎那韦、特拉匹韦、泰利霉素、伏立康唑、胺碘酮、卡维地洛、地尔硫卓、决奈达隆、格卡瑞韦、拉米替坦、雷迪帕韦、莱特莫韦、帕利瑞韦、派仑他韦、奎尼丁、雷诺拉嗪、西美瑞韦、替格瑞洛、维帕他韦、维拉帕米、伏环孢素、伏西瑞韦、丹诺瑞韦、埃替拉韦、奥比他韦和/或达塞布韦、替拉那韦、醋竹桃霉素、艾伐拉利司、拉帕替尼、普拉帕酮
CYP3A4 敏感底物	左炔诺孕酮(LNG)和醋酸乌利司他(UPA)、依伐卡托、阿贝西尼、米哚妥林、来拉替尼、非洛地平、咪达唑仑、丁螺环酮、西地那非、辛伐他汀、布地奈德、氟替卡松、硝苯地平、托伐普坦、艾沙康唑、艾伏尼布、阿帕鲁胺、考比替尼、替西罗莫司、艾代拉里斯、三唑仑、依普利酮、阿普唑仑、阿莫曲坦、阿普斯特、尼索地平、阿伐那非、罗氟司特、甲磺酸溴隐亭、右佐匹克隆、氟班色林、氨氯地平，依拉地平、阿普唑仑，阿普瑞坦，阿托伐他汀，秋水仙碱，利匹韦林，利伐沙班，他达拉非，匹莫齐特、阿芬太尼，考尼伐坦，达非那新，地瑞拉韦，依巴斯汀，依维莫司，依鲁替尼，洛美他派，洛伐他汀、纳洛醇醚，尼索地平，西罗莫司，他克莫司，依地那非，达沙替尼，依来曲坦，鲁拉西酮，马拉韦罗，圭硫平，替格瑞洛，利格列汀，哌替啶, 他莫昔芬
OAT1 敏感底物	阿德福韦，对氨基马尿酸，西多福韦，替诺福韦

表格中列出的是常见的 CYP3A4 和 P-gp 的强效抑制剂和诱导剂，OAT1 和 CYP3A4 敏感底物。如对于其他可能的合并用药有疑问，研究者可与申办方进行沟通。药物相互作用可在 FDA 的官网上进行查询，网址如下：

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table4-1。

附录 5：BOIN 设计的详细参数与模拟性能

使用从 http://www.trialdesign.org 获取的 Shiny app “BOIN”，并考虑以下两种情形：

1. 前两个剂量水平采用加速滴定

BOIN 设计的具体参数如下：

参数	值
剂量组数	5
起始剂量	1
每次入组例数	3
入组次数	10
如果分配到某个剂量组的受试者数达到 m 例且接下来仍将分配受试者到该剂量组，则研究终止。m =	6
目标毒性概率	0.3
使用默认的剂量升降边界值（推荐）	True
使用加速滴定	Yes
加速滴定最高剂量	2
当 3 例受试者中观察到 1 例 DLT 时，将决策由降低剂量改为保持当前剂量	Yes
消除剂量阈值 p_K	0.95
每个情形的重复次数	1000
随机数生成器种子	12345

注：最大样本量 = 每次入组例数 * 入组次数 = 3 * 10 = 30.

该 BOIN 设计的模拟性能如下：

	剂量 1	剂量 2	剂量 3	剂量 4	剂量 5	患者数	提前终止%
情形 1							
真实 DLT 率	0.3	0.46	0.5	0.54	0.58		
选择%	56.6	22.4	11.7	1.6	0		7.7

接受治疗的患者%	44.1	35.1	17.6	2.9	0.3	12.1	
情形 2							
真实 DLT 率	0.16	0.3	0.47	0.54	0.6		
选择%	24.8	47.5	23.8	2.9	0.1		0.9
接受治疗的患者%	26.7	39.7	28.1	5.1	0.4	14.4	
情形 3							
真实 DLT 率	0.04	0.15	0.3	0.48	0.68		
选择%	1.6	22.9	56.7	18	0.8		0
接受治疗的患者%	9.8	23.3	43.4	20.7	2.8	15.3	
情形 4							
真实 DLT 率	0.02	0.07	0.12	0.3	0.45		
选择%	0.2	3.3	23.8	51.2	21.4		0.1
接受治疗的患者%	6.8	9.7	31.8	35.7	15.9	17	
情形 5							
真实 DLT 率	0.02	0.06	0.1	0.13	0.3		
选择%	0.3	2.2	11.1	22.7	63.7		0
接受治疗的患者%	7	9.2	24.3	29.5	30	16.4	

2. 仅考虑后三个剂量水平的 BOIN 设计

BOIN 设计的具体参数如下：

参数	**值**
剂量组数	5
起始剂量	1
每次入组例数	3
入组次数	10

如果分配到某个剂量组的受试者数达到 m 例且接下来仍将分配受试者到该剂量组，则研究终止。m =	6
目标毒性概率	0.3
使用默认的剂量升降边界值（推荐）	True
使用加速滴定	No
当 3 例受试者中观察到 1 例 DLT 时，将决策由降低剂量改为保持当前剂量	Yes
消除剂量阈值 p_K	0.95
每个情形的重复次数	1000
随机数生成器种子	12345

该 BOIN 设计的模拟性能如下：

	剂量 1	剂量 2	剂量 3	患者数	提前终止%
情形 1					
真实 DLT 率	0.3	0.48	0.67		
选择%	70.6	20.4	0.9		8.1
接受治疗的患者%	63.7	32	4.3	10.4	
情形 2					
真实 DLT 率	0.13	0.3	0.44		
选择%	27.7	50.1	21.7		0.5
接受治疗的患者%	39.3	41.7	19	13.9	
情形 3					
真实 DLT 率	0.05	0.13	0.3		
选择%	3.6	26.2	70.1		0.1
接受治疗的患者%	25.1	37.4	37.5	14.7	

根据上述模拟性能结果，本设计可大概率选择准确的 MTD（如果有 MTD），并将更多的患者分配到 DLT 发生率最接近目标概率为 0.3 的剂量水平组。

附录 6：期中分析统计学方法

中期分析采用了贝叶斯预测概率（predictive probability，PP）的方法计算成功率，为早期的无效性判断提供依据。基于中期分析时观察到的有效性数据，对达到最大计划样本量时成功的概率（即认为研究药物有效）进行计算。基于已观察到的数据，高 PP 表示在试验结束时很有可能得到研究治疗有效的结论，与之相反，低 PP 则表示研究治疗或许并没有足够的疗效。

下表展示了通过在线软件（https://www.trialdesign.org/one-page-shell.html#BEMPR）设定的相关参数值和计算结果：

Input Parameter	Input Value	
	NSCLC	PDAC/CRC
Reference response rate (θ_0)	0.23	0.10
Threshold for declaring efficacy at the end of the trial (p_T)	0.7	
Early Stopping for Futility	TRUE	
Probability confidence threshold for futility stopping (p_L)	0.2	
Early Stopping for Efficacy	FALSE	
Prior distribution for θ: Beta(a_0,b_0) a_0	0.5	
Prior distribution for θ: Beta(a_0,b_0) b_0	0.5	
Input Cohort Manually	FALSE	
Maximum number of patients in the trial	73	50
Minimum number of patients before early stopping rule applies	20	
Cohort size	1	

附录 7：中心实验室信息和样本销毁公司信息

中心实验室一：药代动力学检测

名称：上海观合医药科技股份有限公司

统一社会信用代码：91310110MA1G83F27K

地址：上海市杨浦区翔殷路 128 号 12 号楼三楼 C 座 101-110 室

中心实验室二： ctDNA 测序

名称：广州燃石医学检验所有限公司

统一社会信用代码：91440116094098415C

地址：广州市黄埔区广州国际生物岛星岛环北路 5 号

样本销毁公司一：药代动力学样本销毁单位

名称：上海市固体废物处置有限公司

统一社会信用代码：913101147294906145

地址：上海市嘉定区嘉朱公路 2491 号

样本销毁公司二： ctDNA 测序样本销毁单位

名称：广州环保投资集团有限公司

统一社会信用代码：91440101671815024A

地址：广州市越秀区流花路 121 号（南塔）1218 房

STATISTICAL ANALYSIS PLAN

An open-label, phase I/II clinical study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation

Protocol Number:	GFH375X1101
Sponsor:	GenFleet Therapeutics (Shanghai) Inc.
CRO:	ClinChoice Enterprise Management (Shanghai) Co., Ltd.
Version:	0.9
Date:	November 07, 2025

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Document Update Record

Version	Date	Author/Modifier	Comments

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List of Abbreviations

Abbreviation	Term
AE	Adverse event
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the curve
BICR	Blinded Independent Central Review Committee
BID	Twice daily
BMI	Body mass index
BOIN	Bayesian Optimal Interval
BOR	Best overall response
BQL	Below lower limit of quantification
BSA	Body surface area
C_{max}	Maximum concentration
$C_{max,ss}$	Steady-state maximum concentration
$C_{trough,ss}$	Steady-state trough concentration
CI	Confidence interval
CL/F	Apparent clearance
CL/F_{ss}	Steady-state apparent clearance
CR	Complete response
CRC	Colorectal carcinoma
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CV	Coefficient of variation
DCR	Disease control rate
DDS	Dose Determination Set
DLT	Dose-limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FAS	Full Analysis Set
GCV	Geometric coefficient of variation
HR	Heart rate
LLOQ	Lower limit of quantification
KRAS	Kirsten ratsarcoma viral oncogene homolog
MedDRA	Medical Dictionary for Regulatory Activities
NE	Not evaluable
NSCLC	Non-small cell lung cancer
MRT	Mean residence time
MTD	Maximum tolerated dose
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PDAC	Ductal adenocarcinoma of pancreas

Abbreviation	Term
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PN	Preferred name
PPS	Per-Protocol Set
PPoS	Predictive probability of success
PR	Partial response
PT	Preferred term
Q1	First quartile
Q3	Third quartile
QD	Once daily
R^2adj	Adjusted coefficient of determination
R_{ac_AUC}	Accumulation ratio based on $AUC_{0\text{-}tau}$
R_{ac_Cmax}	Accumulation ratio based on C_{max}
$R_{ac_Ctrough}$	Accumulation ratio based on C_{trough}
RECIST	Response Evaluation Criteria in Solid Tumors
RED	Recommended expansion dose
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SMC	Safety Monitoring Committee
SOC	System organ class
SS	Safety Set
$t_{1/2}$	Elimination half-life
T_{max}	Time to maximum concentration
TEAE	Treatment-emergent adverse event
TTR	Time to response
V_z/F	Apparent volume of distribution
V_z/F_{ss}	Steady-state apparent volume of distribution
WHODrug	World Health Organization Drug Dictionary
λ_z	Terminal elimination rate constant

1 Introduction

This study (Protocol No. GFH375X1101) is an open-label, phase I/II clinical study to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation. Based on the clinical study protocol (Version: V2.0, 2025-1-24), this Statistical Analysis Plan (SAP) details the specific statistical methods and data handling principles for analyzing and reporting subject safety assessments, efficacy assessments, PK assessments, and biomarker assessments.

This document will be gradually supplemented and improved to reflect protocol amendments, regulatory and other important changes. The final SAP will be archived after approval by the sponsor and before database lock. Any deviations from the final SAP will be noted in the clinical study report.

1.1 Study Objectives and Endpoints

Table 1 Objectives and Endpoints of the Phase I Study

Study Objectives	Study Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and tolerability of GFH375 in patients with advanced solid tumors with KRAS G12D mutation	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs); changes in vital signs, electrocardiogram (ECG), and laboratory tests
• To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of GFH375	• Incidence of dose-limiting toxicity (DLT) events
Secondary Objectives	**Secondary Endpoints**
• To evaluate the PK characteristics of GFH375 in patients with advanced solid tumors with KRAS G12D mutation	• Plasma concentrations and PK parameters of GFH375, including but not limited to C_{max}, T_{max}, AUC, $t_{1/2}$, CL/F, Vz/F, C_{trough}
• To evaluate the preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation	• Objective response rate (ORR), duration of response (DoR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
	• Overall survival (OS)
Exploratory Objective	**Exploratory Endpoint**
• To explore the molecular mechanisms related to treatment sensitivity or drug resistance	• Mutation analysis of circulating tumor DNA (ctDNA) in blood at baseline and at the end of treatment

Table 2 Objectives and Endpoints of the Phase II Study

Study Objectives	Study Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the efficacy of GFH375 in patients with advanced non-small cell lung cancer (NSCLC), advanced pancreatic carcinoma (PDAC), advanced colorectal cancer (CRC), and other solid tumors with	• ORR as assessed by RECIST 1.1

KRAS G12D mutation

Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation using other efficacy endpoints	• Best overall response (BOR), DoR, DCR, TTR, and PFS as assessed by RECIST 1.1 • OS
• To evaluate the safety of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation	• Incidence and severity of AEs and SAEs; changes in vital signs, ECG, and laboratory tests
• To evaluate the PK characteristics of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation	• Plasma concentrations of GFH375
Exploratory Objective	**Exploratory Endpoint**
• To explore the molecular mechanisms related to treatment sensitivity or drug resistance	• Mutation analysis of blood ctDNA at baseline and at the end of treatment
• For PDAC subjects: Relationship between carbohydrate antigen 19-9 (CA19-9) and treatment response	• For PDAC subjects: Change from baseline in serum CA19-9

1.2 Study Overview

1.2.1 Overall Study Design

This is a study to evaluate the safety/tolerability, PK, and efficacy of GFH375 monotherapy in patients with advanced solid tumors with KRAS G12D mutation. The primary objective of the Phase I study is to evaluate the safety/tolerability, PK, and preliminary efficacy of GFH375 in patients with advanced solid tumors with KRAS G12D mutation, and to determine the MTD and/or RP2D of GFH375. The primary objective of the Phase II study is to evaluate the efficacy of GFH375 in patients with advanced NSCLC, advanced PDAC, advanced CRC, and other advanced solid tumors with KRAS G12D mutation.

Phase I Part

According to the BOIN design, 3-6 subjects will be enrolled in each dose cohort (except during accelerated titration) to receive oral administration of GFH375, with each treatment cycle lasting 21 days. Subjects will be enrolled into sequential dose-escalation cohorts, with a starting dose of 100 mg once daily (QD). A total of 7 or more dose levels are expected to be evaluated in the dose-escalation part, and the planned dose escalation is shown in Table 3. The GFH375 dosing regimen will be comprehensively evaluated during dose escalation. If necessary, dose exploration with a twice daily (BID) dosing frequency will be conducted. Dose escalation can be conducted independently and in parallel for QD and BID dosing regimens.

Based on the data obtained, including safety, PK, and preliminary efficacy results, BID dose exploration may be conducted. The starting dose for BID will be selected from one of the dose cohorts in the table below, and the total daily dose will be consistent with the QD dose being explored.

Table 3 Dose Escalation

Dose Cohort	Planned QD Dose Escalation Cohorts for Phase I[1]
Dose Cohort 1	100 mg QD
Dose Cohort 2	200 mg QD
Dose Cohort 3	400 mg QD
Dose Cohort 4	600 mg QD
Dose Cohort 5	750 mg QD
Dose Cohort 6	1000 mg QD
Dose Cohort 7	1200 mg QD
Dose Cohort	**Potential BID Dose Exploration Cohorts for Phase I[2]**
Dose Cohort 1	100 mg BID
Dose Cohort 2	150 mg BID
Dose Cohort 3	200 mg BID
Dose Cohort 4	300 mg BID
Dose Cohort 5	400 mg BID

Note: [1] Intermediate doses of the above doses, such as 150 mg, 300 mg, 500 mg, 800 mg, 900 mg, 1100 mg QD, etc., may be explored during the escalation process based on the clinical data obtained, including safety, PK, and possible efficacy.
[2] Intermediate doses of the above doses, such as 250 mg BID, etc., may be explored.

Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional subjects for backfilling. These subjects will be treated with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is considered to have potential clinical benefit by the investigator and sponsor, in order to better estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. If the safety of the 750 mg QD dose cohort has been explored and confirmed, backfilling of the 700 mg QD dose cohort may also be conducted. Backfilled subjects will not be included in the DLT evaluation. After backfilling, no more than 30 subjects will be treated in each GFH375 dose cohort (including subjects enrolled in the BOIN dose-escalation phase).

The study schematic is shown in Figure 1.

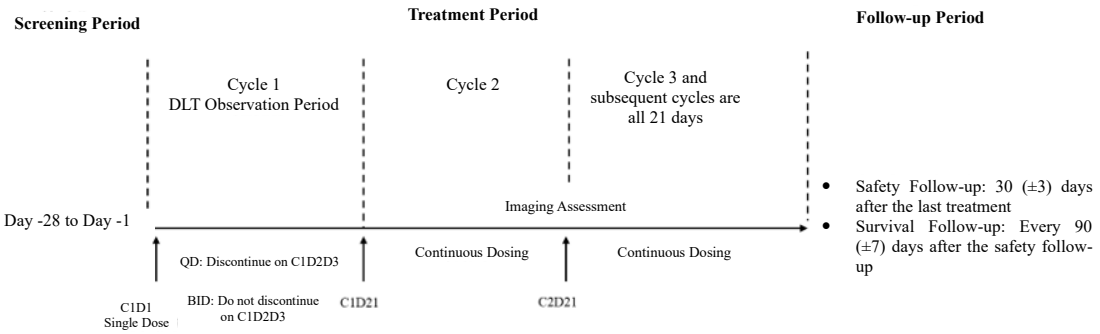

Figure 1 Phase I Study Schematic

Phase II Part

Based on all safety, tolerability, PK, and efficacy data from the Phase I dose-escalation part and some backfilled subjects, the RP2D was determined to be 600 mg QD.

The Phase II study is an open-label, multicenter study. The overall study plan is shown in 错误!未找到引用源。. The objective is to evaluate the efficacy, safety, and PK characteristics of GFH375 in patients with advanced non-small cell lung cancer, advanced pancreatic carcinoma, colorectal cancer, and other advanced solid tumors with KRAS G12D mutation. The Phase II study will enroll approximately 317 subjects with advanced solid tumors with KRAS G12D mutation to receive continuous monotherapy with GFH375 at the RP2D. The treatment cycle is 21 days, until progressive disease (PD), unacceptable toxicity, or discontinuation of study treatment for other reasons.

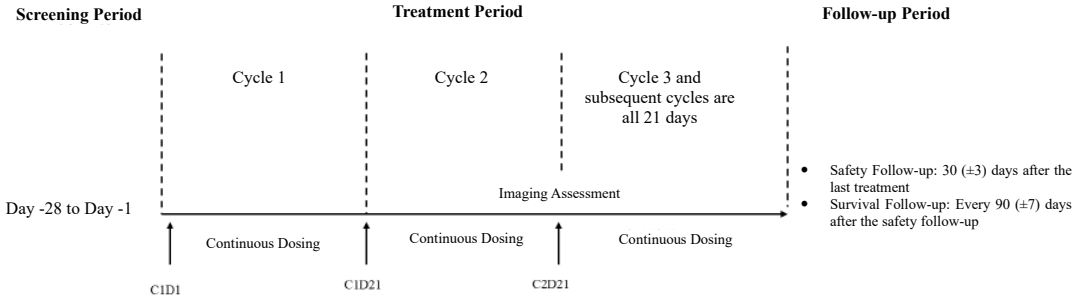

Figure 2 Phase II Study Schematic

1.2.2 Randomization and Blinding

This is a single-arm, open-label study, so randomization and blinding are not applicable.

1.2.3 Sample Size

1.2.3.1 Phase I: Dose-Escalation Part

According to the BOIN design, 3-6 subjects will be enrolled in each dose cohort (except during accelerated titration) for treatment. Based on the safety/tolerability, PK, and preliminary efficacy data obtained, one or more dose cohorts may be selected to enroll additional subjects for backfilling. These

subjects will be treated with a GFH375 monotherapy dose that has been confirmed to be safe and well-tolerated and is considered to have potential clinical benefit by the investigator and sponsor, in order to better estimate the RP2D of GFH375 monotherapy and characterize its safety\tolerability, PK, and efficacy. Backfilled subjects will not be included in the DLT evaluation. After backfilling, no more than 30 subjects will be treated in each GFH375 dose cohort (including subjects enrolled in the BOIN dose-escalation phase). If more dose cohorts or alternative dosing regimens need to be explored, additional subjects may be enrolled.

1.2.3.2 Phase II

A total of approximately 317 subjects are expected to be enrolled, including approximately 73 subjects with advanced NSCLC, approximately 94 subjects with advanced PDAC, 50 subjects with advanced CRC, and 100 subjects with other advanced solid tumors.

Table 2 Phase II Sample Size

Tumor Type	Historical Control ORR	Expected ORR	Sample Size
NSCLC	23%	40%	73
PDAC	15%	30%	94
CRC	10%	30%	50
Other			100
Total			317

For second-line advanced NSCLC, the historical control value for ORR is 23%, and the expected ORR in this study is 40%. The study will be considered successful if the lower limit of the 95% CI for the observed ORR is not less than the historical control of 23%. With a one-sided $\alpha = 0.025$, 73 subjects are required to achieve 89% power. When at least 25 of the 73 subjects have a CR/PR, the lower limit of the exact 95% CI for the observed ORR will be higher than the historical control of 23%. With 25 CR/PRs, the ORR = 34.2%, with a 95% CI of (23.5%, 46.3%).

For second-line advanced PDAC, the historical control value for ORR is set at 15%. The expected ORR with GFH375 treatment is 30%. If the lower limit of the 95% CI for ORR after GFH375 treatment is greater than 15%, the efficacy of GFH375 will be considered statistically significant. With a one-sided $\alpha = 0.025$, 94 subjects will provide 95% power to ensure that the lower limit of the 95% CI for the ORR is greater than 15%. Approximately 94 subjects with PDAC are planned for enrollment. When 22 responses (PR/CR) are observed in 94 subjects, the exact 95% CI for the observed ORR is (15.29%, 33.26%). Therefore, if ≥22 responses are observed in 94 subjects, the efficacy of GFH375 will be considered statistically significant.

For third-line CRC, the historical control value for ORR is 10%, and the expected ORR in this study is 30%. The study will be considered successful if the lower limit of the 95% CI for the observed ORR

is not less than the historical control of 10%. It is planned to enroll 50 subjects, which will provide 96% power with a one-sided $\alpha = 0.025$. When at least 10 of the 50 subjects have a CR/PR, the lower limit of the exact 95% CI for the observed ORR will be higher than the historical control of 10%. With 10 CR/PRs, the ORR = 20.0%, with a 95% CI of (10.0%, 33.7%).

For other solid tumors: Approximately 100 subjects with advanced solid tumors with KRAS G12D mutation, such as bile duct cancer and appendix cancer with KRAS G12D mutation, are planned for enrollment.

The above sample size and ORR (and its 95% exact CI) calculations were performed using the R language. Among them, the sample size was calculated using the "nBinomial1Sample" function in the "gsDesign" package (option: conservative = TRUE); the ORR and its 95% exact CI were calculated using the "binom.exact" function in the "epitools" package (default options).

2 Basic Considerations for Statistical Analysis

2.1 General Rules

All statistical analyses will be performed using SAS 9.4 or a later version.

For continuous variables, the number of subjects, mean, standard deviation, median, minimum, and maximum will be summarized. For categorical variables, the number of subjects and percentage for each category will be summarized. Time-to-event variables will be analyzed using the Kaplan-Meier method, survival curves will be plotted, and the median survival time and its corresponding two-sided 95% confidence interval (CI) will be calculated. Table 3 shows the number of decimal places to be retained for each statistical parameter.

Table 3 Number of Decimal Places for Statistical Parameters

Statistic	**Number of Decimal Places to Retain**
Arithmetic mean, geometric mean, median, Q1, Q3, CI	One more decimal place than the original data, with a maximum of 3 decimal places
Standard deviation, standard error, coefficient of variation (CV%), and geometric coefficient of variation (GCV%)	Two more decimal places than the original data, with a maximum of 3 decimal places.
Maximum, minimum	Same number of decimal places as the original data, with a maximum of 3 decimal places
Percentage	Retain one decimal place. If the percentage is 100%, it will be expressed as "100". If the percentage is 0, it will be expressed as "0"
P-value	Retain 3 decimal places. If the P-value is less than 0.001, it will be expressed as "<0.001". If the P-value is greater than 0.999, it will be expressed as ">0.999".

2.2 Definition of Analysis Sets

- Full Analysis Set (FAS): All subjects who have received at least one dose of GFH375.

- Safety Set (SS): All subjects who have received at least one dose of GFH375 and have at least one valid post-baseline safety assessment.
- Dose Determination Set (DDS): All subjects in the Phase I SS who received unreduced GFH375 for at least 15 cumulative days during the DLT observation period and had adequate safety assessments, or who experienced a DLT during the DLT observation period. The DDS does not include backfilled subjects.
- Per-Protocol Set (PPS): All Phase II subjects in the FAS who are compliant with the protocol. The study team will review all protocol deviations before the final database lock and exclude subjects with major protocol deviations that affect the efficacy evaluation from the PPS.
- Pharmacokinetic Analysis Set (PKAS): All subjects who have received at least one dose of GFH375 and have at least one blood sample providing evaluable PK data.

2.3 Data Handling Principles

2.3.1 Definition of Baseline

Unless otherwise specified, baseline is defined as the last non-missing assessment result (including scheduled and unscheduled visits) before the first dose of GFH375. If a subject does not have an assessment result as defined above, the baseline will be treated as missing. When the assessment occurs on the same day as the first dose of GFH375, if it cannot be confirmed that it occurred after the first dose of GFH375, it will be considered as baseline data by default. However, for AEs, concomitant medications/therapies, etc., when their start date is the same as the date of the first dose of GFH375, if it cannot be confirmed that they occurred before dosing, the AE, concomitant medication/therapy, etc., will be considered to have occurred post-baseline.

2.3.2 Definition of Study Day

The study day is calculated with the date of the first dose of GFH375 as the reference to obtain the time interval (in days) between the date of the event or assessment and the date of the first dose. The study day is calculated as follows:

- If the event or assessment occurs on or after the day of the first dose of GFH375, the study day is: Date of event or assessment - Date of first dose of GFH375 + 1;
- If the event or assessment occurs before the first dose of GFH375, the study day is: Date of event or assessment - Date of first dose of GFH375.

2.3.3 Definition of Analysis Window

All statistical analyses of study data will be based on the nominal visits recorded in the case report form (CRF), and no analysis windows will be set.

2.3.4 Last Known Date of Survival

For subjects whose death is not known as of the analysis date, their last known date of survival will be determined based on the last recorded non-missing date from the following data:

- The dates of all assessments (e.g., vital signs, physical examination, ECOG assessment, laboratory tests, ECG, etc.). If the assessment involves sample collection, the collection date will be used;
- The start and end dates of GFH375 administration, concomitant medications, concomitant non-drug therapies, and new anti-tumor therapies;
- The end date of an AE with an outcome other than “death”;
- The date of the last follow-up visit where the subject's status was “alive” during survival follow-up;
- The date of last contact before being lost to follow-up.

2.3.5 Rules for Handling Missing Data

Unless otherwise specified, missing data in this study will not be imputed.

2.3.5.1 Date of Initial Pathological Diagnosis

Imputation rules for the date of initial pathological diagnosis:

- If the year is missing (or the entire date is missing), it will not be imputed;
- If only the day is missing, it will be imputed as the 1st of that month;
- If both the month and day are missing, it will be imputed as July 1st.

If the imputed date is after the date of informed consent, the imputed date will be revised to the date of informed consent - 1 day.

2.3.5.2 Date of Death

Applicable only to confirmed deaths, the date of death will be imputed using the following rules:

- If the year is missing (or year, month, and day are all missing), the date of death will be imputed as the last known date of survival + 1 day.
- If both the day and month are missing, July 1st of that year will be imputed as the date of death.
- If only the day is missing, the 1st day of that month will be imputed as the date of death.

If the imputed date of death is before the last known date of survival, the imputed date will be revised to the last known date of survival + 1 day.

2.3.5.3 Date of Prior/Concomitant Therapy

Prior/concomitant therapy includes drug and non-drug therapies. The imputation rules for the dates of

prior/concomitant therapy are as follows. If both the start and end dates of a prior/concomitant therapy are missing, the end date will be imputed first, followed by the start date.

End Date of Prior/Concomitant Therapy

- Imputation will only be performed for prior/concomitant therapies for which "No" was selected for "Ongoing";
- If only the day is missing, it will be imputed as the last day of that month;
- If both the month and day are missing, it will be imputed as December 31st of that year;

If the imputed end date of the prior/concomitant therapy is after the study end date, the end date of the prior/concomitant therapy will be revised to the study end date.

Start Date of Prior/Concomitant Therapy

- If only the day is missing, it will be imputed as the 1st of that month;
- If both the month and day are missing, it will be imputed as January 1st of that year;
- If the year, month, and day are all missing, it will be imputed as the date of the first dose of GFH375;

If the imputed start date of the prior/concomitant therapy is later than its end date, it will be revised to the end date of the prior/concomitant therapy.

2.3.5.4 End Date of Prior Anti-tumor Therapy

Prior anti-tumor therapy includes drug therapy, surgery, and radiotherapy. The imputation rules for the end date of prior anti-tumor therapy are as follows:

- If only the day is missing, it will be imputed as the last day of that month;
- If both the month and day are missing, it will be imputed as December 31st of that year;
- If the year, month, and day are all missing, no imputation will be performed;

If the imputed date is after the date of informed consent, the imputed date will be revised to the date of informed consent - 1 day.

2.3.5.5 Date of Progressive Disease on Last Line of Prior Therapy

The imputation rules for the date of PD on the last line of prior therapy are as follows:

- If only the day is missing, it will be imputed as the last day of that month;
- If both the month and day are missing, it will be imputed as December 31st of that year;
- If the year, month, and day are all missing, no imputation will be performed;

If the imputed date is after the date of informed consent, the imputed date will be revised to the date of informed consent - 1 day.

2.3.5.6 Start Date of Adverse Events

Imputation rules for the start date of an AE:

- If the AE start date is completely missing, it will be imputed as the date of the first dose of GFH375;
- If the AE start date is partially missing, the imputation rules are as follows:
  - If the year and month are known and are the same as the year and month of the first dose of GFH375, it will be imputed as the date of the first dose of GFH375;
  - If the year and month are known but are different from the year and month of the first dose of GFH375, it will be imputed as the 1st of that month;
  - If only the year is known and is the same as the year of the first dose of GFH375, it will be imputed as the date of the first dose of GFH375;
  - If only the year is known but is different from the year of the first dose of GFH375, it will be imputed as January 1st of that year.

If the AE end date is not missing and the imputed AE start date is after the AE end date, the AE start date will be imputed as the AE end date.

2.3.5.7 End Date of Investigational Product

If the end date of the last record (i.e., last dose) is missing, it will be imputed with the earliest, complete date from the following that is closest to the start date of that record:

- The last day of the month (if only the day is missing)
- The start time of the AE for which the action taken with study treatment was “drug withdrawn” in the AE record
- Date of decision to end study treatment - 1 day
- Date of death
- Data cutoff date

Missing end date during the study treatment period (not the last dose):

- Start date of the next nearest medication record - 1 day

2.3.6 Other Data Handling Principles

For laboratory test items, all results to be summarized will be presented in tables and listings using SI units. If laboratory test results contain “>” or “<”, the upper or lower limit of the test result will be used as the analysis value for tabulation and summary (the “>” or “<” will be retained in listings). For example, if the test result is “>100”, the analysis value will be assigned as 100.

Unless otherwise specified, only data from scheduled visits will be summarized. However, for the summary analysis of the best/worst post-baseline assessment results, results from both scheduled and unscheduled visits will be included. Results from both unscheduled and scheduled visits will be presented in listings. With the exception of ECG-related assessments, if, during a scheduled visit, an assessment item is tested two or more times within the same visit, the last non-missing result will be used for tabulation analysis; for multiple measurements of ECG-related parameters within the same visit, the mean value will be used for tabulation analysis. If multiple identical best/worst post-baseline assessment results occur, the last assessment result will be used for tabulation analysis. Multiple assessment results from both unscheduled and scheduled visits will be presented in listings.

2.4 Multiplicity Comparison

This study does not involve multiple comparisons.

2.5 Subgroup Analysis

For Phase II subjects with PDAC and NSCLC, a subgroup analysis of ORR will be performed based on the results assessed by BICR where CR/PR requires confirmation.

Subgroups for PDAC include:

- Age (<65 years, ≥65 years);
- Sex (male, female);
- ECOG PS score (0, 1);
- Number of metastatic sites (<2, ≥2);
- CA19-9 level (<40 U/mL, ≥40 U/mL);
- Albumin (<40 g/L, ≥40 g/L);
- Prior radiotherapy (yes, no);
- Prior surgery (yes, no);
- Tumor stage (III, IV, other);
- Metastases to liver (yes, no);
- Body mass index (<median, ≥median);
- Number of prior lines of drug therapy (0, 1, 2, 3);
- Duration of disease (<median, ≥median);
- Time from PD on last line of prior therapy to first treatment (<median, ≥median, <1 month, 1-3 months, 3-6 months, ≥6 months);
- Prior treatment with gemcitabine/gemcitabine hydrochloride (yes, no);
- Prior treatment with albumin-bound paclitaxel/paclitaxel (yes, no);

- Prior treatment with irinotecan (yes, no).

Subgroups for NSCLC include:

- Age (<60 years, ≥60 years, <65 years, ≥65 years);
- Sex (male, female);
- ECOG PS score (0, 1);
- Smoking history (never smoked, former smoker, current smoker);
- Brain metastasis (yes, no);
- Metastases to liver (yes, no);
- Metastases to adrenals (yes, no);
- Metastases to bone (yes, no);
- Number of prior lines of drug therapy (1, 2, 3);
- Prior treatment with anti-PD-1/PD-L1 drugs (yes, no);
- Prior treatment with platinum-containing drugs (yes, no);
- Prior treatment with anti-PD-1/PD-L1 and platinum-containing drugs (yes, no);
- PD-L1 expression level (low expression, medium expression, high expression).

2.6 Pooling of Study Centers

This is a multicenter trial, and data from all centers will be pooled for analysis, without considering center effects.

3 Definition and Derivation Rules for Variables

3.1 Subject Demographics

3.1.1 Prior/Concomitant Medical History

Prior medical history refers to medical history that had resolved at screening, while concomitant medical history refers to medical history that was ongoing at screening. This is determined by the "Ongoing" field on the "Other Medical History" page in the CRF.

3.1.2 Prior/Concomitant Medications

Prior medications refer to non-investigational products that were discontinued before the first dose of GFH375.

Concomitant medications refer to non-investigational products that meet one of the following conditions:

- Started before the first dose of GFH375 and continued after the first dose of GFH375;
- Started on or after the day of the first dose of GFH375.

In addition, if "Yes" is selected for "Ongoing" on the "Prior/Concomitant Medications" page of the CRF, it can be determined to be a concomitant medication.

3.1.3 Prior/Concomitant Non-drug Therapies

Prior non-drug therapies refer to non-drug therapies with a start date before the first dose of GFH375.

Concomitant non-drug therapies refer to non-drug therapies that meet one of the following conditions:

- Started before the first dose of GFH375 and continued after the first dose of GFH375;
- Started on or after the day of the first dose of GFH375.

In addition, if "Yes" is selected for "Ongoing" on the "Prior/Concomitant Non-drug Therapies" page of the CRF, it can be determined to be a concomitant non-drug therapy.

3.2 Efficacy Endpoints

The endpoint indicators in this study are assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Best overall response (BOR) is the best response from the start of the first dose of GFH375 until PD, death from any cause, or the start of new anti-tumor therapy (whichever occurs first). If the start date of the new anti-tumor therapy is the same as the assessment date, the assessment will be considered to have occurred before the start of the new anti-tumor therapy. If a subject has no record of PD or new anti-tumor therapy, all assessment results can be used to determine their BOR. The confirmation criteria for best overall response (BOR) are as follows:

- Confirmed CR: Assessed as CR at least once, and confirmed as CR again in a subsequent assessment (at least 4 weeks later), with no evidence of PD in between.
- Confirmed PR: Assessed as PR at least once, and confirmed as PR or CR again in a subsequent assessment (at least 4 weeks later), with no evidence of PD in between.
- SD: To be assessed as SD, the subject must have had at least 6 weeks (42 days) of follow-up after the first dose of GFH375, and not meet the criteria for CR or PR. If the minimum time criterion is not met, SD will not be recognized. For example, if a patient is assessed as SD on Day 30, it cannot be determined as SD because the condition of ≥42 days is not met.
- PD: Not assessed as confirmed CR, PR, or SD before PD or new anti-tumor therapy, and PD occurs before 91 days (2*6 weeks + 1 week) after the first dose of GFH375.
- NE: No post-baseline tumor assessment; post-baseline tumor assessments have been performed, but none can be judged as CR, PR, SD, or PD; post-baseline tumor assessments have been performed, but occur after new anti-tumor therapy; SD does not meet the minimum of 6 weeks after the first dose of GFH375 and there is no subsequent tumor assessment; PD occurs after 91 days (2*6 weeks + 1 week) after the first dose of GFH375,

and there is no tumor assessment during this period.

3.2.1 Objective Response Rate (ORR)

For the definition of ORR, see section **4.2.1**.

3.2.2 Disease Control Rate (DCR)

For the definition of DCR, see section **4.2.2**.

3.2.3 Progression-Free Survival (PFS)

For the definition of PFS, see section **4.2.3**.

The calculation of PFS will always be based on the imaging examination date corresponding to the efficacy assessment, not the visit or efficacy assessment date. The calculation of TTR and DoR is similar. If imaging examinations within a visit are completed on multiple dates, the following rules will be applied to select the analysis date:

- The date of PD will be determined by the earliest date of the imaging examination of the lesion corresponding to the PD event. For example, for PD based on a new lesion according to RECIST v1.1 criteria, the PD date is the date of the imaging examination where the new lesion was first detected.
- For subjects who have not experienced PD, the censoring date will be determined by the latest imaging examination date within that visit.

For subjects who experience PD or death, the PFS is calculated as: PFS (months) = (Date of earliest imaging examination corresponding to PD or date of death - Date of first dose of GFH375 + 1) / 30.4375.

For censored subjects, the PFS is calculated as: PFS (months) = (Censoring date - Date of first dose of GFH375 + 1) / 30.4375. The censoring rules are shown in Table 7:

Table 7 PFS Censoring Rules

#	Scenario	PD or Censoring Date	Outcome
1	No post-baseline tumor assessment, and death occurs within the first two tumor assessment cycles	Date of death	PD
2	No post-baseline tumor assessment, and no death within the first two tumor assessment cycles	Date of first dose of GFH375	Censored
3	Post-baseline tumor assessment, no PD or death	Date of last valid imaging examination	Censored
4	Post-baseline tumor assessment; PD at first assessment, and the assessment date is more than two consecutive assessment cycles after the first dose date	Date of first dose of GFH375	Censored
5	Post-baseline tumor assessment; PD at first assessment, and the date of first progression is less than or equal to two consecutive assessment cycles after the first dose	Date of PD	PD
6	Post-baseline tumor assessment; PD occurs (not at first assessment), but the date of first PD is more than two	Date of the last valid imaging examination before the date of PD	Censored

	consecutive assessment cycles after the date of the previous imaging examination		
7	Post-baseline tumor assessment; PD occurs (not at first assessment), and the date of first PD is less than or equal to two consecutive assessment cycles after the date of the previous imaging examination	Date of PD	PD
8	Post-baseline tumor assessment; death before PD, and the date of death is more than two consecutive assessment cycles after the date of the previous imaging examination	Date of the last valid imaging examination before death	Censored
9	Post-baseline tumor assessment; death before PD, and the date of death is less than or equal to two consecutive assessment cycles after the date of the previous imaging examination	Date of death	PD
10	Received new anti-tumor therapy before PD or death	Date of the last valid imaging examination on or before the day of receiving new anti-tumor therapy (if no imaging examination, then the date of the first dose of GFH375)	Censored

The rule for determining two consecutive missed/invalid tumor assessment visits is as follows:

- If there is no tumor assessment after the first dose of GFH375, two consecutive missed/invalid tumor assessments are defined as 91 days (2*6 weeks + 7-day window) after the first dose of GFH375;
- If there are tumor assessments after the first dose of GFH375:
  - If PD/death occurs within 48 weeks of the first dose of GFH375, two consecutive missed/invalid tumor assessments are 98 days (2*(6 weeks + 7-day window)) after the previous tumor assessment;
  - If PD/death occurs after 48 weeks of the first dose of GFH375, but the last imaging assessment before PD/death occurred within 48 weeks of the first dose of GFH375, two consecutive missed/invalid tumor assessments are 140 days (6 weeks + 7-day window + 12 weeks + 7-day window) after the previous tumor assessment;
  - If PD/death occurs after 48 weeks of the first dose of GFH375, and the last imaging assessment before PD/death also occurred after 48 weeks of the first dose of GFH375, two consecutive missed/invalid tumor assessments are 182 days ([2*(12 weeks + 7-day window)]) after the previous tumor assessment.

3.2.4 Duration of Response (DoR)

For the definition of DoR, see section **4.2.4**. The end date of DoR should be consistent with the date of PD or death from any cause for the PFS event. For subjects who meet the response criteria and do not experience subsequent PD, the censoring time for their duration of response is the same as the

PFS censoring time (see Section 3.2.3).

For subjects with a BOR of confirmed CR or PR, the DoR is calculated as: DoR (months) = (Date of PD or death or censoring date - Date of imaging examination corresponding to the first confirmed CR or PR + 1) / 30.4375. DoR will also be calculated without requiring confirmation of CR or PR.

3.2.5 Time to Response (TTR)

For the definition of TTR, see section **4.2.5**.

For subjects with a BOR of confirmed CR or PR, the TTR is calculated as: TTR (months) = (Date of imaging examination corresponding to the first confirmed CR or PR - Date of first dose of GFH375 + 1) / 30.4375. TTR will also be calculated without requiring confirmation of CR or PR.

3.2.6 Overall Survival (OS)

For the definition of OS, see section **4.2.6**.

Overall survival (months) = (Date of death/censoring date - Date of first dose of GFH375 + 1) / 30.4375.

3.3 PK Endpoints

The non-compartmental analysis module in Phoenix WinNonlin (version 8.2 or later) software will be used to calculate PK parameters from blood concentration data based on actual sampling times. PK parameters include: C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, T_{max}, T_{last}, $t_{1/2}$, V_z/F, CL/F, λ_z, MRT, $AUC_{\%_Extrap}$, $C_{trough,ss}$, $C_{max,ss}$, $AUC_{0\text{-}t,ss}$, $AUC_{0\text{-}tau,ss}$, $AUC_{0\text{-}inf,ss}$, CL/F_{ss}, V_z/F_{ss}, R_{ac_Cmax}, $R_{ac_Ctrough}$, R_{ac_AUC}. For the specific definitions and calculation methods of PK parameters, see Table 11 in section **4.4.2**. The planned PK blood sampling time points are shown in 错误!未找到引用源。 8 and 错误!未找到引用源。 9.

Table 8 Phase I PK Sample Collection Schedule

Cycle	Day	Planned Sampling Time Point (h)	Time Window
1	1	Predose	-1 h
1	1	1 h postdose	±5min
1	1	2 h postdose	±10min
1	1	4 h postdose	±15min
1	1	6 h postdose	±30min
1	1	8 h postdose	±30min
1	1[1]	12 h postdose	±30min
1	2[2]	24 h postdose	±1h
1	3[2]	48 h postdose	±2h
1	4[2]	72 h postdose (collected before dosing on D4)	±3h
1	8	Predose	-1h
1	15	Predose	-1h
1	21	Predose	-1h
1	21	1 h postdose	±5min
1	21	2 h postdose	±10min
1	21	4 h postdose	±15min

1	21	6 h postdose	±30min
1	21	8 h postdose	±30min
1	21[1]	12 h postdose	±30min
1	21[2]	24 h postdose	±1h
2	10	Predose	-1h
4	1	Predose	-1h
5	1	Predose	-1h
6	1	Predose	-1h

1. If BID dosing is used, the PK samples at 12 h postdose on C1D1 and C1D21 must be collected before the second dose of the day. 2. Only applicable to QD dosing, collection is required before dosing.

Table 9 Phase II PK Sample Collection Schedule

Cycle	**Day**	**Planned Sampling Time Point (h)**	**Time Window**
1	10	Predose	-1 h
1	10	Postdose	2-4 h
2	1	Predose	-1 h
2	1	Postdose	1-3 h
3	1	Predose	-1 h
3	1	Postdose	2-4 h
4	1	Predose	-1 h
5	1	Predose	-1 h
6	1	Predose	-1 h

3.4 Safety Analysis

3.4.1 Study Treatment Exposure

- Actual exposure duration (months): (Date of last dose of GFH375 - Date of first dose of GFH375 + 1) / 30.4375
- Total actual exposure dose (mg): The total dose of GFH375 actually taken by the subject during the study, which is the sum of the total daily actual dose collected on the study drug administration record page in the eCRF.
- Number of dosing days (days): Actual exposure duration (days) - Number of days with zero actual dose (days)
- Average daily exposure (mg/day): Total actual exposure dose (mg) / Number of dosing days (days)
- Actual dose intensity (mg/day): Total actual exposure dose (mg) / Actual exposure duration (days)
- Relative dose intensity (%): 100% * Actual dose intensity (mg/day) / Planned dose intensity (mg/day). Where, the planned dose intensity (mg/day) is the treatment dose group to which the subject was assigned at enrollment. For example, the planned dose intensity for a subject assigned to the 100 mg QD dose group is 100 mg/day, and the planned dose intensity for a

subject assigned to the 300 mg BID dose group is 600 mg/day.

- Dosing compliance (%): 100% * Total actual exposure dose (mg) / Total planned exposure dose (mg). Where, the total planned exposure dose is the sum of the total daily planned dose collected on the study drug administration record page in the eCRF.

3.4.2 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an event that was not present before treatment and occurred during the treatment period (defined as from the first dose of the study drug to within 30 days after the last dose) or worsened compared to the pre-treatment state. If the AE start date for a subject is incompletely recorded, the imputation rules in section 2.3.5.6 will be used to determine if it is a TEAE.

The relationship between a TEAE and the study drug is assessed as related or not related. TEAEs related to the study drug will be defined as TEAEs that the investigator considers related, probably related, or possibly related; TEAEs unrelated to the study drug include not related and unlikely related TEAEs. If the relationship to the study drug is missing, it will be considered "related" to the study drug.

3.4.3 Laboratory Test Indicators

Laboratory tests in this study include hematology, blood chemistry, urinalysis, coagulation function, viral serology tests, and pregnancy tests.

When creating cross-tabulations of the clinical evaluation (normal, abnormal but not clinically significant, abnormal and clinically significant) for each test, the worst post-baseline result is defined as the worst clinical assessment of the subject at all post-baseline visits (including scheduled and unscheduled visits), with results ranked from best to worst as normal, abnormal but not clinically significant, and abnormal and clinically significant.

3.4.4 Vital Signs, Physical Examination, and ECGs

3.4.4.1 Vital Signs

Vital sign assessments include body temperature (°C), pulse (beats/min), respiration (breaths/min), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg).

When creating cross-tabulations of the clinical evaluation of vital signs (normal, abnormal but not clinically significant, abnormal and clinically significant), the worst post-baseline result is defined as the worst clinical assessment of the subject at all post-baseline visits (including scheduled and unscheduled visits), where "normal" is better than "abnormal but not clinically significant", and "abnormal but not clinically significant" is better than "abnormal and clinically significant". In

addition, whether there are abnormal changes in the subject's post-dosing vital sign indicators will be determined according to Table 10.

Table 10 Criteria for Determining Significant Changes in Vital Sign Indicators from Baseline

	Above normal	**Below normal**
Systolic blood pressure (mmHg)	Increase from baseline >=20 and value >=160	Decrease from baseline >=20 and value <=90
Diastolic blood pressure (mmHg)	Increase from baseline >=10 and value >=100	Decrease from baseline >=10 and value <=50
Pulse (beats/min)	Increase from baseline >25% and value >120	Decrease from baseline >25% and value <50
Respiration (breaths/min)	Measured value < 8	Measured value > 35
Body temperature (C)	Measured value >=39.1	-

3.4.4.2 Physical Examination

A complete physical examination includes general condition, skin, neck (thyroid), eyes, ears, nose, throat, chest (including lungs), heart, abdomen, back, lymph nodes, extremities, and vascular and nervous systems; breast, pelvic, rectal, and external genitalia examinations will be performed if clinically indicated. When creating cross-tabulations of the clinical evaluation of physical examinations (normal, abnormal but not clinically significant, abnormal and clinically significant), the worst post-baseline result is defined as the worst clinical assessment of the subject at all post-baseline visits (including scheduled and unscheduled visits), where “normal” is better than “abnormal but not clinically significant”, and “abnormal but not clinically significant” is better than “abnormal and clinically significant”.

3.4.4.3 ECGs

12-lead ECG assessments include: heart rate (HR), PR interval, QRS interval, QT interval, and QTcF (Fridericia's formula) interval, and overall clinical significance assessment.

If multiple assessments are performed during the same visit, the mean of the quantitative results will be used for analysis. In addition, all 12-lead ECG results will be listed.

When creating cross-tabulations of the clinical evaluation of ECGs (normal, abnormal but not clinically significant, abnormal and clinically significant), the best result of multiple measurements will be used for baseline, and the worst result of multiple measurements will be used for post-baseline visits. The worst post-baseline result is defined as the worst clinical assessment of the subject at all post-baseline visits (including scheduled and unscheduled visits), where “normal” is better than “abnormal but not clinically significant”, and “abnormal but not clinically significant” is better than “abnormal and clinically significant”. In addition, whether there are abnormal changes in the subject's

post-dosing ECG indicators will be determined according to Table 11.

Table 11 Criteria for Determining Significant Changes in ECG Indicators from Baseline

	Above normal	Below normal
QTcF (ms)	Value >450 and <=480	-
	Value >480 and <=500	-
	Value >=501	-
QTcF (ms) maximum change from baseline	Increase from baseline >30 and <=60	-
	Increase from baseline >60	-
Heart rate (beats/min)	Increase from baseline >25% and value >=100	Decrease from baseline >25% and value <=50
PR (ms)	Increase from baseline >25% and value >200	Decrease from baseline >25% and value <120
QRS (ms)	Increase from baseline >25% and value >110	-

3.4.5 Other Safety Indicators

Other safety indicators include the ECOG score.

3.5 Biomarker Indicators

Biomarker indicators include only CA19-9 for Phase II PDAC subjects.

4 Statistical Analysis

Unless otherwise specified, the Phase I and Phase II data of this study will be analyzed separately. The Phase I data will be analyzed and summarized by different dose levels and dosing regimens; the Phase II data will be analyzed and summarized by tumor type. Unless otherwise specified, the same statistical methods will be used to analyze the Phase I and Phase II data.

For post hoc analyses, in Phase I subjects, demographic and baseline characteristics, as well as efficacy, will also be analyzed by tumor type. The ORR across different tumor types at the target dose will be summarized.

4.1 Subject General Characteristics

4.1.1 Subject Disposition

Based on all subjects who have signed the informed consent form, the number and percentage of subjects who have been successfully screened and who failed screening will be summarized, and the reasons for screening failure will be summarized by category. Based on successfully screened subjects, the number and percentage of subjects in each analysis set will be summarized, and the number and percentage of subjects in the Phase I dose-escalation and backfilling cohorts will also be summarized. In addition, based on the FAS, the main reasons for treatment discontinuation and study termination will be summarized by category. The above analyses will be summarized separately for Phase I and

Phase II data.

A listing of screening and screening failure reasons, treatment discontinuation, and study termination will be provided for all subjects.

4.1.2 Protocol Deviations

To measure how well the protocol is followed, all protocol deviations will be determined before database lock based on the information collected and in conjunction with the protocol requirements. These protocol deviations will be evaluated by the study team and classified as major or minor protocol deviations. Based on successfully screened subjects, all major protocol deviations will be summarized.

In addition, based on successfully screened subjects, a listing of all protocol deviations will be provided.

4.1.3 Demographics and Baseline Characteristics

Based on the FAS, descriptive statistics will be performed on the subjects' demographics and baseline characteristics. The indicators to be counted include:

Demographics

- Sex
- Age
- Age group (<65 and >=65 years, <60 and >=60 years)
- Race: Han, Other
- Body height
- Baseline weight
- Baseline body mass index (BMI) = weight (kg) / (body height (cm) / 100)^2, rounded to 1 decimal place.

Baseline Characteristics

- Baseline tumor diagnosis information
  - Diagnosis name: non-small cell lung cancer (NSCLC), ductal adenocarcinoma of pancreas (PDAC), colorectal cancer (CRC), bile duct cancer, endometrial cancer, other
  - Pathological type (applicable to NSCLC, PDAC, and CRC)
  - Histological grade: G1 (well-differentiated), G2 (moderately differentiated), G3 (poorly differentiated), G4 (undifferentiated), not assessed, other
  - Tumor stage at enrollment
  - TNM stage at enrollment - T stage

- TNM stage at enrollment - N stage
- TNM stage at enrollment - M stage
- Presence of metastasis at enrollment
- Metastatic sites at enrollment

- Duration of disease (months) = (Date of first dose of GFH375 - Date of initial pathological diagnosis + 1) / 30.4375
- PD on last line of therapy: Yes, No
- Time from PD on last line of therapy to first treatment (months) = (Date of first dose of GFH375 - Date of last PD + 1) / 30.4375
- Time from PD on last line of therapy to first treatment category: <1 month, 1-3 months, 3-6 months, ≥6 months
- ECOG performance status score: 0, 1
- Smoking history: Never smoked, former smoker, current smoker (Phase II NSCLC subjects)
- PD-L1 expression level at baseline (applicable to NSCLC): Low expression (TPS<1%), Medium expression (TPS 1-49%), High expression (TPS>=50%), Non-TPS, Unknown
- KRAS G12D mutation status: Negative, Positive, Unknown
- KRAS G12D mutation rate: <5%, 5-20%, 20-50%, ≥50%
- NRS score: 0, 1, 2, 3

In addition, based on the FAS, a listing of subject demographics and baseline characteristics will be provided.

4.1.4 Prior and Concomitant Medical History

The Medical Dictionary for Regulatory Activities (MedDRA version 26.0 or later) will be used to code the prior and concomitant medical history of subjects. Based on the FAS, the number and percentage of subjects in each disease category will be summarized by System Organ Class (SOC) and Preferred Term (PT).

Based on the FAS, a listing of all prior and concomitant medical history details will be provided.

4.1.5 Prior and Concomitant Therapies

4.1.5.1 Prior and Concomitant Medications

The World Health Organization Drug Dictionary (WHODrug, version B3 March 1, 2023 or later) will be used to code the prior and concomitant medications of subjects. Based on the FAS, the number and percentage of subjects will be calculated according to the Anatomical Therapeutic Chemical (ATC) classification level II and Preferred Name (PN).

Based on the FAS, listings of prior and concomitant medication data will be provided.

4.1.5.2 Prior/Concomitant Non-drug Therapies

MedDRA version 26.0 or later will be used to code all prior/concomitant non-drug therapies for subjects. Based on the FAS, prior and concomitant non-drug therapies will be summarized by SOC and PT.

In addition, a listing of all prior/concomitant non-drug therapy information will be provided.

4.1.5.3 Prior Anti-tumor Therapy History

Based on the FAS, the following prior anti-tumor therapy categories will be summarized.

- Summary of prior anti-tumor drug therapy history:
  - History of prior anti-tumor therapy: Yes, No
  - Total number of prior lines of drug therapy: 0, 1, 2, 3, ≥4
  - Type of last line of drug therapy: 1st line, 2nd line, 3rd line, 4th line, 5th line, ≥6th line, adjuvant, neoadjuvant, unknown, other
  - Best response to last line of drug therapy: Complete Response (CR), Partial Response (PR), Stable Disease (SD), PD (PD), Not Assessed (NA), Not Evaluable (NE), Unknown (UN)
  - Reason for discontinuation of last line of drug therapy: Completed treatment plan, PD/relapse, intolerable toxicity, other
  - Time from end of last line of drug therapy to first dose of GFH375 (months)
- Summary of prior anti-tumor surgery history (excluding surgery for diagnostic purposes):
  - History of prior anti-tumor surgery: Yes, No
  - Purpose of last surgery: Palliative, curative, other
  - Time from last surgery to first dose of GFH375 (months)
- Summary of prior anti-tumor radiotherapy history:
  - History of prior anti-tumor radiotherapy: Yes, No
  - Site of prior radiotherapy
  - Purpose of prior radiotherapy: Neoadjuvant, adjuvant, palliative, curative, other
  - Best response to last radiotherapy: Complete Response (CR), Partial Response (PR), Stable Disease (SD), PD (PD), Not Assessed (NA), Not Evaluable (NE), Unknown (UN)
  - Reason for discontinuation of last radiotherapy: Completed treatment plan, PD/relapse, intolerable toxicity, other
  - Time from end of last radiotherapy to first dose of GFH375 (months)

The World Health Organization Drug Dictionary (WHODrug, version B3 March 1, 2023 or later) will be used to code the prior anti-tumor therapy drugs of subjects. Based on the FAS, the number and percentage of subjects will be calculated according to the ATC classification level II and PN.

MedDRA version 26.0 or later will be used to code all prior anti-tumor surgery for subjects. Based on the FAS, prior anti-tumor surgery will be summarized by SOC and PT. In addition, a listing of all prior anti-tumor therapy related information for subjects will be provided.

4.1.5.4 Subsequent Anti-tumor Therapy

Based on the FAS, information related to subjects' new anti-tumor therapies will be summarized, including:

- Number and percentage of subjects who received subsequent new anti-tumor therapy
- Time from end of study treatment to start of new anti-tumor therapy (months) = (Start date of new anti-tumor therapy - Date of last dose of GFH375 + 1) / 30.4375
- Therapy category: drug therapy, radiotherapy, surgery

The World Health Organization Drug Dictionary (WHODrug, version B3 March 1, 2023 or later) will be used to code the subsequent anti-tumor therapy drugs of subjects. Based on the FAS, the number and percentage of subjects will be calculated according to the ATC classification level II and PN.

MedDRA version 26.0 or later will be used to code all subsequent anti-tumor surgery for subjects. Based on the FAS, subsequent anti-tumor surgery will be summarized by SOC and PT.

In addition, a listing of detailed information on subjects' subsequent anti-tumor therapies will be provided.

4.2 Efficacy Analysis

4.2.1 Objective Response Rate (ORR)

4.2.1.1 Primary Analysis

The same analysis method will be used for Phase I and Phase II subjects.

Definition of Estimand:

- **Treatment:** GFH375.
- **Study Population:** Subjects with advanced solid tumors with KRAS G12D mutation (FAS).
- **Variable:** Whether confirmed CR or PR is achieved, as assessed by RECIST 1.1 criteria. If a subject has no post-baseline assessment results, the subject will be considered a non-responder. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.

- **Intercurrent Events and Handling Strategy:**

Intercurrent Event		**Handling Strategy**
Inc1	Start of new anti-tumor therapy	On-treatment strategy (Assessment results after the start of anti-tumor therapy will not be included in the analysis)

- **Population-level Summary:** ORR and its 90% and 95% CIs.

Analysis Method of Estimand:

The BOR of subjects will be summarized, the number of subjects who have achieved confirmed CR or PR and the ORR of subjects will be summarized, and the Clopper-Pearson exact method will be used to estimate the 90% and 95% CIs for the ORR. At the same time, BOR and ORR will be summarized without requiring confirmation of CR or PR, and the 90% and 95% CI for ORR will be provided. BOR and ORR will be analyzed based on subjects with measurable lesions at baseline as assessed by the investigator or BIRC. In addition, a swimmer plot of efficacy assessment results during treatment for all subjects, a waterfall plot of the minimum percentage change from baseline in the sum of diameters of target lesions, and a spider plot of the percentage change from baseline in the sum of diameters of target lesions at different time points during treatment for all subjects will be generated. For NSCLC and PDAC subjects, the consistency of BOR results between BICR and investigator assessments will be summarized.

4.2.1.2 Supportive Analysis

1) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC subjects in the FAS.
- **Variable:** Whether confirmed CR or PR is achieved, as assessed by the investigator according to RECIST 1.1 criteria. If a subject has no post-baseline assessment results, the subject will be considered a non-responder.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

2) Adjustments to the study population

- **Study Population:** Phase II subjects with advanced solid tumors with KRAS G12D mutation (PPS).
- **Other Attributes:** Same as the primary analysis.

Except for plotting, the analysis method is the same as the primary analysis.

3) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC subjects in the Phase II PPS.

- **Variable:** Whether confirmed CR or PR is achieved, as assessed by the investigator according to RECIST 1.1 criteria. If a subject has no post-baseline assessment results, the subject will be considered a non-responder.
- **Other Attributes:** Same as the primary analysis.

Except for plotting, the analysis method is the same as the primary analysis.

4.2.1.3 Subgroup Analysis

For Phase II PDAC and NSCLC subjects, a subgroup analysis of ORR will be performed based on the results assessed by BICR where CR/PR requires confirmation, and the results of the subgroup analysis will be displayed in a forest plot. For specific subgroups, see section **2.5**.

4.2.2 Disease Control Rate (DCR)

4.2.2.1 Primary Analysis

The same analysis method will be used for Phase I and Phase II subjects.

Definition of Estimand:

- **Variable:** The percentage of subjects who have achieved confirmed CR or PR, SD, as assessed by RECIST 1.1 criteria. If a subject has no post-baseline assessment results, the subject will be considered as not having achieved CR/PR/SD. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Population-level Summary:** DCR and its 90% and 95% CIs.
- **Other Attributes:** Same as the estimand for the primary analysis of objective response rate.

Analysis Method of Estimand:

The number of subjects who have achieved confirmed CR or PR, SD in BOR, and the DCR will be summarized. The Clopper-Pearson exact method will be used to estimate the two-sided 90% and 95% CI for the DCR. At the same time, without requiring confirmation of CR or PR, the number of subjects who have achieved CR or PR, SD in BOR, and the DCR will be summarized, and the 90% and 95% CI for the DCR will be provided. BOR and DCR will be analyzed based on subjects with measurable lesions at baseline as assessed by the investigator or BIRC.

4.2.2.2 Supportive Analysis

1) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC subjects in the FAS.
- **Variable:** Whether confirmed CR or PR, SD is achieved, as assessed by the investigator

according to RECIST 1.1 criteria. If a subject has no post-baseline assessment results, the subject will be considered as not having achieved CR/PR/SD.

- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

2) Adjustments to the study population

- **Study Population:** Phase II subjects with advanced solid tumors with KRAS G12D mutation (PPS).
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

3) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC subjects in the Phase II PPS.
- **Variable:** Whether confirmed CR or PR, SD is achieved, as assessed by the investigator according to RECIST 1.1 criteria. If a subject has no post-baseline assessment results, the subject will be considered as not having achieved CR/PR/SD.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

4.2.3 Progression-Free Survival (PFS)

4.2.3.1 Primary Analysis

The same analysis method will be used for Phase I and Phase II subjects.

Definition of Estimand:

- **Treatment:** GFH375.
- **Study Population:** Subjects with advanced solid tumors with KRAS G12D mutation (FAS).
- **Variable:** Time from the first dose of GFH375 to the first occurrence of PD or death from any cause, whichever occurs first. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Intercurrent Events and Handling Strategy:**

Intercurrent Event		**Handling Strategy**
Inc2	Subjects who have received new anti-tumor therapy without PD or death.	Hypothetical strategy (Censored at the date of the last valid imaging examination before the start of new anti-tumor therapy)
Inc3	The date of PD or death is more than two consecutive assessment cycles after the date of the previous imaging examination	Hypothetical strategy (Censored at the date of the last valid imaging examination before two or more consecutive missed assessments; if there are no prior valid imaging

		examination results, censored at the date of the first dose of GFH375)

- **Population-level Summary:** Quartiles of PFS and PFS rates at different time points.

Analysis Method of Estimand:

The occurrence of events and censoring for subjects will be summarized. The Kaplan-Meier method will be used to estimate the quartiles of PFS and the two-sided 90% and 95% CI estimated using the Brookmeyer and Crowley method, and the PFS rate and its two-sided 90% and 95% CI at each time point will be calculated. The Kaplan-Meier survival curve will be plotted.

In addition, the Reverse Kaplan-Meier method will be used to estimate the median follow-up time for PFS and the two-sided 90% and 95% CI will be estimated using the Brookmeyer and Crowley method. The follow-up time for PFS refers to the time from the first dose of GFH375 to the last tumor assessment. If PD or death occurs, the PFS follow-up time will be censored at the date of PD or death (whichever occurs first).

For the Phase I stage, when the sample size of the analysis group is less than 10, PFS will be listed individually for each subject and will not be analyzed using the Kaplan-Meier method.

4.2.3.2 Supportive Analysis

1) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC subjects in the FAS.
- **Variable:** Based on the investigator's assessment, the time from the first dose of GFH375 to the first occurrence of PD or death from any cause, whichever occurs first.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

4.2.4 Duration of Response (DoR)

4.2.4.1 Primary Analysis

Definition of Estimand:

- **Treatment:** GFH375.
- **Study Population:** Subjects in the FAS who have achieved confirmed CR or PR in BOR. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Variable:** Time from the first achievement of CR or PR to the first occurrence of PD or death from any cause, whichever occurs first. Note: For NSCLC and PDAC, the results will be

based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.

- **Intercurrent Events and Handling Strategy:** Same as for PFS.
- **Population-level Summary:** Quartiles of DoR and DoR rates at different time points.

Analysis Method of Estimand:

The occurrence of events and censoring for subjects will be summarized. The Kaplan-Meier method will be used to estimate the quartiles of DoR and the two-sided 90% and 95% CI estimated using the Brookmeyer and Crowley method, and the DoR rate and its two-sided 90% and 95% CI at each time point will be calculated. The Kaplan-Meier survival curve will be plotted. DoR will be analyzed based on subjects with measurable lesions at baseline as assessed by the investigator or BIRC.

For the Phase I stage, when the sample size of the analysis group is less than 10, DoR will be listed individually for each subject and will not be analyzed using the Kaplan-Meier method.

4.2.4.2 Supportive Analysis

1) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC subjects in the FAS who have achieved confirmed CR or PR in BOR, based on the investigator's assessment.
- **Variable:** Based on the investigator's assessment, the time from the first achievement of CR or PR to the first occurrence of PD or death from any cause, whichever occurs first.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

2) Adjustments to the study population

- **Study Population:** Subjects in the FAS who have achieved CR or PR in BOR, where CR and PR do not require confirmation according to RECIST 1.1 rules. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

3) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC subjects in the FAS who have achieved CR or PR in BOR based on the investigator's assessment, where CR and PR do not require confirmation according to RECIST 1.1 rules.

- **Variable:** Based on the investigator's assessment, the time from the achievement of CR or PR to the first occurrence of PD or death from any cause, whichever occurs first.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

4.2.5 Time to Response (TTR)

4.2.5.1 Primary Analysis

Definition of Estimand:

- **Treatment:** GFH375.
- **Study Population:** Subjects in the FAS who have achieved confirmed CR or PR. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Variable:** Time from the start of study drug administration to the first achievement of confirmed CR or PR, based on the earliest time CR or PR is observed. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Intercurrent Events and Handling Strategy:** Same as for ORR.
- **Population-level Summary:** Mean, standard deviation, median, Q1, Q3, minimum, and maximum.

Analysis Method of Estimand:

A descriptive analysis of TTR will be performed, including the number of subjects who have achieved CR or PR, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

For the Phase I stage, when the sample size of the analysis group is less than 10, TTR will be listed individually for each subject.

4.2.5.2 Supportive Analysis

1) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC subjects in the FAS who have achieved confirmed CR or PR in BOR, based on the investigator's assessment.
- **Variable:** Based on the investigator's assessment, the time from the start of study drug administration to the first achievement of confirmed CR or PR, based on the earliest time CR or PR is observed.

- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

2) Adjustments to the study population

- **Study Population:** Subjects in the FAS who have achieved CR or PR in BOR, where CR and PR do not require confirmation according to RECIST 1.1 rules. Note: For NSCLC and PDAC, the results will be based on the assessment by the Blinded Independent Central Review Committee (BICR); for other tumor types, the results will be based on the investigator's assessment.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

3) Adjustments to the study population and variable

- **Study Population:** NSCLC and PDAC subjects in the FAS who have achieved CR or PR in BOR based on the investigator's assessment, where CR and PR do not require confirmation according to RECIST 1.1 rules.
- **Variable:** Based on the investigator's assessment, the time from the start of study drug administration to the first achievement of confirmed CR or PR, based on the earliest time CR or PR is observed.
- **Other Attributes:** Same as the primary analysis.

The analysis method is the same as the primary analysis.

4.2.6 Overall Survival (OS)

Definition of Estimand:

- **Treatment:** GFH375.
- **Study Population:** Subjects with advanced solid tumors with KRAS G12D mutation (FAS).
- **Variable:** Time from the start of study drug administration to death from any cause. For subjects in whom a death event is not observed, they will be censored at the last known date of survival.
- **Intercurrent Events and Handling Strategy:**

Intercurrent Event		**Handling Strategy**
Inc1	Start of new anti-tumor therapy	Treatment policy strategy (If death occurs, it will be treated as a death event; if no death, it will be censored at the last known date of survival)

- **Population-level Summary:** Quartiles of OS and PFS rates at different time points.

Analysis Method of Estimand:

The occurrence of events and censoring for subjects will be summarized. The Kaplan-Meier method will be used to estimate the quartiles of OS and the two-sided 90% and 95% CI estimated using the Brookmeyer and Crowley method, and the OS rate and its two-sided 90% and 95% CI at each time point will be calculated. The Kaplan-Meier survival curve will be plotted.

In addition, the Reverse Kaplan-Meier method will be used to estimate the median OS follow-up time and the two-sided 90% and 95% CI will be estimated using the Brookmeyer and Crowley method. OS follow-up time refers to the time from the start of study drug administration to the last known date of survival. If death occurs, the OS follow-up time will be censored at the date of death.

For the Phase I stage, when the sample size of the analysis group is less than 10, OS will be listed individually for each subject and will not be analyzed using the Kaplan-Meier method.

4.3 Safety Analysis

DLT analysis will be based on the DDS, and all other safety analyses will be based on the SS.

4.3.1 Drug Exposure

Descriptive statistics will be performed on the actual exposure duration (months), total actual exposure dose (mg), number of dosing days (days), average daily exposure (mg/day), actual dose intensity (mg/day), relative dose intensity (%), and dosing compliance (%) of GFH375. Relative dose intensity and dosing compliance will be categorized and summarized as < 80%, 80% to 120%, and >120%.

The number and percentage of subjects who have planned dose adjustments and dose reductions will be summarized, and the corresponding reasons will be provided. A planned dose adjustment refers to a change in the planned dose compared to the previous planned dose. A planned dose reduction refers to a planned dose that is less than the previous non-zero planned dose (i.e., the comparison between two planned doses does not consider drug holidays in between), and the reduced planned dose is not zero. The number and percentage of subjects whose actual administered dose is inconsistent with the planned dose will be summarized, and the corresponding reasons will be provided.

The number of occurrences of planned dose reductions and planned dose interruptions will be summarized, and the number and percentage of subjects for different numbers of occurrences will also be summarized.

The GFH375 medication status of subjects will be listed.

4.3.2 Dose-Limiting Toxicities (DLTs)

The number and percentage of subjects who have experienced DLTs in the Phase I study will be summarized, and the types of DLTs will also be summarized.

DLTs will be coded using MedDRA version 26.0 or later. The number and percentage of DLTs will be

summarized by SOC, PT, and severity.

Based on a prior non-informative probability distribution of $beta$ (0.05, 0.05), the posterior probability distribution for the DLT rate in each group is $beta$ $(y_j + 0.05, n_j - y_j + 0.05))$, and the posterior mean DLT rate for each group is then calculated. The formula for calculating the posterior mean DLT rate is $p_j = \frac{y_j+0.05}{n_j+0.1}$, where n_j is the number of subjects in each group, and y_j is the number of subjects who have experienced a DLT in each group.

The DLT rate and the posterior mean DLT rate for each group will be estimated using isotonic regression, where the weight for the DLT rate is the number of subjects in each group, and the weight for the posterior mean DLT rate is the reciprocal of the posterior distribution variance (according to the BOIN design)$w_j = \frac{(n_j+0.1)^2 (n_j+0.1+1)}{(y_j+0.05)(n_j-y_j+0.05)}$, where n_j is the number of subjects in each group, and y_j is the number of subjects who have experienced a DLT in each group.

All DLTs will be listed.

4.3.3 Adverse Events

AEs will be coded using MedDRA version 26.0 or later, and the severity of AEs will be graded based on NCI CTCAE V5.0. TEAEs will be summarized in tables and all AEs will be listed.

The number and percentage of subjects will be summarized based on the following categories:

- TEAE
  - Any TEAE
  - TEAE of CTCAE Grade 3 or higher
  - TEAE leading to dose reduction of GFH375
  - TEAE leading to dose interruption of GFH375
  - TEAE leading to discontinuation of GFH375
  - Treatment-emergent serious adverse event (TESAE)
  - TEAE of CTCAE=Grade 5
  - TEAE meeting Hy's Law criteria
- TEAE related to GFH375 (TRAE)
  - Any TRAE
  - TRAE of CTCAE Grade 3 or higher
  - TRAE leading to dose reduction of GFH375
  - TRAE leading to dose interruption of GFH375

- TRAE leading to discontinuation of GFH375
- Treatment-related serious adverse event during treatment (TRSAE)
- TRAE of CTCAE=Grade 5
- TRAE meeting Hy's Law criteria

The number and percentage of subjects who have experienced the following types of events will be summarized by SOC, PT, and severity:

- TRAE
- TEAE
- TEAE of CTCAE Grade 3 or higher
- TRAE of CTCAE Grade 3 or higher
- TESAE
- TRSAE
- TEAE leading to dose reduction of GFH375
- TRAE leading to dose reduction of GFH375
- TEAE leading to dose interruption of GFH375
- TRAE leading to dose interruption of GFH375
- TEAE leading to discontinuation of GFH375
- TRAE leading to discontinuation of GFH375
- TEAE meeting Hy's Law criteria
- TRAE meeting Hy's Law criteria

The number and percentage of subjects who have experienced the following types of events will be summarized by SOC and PT:

- TEAE
- TRAE
- TESAE of CTCAE Grade 3 or higher
- TRSAE of CTCAE Grade 3 or higher
- TEAE of CTCAE Grade 3 or higher leading to dose reduction of GFH375
- TRAE of CTCAE Grade 3 or higher leading to dose reduction of GFH375
- TEAE of CTCAE Grade 3 or higher leading to dose interruption of GFH375
- TRAE of CTCAE Grade 3 or higher leading to dose interruption of GFH375
- TEAE of CTCAE Grade 3 or higher leading to discontinuation of GFH375
- TRAE of CTCAE Grade 3 or higher leading to discontinuation of GFH375

- TEAE of CTCAE=Grade 5
- TRAE of CTCAE=Grade 5

The number and percentage of subjects who have experienced the following types of events will be summarized by PT:

- TEAE with an incidence of ≥10% in any group
- TRAE with an incidence of ≥10% in any group
- TEAE of CTCAE Grade 3 or higher with an incidence of ≥5% in any group
- TRAE of CTCAE Grade 3 or higher with an incidence of ≥5% in any group

The number and percentage of subjects who have experienced hepatotoxicity will be summarized by PT, including alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hepatic function abnormal, hyperbilirubinaemia, liver injury, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, and blood lactate dehydrogenase increased.

When counting the number of AE occurrences, if a subject experiences the same AE (same PT) more than once, it will be counted only once under that PT. Similarly, if a subject experiences more than one AE in the same SOC classification, it will be counted only once under that SOC classification. When summarizing AEs by severity, if the same AE occurs more than once in the same subject during the study, the one with the highest grade will be used for calculation.

All AEs will be presented in a listing. In addition, SAEs and AEs with an outcome of death will be listed separately.

4.3.4 Laboratory Tests

Viral serology test and pregnancy test results will only be listed. For other test items, the results from each visit will be analyzed with descriptive statistics and listed.

For quantitative test results, summaries will be provided for each scheduled visit and their change from baseline, calculating statistics such as number of subjects, mean, standard deviation, median, minimum, and maximum. For qualitative results of clinical assessments, a cross-tabulation will be used to show the change of the worst post-baseline result relative to the baseline result and the result at the last post-baseline visit.

For laboratory test parameters whose abnormalities can be graded for severity according to NCI CTCAE (version 5.0) (Grade 0 to 4, where Grade 0 indicates normal), such as hematology, blood chemistry, and coagulation function, a cross-tabulation will be used to summarize the maximum change in CTCAE grade from baseline and the result at the last post-baseline visit. The increase in

CTCAE grade for laboratory test parameters post-baseline will be summarized. See Appendix 1 for the CTCAE grading rules for laboratory test parameters to be evaluated. For quantitative parameters from hematology, blood chemistry, urinalysis, and coagulation function that do not have a corresponding CTCAE grade, they will be categorized according to their normal range (below normal, normal, above normal, below & above normal [both below and above normal values occurred post-baseline]). A cross-tabulation will be used to summarize the change of the worst post-baseline situation from baseline and the result at the last post-baseline visit.

Based on the liver function-related test results from blood chemistry, the number and percentage of subjects in the following categories post-baseline will be summarized (ULN: upper limit of normal):

ALT > 3 * ULN, ALT > 5 * ULN, ALT > 10 * ULN, ALT > 20 * ULN;

AST > 3 * ULN, AST > 5 * ULN, AST > 10 * ULN, AST > 20 * ULN;

(ALT or AST) > 3 * ULN, (ALT or AST) > 5 * ULN, (ALT or AST) > 10 * ULN, (ALT or AST) > 20 * ULN;

TBIL > 2 * ULN;

AKP > 1.5 * ULN;

Concurrent ALT > 3 * ULN and TBIL > 2 * ULN;

Concurrent AST > 3 * ULN and TBIL > 2 * ULN;

Concurrent (ALT or AST) > 3 * ULN and TBIL > 2 * ULN;

Concurrent (ALT or AST) > 3 * ULN and TBIL > 1.5 * ULN;

Concurrent (ALT or AST) > 3 * ULN, TBIL > 2 * ULN, and AKP ≥ 2 * ULN;

Concurrent (ALT or AST) > 3 * ULN, TBIL > 2 * ULN, and (AKP < 2 * ULN or missing).

4.3.5 Vital Signs, Physical Examination, and ECGs

4.3.5.1 Vital Signs

The observed values of vital sign test items at each scheduled visit and their change from baseline will be summarized. Based on the overall clinical evaluation of vital signs (normal, abnormal but not clinically significant, abnormal and clinically significant), a cross-tabulation of the worst post-baseline evaluation (including unscheduled visits) and the last visit relative to baseline will be summarized.

In addition, the number and percentage of subjects with abnormal changes in post-dosing ECG indicators (Table 10) will be summarized (based on the worst post-dosing result).

In addition, all vital signs measurement results for subjects will be listed.

4.3.5.2 Physical Examination

For the clinical evaluation results of physical examinations (normal, abnormal but not clinically significant, abnormal and clinically significant), a cross-tabulation of the worst post-baseline result (including unscheduled visits) and the change from baseline result at the last visit will be created.

In addition, all physical examination results for subjects will be listed.

4.3.5.3 ECGs

For quantitative test results, the observed values at each scheduled visit and their change from baseline will be summarized. For clinical significance (normal, abnormal but not clinically significant, abnormal and clinically significant), a cross-tabulation of the worst post-baseline assessment result (including scheduled and unscheduled visits) and the result relative to the baseline examination at the last visit will be created.

In addition, the number and percentage of subjects with abnormal changes in post-dosing ECG indicators (Table 11) will be summarized (based on the worst post-dosing result).

All ECG results will be presented in listings.

4.3.6 Death

The number of deceased subjects and the cause of death will be summarized by study observation period (during the study, on-treatment period, post-treatment period), and the death cases will be listed.

Deaths during the study are classified by study observation period as:

- Death during the study: Death occurring from the first study treatment to the end of the study (including survival follow-up).
- On-treatment death: Death occurring from the first study treatment to within 30 days after the last study drug administration;
  - Death after initiation of new anti-tumor therapy.
- Post-treatment death: Death occurring from more than 30 days after the last study drug administration until the end of the study.

4.3.7 Other Safety Analyses

For ECOG performance status, a cross-tabulation of the status at each scheduled visit, the worst post-baseline assessment result (including scheduled and unscheduled visits), and the result at the last visit relative to the baseline examination will be created. In addition, all ECOG score results for subjects will be listed.

4.4 PK Analysis

PK analysis will be based on the PKAS. Data below the lower limit of quantification (LLOQ) will be

marked as BQL.

PK analysis will be handled according to the following rules:

- PK parameters will be calculated based on actual sampling times;
- All blood drug concentration values below the lower limit of quantification (LLOQ) will be treated as "0" before T_{max} and as missing after T_{max} for PK parameter calculation and plotting; however, for descriptive statistical analysis, all will be treated as "0", and the number of BQLs at each time point will be noted;
- When calculating descriptive statistics for concentrations at each time point, out-of-window data will not be included; statistics such as mean, standard deviation, and coefficient of variation will only be calculated if at least two-thirds of the individual data at a specific sampling time point are at or above BQL, otherwise the descriptive statistics for that sampling point will not be calculated and will be represented as "NC". When plotting the mean drug concentration-time curve, out-of-window data will not be included; if at least one-third of the individual data at a specific post-dose sampling time point are below BQL, that point will not be displayed on the graph.

For each PK sampling cycle, if a subject meets the following conditions, the blood drug concentration data for that PK sampling cycle will not be included in the summary analysis (including descriptive statistics by group and plotting of the mean blood drug concentration-time curve), but individual blood drug concentration-time curves still need to be plotted and listed. PK parameters calculated based on this blood drug concentration data will not be included in the analysis, but will only be listed and marked.

- If the subject experiences vomiting within 3 hours after taking the investigational drug;
- Other protocol deviations or AEs that significantly affect the PK evaluation.

4.4.1 Blood Drug Concentration Analysis

In the PK analysis, concentrations will be as provided by the laboratory. Concentration data and units will be presented as the raw data received from the laboratory.

Descriptive statistics will be performed on the GFH375 blood drug concentration data according to the sampling times specified in the protocol. The Phase I summary will be presented by different dose groups and dosing frequencies, and the Phase II summary will be presented by different tumor types, including number of subjects, number of BQLs, arithmetic mean, standard deviation, arithmetic coefficient of variation (CV%), median, minimum, maximum, geometric mean, and geometric coefficient of variation (GCV%).

Drug concentration-time curves for Phase I blood drug concentration data will be plotted, including drug concentration-time curves after the first dose and multiple doses. Mean blood drug concentration-time curves (linear and semi-logarithmic) will be plotted based on planned blood sampling time points; individual blood drug concentration-time curves (linear and semi-logarithmic) will be plotted based on actual blood sampling time points.

The formula for calculating GCV% is as follows:

$$GCV\%=\sqrt{\exp^{(\ln(\text{Geo SD}))^2}-1}\times 100\%$$

The reference SAS program for GCV% is as follows:

GCV%=sqrt(exp(SD**2)-1)*100, where SD is the standard deviation of the natural logarithm of the original data.

The blood drug concentration-time data will be listed for all subjects, and BQL will be marked in the listing.

4.4.2 PK Parameter Analysis

PK parameter analysis is only for Phase I data. PK parameters will be summarized and analyzed by different dose groups and dosing frequencies, including number of subjects and missing cases, arithmetic mean, standard deviation, arithmetic coefficient of variation (CV%), median, Q1, Q3, minimum, maximum, as well as geometric mean and geometric coefficient of variation (GCV%). However, T_{max} and T_{last} will only be described by number of subjects and missing cases, median, Q1, Q3, minimum, and maximum. For specific PK parameters, see Table 12.

Table 12 List of PK Parameters

Parameter	**WNL Term**	**Definition**	**Calculation Method**
C_{max}	Cmax	Maximum concentration	Obtained directly from observed data
AUC_{0-t}	AUC_{last}	Area under the drug concentration-time curve from time 0 to the last measurable concentration collection time t	Linear-up/log-down trapezoidal method†
AUC_{0-tau}	AUC_{0-12h} or AUC_{0-24h}	Area under the drug concentration-time curve from time 0 to 12 h (BID group) or 24 h (QD group)	Linear-up/log-down trapezoidal method†
AUC_{0-inf}	AUCINF_obs	Area under the drug-time curve from time 0 extrapolated to infinity	$AUC_{0-inf} = AUC_{0-t} + C_t/\lambda_z$, where C_t is the blood drug concentration corresponding to the last measurable time point
T_{max}	T_{max}	Time to maximum concentration	Obtained directly from observed data

T_{last}	T_{last}	Time of last measurable concentration	Obtained directly from observed data
$t_{1/2}$	HL_Lambda_z	Elimination half-life	$t_{1/2} = \ln(2)/\lambda_z$, Note: Only data points in the log-linear decline phase can be used in the regression
V_z/F	Vz_F_obs	Apparent volume of distribution	$V_z/F = Dose/(AUC_{0\text{-}inf} * \lambda_z)$
CL/F	Cl_F_obs	Apparent clearance	Single dose: $CL/F = Dose/AUC_{0\text{-}inf}$
λ_z	Lambda_z	Terminal elimination rate constant	Calculated by linear regression of the elimination phase of the log concentration-time curve
MRT	MRTINF_obs	Mean residence time	$MRT=AUMC_{0\text{-}inf} / AUC_{0\text{-}inf}$
$AUC_{\%_Extrap}$	AUC_%Extrap_obs	Percentage of area extrapolated	$AUC_{\%_Extrap} = (AUC_{0\text{-}inf} - AUC_{0\text{-}t}) / AUC_{0\text{-}inf} *100\%$
$C_{trough,ss}$	C_{tau}	Steady-state trough concentration	Obtained directly from observed data
$C_{max,ss}$	C_{max}	Steady-state maximum concentration	Obtained directly from observed data
$AUC_{0\text{-}t,ss}$	AUC_{last}	Area under the steady-state plasma concentration-time curve from time zero to the time of the last quantifiable concentration (C0-t)	Linear-up/log-down trapezoidal method†
$AUC_{0\text{-}tau,ss}$	AUC_TAU	Area under the plasma concentration-time curve from time zero to tau, where tau is the dosing interval.	Linear-up/log-down trapezoidal method†
$AUC_{0\text{-}inf,ss}$	AUCINF_obs	Area under the steady-state plasma concentration-time curve from time zero extrapolated to infinity	$AUC_{0\text{-}inf,ss} = AUC_{0\text{-}t,ss} + C_{ss,last}/\lambda_z$, where $C_{ss,last}$ is the plasma concentration corresponding to the last measurable time point (T_{last})
$T_{max,ss}$	T_{max}	Time to steady-state peak concentration	Obtained directly from observed data
CL/F_{ss}	CLss_F	Steady-state apparent clearance	$CL/F_{ss} =Dose/ AUC_{0\text{-}tau,ss}$
V_z/F_{ss}	V_z_F	Steady-state apparent volume of distribution	$V_z/F_{ss} = MRT_{0\text{-}inf}* CL/F_{ss}$
R_{ac_Cmax}	R_{acCmax}	Accumulation ratio based on C_{max}	$R_{ac_Cmax} = C_{max,ss}$ (multiple doses)/C_{max} (first dose)
$R_{ac_Ctrough}$	$R_{acCtrough}$	Accumulation ratio based on C_{trough}	$C_{trough,ss}$ (multiple doses)/C_{trough} (first dose)
R_{ac_AUC}	R_{acAUC}	Accumulation ratio based on $AUC_{0\text{-}tau}$	$R_{ac_AUC} = AUC_{0\text{-}tau}$ (multiple doses)/$AUC_{0\text{-}tau}$ (first dose)

†For the ascending concentration phase, the area under the curve will be calculated using the linear trapezoidal rule, and for the descending concentration phase, the log-linear trapezoidal rule will be used (linear-up/log-down trapezoidal rule).

The calculation of λ_z follows the following rules:

- The elimination phase has at least 3 measurable sampling points (the first sample point must be after T_{max});
- The concentration is decreasing (λ_z must be a positive value);
- Adjusted coefficient of determination (R^2_{adj}) ≥ 0.8;
- $AUC_{\%_Extrap}$ ≤20%.

When R^2_{adj} < 0.8 or $AUC_{\%_Extrap}$ > 20%, or when the λ_z value cannot be accurately calculated (missing), λ_z and other related PK parameters ($t_{1/2}$, $AUC_{0\text{-inf}}$, CL/F, V_z/F, $AUC_{\%_Extrap}$, MRT) will not be summarized, but will still be presented in the listing and marked.

4.4.3 Dose Proportionality Analysis

Dose proportionality analysis is only for Phase I data. Using the Power model, a linear regression model will be fitted after natural logarithmic transformation of the PK parameters (C_{max}, $AUC_{0\text{-t}}$, and $AUC_{0\text{-inf}}$) and dose for both single and multiple doses to analyze the linear relationship between drug exposure and dose.

The formula for the Power model is:

ln [PK]=α+β*ln [Dose] +ε

where PK represents the PK parameters above, α is the intercept, β is the slope, ε is the random error, and Dose is the administered dose group.

The reference SAS program is as follows:

```
proc glm data = pkdata;
model ln[pk] = ln[dose] / clparm alpha=0.1;
ods output parameterestimates=parameterestimates;
run;
```

The CI method will be used to evaluate the linear relationship between PK parameters and dose. The 90% CI of the slope (β) will be compared with the decision region. If the 90% CI of β falls completely within the decision region, the linear relationship between the PK parameter and dose is considered to be established, i.e.:

$$1+\frac{\ln(\theta_L)}{\ln(r)} < \beta < 1+\frac{\ln(\theta_H)}{\ln(r)}$$

where θ_L=0.8, θ_H=1.25, and r is the ratio of the highest dose group to the lowest dose group.

4.5 Biomarker Analysis

For Phase II PDAC subjects, CA19-9 will be summarized. For quantitative indicators, the number of subjects, mean, standard deviation, median, minimum, and maximum will be summarized; for

categorical indicators, the number of subjects and percentage for each category will be summarized. CA19-9 will be presented in a listing.

5 Interim Analysis and Safety Monitoring Committee (SMC)

5.1 Interim Analysis

A futility interim analysis will be performed separately for NSCLC, PDAC, and CRC. For a single tumor type, it is planned to be conducted when approximately 35 subjects (including Phase I subjects treated with RP2D and Phase II subjects) have had at least one post-baseline imaging tumor assessment or have withdrawn from the study early. Due to practical clinical operational reasons, the number of subjects at the time of the interim analysis is allowed to differ from the planned number. During the interim analysis, enrollment will not be stopped.

At the interim analysis, a futility analysis will be conducted for the ORR of NSCLC, PDAC, and CRC, respectively, using the Bayesian predictive probability method. Early termination of the study for the corresponding tumor type due to lack of efficacy evidence is permitted (but not mandatory).

The predictive probability of success (PPoS) will be calculated based on the observed number of Phase II subjects who have achieved a response (CR/PR). If the PPoS is < 0.2, early termination of enrollment due to lack of efficacy evidence is permitted (but not mandatory). The corresponding termination criteria for PPoS < 0.2 are shown in the table below:

Tumor Type	Number of Subjects	Recommended to terminate the study when the number of responding subjects is ≤
NSCLC	20 ~ 21	3
	22 ~ 25	4
	26 ~ 29	5
	30 ~ 33	6
	34 ~ 37	7
	38 ~ 41	8
	42 ~ 45	9
PDAC	25 ~ 26	2
	27 ~ 33	3
	34 ~ 39	4
	40 ~ 45	5
CRC	20 ~ 23	1
	24 ~ 30	2
	31 ~ 37	3
	38 ~ 43	4
	44 ~ 48	5

*Number of subjects: Number of Phase I subjects treated with RP2D and Phase II subjects who have had at least one post-baseline imaging tumor assessment or have withdrawn from the study early (at least one of the two is met).

The interim analysis planned above is not mandatory. If there is sufficient comprehensive safety and efficacy data to support it before the planned time point for the interim analysis, this interim futility

analysis may be omitted.

5.2 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) composed of investigators and the sponsor will be established for this study. The SMC will continuously review safety data from the first dose of the first subject until the end of the study. During the dose-escalation and expansion phases, SMC members will review safety data, PK data, etc., to decide on enrollment for the next dose or to explore other potential dose cohorts, and to recommend the appropriate RDE and RP2D.

During the study, if both the investigator and the sponsor believe that a subject is at a safety risk or has reached the limit of tolerability, dose escalation or study treatment will be stopped immediately. For details, please refer to the SMC charter.

6 Modifications to the Original Analysis Plan

None.

7 References

None.

Appendix 1 CTCAE (V5.0) Grading Rules for Laboratory Test Parameters to be Evaluated

Parameter	CTCAE V5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin concentration (HGB)	Anaemia	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	-
Haemoglobin concentration (HGB)	Hemoglobin increased	Increase of 0 - 2 g/dL relative to ULN	Increase of 2 - 4 g/dL relative to ULN	Increase of >4 g/dL relative to ULN	-
White blood cell count (WBC)	Leukocyte count decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000 - 1000/mm^3; <2.0 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
White blood cell count (WBC)	Leukocytosis	-	-	>100,000/mm^3;	
Lymphocyte (LY) count	Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
Lymphocyte (LY) count	Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3, >4 x 10^9/L - 20 x 10^9/L	>20,000/mm^3; >20 x 10^9/L	-
Neutrophil count (ANC)	Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000 - 500/mm^3; <1.0 - 0.5 x 10^9 /L	<500/mm^3; <0.5 x 10^9 /L
Platelet count (PLT)	Thrombocyte count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10^9 /L	<25,000/mm^3; <25.0 x 10^9 /L
Alanine aminotransferase (ALT)	Alanine aminotransferase increased	>ULN - 3.0 × ULN (if baseline normal); 1.5-3.0 × baseline (if baseline abnormal)	>3.0 - 5.0 × ULN (if baseline normal); 3.0-5.0 × baseline (if baseline abnormal)	>5.0 - 20.0 × ULN (if baseline normal); 5.0 - 20.0 × baseline (if baseline abnormal)	>20.0 × ULN (if baseline normal); >20.0 × baseline (if baseline abnormal)
Aspartate aminotransferase (AST)	Aspartate aminotransferase increased	>ULN - 3.0 × ULN (if baseline normal); 1.5-3.0 × baseline (if baseline abnormal)	>3.0 - 5.0 × ULN (if baseline normal); 3.0-5.0 × baseline (if baseline abnormal)	>5.0 - 20.0 × ULN (if baseline normal); 5.0 - 20.0 × baseline (if baseline abnormal)	>20.0 × ULN (if baseline normal); >20.0 × baseline (if baseline abnormal)
Alkaline phosphatase (ALP)	Alkaline phosphatase increased	>ULN - 2.5 × ULN (if baseline normal); 2.0-2.5 × baseline (if baseline abnormal)	>2.5 - 5.0 × ULN (if baseline normal); 2.5 - 5.0 × baseline (if baseline abnormal)	>5.0 - 20.0 × ULN (if baseline normal); 5.0 - 20.0 × baseline (if baseline abnormal)	>20.0 × ULN (if baseline normal); >20.0 × baseline (if

Parameter	CTCAE V5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
					baseline abnormal)
Creatine kinase (CK)	Creatine phosphokinase increased	> ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10 x ULN
Blood creatinine (CREA)	Creatinine increased	>ULN - 1.5 x ULN;	>1.5 - 3.0 × ULN; >1.5 - 3 × baseline	>3.0 - 6.0 × ULN; >3 × baseline	>6.0 x ULN
Total bilirubin (TBIL)	Blood bilirubin increased	>ULN - 1.5 × ULN (if baseline normal); >1-1.5 × baseline (if baseline abnormal)	>1.5 - 3.0 × ULN (if baseline normal); 1.5 - 3.0 × baseline (if baseline abnormal)	>3.0 - 10.0 × ULN (if baseline normal); 3.0 - 10.0 × baseline (if baseline abnormal)	>10.0 × ULN (if baseline normal); >10.0 × baseline (if baseline abnormal)
Total cholesterol (TCHO)	Hypercholesteremia	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92mmol/L
Gamma-glutamyltransferase (GGT)	Gamma-glutamyltransferase increased	>ULN - 2.5 × ULN (if baseline normal); >2-2.5 × baseline (if baseline abnormal)	>2.5 - 5.0 × ULN (if baseline normal); 2.5 - 5.0 × baseline (if baseline abnormal)	>5.0 - 20.0 × ULN (if baseline normal); 5.0 - 20.0 × baseline (if baseline abnormal)	>20.0 × ULN (if baseline normal); >20.0 × baseline (if baseline abnormal)
Triglycerides (TG)	Hypertriglyceridaemia	>150 - 300 mg/dL; >1.71 - 3.42 mmol/L	>300 - 500 mg/dL; >3.42 - 5.7 mmol/L	>500 - 1000 mg/dL; >5.7 - 11.4 mmol/L	
Potassium	Hyperkalaemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Potassium	Kaliopenia	-	<LLN - 3.0 mmol/L	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Sodium	Hypernatraemia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Sodium	Hyponatraemia	<LLN - 130 mmol/L	<125 - 129 mmol/L	<120 - 124 mmol/L	<120 mmol/L
Blood glucose	Hypoglycaemia	<lower limit of normal (LLN) - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Albumin (ALB)	Hypoalbuminaemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	-
International normalised ratio (INR)	INR increased	>1.2-1.5; >1-1.5 × baseline	>1.5-2.5; >1.5-2.5 × baseline	>2.5; >2.5 × baseline	-

Parameter	**CTCAE V5.0 Term**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Activated partial thromboplastin time (APTT)	Activated partial thromboplastin time prolonged	> ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 × ULN;	-
Eosinophils	Eosinophilia	For baseline visit: AVAL > ANRHI; For post-baseline visit: AVAL > ANRHI and AVAL > BASE	-	-	-
Lactate dehydrogenase	Blood lactate dehydrogenase increased	AVAL> ANRHI	-	-	-
Calcium (mmol/L)	Hypocalcaemia	2.0 mmol/L<=AVAL<ANRLO	1.75 mmol/L<=AVAL<2.0 mmol/L	1.5 mmol/L<=AVAL<1.75 mmol/L	AVAL<1.5 mmol/L
Calcium (mmol/L)	Hypercalcaemia	ANRHI<AVAL<=2.9 mmol/L	2.9 mmol/L<AVAL<=3.1 mmol/L	3.1 mmol/L<AVAL<=3.4 mmol/L	AVAL>3.4 mmol/L

统计分析计划

一项评估GFH375治疗KRAS G12D突变型晚期实体瘤患者的安全性、耐受性、药代动力学和疗效的开放 标签、I/II期临床研究

方案编号：	GFH375X1101
申办方：	劲方医药科技（上海）股份有限公司
CRO：	昆翎企业管理（上海）有限公司
版本号：	0.9
日期：	2025-11-07

签字页

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文档更新记录

版本	日期	作者/修改人	注释

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缩略词表

缩略词	术语
AE	不良事件
ATC	解剖学治疗学及化学分类系统
AUC	曲线下面积
BICR	盲态独立中心审查委员会
BID	每日二次
BMI	体重指数
BOIN	贝叶斯最优区间
BOR	最佳总缓解
BQL	低于定量下限
BSA	体表面积
C_{max}	峰浓度
$C_{max,ss}$	稳态峰浓度
$C_{trough,ss}$	稳态谷浓度
CI	置信区间
CL/F	表观清除率
CL/F_{ss}	稳态表观清除率
CR	完全缓解
CRC	结直肠癌
CRF	病例报告表
CTCAE	不良事件通用术语评价标准
ctDNA	肿瘤循环 DNA
CV	变异系数
DCR	疾病控制率
DDS	剂量确定分析集
DLT	剂量限制性毒性
DoR	缓解持续时间
ECG	心电图
ECOG	美国东部肿瘤协作组
eCRF	电子病例报告表
FAS	全分析集
GCV	几何变异系数
HR	心率
LLOQ	定量下限
KRAS	鼠类肉瘤病毒癌基因
MedDRA	监管活动医学词典
NE	无法评估
NSCLC	非小细胞肺癌
MRT	平均滞留时间
MTD	最大耐受剂量
ORR	客观缓解率
OS	总生存期

缩略词	术语
PD	疾病进展
PDAC	胰腺导管腺癌
PD-L1	程序性死亡配体 1
PFS	无进展生存期
PK	药代动力学
PKAS	药代动力学分析集
PN	首选药名
PPS	符合方案集
PPoS	预测成功率
PR	部分缓解
PT	首选术语
Q1	第一分位数
Q3	第三分位数
QD	每日一次
R^2adj	校正的决定系数
R_{ac_AUC}	基于 $AUC_{0\text{-}tau}$ 计算的蓄积比
R_{ac_Cmax}	基于 C_{max} 计算的蓄积比
$R_{ac_Ctrough}$	基于 C_{trough} 计算的蓄积比
RECIST	实体肿瘤疗效评价标准
RED	推荐的扩展剂量
RP2D	II期推荐剂量
SAE	严重不良事件
SAP	统计分析计划
SD	疾病稳定
SMC	安全监查委员会
SOC	系统器官分类
SS	安全性分析集
$t_{1/2}$	消除半衰期
T_{max}	达峰时间
TEAE	治疗期间不良事件
TTR	至缓解时间
V_z/F	表观分布容积
V_z/F_{ss}	稳态表观分布容积
WHODrug	世界卫生组织药物词典
λ_z	末端消除速率常数

1 介绍

本研究（方案编号 GFH375X1101）是一项评估 GFH375 治疗 KRAS G12D 突变型晚期实体瘤患者的安全性、耐受性、药代动力学和疗效的开放标签的 I/II 期临床研究。基于该研究的临床研究方案（版本：V2.0, 2025-1-24），本统计分析计划（SAP）详细描述了用于分析和报告受试者安全性评估、有效性评估、药代动力学（PK）评估、生物标志物评估的具体统计方法和数据处理原则。

本文件将会逐渐补充完善，以用于展现方案修正、监管和其他重要变化。定稿的 SAP 将会在申办方审批通过后，数据锁库之前，进行归档保存。任何偏离定稿 SAP 的内容都将在临床研究报告中进行备注说明。

1.1 研究目的与研究终点

表 1 I期研究部分的目的和终点

研究目的	研究终点
主要目的	**主要终点**
• 评估GFH375在KRAS G12D突变的晚期实体瘤患者中的安全性和耐受性	• 不良事件（AE）和严重不良事件（SAE）的发生率和严重程度；生命体征、心电图（ECG）和实验室检查的改变
• 确定GFH375的最大耐受剂量（MTD）和II期推荐剂量（RP2D）	• 剂量限制性毒性（DLT）事件的发生率
次要目的	**次要终点**
• 评估GFH375在KRAS G12D突变的晚期实体瘤患者中的PK特征	• GFH375的血浆浓度和PK参数，包括但不限于C_{max}、T_{max}、AUC、$t_{1/2}$、CL/F、Vz/F、C_{trough}
• 评估GFH375在KRAS G12D突变型晚期实体瘤患者中的初步疗效	• 根据实体瘤疗效评价标准（RECIST）1.1评估的客观缓解率（ORR）、缓解持续时间（DoR）、疾病控制率（DCR）、至缓解时间（TTR）、无进展生存期（PFS） • 总生存期（OS）
探索目的	**探索终点**
• 探索与治疗敏感或耐药相关的分子机制	• 基线和治疗结束时血液循环肿瘤DNA（ctDNA）的突变分析

表 2 II期研究部分的目的和终点

研究目的	研究终点
主要目的	**主要终点**
• 评估GFH375在KRAS G12D突变的晚期非小细胞肺癌（NSCLC）、晚期胰腺癌（PDAC）、晚期结直肠癌（CRC）和其他实体瘤患者中的疗效	• 根据RECIST 1.1评估的ORR
次要目的	**次要终点**
• 使用其他疗效指标评估GFH375在	• 根据RECIST 1.1评估的最佳总体缓解

KRAS G12D突变的晚期NSCLC、晚期PDAC、晚期CRC和其他晚期实体瘤患者中的疗效 • 评估GFH375在KRAS G12D突变的晚期NSCLC、晚期PDAC、晚期CRC和其他晚期实体瘤患者中的安全性 • 评估GFH375在KRAS G12D突变的晚期NSCLC、晚期PDAC、晚期CRC和其他晚期实体瘤患者中的PK特征	（BOR）、DoR、DCR、TTR、PFS • OS • AE、SAE 的发生率和严重程度；生命体征、ECG和实验室检查的改变 • GFH375的血浆浓度
探索目的	**探索终点**
• 探索与治疗敏感或耐药相关的分子机制 • 针对PDAC受试者：糖类抗原19-9（CA19-9）与治疗应答的关系	• 基线和治疗结束时血液ctDNA的突变分析 • 针对PDAC受试者：血清CA19-9相对基线的变化

1.2 试验概述

1.2.1 总体试验设计

本研究是一项评估 GFH375 单药在携带 KRAS G12D 突变的晚期实体瘤患者中的安全性/耐受性、PK 及有效性。I 期研究的主要目的是评估 GFH375 在携带 KRAS G12D 突变的晚期实体瘤患者中的安全性/耐受性、PK 和初步有效性，并确定 GFH375 的 MTD 和/或 RP2D。II 期研究的主要目的是评估 GFH375 在携带 KRAS G12D 突变的晚期 NSCLC、晚期 PDAC、晚期 CRC 和其他晚期实体瘤患者中的有效性。

I 期部分

将根据 BOIN 设计，在每个剂量组入组 3-6 例受试者（加速滴定时除外）接受 GFH375 口服给药治疗，每 21 天为一个治疗周期。受试者将入组至顺序递增的不同剂量组，起始剂量为 100 mg 每日一次（QD）。预计在剂量递增部分共进行 7 个或更多给药剂量的评估，计划的递增剂量参见表 3。剂量递增过程中将综合评估 GFH375 给药方案，必要时将进行给药频率为每日 2 次（BID）的剂量探索，剂量递增可在 QD 和 BID 给药方案上独立并行进行。

基于所获得的数据包括安全性、PK、初步疗效结果，可能会进行 BID 剂量探索。BID 起始剂量将选择下表其中一个剂量组，每日总剂量与正在探索的 QD 剂量一致。

表 3 剂量递增表格

剂量组	**I期计划进行递增的QD剂量组[1]**
剂量组1	100 mg QD
剂量组2	200 mg QD
剂量组3	400 mg QD
剂量组4	600 mg QD
剂量组5	750 mg QD
剂量组6	1000 mg QD
剂量组7	1200 mg QD
剂量组	**I期可能探索的BID剂量组[2]**

剂量组1	100 mg BID
剂量组2	150 mg BID
剂量组3	200 mg BID
剂量组4	300 mg BID
剂量组5	400 mg BID

注：[1] 可能会在爬坡过程中基于获得的临床数据包括安全性、PK、可能的有效性进行上述剂量的中间剂量探索，如 150mg、300mg、500mg、800mg、900mg、1100mg QD 等。
[2] 可能会进行上述剂量的中间剂量探索，如 250mg BID 等。

将根据已获得的安全性/耐受性、PK 及初步有效性数据，可能选择一个或多个剂量组入组额外的受试者作为回填，接受已确认安全且耐受性良好的、经研究者及申办方评估可能临床获益的 GFH375 单药剂量组进行治疗，以更好地估计 GFH375 单药的 RP2D 以及表征其安全性\耐受性、PK 及有效性。如探索并确认过 750mg QD 剂量组的安全性，亦可进行 700mg QD 剂量组回填。回填的受试者不被纳入 DLT 的评估。回填后，接受 GFH375 每个剂量组治疗的受试者不超过 30 例（包括 BOIN 剂量递增阶段入组的受试者）。

研究计划示意图见图 1。

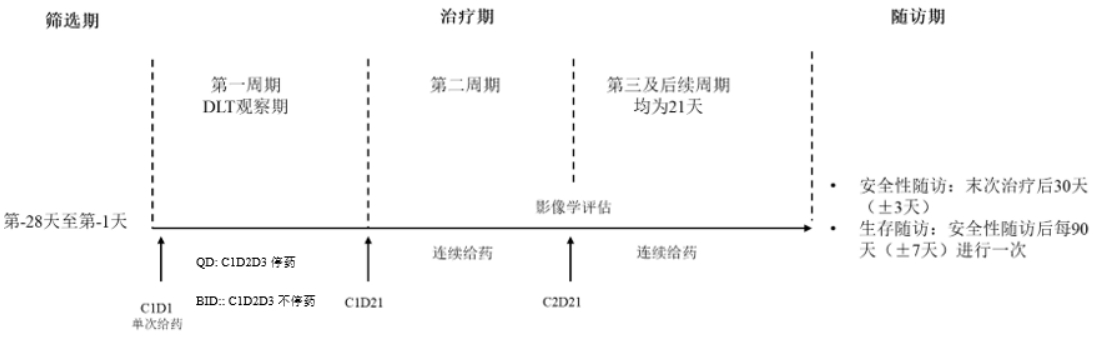

图 1 I 期研究计划示意图

II 期部分

根据 I 期剂量递增部分以及部分回填受试者的所有安全性、耐受性、PK 和疗效数据，确定 RP2D 为 600 mg QD。

II 期研究为开放标签、多中心的研究，总体研究计划见**错误!未找到引用源。**。目的是评估 GFH375 治疗携带 KRAS G12D 突变的晚期非小细胞肺癌、晚期胰腺癌、结直肠癌和其他晚期实体瘤患者的有效性、安全性和 PK 特征。II 期研究将入组约 317 例 KRAS G12D 突变的晚期实体瘤受试者，以接受 RP2D 的 GFH375 连续单药治疗，治疗周期为 21 天，直至疾病进展、出现不可耐受的毒性或因其他原因结束研究治疗。

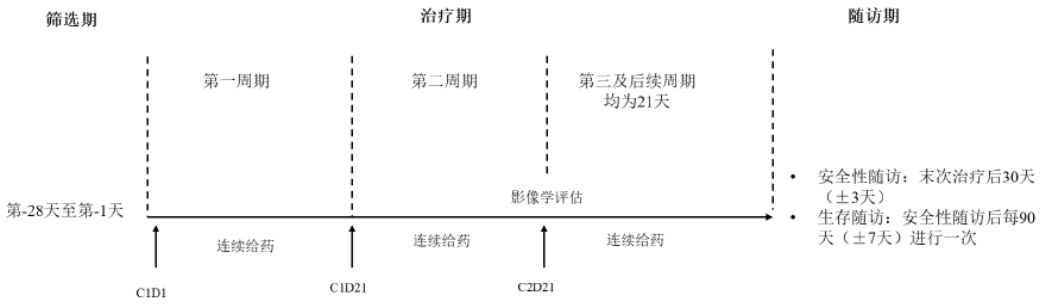

图 2 II 期研究计划示意图

1.2.2 随机化和盲法

本试验为单臂开放性研究，因此随机化和盲法不适用。

1.2.3 样本量

1.2.3.1 I 期：剂量递增部分

将根据 BOIN 设计，在每个剂量组入组 3-6 例受试者（加速滴定时除外）接受治疗。将根据已获得的安全性/耐受性、PK 及初步有效性数据，可能选择一个或多个剂量组入组额外的受试者作为回填， 接受已确认安全且耐受性良好的、经研究者及申办方评估可能临床获益的 GFH375 单药剂量进行治疗，以更好的估计 GFH375 单药的 RP2D 以及表征其安全性\耐受性、PK 及有效性。回填的受试者不被纳入 DLT 的评估。回填后，接受 GFH375 每个剂量组治疗的受试者不超过 30 例（包括 BOIN 剂量递增阶段入组的受试者）。如果需要探索更多的剂量组或替代给药方案，则可以入组额外的受试者。

1.2.3.2 II 期

总共预计入组约 317 例受试者，其中约 73 例晚期 NSCLC 受试者、约 94 例晚期 PDAC 受试者、50 例晚期 CRC 受试者、100 例晚期其他实体瘤受试者。

表 2 II 期样本量

肿瘤类型	历史对照ORR	预期ORR	样本量
NSCLC	23%	40%	73
PDAC	15%	30%	94
CRC	10%	30%	50
其他			100
合计			317

对于晚期二线 NSCLC，ORR 的历史对照值为 23%，预计本研究 ORR 可达到 40%。若观测到的 ORR 的 95% CI 下限不低于历史对照 23%，则视为成功。单侧 α= 0.025，要达到 89%把握度，则需要 73 例受试者。当 73 例受试者中有至少 25 例 CR/PR 时，ORR 观测值的 exact 95%CI 下限高于历史对照 23%。25 例 CR/PR 时，ORR = 34.2% ，其 95% CI 为（23.5%, 46.3%）。

对于晚期二线 PDAC，ORR 的历史对照值设定值为 15%，预计 GFH375 治疗下 ORR 可达到 30%，若采用 GFH375 治疗后 ORR 的 95%CI 下限大于 15%，则认为 GFH375 的疗效具有统计学显著意义。当单侧 α = 0.025，94 例受试者可

获得 95%的把握度以保证试验数据获得 ORR 的 95%CI 下限大于 15%。计划入组 PDAC 受试者约 94 例。当 94 例受试者中观察到 22 例获得缓解（PR/CR）时，ORR 观测值的 exact 95% 为（15.29%，33.26%）。因此 94 例受试者中观察到 ≥ 22 例缓解时，则认为 GFH375 的疗效具有统计学意义。

对于三线 CRC，ORR 的历史对照值为 10%，预计本研究 ORR 可以达到 30%。若观测到的 ORR 的 95% CI 下限不低于历史对照 10%，则视为成功。计划入组 50 例受试者，在单侧 α = 0.025 的情况下，把握度可达到 96%。当 50 例受试者中有至少 10 例 CR/PR 时，ORR 观测值的 exact 95% CI 下限高于历史对照 10%。10 例 CR/PR 时，ORR = 20.0% ，其 95% CI 为 (10.0%, 33.7%)。

对于其他实体瘤：计划入组约 100 例 KRAS G12D 突变的晚期实体瘤受试者，如携带 KRAS G12D 突变的胆管癌、阑尾癌等。

以上样本量和 ORR（及其 95% exact CI） 的计算使用了 R 语言。其中，样本量计算使用了“gsDesign”package 中的“nBinomial1Sample”function（option：conservative = TRUE）；ORR 及其 95% exact CI 使用了“epitools”package 中的“binom.exact”function（default options）。

2 统计分析基本考虑

2.1 一般规则

所有统计分析将使用 SAS 9.4 或更新版本进行。

对连续变量，总结例数、平均值、标准差、中位数、最小值和最大值。对分类变量，总结各类例数及百分比。对时间-事件变量采用 Kaplan-Meier 法进行分析，绘制生存曲线图，并计算中位生存时间及对应的双侧 95%置信区间（CI）。表 3 为各统计参数的小数点保留位数情况。

表 3 统计参数的小数保留位数

统计量	保留的小数位数
算术均值、几何均值、中位数、Q1、Q3、置信区间（CI）	比原始数据多保留 1 位小数，最多不超过 3 位小数
标准差、标准误、变异系数（CV%）和几何变异系数（GCV%）	比原始数据多保留 2 位小数，最多不超过 3 位小数。
最大值、最小值	与原始数据保留相同的小数位数，最多不超过 3 位小数
百分比	保留一位小数，若百分比达百分之百则表示为“100”，若百分比为 0 则表示为“0”
P 值	保留 3 位小数，如果 P 值小于 0.001，将被表示为“<0.001”。如果 P 值大于 0.999，将被表示为“>0.999”。

2.2 分析集定义

- 全分析集（FAS）：至少接受 1 次 GFH375 给药的所有受试者。
- 安全性分析集（SS）：至少接受 1 次 GFH375 给药且至少有 1 次有效的基线后安全性评估的所有受试者。

- 剂量确定分析集（DDS）： I 期 SS 中在 DLT 观察期间至少累计 15 天接受未减量的 GFH375 的所有受试者且有充分的安全性评估，或在 DLT 观察期间发生 DLT。DDS 不包含回填（backfill）的受试者
- 符合方案集（PPS）： FAS 中符合方案的所有 II 期受试者。研究团队将在最终数据库锁定前对所有方案偏离进行审查，据此将发生影响疗效评价的重大方案偏离的受试者从 PPS 中排除。
- 药代动力学分析集（PKAS）：至少接受 1 次 GFH375 给药且至少有 1 份血样提供可评价 PK 数据的所有受试者。

2.3 数据处理原则

2.3.1 基线定义

若无特殊说明，基线定义为 GFH375 首次给药前的最后一次非缺失检查结果（包括计划和非计划访视）。如果受试者没有上述定义的检查结果，则基线当作缺失处理。当该检查与 GFH375 首次给药发生于同一天时，若不能确认其发生于 GFH375 首次给药之后，则默认其为基线数据。但是对于不良事件，合并用药/治疗等，当其开始日期与 GFH375 首次给药日期一致时，如不能确认发生在给药之前，认为该不良事件，合并用药/治疗等是基线后发生的。

2.3.2 研究日的定义

研究日的计算以 GFH375 首次给药日期作为参照，计算事件发生日期或评估日期相对于首次给药日期的时间间隔（天）。研究日计算方法如下：

- 若事件发生或评估在 GFH375 首次给药当天或之后，则研究日为：事件发生或评估日期 - GFH375 首次给药日期 + 1；
- 若事件发生或评估在 GFH375 首次给药之前，则研究日为：事件发生或评估日期 - GFH375 首次给药日期。

2.3.3 分析窗口期的定义

对研究数据的统计分析都将基于病例报告表（CRF）记录的名义访视，不设置分析窗口期。

2.3.4 最后已知的生存日期

对于截至分析日期还未获知死亡的受试者，将根据以下数据中最后一次记录到的非缺失日期来判断其最后已知的存活日期：

- 所有检查项目的检查日期（如生命体征检查、体格检查、ECOG 评估、实验室检查、心电图等），如该检查涉及到样本采集，则以采样日期为准；
- GFH375 给药、伴随用药、伴随非药物治疗、新的抗肿瘤治疗的开始和结束日期；
- 不良事件的发生和转归不为“死亡”的结束日期；
- 生存随访中受试者状态为“生存”的最后一次随访日期；

- 失访前最后一次取得联系的日期。

2.3.5 缺失数据的处理规则

除非特殊说明，本试验对缺失数据将不进行填补。

2.3.5.1 初始病理学诊断日期

初始病理学诊断日期的填补规则：

- 如果年缺失（或者完全缺失），则不填补；
- 如果仅有日缺失，填补为当月的 1 号；
- 如果月和日同时缺失，则填补为 7 月 1 号。

如果填补后的日期在知情同意日期之后，则填补日期修正为知情同意日期-1 天。

2.3.5.2 死亡日期

仅适用于确认死亡的病例，死亡日期采用如下填补规则：

- 如果年份缺失（或年、月、日均缺失），死亡日期填补为最后已知存活日期+1 天。
- 如果日和月份都缺失，那么当年 7 月 1 日填补为死亡日期。
- 如果仅日期缺失，那么当月的第 1 天填补为死亡日期。

如果填补后的死亡日期在最后已知的生存日期之前，则填补日期修正为最后已知的生存日期+1 天。

2.3.5.3 既往/伴随治疗日期

既往/伴随治疗包括药物和非药物治疗。既往/伴随治疗日期的填补规则如下。若既往/伴随治疗开始日期和结束日期都存在缺失，将先进行结束日期的填补，后进行开始日期的填补。

既往/伴随治疗结束日期

- 仅对是否持续选择“否”的既往/合并治疗进行填补；
- 如果仅有日缺失，则填补为当月的最后一天；
- 如果月和日同时缺失，则填补为当年的 12 月 31 日；

如果填补后的既往/伴随治疗结束日期在研究结束日期之后，则将既往/伴随治疗结束日期修正为研究结束日期。

既往/伴随治疗开始日期

- 如果仅有日缺失，则填补为当月的 1 日；
- 如果月和日同时缺失，则填补为当年的 1 月 1 日；
- 如果年、月和日全部缺失，则填补为 GFH375 首次给药日期；

如果填补后的既往/伴随治疗开始日期晚于既往/伴随治疗结束日期，则修正为既往/伴随治疗结束日期。

2.3.5.4 既往抗肿瘤治疗结束日期

既往抗肿瘤治疗包括药物、手术和放射治疗。既往抗肿瘤治疗结束日期的填补规则如下：

- 如果仅有日缺失，则填补为当月的最后一天；
- 如果月和日同时缺失，则填补为当年的 12 月 31 日；
- 如果年、月和日全部缺失，则不进行填补；

如果填补后的日期在知情同意日期之后，则填补日期修正为知情同意日期-1 天。

2.3.5.5 既往末线治疗疾病进展日期

既往末线治疗疾病进展日期的填补规则如下：

- 如果仅有日缺失，则填补为当月的最后一天；
- 如果月和日同时缺失，则填补为当年的 12 月 31 日；
- 如果年、月和日全部缺失，则不进行填补；

如果填补后的日期在知情同意日期之后，则填补日期修正为知情同意日期-1 天。

2.3.5.6 不良事件开始日期

不良事件的开始日期填补规则：

- 如果 AE 开始日期全部缺失，则填补为 GFH375 首次给药日期；
- 如果 AE 开始日期部分缺失，则填补规则如下：
  - 如果年和月已知，且年和月与 GFH375 首次给药日期的年和月相同，则填补为 GFH375 首次给药日期；
  - 如果年和月已知，但年和月与 GFH375 首次给药日期的年和月不同，则填补为当月的 1 号；
  - 如果仅有年已知，且年与 GFH375 首次给药日期的年份相同，则填补为 GFH375 首次给药日期；
  - 如果仅有年已知，但年与 GFH375 首次给药日期的年份不同，则填补为当年 1 月 1 号。

如果 AE 结束日期非缺失，填补后的 AE 开始日期在 AE 结束日期之后，则将 AE 开始日期填补为 AE 结束日期。

2.3.5.7 试验用药结束日期

最后一条记录（即末次用药）结束日期缺失，取下列日期中距离该条记录

用药开始日期最近，最先发生且完整的日期进行填补：

- 当月最后一天（仅日缺失）
- AE 记录中对研究治疗采取的措施为“终止给药”的 AE 的开始时间
- 决定结束研究治疗日期-1 天
- 死亡日期
- 数据截止日期

研究用药期间（非末次用药）结束日期缺失：

- 最近的下一条用药记录的开始日期-1 天

2.3.6 其它数据处理原则

对于实验室检查项目，所有需总结的结果都将使用国际标准单位在表格和列表中进行展示。若实验室检查结果存在“>”或“<”时，则将检查结果上限或下限作为制表总结的分析值（列表中保留“>”或“<”）。如：检查结果为“>100”，则分析值赋值为100。

若无特殊说明，仅总结计划访视的数据内容，但对于基线后最佳/最差检查结果的汇总分析，将同时包括计划访视与非计划访视的结果。非计划访视及计划访视内的检查结果均列表展示。除心电图相关检查外，若在计划访视中，某一检查项目在同一访视内进行了两次或更多次的检测，则取末次非缺失检查结果作为制表分析数据；心电图相关指标同一访视内的多次检测结果以均值作为制表分析数据。基线后若出现多条相同的最佳/最差检查结果，则取末次检查结果作为制表分析数据。非计划访视及计划访视内的多次检查结果均在列表中进行展示。

2.4 多重性比较

本研究不涉及多重比较。

2.5 亚组分析

对于 II 期 PDAC 和 NSCLC 受试者，基于 BICR 评估的结果对 CR/PR 需确认情况下的 ORR 进行亚组分析。

PDAC 的亚组包括：

- 年龄（<65 岁，≥65 岁）；
- 性别（男性，女性）；
- ECOG PS 评分（0 分，1 分）；
- 转移部位数（<2，≥2）；
- CA19-9 水平（<40 U/mL, ≥40 U/mL）；
- 白蛋白（<40 g/L, ≥40 g/L）；

- 既往接受放疗（是，否）；
- 既往接受手术治疗（是，否）；
- 肿瘤分期（III，IV，其他）；
- 肝转移（是，否）；
- 体重指数（<中位数，≥中位数）；
- 既往药物治疗线数（0 线，1 线，2 线，3 线）；
- 病程（<中位数，≥中位数）；
- 既往末线治疗疾病进展至首次治疗时间（<中位数，≥中位数，<1 个月，1-3 个月，3-6 个月，≥6 个月）；
- 既往接受吉西他滨/盐酸吉西他滨 治疗（是，否）；
- 既往接受白蛋白紫杉醇/紫杉醇治疗（是，否）；
- 既往接受伊立替康治疗（是，否）。

NSCLC 亚组包括：

- 年龄（<60 岁，≥60 岁，<65 岁，≥65 岁）；
- 性别（男性，女性）；
- ECOG PS 评分（0 分，1 分）；
- 吸烟史（从未吸烟，既往吸烟，现在吸烟）；
- 脑转移（是，否）；
- 肝转移（是，否）；
- 肾上腺转移（是，否）；
- 骨转移（是，否）；
- 既往药物治疗线数（1 线，2 线，3 线）；
- 既往接受抗 PD-1/PD-L1 药物治疗（是，否）；
- 既往接受含铂药物治疗（是，否）；
- 既往接受抗 PD-1/PD-L1 与含铂药物治疗（是，否）；
- PD-L1 表达水平（低表达，中表达，高表达）。

2.6 研究中心合并

本试验为多中心试验，所有中心数据将合并进行分析，不考虑中心效应。

3 指标的定义及衍生规则

3.1 受试者基本信息

3.1.1 既往/伴随病史

既往病史指筛选时已结束的病史，伴随病史指筛选时仍在持续的病史。通过 CRF 中“其他病史”页面“是否持续”进行判断。

3.1.2 既往/合并用药

既往用药指结束于GFH375首次给药之前的非试验用药品。

合并用药是指满足下面条件之一的非试验用药品：

- 开始于 GFH375 首次给药之前，并且在 GFH375 首次给药之后继续使用；
- 开始于 GFH375 首次给药当天及之后。

此外，如果 CRF“既往/伴随用药”页面“是否持续”选择“是”，则可判断为属于合并用药。

3.1.3 既往/合并非药物治疗

既往非药物治疗是指开始日期在 GFH375 首次给药之前的非药物治疗。

合并非药物治疗是指满足下面条件之一的非药物治疗：

- 开始于 GFH375 首次给药之前，并且在 GFH375 首次给药之后持续；
- 开始于 GFH375 首次给药当天及之后。

此外，如果 CRF“既往/伴随非药物治疗”页面“是否持续”选择“是”，则可判断为属于合并非药物治疗。

3.2 疗效终点

本研究的终点指标根据实体瘤疗效评价标准 1.1 版（RECIST1.1）进行评估。肿瘤最佳总缓解（BOR）为从 GFH375 首次给药开始到疾病进展、任何原因导致的死亡以及开始新的抗肿瘤（以先发生为准）的最佳缓解情况。若新的抗肿瘤治疗开始日期和评价日期为同一天，则将认为评价发生在开始新的抗肿瘤治疗之前。若受试者无疾病进展或无新的抗肿瘤治疗记录，则所有的评估结果均可用于决定其 BOR。最佳总缓解（BOR）的确认标准如下：

- 确认的 CR：至少一次被评价为 CR，且在随后（至少 4 周后）的评价中再次被确认为 CR，其间未出现疾病进展证据。
- 确认的 PR：至少一次被评价为 PR，且在随后（至少 4 周后）的评价中再次确认为 PR 或 CR，其间未出现疾病进展证据。
- SD：当被评价为 SD 时，需满足从 GFH375 首次给药后最少 6 周（42 天），而且不满足 CR 或 PR。若没有达到最短时间的标准，则 SD 不被认可。例如，某患者第 30 天评价为 SD，因为没有满足≥42 天的条件，不能判定为 SD。

- PD：在疾病进展或新的抗肿瘤治疗之前未被评价确认为 CR、PR 或 SD，且 PD 发生在 GFH375 首次给药后 91 天（2*6 周+1 周）之前。
- NE：无基线后肿瘤评价；基线后进行过肿瘤评价，但所有评价均不能判断为 CR，PR，SD 和 PD；基线后进行过肿瘤评价，但发生在新的抗肿瘤治疗之后；SD 不满足从 GFH375 首次给药后最少 6 周且无后续肿瘤评价；PD 发生在 GFH375 首次给药后 91 天（2*6 周+1 周）之后，且期间无肿瘤评价。

3.2.1 客观缓解率（ORR）

ORR 定义参见 **4.2.1** 章节。

3.2.2 疾病控制率（DCR）

DCR 定义参见 **4.2.2** 章节。

3.2.3 无进展生存期（PFS）

PFS 定义参见 **4.2.3** 章节。

PFS 的计算将始终基于疗效评估对应的影像学检查日期，而非访视或疗效评估日期。TTR、DoR 的计算同理。如果某访视内影像学检查在多个日期完成，将应用以下规则选取分析日期：

- 进展日期将根据判定该进展事件对应病灶的影像学检查的最早日期确定。例如，对于基于 RECIST v1.1 标准新病灶的 PD，PD 日期是首次检测到新病灶的影像学检查日期。
- 对于未出现疾病进展的受试者，删失日期将根据该访视内最晚一次影像学检查日期确定。

对于出现疾病进展或死亡的受试者，PFS 计算方法为：PFS（月）=（最早的疾病进展对应的影像学检查日期或死亡日期 - GFH375 首次给药日期+1）/ 30.4375。

对于删失的受试者，PFS 计算方法为：PFS（月）=（删失日期-GFH375 首次给药日期+1）/ 30.4375。删失规则如表 7 所示：

表 7 PFS 删失规则

#	情况	进展或删失日期	结果
1	基线后无肿瘤评估，并于前两个肿瘤评估周期内死亡	死亡日期	进展
2	基线后无肿瘤评估，且前两个肿瘤评估周期内未死亡	GFH375 首次给药日期	删失
3	基线后有肿瘤评估，未出现疾病进展或死亡	最后一次有效的影像学检查日期	删失
4	基线后有肿瘤评估，首次评估发生 PD，且评估日期距首次给药日期大于两个连续的评估周期	GFH375 首次给药日期	删失
5	基线后有肿瘤评估，首次评估发生 PD，且首次进展日期距首次给药小于等于两	进展日期	进展

	个连续的评估周期		
6	基线后有肿瘤评估，发生 PD（非首次评估），但首次进展日期距上一次影像学检查日期大于两个连续的评估周期	在进展日期之前的最后一次有效的影像学检查日期	删失
7	基线后有肿瘤评估，发生 PD（非首次评估），且首次进展日期距上一次影像学检查日期小于等于两个连续的评估周期	进展日期	进展
8	基线后有肿瘤评估，进展前死亡，且死亡日期距上一次影像学检查日期大于两个连续的评估周期	死亡前最后一次有效的影像学检查日期	删失
9	基线后有肿瘤评估，进展前死亡，且死亡日期距上一次影像学检查日期小于等于两个连续的评估周期	死亡日期	进展
10	在疾病进展或死亡前接受了新的抗肿瘤治疗	接受新的抗肿瘤治疗当天或之前最后一次有效的影像学检查日期（若无影像学检查，则为 GFH375 首次给药日期）	删失

连续两次缺失/无效的肿瘤评估访视判断规则如下：

- 如果 GFH375 首次给药后无任一次肿瘤评价，则连续两次缺失/无效的肿瘤评估定义为是 GFH375 首次给药后 91 天（2*6 周+7 天时间窗）；
- 如果 GFH375 首次给药后有肿瘤评估：
  - 在 GFH375 首次给药 48 周内发生进展/死亡，则连续两次缺失/无效的肿瘤评估是前一次肿瘤评价后 98 天（2*（6 周+7 天时间窗））；
  - 在 GFH375 首次给药 48 周后发生进展/死亡，但进展/死亡前最后一次影像学评估发生在 GFH375 首次给药后 48 周内，则连续两次缺失/无效的肿瘤评估是前一次肿瘤评价后 140 天（6 周+7 天时间窗+12 周+7 天时间窗）；
  - 在 GFH375 首次给药 48 周后发生进展/死亡，且进展/死亡前最后一次影像学评估也发生在 GFH375 首次给药 48 周后，则连续两次缺失/无效的肿瘤评估是前一次肿瘤评价后 182 天（[2*（12 周+7 天时间窗）]）。

3.2.4 缓解持续时间（DoR）

DoR 定义参见 **4.2.4** 章节。DoR 的结束日期应与 PFS 事件的疾病进展或因任何原因导致的死亡的日期一致。对于符合缓解条件之后未出现疾病进展的受试者，则其缓解持续时间的删失时间与 PFS 删失时间相同（参见 3.2.3 节）。

对于 BOR 达确认的 CR 或 PR 的受试者，DoR 的计算方法为：DoR（月）=（PD 或死亡日期或删失日期 – 首次达确认的 CR 或 PR 对应的影像学检查日期 + 1）/30.4375。同时在无需确认 CR 或 PR 的情况下，对 DoR 进行计算。

3.2.5 至缓解时间（TTR）

TTR 定义参见 **4.2.5** 章节。

对于 BOR 达确认的 CR 或 PR 的受试者，TTR 计算方法为：TTR（月）=（首次达确认的 CR 或 PR 对应的影像学检查日期 – GFH375 首次给药日期+1）/ 30.4375。同时在无需确认 CR 或 PR 的情况下，对 TTR 进行计算。

3.2.6 总生存期（OS）

OS 定义参见 **4.2.6** 章节。

总生存期（月）=（死亡日期/删失日期 –GFH375 首次给药日期+ 1）/ 30.4375。

3.3 药代动力学指标

将使用 Phoenix WinNonlin（8.2 版或以上版本）软件中的非房室分析模块，根据实际采样时间对血药浓度数据计算 PK 参数， PK 参数包括：C_{max}、AUC_{0-t}、AUC_{0-inf}、T_{max}、T_{last}、$t_{1/2}$、V_z/F、CL/F、λ_z、MRT、$AUC_{\%_Extrap}$、$C_{trough,ss}$、$C_{max,ss}$、$AUC_{0-t,ss}$、$AUC_{0-tau,ss}$、$AUC_{0-inf,ss}$、CL/F_{ss}、V_z/F_{ss}、R_{ac_Cmax}、$R_{ac_Ctrough}$、R_{ac_AUC}。PK 参数的具体定义以及计算方法参见 **4.4.2** 章节表 11。药代动力学血样计划采集时间点见**错误!未找到引用源。**8 和**错误!未找到引用源。**9。

表 8 I 期药代动力学（PK）样本采集计划表

周期	日	计划采样点（h）	时间窗
1	1	给药前	-1 h
1	1	给药后 1h	±5min
1	1	给药后 2h	±10min
1	1	给药后 4h	±15min
1	1	给药后 6h	±30min
1	1	给药后 8h	±30min
1	1[1]	给药后 12h	±30min
1	2[2]	给药后 24h	±1h
1	3[2]	给药后 48h	±2h
1	4[2]	给药后 72h（D4 给药前采集）	±3h
1	8	给药前	-1h
1	15	给药前	-1h
1	21	给药前	-1h
1	21	给药后 1h	±5min
1	21	给药后 2h	±10min
1	21	给药后 4h	±15min
1	21	给药后 6h	±30min
1	21	给药后 8h	±30min
1	21[1]	给药后 12h	±30min
1	21[2]	给药后 24h	±1h
2	10	给药前	-1h
4	1	给药前	-1h
5	1	给药前	-1h
6	1	给药前	-1h

1. 若为 BID 给药，C1D1 和 C1D21 给药后 12h 的 PK 样本，需在当天第二次给药前采集。
2. 仅适用于 QD 给药，需要给药前采集。

表 9 II 期药代动力学（PK）样本采集计划表

周期	日	计划采样点（h）	时间窗
1	10	给药前	-1 h
1	10	给药后	2-4 h
2	1	给药前	-1 h
2	1	给药后	1-3 h
3	1	给药前	-1 h
3	1	给药后	2-4 h
4	1	给药前	-1 h
5	1	给药前	-1 h
6	1	给药前	-1 h

3.4 安全性分析

3.4.1 研究治疗暴露情况

- 实际暴露时间（月）：（GFH375 末次给药日期 – GFH375 首次给药日期 + 1）/30.4375
- 实际暴露总剂量（mg）：在研究中受试者实际服用的 GFH375 的总剂量，即按照 eCRF 中研究药物服药记录页收集的每日实际服药总剂量求和。
- 服药天数（天）：实际暴露时间（天） – 实际服药量为 0 的天数（天）
- 平均每日暴露量（mg/天）：实际暴露总剂量（mg）/ 服药天数（天）
- 实际剂量强度（mg/天）：实际暴露总剂量（mg）/ 实际暴露时间（天）
- 相对剂量强度（%）：100 % * 实际剂量强度（mg/天）/ 计划剂量强度（mg/天）。其中，计划剂量强度（mg/天）为受试者入组时被分配的治疗剂量组，例如，被分配至 100mg QD 剂量组的受试者的计划剂量强度即为 100mg/天，被分配至 300mg BID 剂量组的受试者的计划剂量强度为 600mg/天。
- 服药依从性（%）：100 % *实际暴露总剂量（mg）/计划暴露总剂量（mg）。其中，计划暴露总剂量按照 eCRF 中研究药物服药记录页收集的每日计划服药总剂量求和。

3.4.2 不良事件

治疗期间不良事件（TEAE）定义为在治疗前未出现，在治疗期间（定义为从研究药物首次给药到末次给药后 30 天内出现或相对于治疗前状态加重的事件。如果受试者 AE 开始日期记录不完整，则依据章节 2.3.5.6 填补规则判断是否属于 TEAE。

TEAE 和研究药物之间的关系被评估为相关或不相关。研究药物相关的 TEAE 将被定义为研究人员认为有关、很可能有关或可能有关的 TEAE；研究药物不相关的 TEAE 包括无关、可能无关的 TEAE。若缺失与研究药物的关系，将被视为与研究药物“相关”。

3.4.3 实验室检查指标

本研究中实验室检查包括血常规、血生化、尿常规、凝血功能、病毒血清学检查、妊娠试验等。

在制作各检查临床评价（正常、异常无临床意义、异常有临床意义）交叉表时，基线后最差结果定义为整个基线后各访视中（包括计划访视与计划外访视）受试者临床评估最差情况，结果从好到差依次为正常、异常无临床意义、异常有临床意义。

3.4.4 生命体征、体格检查及心电图

3.4.4.1 生命体征

生命体征检查的项目包括体温（℃）、脉搏（次/分）、呼吸（次/分）、收缩压（mmHg）以及舒张压（mmHg）。

在制作生命体征的临床评价（正常、异常无临床意义、异常有临床意义）交叉表时，基线后最差结果定义为整个基线后各访视中（包括计划访视与计划外访视）受试者临床评估最差情况，其中“正常”优于“异常无临床意义”，“异常无临床意义”优于“异常有临床意义”。此外，根据表 10 对受试者给药后的生命体征指标是否出现异常变化进行判断。

表 10 生命体征指标较基线发生显著改变判断标准

	高于正常值	低于正常值
收缩压(mmHg)	较基线值增加>=20且数值>=160	较基线值降低>=20且数值<=90
舒张压(mmHg)	较基线值增加>=10且数值>=100	较基线值降低>=10且数值<=50
脉搏 （次/分）	较基线值增加>25%且数值>120	较基线值降低>25%且数值<50
呼吸（次/分）	测量值 < 8	测量值 > 35
体温（C）	测量值>=39.1	-

3.4.4.2 体格检查

完整的体格检查包括一般情况、皮肤、颈部（甲状腺）、眼、耳、鼻、喉、胸部（包括肺）、心脏、腹部、背部、淋巴结、四肢、血管神经系统；如有临床指征，将进行乳房、盆腔、直肠、外生殖器检查。在制作体格检查的临床评价（正常、异常无临床意义、异常有临床意义）交叉表时，基线后最差结果定义为整个基线后各访视中（包括计划访视与计划外访视）受试者临床评估最差情况，其中“正常”优于“异常无临床意义”，“异常无临床意义”优于“异常有临床意义”。

3.4.4.3 心电图

12 导联心电图检查包括：心率（HR）、PR 间期、QRS 间期、QT 间期和 QTcF（Frederica 公式）间期和总体临床意义评估。

若同一访视进行多次检查，对于定量检查结果取平均值进行分析，此外，列表展示所有 12 导联心电图检查结果。

在制作心电图检查的临床评价（正常、异常无临床意义、异常有临床意义）交叉表时，基线取多次测量的最佳结果，基线后访视取多次测量的最差结果，

基线后最差结果定义为整个基线后各访视中（包括计划访视与计划外访视）受试者临床评估最差情况，其中“正常”优于“异常无临床意义”，“异常无临床意义”优于“异常有临床意义”。此外，根据表 11 对受试者给药后的心电图指标是否出现异常变化进行判断。

表 11 心电图指标较基线发生显著改变判断标准

	高于正常值	低于正常值
QTcF(ms)	数值>450且<=480	-
	数值>480且<=500	-
	数值>=501	-
QTcF (ms)相对基线变化最大值	较基线增加>30且<=60	-
	较基线增加>60	-
心率（次/分）	较基线值增加>25%且数值>=100	较基线值降低>25%且数值<=50
PR (ms)	较基线值增加>25%且数值>200	较基线值降低>25%且数值<120
QRS (ms)	较基线值增加>25%且数值>110	-

3.4.5 其他安全性指标

其他安全性指标包括 ECOG 评分。

3.5 生物标志物指标

仅包括针对 II 期 PDAC 受试者的 CA19-9。

4 统计分析

若无特殊说明，本试验 I 期数据和 II 期数据分别单独分析。其中，I 期的数据将按照不同剂量水平和给药方案进行分析汇总；II 期的数据将按照肿瘤类型进行分析汇总。若无特殊说明，对 I 期和 II 期的数据采用相同的统计方法进行分析。

对于事后分析（post hoc analysis），将按瘤种对 I 期受试者的人口学，基线特征，以及疗效指标进行汇总分析。并总结目标剂量下各瘤种的 ORR 结果。

4.1 受试者一般特征

4.1.1 受试者分布

基于所有签署知情同意的受试者，总结受试者筛选成功和筛选失败的例数、百分比，并分类总结筛选失败的原因。基于筛选成功受试者，总结进入各分析集受试者的例数和百分比，同时汇总 I 期剂量递增和回填受试者的例数和百分比。此外，基于 FAS，分类总结受试者终止治疗和结束研究的主要原因。以上分析将对 I 期和 II 期数据分别进行汇总。

对所有受试者筛选及筛选失败原因、终止治疗和结束研究情况列表展示。

4.1.2 方案偏离

为了衡量方案是否被很好地执行，在数据库锁库之前，根据已经收集的信息，结合方案要求，确定所有的方案偏离情况。这些方案偏离情况将由研究团

队评估并归类为重大或轻微方案偏离。基于筛选成功受试者，总结受试者所有重大方案偏离情况。

此外，基于筛选成功受试者，列表展示所有受试者方案偏离情况。

4.1.3 人口统计学信息和基线特征

基于 FAS 分别对受试者人口统计学信息与基线特征进行描述统计，需统计的指标包括：

人口统计学信息

- 性别
- 年龄
- 年龄分层（<65 和>=65 岁，<60 和>=60 岁）
- 民族：汉族、其他
- 身高
- 基线体重
- 基线体重指数（BMI）=体重（kg）/（身高（cm）/100）^{2}，保留 1 位小数。

基线特征

- 基线肿瘤诊断信息
  - 诊断名称：非小细胞肺癌（NSCLC）、胰腺导管腺癌（PDAC）、结直肠癌（CRC）、胆管癌、子宫内膜癌、其他
  - 病理类型（NSCLC、PDAC 和 CRC 适用）
  - 组织学分级：G1（高分化）、G2（中分化）、G3（低分化）、G4（未分化）、未评估、其他
  - 入组时的肿瘤分期
  - 入组时 TNM 阶段-T 分期
  - 入组时 TNM 阶段-N 分期
  - 入组时 TNM 阶段-M 分期
  - 入组时是否有转移
  - 入组时的转移部位
- 病程（月）=（首次接受 GFH375 用药日期-初始病理学诊断日期+1）/30.4375
- 末线治疗发生疾病进展：是、否
- 末线治疗疾病进展至首次治疗时间（月）=（首次接受 GFH375 用药日

期-末次疾病进展日期+1）/30.4375

- 末线治疗疾病进展至首次治疗时间分类：<1 个月，1-3 个月，3-6 个月，≥6 个月
- ECOG 体能状态评分：0 分、1 分
- 吸烟史：从未吸烟、既往吸烟、现在吸烟（II 期 NSCLC 受试者）
- 基线时 PD-L1 表达水平（NSCLC 适用）：低表达 (TPS<1%)、中表达 (TPS 1-49%)、高表达 (TPS>=50%)、非 TPS、未知
- KRAS G12D 突变状态：阴性、阳性、未知
- KRAS G12D 突变率：<5%, 5-20%, 20-50%, ≥50%
- NRS 评分：0 分、1 分、2 分、3 分

此外，基于 FAS，列表展示受试者人口统计学信息、基线特征。

4.1.4 既往及伴随病史

将使用国际医学用语词典（MedDRA 26.0 或更高版本）对受试者的既往及伴随病史进行编码。基于 FAS，根据系统器官分类（SOC）和首选术语（PT）汇总各疾病分类下的受试者例数及百分比。

基于 FAS，列表展示受试者所有既往及伴随病史详情。

4.1.5 既往及合并治疗

4.1.5.1 既往及合并用药

将使用世界卫生组织药物词典（WHODrug ，版本 B3 March 1，2023 或更高版本）对受试者既往及合并用药编码。基于 FAS，根据解剖治疗化学（ATC）分类第 II 级和首选名称（PN）计算受试者例数及百分比。

基于 FAS，对既往用药和合并用药数据进行列表展示。

4.1.5.2 既往/合并非药物治疗

使用 MedDRA 26.0 或更高版本对受试者所有既往/合并非药物治疗编码。基于 FAS，根据系统器官分类（SOC）和首选术语（PT）汇总既往及合并非药物治疗。

此外，列表展示所有既往/合并非药物治疗信息。

4.1.5.3 既往抗肿瘤治疗史

基于 FAS，对以下既往抗肿瘤治疗类别进行总结。

- 既往抗肿瘤药物治疗史总结：
  - 是否有既往抗肿瘤治疗史：是、否
  - 既往药物治疗总线数：0、1、2、3、≥4

- 末次药物治疗类型：1 线、2 线、3 线、4 线、5 线、≥6 线、辅助、新辅助、未知、其他
- 末次药物治疗最佳疗效：完全缓解（CR）、部分缓解（PR）、疾病稳定（SD）、疾病进展（PD）、未评估（NA）、不能评估（NE）、未知（UN）
- 末次药物治疗结束原因：完成治疗计划、疾病进展/复发、毒性不能耐受、其他
- 末次药物治疗结束至首次接受 GFH375 治疗时间（月）

• 既往抗肿瘤手术治疗史总结（不纳入手术目的为诊断性的手术治疗史）：
  - 是否有既往抗肿瘤手术史：是、否
  - 末次手术目的：姑息性、根治性、其他
  - 末次手术治疗至首次接受 GFH375 治疗时间（月）

• 既往抗肿瘤放射治疗史总结：
  - 是否有既往抗肿瘤放射治疗史：是、否
  - 既往放射治疗部位
  - 既往放射治疗目的：新辅助、辅助、姑息性、根治性、其他
  - 末次放射治疗最佳疗效：完全缓解（CR）、部分缓解（PR）、疾病稳定（SD）、疾病进展（PD）、未评估（NA）、不能评估（NE）、未知（UN）
  - 末次放射治疗结束原因：完成治疗计划、疾病进展/复发、毒性不能耐受、其他
  - 末次放射治疗结束至首次接受 GFH375 治疗时间（月）

将使用世界卫生组织药物词典（WHODrug ，版本 B3 March 1，2023 或更高版本）对受试者既往抗肿瘤治疗药物进行编码。基于 FAS，根据解剖治疗化学（ATC）分类第Ⅱ级和首选名称（PN）计算受试者例数及百分比。

使用 MedDRA 26.0 或更高版本对受试者所有既往抗肿瘤手术治疗进行编码。基于 FAS，根据系统器官分类（SOC）和首选术语（PT）汇总既往抗肿瘤手术治疗。此外，列表展示受试者所有既往抗肿瘤治疗相关信息。

4.1.5.4 后续抗肿瘤治疗

基于 FAS，总结受试者的新的抗肿瘤治疗相关信息，包括：

• 接受后续新的抗肿瘤治疗的受试者的例数和百分比
• 研究治疗结束至开始新的抗肿瘤治疗的时间（月）=（新的抗肿瘤治疗开始日期 - GFH375 末次给药日期 + 1）/30.4375
• 治疗类别：药物治疗、放疗、手术

将使用世界卫生组织药物词典（WHODrug，版本 B3 March 1，2023 或更高版本）对受试者后续抗肿瘤治疗药物进行编码。基于 FAS，根据解剖治疗化学（ATC）分类第Ⅱ级和首选名称（PN）计算受试者例数及百分比。

使用 MedDRA 26.0 或更高版本对受试者所有后续抗肿瘤手术治疗进行编码。基于 FAS，根据系统器官分类（SOC）和首选术语（PT）汇总后续抗肿瘤手术治疗。

此外，列表展示受试者后续抗肿瘤治疗的详细信息。

4.2 疗效分析

4.2.1 客观缓解率（ORR）

4.2.1.1 主要分析

I 期和 II 期受试者采用相同的分析方法。

估计目标定义：

- **治疗：**GFH375。
- **研究人群：**KRAS G12D 突变型晚期实体瘤受试者（FAS）。
- **变量：**根据 RECIST 1.1 标准评估是否达到确认的 CR 或 PR。若受试者基线后无任何评价结果，则认为该受试者未缓解。注：对于 NSCLC 和 PDAC，将基于盲态独立中心审查委员会（BICR）评估的结果，其余肿瘤类型基于研究者评估的结果。
- **伴发事件及处理策略：**

伴发事件		处理策略
Inc1	开始新的抗肿瘤治疗	在治策略 （开始抗肿瘤治疗后的评估结果不纳入分析）

- **群体层面汇总：**ORR 及其 90%和 95% 置信区间。

估计目标分析方法：

汇总受试者 BOR 情况，总结 BOR 达到确认的 CR 或 PR 的受试者例数和 ORR，采用 Clopper-Pearson 精确概率法估计 ORR 的 90%和 95% 置信区间（CI）。同时在无需确认 CR 或 PR 的情况下，总结 BOR 情况和 ORR，并提供 ORR 的 90%和 95%CI。将基于研究者或 BIRC 评估基线有可测量病灶的受试者对 BOR 和 ORR 进行分析。此外，绘制所有受试者治疗期间疗效评估结果泳道图、靶病灶直径总和较基线变化率最小的瀑布图，以及所有受试者在治疗期间不同时间点靶病灶直径总和较基线变化率的蜘蛛图。

针对 NSCLC 和 PDAC 受试者，对 BICR 和研究者评估的 BOR 结果的一致性进行汇总。

4.2.1.2 补充分析

1) 对研究人群和变量进行调整

- **研究人群：** FAS 中 NSCLC 和 PDAC 受试者。
- **变量：**研究者根据 RECIST 1.1 标准评估是否达到确认的 CR 或 PR。若受试者基线后无任何评价结果，则认为该受试者未缓解。
- **其他属性：**同主要分析。

分析方法与主要分析相同。

2) 对研究人群进行调整

- **研究人群：** II 期 KRAS G12D 突变型晚期实体瘤受试者（PPS）。
- **其他属性：**同主要分析。

除作图外，分析方法与主要分析相同。

3) 对研究人群和变量进行调整

- **研究人群：** II 期 PPS 中 NSCLC 和 PDAC 受试者。
- **变量：**研究者根据 RECIST 1.1 标准评估是否达到确认的 CR 或 PR。若受试者基线后无任何评价结果，则认为该受试者未缓解。
- **其他属性：**同主要分析。

除作图外，分析方法与主要分析相同。

4.2.1.3 亚组分析

针对 II 期 PDAC 和 NSCLC 受试者，基于 BICR 评估的结果对 CR/PR 需确认情况下的 ORR 进行亚组分析，并采用森林图对亚组分析的结果进行展示。具体亚组参见 **2.5 章节**。

4.2.2 疾病控制率（DCR）

4.2.2.1 主要分析

I 期和 II 期受试者采用相同的分析方法。

估计目标定义：

- **变量：**根据 RECIST 1.1 标准评估达到确认的 CR 或 PR、SD 的受试者百分比。若受试者基线后无评价结果，则认为该受试者为未达 CR/PR/SD。注：对于 NSCLC 和 PDAC，将基于盲态独立中心审查委员会（BICR）评估的结果，其余肿瘤类型基于研究者评估的结果。
- **群体层面汇总：**DCR 及其 90%和 95% 置信区间。
- **其他属性：**同客观缓解率主要分析估计目标。

估计目标分析方法：

总结 BOR 达到确认的 CR 或 PR、SD 的受试者例数和 DCR，采用 Clopper-Pearson 精确概率法估计 DCR 的双侧 90%和 95% CI。同时在无需确认 CR 或 PR 的情况下，总结 BOR 达到确认的 CR 或 PR、SD 的受试者例数和 DCR，并提供

DCR 的 90%和 95%CI。将基于研究者或 BIRC 评估基线有可测量病灶的受试者对 BOR 和 DCR 进行分析。

4.2.2.2 补充分析

1) 对研究人群和变量进行调整

- **研究人群：** FAS 中 NSCLC 和 PDAC 受试者。
- **变量：**研究者根据 RECIST 1.1 标准评估是否达到确认的 CR 或 PR、SD。若受试者基线后无任何评价结果，则认为该受试者未达 CR/PR/SD。
- **其他属性：**同主要分析。

分析方法与主要分析相同。

2) 对研究人群进行调整

- **研究人群：**II 期 KRAS G12D 突变型晚期实体瘤受试者（PPS）。
- **其他属性：**同主要分析。

分析方法与主要分析相同。

3) 对研究人群和变量进行调整

- **研究人群：** II 期 PPS 中 NSCLC 和 PDAC 受试者。
- **变量：**研究者根据 RECIST 1.1 标准评估是否达到确认的 CR 或 PR、SD。若受试者基线后无任何评价结果，则认为该受试者未达 CR/PR/SD。
- **其他属性：**同主要分析。

分析方法与主要分析相同。

4.2.3 无进展生存期（PFS）

4.2.3.1 主要分析

I 期和 II 期受试者采用相同的分析方法。

估计目标定义：

- **治疗：**GFH375。
- **研究人群：**KRAS G12D 突变型晚期实体瘤受试者（FAS）。
- **变量：**自 GFH375 首次给药开始至首次出现疾病进展，或因任何原因导致死亡的时间，以先发生为准。注：对于 NSCLC 和 PDAC，将基于盲态独立中心审查委员会（BICR）评估的结果，其余肿瘤类型基于研究者评估的结果。
- **伴发事件及处理策略：**

伴发事件		处理策略
Inc2	未发生进展或死亡的情况下，接受新的抗肿瘤治疗。	假想策略 （删失在开始新的抗肿瘤治疗前的末次有

		效的影像学检查日期）
Inc3	疾病进展或死亡日期距上一次影像学检查日期大于两个连续的评估周期	假想策略 （删失在连续两次或以上缺失评估之前的末次有效的影像学检查日期，若此前无任何有效的影像学检查结果，则删失在GFH375首次给药日期）

- **群体层面汇总：**PFS 的四分位数及不同时间点的 PFS 率。

估计目标分析方法：

总结受试者事件发生及删失情况。采用 Kaplan-Meier 法估计 PFS 的四分位数及采用 Brookmeyer and Crowley 法估计的双侧 90%和 95%CI，计算各时间点对应的 PFS 率及其双侧 90%和 95%置信区间。绘制 Kaplan-Meier 生存曲线。

此外，使用 Reverse Kaplan-Meier 法估计 PFS 的中位随访时间以及采用 Brookmeyer and Crowley 法估计的双侧 90%和 95％置信区间。无进展生存期的随访时间指自 GFH375 首次给药开始到末次肿瘤评价的时间。如果出现疾病进展或死亡，则 PFS 随访时间将删失至疾病进展或死亡日期（以先出现为准）。

对于 I 期阶段，当分析组的样本量小于 10 例时，将按受试者单独列出 PFS，不采用 Kaplan-Meier 方法进行分析。

4.2.3.2 补充分析

1) 对研究人群和变量进行调整

- **研究人群：** FAS 中 NSCLC 和 PDAC 受试者。
- **变量：**基于研究者评估的结果，自 GFH375 首次给药开始至首次出现疾病进展，或因任何原因导致死亡的时间，以先发生为准。
- **其他属性：**同主要分析。

分析方法与主要分析相同。

4.2.4 缓解持续时间（DoR）

4.2.4.1 主要分析

估计目标定义：

- **治疗：**GFH375。
- **研究人群：** FAS 中 BOR 达到确认的 CR 或 PR 的受试者。注：对于 NSCLC 和 PDAC，将基于盲态独立中心审查委员会（BICR）评估的结果，其余肿瘤类型基于研究者评估的结果。
- **变量：**自首次获得 CR 或 PR 时，至首次出现疾病进展，或发生因任何原因导致的死亡的时间，以先发生者为准。注：对于 NSCLC 和 PDAC，将基于盲态独立中心审查委员会（BICR）评估的结果，其余肿瘤类型基于研究者评估的结果。
- **伴发事件及处理策略：**同 PFS。

- **群体层面汇总：**DoR 的四分位数及不同时间点的 DoR 率。

估计目标分析方法：

总结受试者事件发生及删失情况。采用 Kaplan-Meier 法估计 DoR 的四分位数及采用 Brookmeyer and Crowley 法估计的双侧 90%和 95%CI，计算各时间点对应的 DoR 率及其双侧 90%和 95%置信区间。绘制 Kaplan-Meier 生存曲线。将基于研究者或 BIRC 评估基线有可测量病灶的受试者对 DoR 进行分析。

对于 I 期阶段，当分析组的样本量小于 10 例时，将按受试者单独列出 DoR，不采用 Kaplan-Meier 方法进行分析。

4.2.4.2 补充分析

1) 对研究人群和变量进行调整

- **研究人群：**基于研究者评估的结果，FAS 中 BOR 达到确认的 CR 或 PR 的 NSCLC 和 PDAC 受试者。
- **变量：**基于研究者评估的结果，自首次获得 CR 或 PR 时，至首次出现疾病进展，或发生因任何原因导致的死亡的时间，以先发生者为准。
- **其他属性：**同主要分析。

分析方法与主要分析相同。

2) 对研究人群进行调整

- **研究人群：**FAS 中 BOR 达到 CR 或 PR 的受试者，其中 CR 和 PR 无需按照 RECIST1.1 规则进行确认。注：对于 NSCLC 和 PDAC，将基于盲态独立中心审查委员会（BICR）评估的结果，其余肿瘤类型基于研究者评估的结果。
- **其他属性：**同主要分析。

分析方法与主要分析相同。

3) 对研究人群和变量进行调整

- **研究人群：**基于研究者评估的结果，FAS 中 BOR 达到 CR 或 PR 的 NSCLC 和 PDAC 受试者，其中 CR 和 PR 无需按照 RECIST1.1 规则进行确认。
- **变量：**基于研究者评估的结果，自获得 CR 或 PR 时，至首次出现疾病进展，或发生因任何原因导致的死亡的时间，以先发生者为准。
- **其他属性：**同主要分析。

分析方法与主要分析相同。

4.2.5 至缓解时间（TTR）

4.2.5.1 主要分析

估计目标定义：

- **治疗**：GFH375。
- **研究人群**：FAS 中达到确认的 CR 或 PR 的受试者。注：对于 NSCLC 和 PDAC，将基于盲态独立中心审查委员会（BICR）评估的结果，其余肿瘤类型基于研究者评估的结果。
- **变量**：自接受研究用药开始至首次达到确认的 CR 或 PR 的时间，并以最早观察到 CR 或 PR 的时间为准。注：对于 NSCLC 和 PDAC，将基于盲态独立中心审查委员会（BICR）评估的结果，其余肿瘤类型基于研究者评估的结果。
- **伴发事件及处理策略**：同 ORR。
- **群体层面汇总**：平均值、标准差、中位数、Q1、Q3、最小值和最大值。

估计目标分析方法：

对 TTR 进行描述性分析，包括获得 CR 或 PR 的受试者例数，平均值、标准差、中位数、Q1、Q3、最小值和最大值。

对于 I 期阶段，当分析组的样本量小于 10 例时，将按受试者单独列出 TTR。

4.2.5.2 补充分析

1) 对研究人群和变量进行调整

- **研究人群**：基于研究者评估的结果，FAS 中 BOR 达到确认的 CR 或 PR 的 NSCLC 和 PDAC 受试者。
- **变量**：基于研究者评估的结果，自接受研究用药开始至首次达到确认的 CR 或 PR 的时间，并以最早观察到 CR 或 PR 的时间为准。
- **其他属性**：同主要分析。

分析方法与主要分析相同。

2) 对研究人群进行调整

- **研究人群**：FAS 中 BOR 达到 CR 或 PR 的受试者，其中 CR 和 PR 无需按照 RECIST1.1 规则进行确认。注：对于 NSCLC 和 PDAC，将基于盲态独立中心审查委员会（BICR）评估的结果，其余肿瘤类型基于研究者评估的结果。
- **其他属性**：同主要分析。

分析方法与主要分析相同。

3) 对研究人群和变量进行调整

- **研究人群**：基于研究者评估的结果，FAS 中 BOR 达到 CR 或 PR 的 NSCLC 和 PDAC 受试者，其中 CR 和 PR 无需按照 RECIST1.1 规则进行确认。
- **变量**：基于研究者评估的结果，自接受研究用药开始至首次达到确认

的 CR 或 PR 的时间，并以最早观察到 CR 或 PR 的时间为准。

- **其他属性：**同主要分析。

分析方法与主要分析相同。

4.2.6 总生存期（OS）

估计目标定义：

- **治疗：**GFH375。
- **研究人群：**KRAS G12D 突变型晚期实体瘤受试者（FAS）。
- **变量：**自接受研究用药开始至因任何原因导致的死亡的时间。对于未观察到死亡事件的受试者，删失在末次获知生存时。
- **伴发事件及处理策略：**

伴发事件		处理策略
Inc1	开始新的抗肿瘤治疗	疗法策略 （若死亡，按照死亡事件处理；若未死亡，删失在末次获知生存时）

- **群体层面汇总：**OS 的四分位数及不同时间点的 PFS 率。

估计目标分析方法：

总结受试者事件发生及删失情况。采用 Kaplan-Meier 法估计 OS 的四分位数及采用 Brookmeyer and Crowley 法估计的双侧 90%和 95%CI，计算各时间点对应的 OS 率及其双侧 90%和 95%置信区间。绘制 Kaplan-Meier 生存曲线。

此外，采用 Reverse Kaplan-Meier 法估计 OS 随访时间的中位数及采用 Brookmeyer and Crowley 法估计的双侧 90%和 95%CI。OS 随访时间指自接受研究用药开始到最后已知生存日期的时间。如果出现死亡，则 OS 随访时间将删失至死亡日期。

对于 I 期阶段，当分析组的样本量小于 10 例时，将按受试者单独列出 OS，不采用 Kaplan-Meier 方法进行分析。

4.3 安全性分析

DLT 分析基于 DDS，其余所有安全性分析基于 SS。

4.3.1 药物暴露情况

对 GFH375 的实际暴露时间（月），实际暴露剂量（mg），服药天数（天），平均每日暴露剂量（mg/天），实际剂量强度（mg/天），相对剂量强度（%），服药依从性（%）进行描述性统计。并按照< 80%，80% ~120%，>120%对相对剂量强度和服药依从性进行分类汇总。

汇总发生计划剂量调整和剂量降低的受试者例数及百分比，并总结相应的

原因。计划剂量调整指计划给药剂量相较于前一次计划给药剂量发生变化，计划剂量降低指计划给药剂量小于前一次不为 0 的计划给药剂量（即两次计划给药间的比较不考虑期间暂停用药的情况），且降低后的计划给药剂量不为 0。汇总发生实际给药剂量与计划剂量不一致的受试者例数及百分比，并总结相应的原因。

汇总发生计划剂量降低与计划剂量暂停的次数，并总结不同次数下的受试者例数和百分比。

列表展示受试者 GFH375 的用药情况。

4.3.2 剂量限制毒性（DLT）

汇总 I 期试验中出现 DLT 的受试者例数和百分比，同时对 DLT 的类型进行汇总。

将使用 MedDRA 26.0 或更高版本字典对 DLT 进行编码。按照 SOC、PT 和严重程度对 DLT 的例数和百分比进行汇总。

基于先验无信息概率分布$beta(0.05,0.05)$，则每组 DLT 率的后验概率分布为$beta\,(y_j + 0.05, n_j - y_j + 0.05)$，进而计算每组后验平均DLT率。后验平均DLT率的计算公式为$p_j = \frac{y_j+0.05}{n_j+0.1}$，其中$n_j$为每组的受试者例数，$y_j$为每组发生 DLT 的受试者例数。

每组 DLT 率和后验平均 DLT 率分别采用保序回归进行估计，其中 DLT 率的权重选择每组受试者例数，后验平均 DLT 率的权重选择后验分布方差的倒数（按照 BOIN 设计）$w_j = \frac{(n_j+0.1)^2（n_j+0.1+1）}{（y_j+0.05）（n_j-y_j+0.05）}$，其中$n_j$为每组的受试者例数，$y_j$为每组发生 DLT 的受试者例数。

所有 DLT 情况都将进行列表展示。

4.3.3 不良事件

将使用 MedDRA 26.0 或更高版本字典对 AE 进行编码，并基于 NCI CTCAE V5.0 对 AE 的严重程度进行分级。对 TEAE 进行表格总结并对所有 AE 进行列表展示。

基于以下分类汇总受试者例数和百分比：

- TEAE
  - 任何TEAE
  - CTCAE 3级或以上的TEAE
  - 导致GFH375降低剂量的TEAE

- 导致GFH375暂停给药的TEAE
- 导致GFH375终止给药的TEAE
- 治疗期间严重不良事件（TESAE）
- CTCAE=5级的TEAE
- 符合海氏法则的TEAE

• 与 GFH375 相关的 TEAE（TRAE）

- 任何TRAE
- CTCAE 3级或以上的TRAE
- 导致GFH375降低剂量的TRAE
- 导致GFH375暂停给药的TRAE
- 导致GFH375终止给药的TRAE
- 治疗期间治疗相关严重不良事件（TRSAE）
- CTCAE=5级的TRAE
- 符合海氏法则的TRAE

将基于SOC，PT和严重程度总结发生以下各类事件的受试者例数和百分比：

- TRAE
- TEAE
- CTCAE 3级或以上的TEAE
- CTCAE 3级或以上的TRAE
- TESAE
- TRSAE
- 导致GFH375降低剂量的TEAE
- 导致GFH375降低剂量的TRAE
- 导致GFH375暂停给药的TEAE
- 导致GFH375暂停给药的TRAE

- 导致GFH375终止给药的TEAE
- 导致GFH375终止给药的TRAE
- 符合海氏法则的TEAE
- 符合海氏法则的TRAE

将基于SOC和PT总结发生以下各类事件的受试者例数和百分比：

- TEAE
- TRAE
- CTCAE 3级或以上的TESAE
- CTCAE 3级或以上的TRSAE
- 导致GFH375降低剂量的CTCAE 3级或以上的TEAE
- 导致GFH375降低剂量的CTCAE 3级或以上的TRAE
- 导致GFH375暂停给药的CTCAE 3级或以上的TEAE
- 导致GFH375暂停给药的CTCAE 3级或以上的TRAE
- 导致GFH375终止给药的CTCAE 3级或以上的TEAE
- 导致GFH375终止给药的CTCAE 3级或以上的TRAE
- CTCAE=5级的TEAE
- CTCAE=5级的TRAE

将基于 PT 总结发生以下各类事件的受试者例数和百分比：

- 任一组别发生率≥10%的 TEAE
- 任一组别发生率≥10%的 TRAE
- 任一组别发生率≥5%的 CTCAE 3 级或以上的 TEAE
- 任一组别发生率≥5%的 CTCAE 3 级或以上的 TRAE

将基于 PT 总结发生肝脏毒性的受试者例数和百分比，PT 包括丙氨酸氨基转移酶升高、天门东氨酸氨基转移酶升高、血胆红素升高、肝功能异常、高胆红素血症、肝损伤、γ-谷氨酰转移酶升高、血碱性磷酸酶升高、血乳酸脱氢酶升高。

在计算 AE 发生的例数时，如果某个受试者发生相同的 AE（相同的 PT）超过一次，则在该 PT 下只计算一次。类似地，如果某个受试者在相同 SOC 分类

中发生的 AE 超过一次，在该 SOC 分类下也只计算一次。在基于严重程度总结 AE 时，对于同一受试者，如果在研究过程中发生相同的 AE 超过一次，则取级数最高的那次参与计算。

所有不良事件的发生情况将以列表展示。此外，对于严重不良事件、死亡的不良事件还将单独列表展示。

4.3.4 实验室检查

病毒血清学检查、妊娠试验结果仅列表展示，其余检查项目将各访视检测结果进行描述统计分析并列表展示。

对于定量检查结果，将基于各计划访视和其相对基线变化分别总结，计算例数、均值、标准差、中位数、最小值、最大值等统计量。对于临床评估的定性结果，以交叉表的形式展示基线后最差结果相对基线结果的变化情况和基线后末次访视结果情况。

对于血常规、血生化、凝血功能等可以依据 NCI CTCAE（5.0 版）对异常情况的严重程度分级（0 至 4 级，其中 0 级表示正常）的实验室检查参数，以交叉表的形式总结基线后 CTCAE 分级较基线最大变化情况和基线后末次访视结果情况。汇总基线后实验室检查参数 CTCAE 分级增加的情况。待评估的实验室检查参数 CTCAE 分级规则参见附录 1。对于没有相对应 CTCAE 分级的血常规、血生化、尿常规、凝血功能的定量参数，将根据其正常值范围分类（低于正常值，正常，高于正常值，低于&高于正常值[基线后低于正常值和高于正常值的情况都出现过]），以交叉表的形式总结基线后最差情况较基线的变化情况和基线后末次访视结果情况。

基于血生化中肝功能相关的检查结果，汇总基线后以下类别的受试者例数和百分比（ULN：正常值上线）：

ALT > 3 * ULN，ALT > 5 * ULN，ALT > 10 * ULN，ALT > 20 * ULN；

AST > 3 * ULN，AST > 5 * ULN，AST > 10 * ULN，AST > 20 * ULN；

（ALT 或 AST）> 3 * ULN，（ALT 或 AST）> 5 * ULN，（ALT 或 AST）> 10 * ULN，（ALT 或 AST）> 20 * ULN；

TBIL > 2 * ULN；

AKP > 1.5 * ULN；

ALT > 3 * ULN 且 TBIL > 2 * ULN 同时发生；

AST > 3 * ULN 且 TBIL > 2 * ULN 同时发生；

（ALT 或 AST）> 3 * ULN 且 TBIL > 2 * ULN 同时发生；

（ALT 或 AST）> 3 * ULN 且 TBIL > 1.5 * ULN 同时发生；

（ALT 或 AST）> 3 * ULN，TBIL > 2 * ULN 且 AKP ≥ 2 * ULN 同时发生；

（ALT 或 AST）> 3 * ULN，TBIL > 2 * ULN 且（AKP < 2 * ULN 或缺失）同时发生。

4.3.5 生命体征、体格检查及心电图

4.3.5.1 生命体征

将总结生命体征检查项目各计划访视的观测值及其相对基线变化。基于生命体征的整体临床评价（正常、异常无临床意义、异常有临床意义）总结基线后最差评价（包含非计划访视）和末次访视时相对基线的交叉表。

此外，总结给药后心电图指标出现异常变化（表 10）的受试者例数和百分比（以给药后最差结果进行汇总）。

此外，列表展示受试者所有生命体征测量结果。

4.3.5.2 体格检查

对于体格检查的临床评价结果（正常、异常无临床意义、异常有临床意义），制作基线后最差结果（包含非计划访视）和末次访视时相对基线结果变化的交叉表。

此外，列表展示受试者所有体格检查结果。

4.3.5.3 心电图

对于定量检查结果，总结各计划访视的观测值及其相对基线的变化。对临床意义（正常、异常无临床意义、异常有临床意义），制作基线后最差评估结果（包括计划访视和计划外访视）和末次访视时相对基线检查结果的交叉表。

此外，总结给药后心电图指标出现异常变化（表 11）的受试者例数和百分比（以给药后最差结果进行汇总）。

所有心电图检查结果将在列表中展示。

4.3.6 死亡情况

按试验观察期（试验期间，治疗期，治疗后期）对死亡受试者的例数和死亡原因进行总结，并对死亡情况进行列表。试验期间的死亡按试验观察期分为：

- 试验期间死亡：首次研究治疗至试验结束（包括生存随访）期间的死亡。
- 治疗期死亡：首次研究治疗至末次研究用药后 30 天内的死亡；
  - 开始新抗肿瘤治疗之后的死亡。
- 治疗后期死亡：末次研究用药后 30 天之后直至试验结束期间的死亡。

4.3.7 其他安全性分析

对 ECOG 评分状态制作各计划访视和基线后最差评估结果（包括计划访视和计划外访视）和末次访视时相对基线检查结果的交叉表。此外，列表展示受试者所有 ECOG 评分结果。

4.4 药代动力学分析

PK 分析将基于 PKAS。低于定量下限（LLOQ）的数据以 BQL 标记。

PK 分析按照以下规则进行处理：

- 按照实际采样时间计算 PK 参数；
- 低于定量下限（LLOQ）的所有血药浓度值，在进行 PK 参数计算、绘图时在 T_{max} 之前的按照“0”处理，在 T_{max} 之后，按照缺失处理；但描述性统计分析时，均按“0”处理，并注明每个时间点 BQL 数量；
- 在计算各时间点浓度的描述性统计量时，不纳入超窗的数据；只有在特定采样时间点有至少三分之二的个体数据达到或超过 BQL，才会计算平均值、标准差和变异系数等，否则该采样点的描述性统计量不被计算，并以“NC”表示。在绘制平均药时曲线图时，不纳入超窗的数据；若给药后特定采样时间点有至少三分之一的个体数据低于 BQL，则该点不在图上进行展示。

对于每个 PK 采样周期，满足以下条件的受试者，该 PK 采样周期的血药浓度数据将不纳入汇总分析（包括按组别进行的描述性统计和平均血药浓度-时间曲线的绘制），但仍需绘制个体血药浓度-时间曲线，并进行列表展示。基于该血药浓度数据计算的 PK 参数将不纳入分析，仅进行列表展示并标记。

- 如果受试者服用试验药物后，在给药后 3h 内发生呕吐；
- 其他显著影响 PK 评价的方案偏离或 AE。

4.4.1 血药浓度分析

在 PK 分析中，浓度以实验室提供的为准。浓度数据及单位将按从实验室收到的原始数据展现。

对 GFH375 血药浓度数据按照方案规定的采样时间做描述性统计，I 期汇总将按照不同剂量组和给药频率呈现，II 期汇总将按照不同瘤种呈现。包括受试者例数、BQL 例数、算术均值、标准差、算术变异系数（CV%）、中位数、最小值、最大值、几何均值和几何变异系数（GCV%）。

对 I 期血药浓度数据绘制药-时曲线，包括首次给药和多次给药后的药-时曲线。按计划采血时间点，绘制平均血药浓度-时间曲线（线性和半对数）；按实际采血时间点，绘制个体血药浓度-时间曲线图（线性和半对数）。

GCV%的计算公式如下：

$$GCV\%=\sqrt{\exp^{(\ln(Geo\ SD))^2}-1}\times 100\%$$

GCV%的参考 SAS 程序如下：

GCV%=sqrt(exp(SD**2)-1)*100，SD 为原始数据取自然对数后的标准差。

列表展示所有受试者的血药浓度-时间数据，并在列表中标注 BQL。

4.4.2 药代动力学参数分析

PK 参数分析仅针对 I 期数据。对 PK 参数按照不同剂量组和给药频率进行汇总分析，包括例数和缺失数、算术均值、标准差、算术变异系数（CV%）、

中位数、Q1、Q3、最小值、最大值以及几何均值和几何变异系数（GCV%）。但 T_{max} 和 T_{last} 将仅以例数和缺失数、中位数、Q1、Q3、最小值和最大值进行描述。具体 PK 参数见表 12。

表 12 PK 参数列表

参数	WNL 术语	定义	计算方法
C_{max}	Cmax	峰浓度	由观测数据直接得出
AUC_{0-t}	AUClast	从0时到最后一个可测定浓度的采集时间 t 的药物浓度-时间曲线下面积	线性/对数梯形法（Linear Up Log Down）†
AUC_{0-tau}	AUC0-12h 或 AUC0-24h	从 0 时到 12h（BID 组）或 24h（QD 组）的药物浓度-时间曲线下面积	线性/对数梯形法（Linear Up Log Down）†
AUC_{0-inf}	AUCINF_obs	从0时推算到无穷大时间点的药-时曲线下面积	$AUC_{0-inf} = AUC_{0-t} + C_t/\lambda_z$，$C_t$ 是最后一个可测量的时间点对应的血药浓度
T_{max}	Tmax	达峰时间	由观测数据直接得出
T_{last}	Tlast	最后一个可测定浓度的采集时间	由观测数据直接得出
$t_{1/2}$	HL_Lambda_z	消除半衰期	$t_{1/2} = \ln（2）/\lambda_z$，注：只有在 log-线性下降时的数据点可在回归中使用
V_z/F	Vz_F_obs	表观分布容积	$V_z/F = Dose/（AUC_{0-inf} * \lambda_z）$
CL/F	Cl_F_obs	表观清除率	单次给药：CL/F =Dose/ AUC_{0-inf}
λ_z	Lambda_z	末端消除速率常数	基于对数浓度-时间曲线的消除相进行线性回归计算
MRT	MRTINF_obs	平均滞留时间	$MRT=AUMC_{0-inf} / AUC_{0-inf}$
$AUC_{\%_Extrap}$	AUC_%Extrap_obs	外推面积百分比	$AUC_{\%_Extrap} = (AUC_{0-inf} - AUC_{0-t}) / AUC_{0-inf} *100\%$
$C_{trough,ss}$	Ctau	稳态谷浓度	由观测数据直接得出
$C_{max,ss}$	Cmax	稳态峰浓度	由观测数据直接得出
$AUC_{0-t,ss}$	AUClast	从零点时间到最后一个计量浓度（C0-t）时间的稳态血药浓度-时间曲线下面积	线性/对数梯形法（Linear Up Log Down）†
$AUC_{0-tau,ss}$	AUC_TAU	从零时至 tau 时的血药浓度-时间曲线下面积，其中 tau 为给药间隔。	线性/对数梯形法（Linear Up Log Down）†

$AUC_{0\text{-}inf,ss}$	AUCINF_obs	从零点时间到推算的无穷时间的稳态血药浓度-时间曲线下面积	$AUC_{0\text{-}inf,ss} = AUC_{0\text{-}t,ss} + C_{ss,last}/\lambda_z$，$C_{ss,last}$是最后一个可测量的时间点（$T_{last}$）对应的血药浓度
$T_{max,ss}$	Tmax	稳态达峰时间	由观测数据直接得出
CL/F_{ss}	CLss_F	稳态表观清除率	CL/F_{ss} =Dose/ $AUC_{0\text{-}tau,ss}$
V_z/F_{ss}	Vz_F	稳态表观分布容积	$V_z/F_{ss} = MRT_{0\text{-}inf}$* CL/F_{ss}
R_{ac_Cmax}	RacCmax	基于 C_{max} 计算的蓄积比	$R_{ac_Cmax} = C_{max,ss}$（多次给药）/C_{max}（首次给药）
$R_{ac_Ctrough}$	RacCtrough	基于 C_{trough} 计算的蓄积比	$C_{trough,ss}$（多次给药）/C_{trough}（首次给药）
R_{ac_AUC}	RacAUC	基于 $AUC_{0\text{-}tau}$ 计算的蓄积比	R_{ac_AUC} = $AUC_{0\text{-}tau}$（多次给药）/$AUC_{0\text{-}tau}$（首次给药）

†对于浓度上升段，曲线下面积将会使用线性梯形法则来计算，对于浓度下降段，将使用对数线性梯形法则（线性向上-对数向下梯形法则）。

λ_z的计算遵循以下规则：

- 消除相至少有 3 个可测量采样点（第一个样点必须大于 T_{max}）；
- 浓度是下降的（λ_z必须是正值）；
- 校正的决定系数（R^2_{adj}）≥ 0.8；
- $AUC_{\%_Extrap}$ ≤20%。

当R^2_{adj} < 0.8或$AUC_{\%_Extrap}$>20%，或 λ_z 值无法准确计算时（缺失为空），将不汇总 λ_z及与其相关的其他PK参数（$t_{1/2}$、$AUC_{0\text{-}inf}$、CL/F、V_z/F、$AUC_{\%_Extrap}$、MRT），但仍将在列表中展示，并标记。

4.4.3 剂量比例化关系分析

剂量比例化关系分析仅针对 I 期数据。采用 Power 模型，对首次给药和多次给药药代动力学参数（C_{max}、$AUC_{0\text{-}t}$ 和 $AUC_{0\text{-}inf}$）和剂量做自然对数转化后拟合线性回归模型，分析药物暴露和剂量的线性关系。

Power 模型的公式为：

$\ln [PK]=\alpha+\beta*\ln [Dose] +\varepsilon$

其中 PK 为以上各药代动力学参数，α 为截距，β 为斜率，ε 为随机误差，Dose 为给药剂量组。

参考 SAS 程序如下：

```
proc glm data = pkdata;
    model ln[pk] = ln[dose] / clparm alpha=0.1;
    ods output parameterestimates=parameterestimates;
run;
```

将使用置信区间法对药代动力学参数与剂量之间的线性关系进行评价，对斜率（β）的 90%置信区间与判定区域进行比较，如果 β 的 90%置信区间完全落在判定区域内，则认为药代动力学参数与剂量之间的线性关系成立，即：

$$1+\frac{\ln(\theta_L)}{\ln(r)}< \beta <1+\frac{\ln(\theta_H)}{\ln(r)}$$

其中，θ_L=0.8，θ_H=1.25，r 为最高剂量组与最低剂量组的比值。

4.5 生物标志物分析

针对 II 期 PDAC 受试者，对 CA19-9 进行汇总。对定量指标，总结例数、平均值、标准差、中位数、最小值和最大值；对分类指标，总结各类例数及百分比。

对 CA19-9 进行列表展示。

5 期中分析与安全监查委员会（SMC）

5.1 期中分析

将分别对 NSCLC、PDAC、CRC 进行无效性中期分析。对于单个瘤种，计划在约 35 例受试者（包括 I 期接受 RP2D 治疗的受试者和 II 期受试者）至少有一次基线后影像学肿瘤评估或提前退出研究时进行。考虑实际临床操作的原因，允许中期分析时的受试者例数与计划例数有所差别。期中分析过程中，项目不停止入组。

期中分析时，将分别针对 NSCLC、PDAC、CRC 的 ORR，采用贝叶斯预测概率的方法进行无效性分析。允许（但不强制）因缺乏有效性证据而提前终止对相应瘤种的研究。

基于观察到的获得缓解（CR/PR）的 II 期受试者例数计算预测成功概率（PPoS），如果 PPoS < 0.2，则允许（但不强制）因为缺少有效性证据而提前终止入组。PPoS < 0.2 的对应的终止标准见下表：

瘤种	受试者例数	建议终止试验，当缓解受试者例数≤
NSCLC	20 ~ 21	3
	22 ~ 25	4
	26 ~ 29	5
	30 ~ 33	6
	34 ~ 37	7
	38 ~ 41	8
	42 ~ 45	9
PDAC	25 ~ 26	2

	27 ~ 33	3
	34 ~ 39	4
	40 ~ 45	5
CRC	20 ~ 23	1
	24 ~ 30	2
	31 ~ 37	3
	38 ~ 43	4
	44 ~ 48	5

*受试者例数：至少有一次基线后影像学肿瘤评估或提前退出研究（至少满足其一）的 I 期接受 RP2D 治疗的受试者和 II 期受试者数。

上述计划的中期分析不强制进行，在达到中期分析计划的时间点前，如果有足够的安全性和有效性综合数据支持，可以省略该中期无效性分析。

5.2 安全监查委员会

本研究将成立由研究者及申办方组成的安全性监查委员会（SMC）。SMC 将从第一位受试者首次给药开始持续审查安全性数据，直至研究结束。在剂量递增及扩展阶段，SMC 成员将审阅安全性数据、PK 数据等，以决定下一个剂量的入组或者探索潜在的其他剂量组，并推荐合适的 RDE 及 RP2D。

研究期间，若研究者及申办方均认为受试者存在安全性风险或已达到耐受限度，剂量递增或研究治疗将立即停止。

详细信息请参阅 SMC 章程。

6 对原分析计划的修改

暂无。

7 参考文献

暂无。

附录 1 待评估的实验室检查参数 CTCAE（V5.0）分级规则

参数	CTCAE V5.0 名称	分级 1	分级 2	分级 3	分级 4
血红蛋白浓度（HGB）	贫血	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	-
血红蛋白浓度（HGB）	血红蛋白增高	相对ULN增加 0 -2 g/dL	相对ULN增加 2 -4 g/dL	相对ULN增加 ＞4 g/dL	-
白细胞计数（WBC）	白细胞数降低	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000 - 1000/mm^3; <2.0 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
白细胞计数（WBC）	白细胞数增多	-	-	>100,000/mm^3;	
淋巴细胞（LY）计数	淋巴细胞计数降低	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
淋巴细胞（LY）计数	淋巴细胞计数增高	-	>4000/mm^3 - 20,000/mm^3, >4 x 10^9/L – 20 x 10^9/L	>20,000/mm^3; >20 x 10^9/L	-
中性粒细胞计数（ANC）	中性粒细胞计数降低	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000 - 500/mm^3; <1.0 - 0.5 x 10^9 /L	<500/mm^3; <0.5 x 10^9 /L
血小板计数（PLT）	血小板计数降低	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10^9 /L	<25,000/mm^3; <25.0 x 10^9 /L
丙氨酸氨基转移酶（ALT）	丙氨酸氨基转移酶增高	>ULN - 3.0 x ULN（基线值正常）；基线值的 1.5～3.0 倍（如基线值不正常）	>3.0 - 5.0 x ULN （基线值正常）；基线值的 3.0～5.0 倍（如基线值不正常）	>5.0 - 20.0 x ULN （基线值正常）；基线值的 5.0～20.0 倍（如基线值不正常）	>20.0 x ULN（基线值正常）；>基线值的 20.0 倍（如基线值不正常）
天冬氨酸氨基转移酶（AST）	天冬氨酸氨基转移酶增高	>ULN - 3.0 x ULN （基线值正常）；基线值的 1.5～3.0 倍（如基线值不正常）	>3.0 - 5.0 x ULN（基线值正常）；基线值的 3.0～5.0 倍（如基线值不正常）	>5.0 - 20.0 x ULN（基线值正常）；基线值的 5.0～20.0 倍（如基线值不正常）	>20.0 x ULN（基线值正常）；>基线值的 20.0 倍

参数	CTCAE V5.0 名称	分级 1	分级 2	分级 3	分级 4
					（如基线值不正常）
碱性磷酸酶（ALP）	碱性磷酸酶增高	>ULN - 2.5 x ULN（基线值正常）；基线值的 2.0～2.5 倍（如基线值不正常）	>2.5 - 5.0 x ULN（基线值正常）；基线值的 2.5～5.0 倍（如基线值不正常）	>5.0 - 20.0 x ULN（基线值正常）；基线值的 5.0～20.0 倍（如基线值不正常）	>20.0 x ULN（基线值正常）；>基线值的 20.0 倍（如基线值不正常）
肌酸激酶（CK）	肌酸磷酸激酶增高	> ULN – 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10 x ULN
血肌酐（CREA）	肌酐增高	>ULN - 1.5 x ULN;	>1.5 - 3.0 x ULN ; >1.5 – 3 x 基线值	>3.0 - 6.0 x ULN; > 3 x 基线值	>6.0 x ULN
总胆红素（TBIL）	血胆红素增高	>ULN - 1.5 x ULN（基线值正常）；大于 1～1.5 倍基线值（基线值不正常）	>1.5 - 3.0 x ULN（基线值正常）；基线值的 1.5～3.0 倍（如基线值不正常）	>3.0 - 10.0 x ULN（基线值正常）；基线值的 3.0～10.0 倍（如基线值不正常）	>10.0 x ULN（基线值正常）；>基线值的 10.0 倍（如基线值不正常）
总胆固醇（TCHO）	高胆固醇血症	>ULN - 300 mg/dL；>ULN - 7.75 mmol/L	>300 - 400 mg/dL；>7.75 - 10.34 mmol/L	>400 – 500 mg/dL；>10.34 – 12.92 mmol/L	>500 mg/dL；>12.92mmol/L
谷氨酰转肽酶（GGT）	γ谷氨酰转移酶增高	>ULN - 2.5 x ULN（基线值正常）；大于 2～2.5 倍基线值（基线值不正常）	>2.5 - 5.0 x ULN（基线值正常）；基线值的 2.5～5.0 倍（如基线值不正常）	>5.0 - 20.0 x ULN（基线值正常）；基线值的 5.0～20.0 倍（如基线值不正常）	>20.0 x ULN（基线值正常）；>基线值的 20.0 倍（如基线值不正常）
甘油三酯（TG）	高甘油三酯血症	>150 - 300 mg/dL；>1.71 – 3.42 mmol/L	>300 - 500 mg/dL；>3.42 – 5.7 mmol/L	>500 – 1000 mg/dL；>5.7 – 11.4 mmol/L	

参数	CTCAE V5.0 名称	分级 1	分级 2	分级 3	分级 4
钾	高钾血症	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
钾	低钾血症	-	<LLN - 3.0 mmol/L	<3.0 - 2.5 mmol/L	<2.5 mmol/L
钠	高钠血症	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
钠	低钠血症	<LLN - 130 mmol/L	<125 - 129 mmol/L	<120 - 124 mmol/L	<120 mmol/L
血糖	低糖血症	<LLN – 55 mg/dL；<LLN – 3.0 mmol/L	<55 – 40 mg/dL； <3.0 – 2.2 mmol/L	<40 - 30 mg/dL；< 2.2 - 1.7 mmol/L	<30 mg/dL；<1.7 mmol/L
白蛋白（ALB）	低白蛋白血症	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	-
国际标准化比率（INR）	INR 增高	>1.2～1.5；>1～1.5 倍基线水平	>1.5～2.5；>1.5～2.5 倍基线水平	>2.5；>2.5 倍基线水平	-
活化部分凝血活酶时间（APTT）	活化部分凝血活酶时间延长	> ULN – 1.5 x ULN	>1.5 – 2.5 x ULN	>2.5 x ULN；	-
嗜酸性粒细胞	嗜酸性粒细胞增高	对于基线访视：AVAL> ANRHI； 对于基线后访视： AVAL> ANRHI 并且 AVAL> BASE	-	-	-
乳酸脱氢酶	血乳酸脱氢酶升高	AVAL> ANRHI	-	-	-
钙（mmol/L）	低钙血症	2.0 mmol/L<=AVAL<ANRLO	1.75 mmol/L<=AVAL<2.0 mmol/L	1.5 mmol/L<=AVAL<1.75 mmol/L	AVAL<1.5 mmol/L
钙（mmol/L）	高钙血症	ANRHI<AVAL<=2.9 mmol/L	2.9 mmol/L<AVAL<=3.1 mmol/L	3.1 mmol/L<AVAL<=3.4 mmol/L	AVAL>3.4 mmol/L