Supplementary materials

The anti-PD-L1/CTLA-4 bispecific antibody KN046 plus lenvatinib in advanced unresectable or metastatic hepatocellular carcinoma: a phase II trial

Methods

1. Inclusion Criteria

- Has a diagnosis of hepatocellular carcinoma confirmed by histology or cytology;
- Barcelona Clinic Liver Cancer (BCLC) Stage B or C;
- Age ≥18 years or ≤75 years for both genders;
- Eastern Cooperative Oncology Group (ECOG) performance status: 0-1;
- Child Pugh score ≤7;
- Left ventricular ejection fraction (LVEF) ≥50% or above lower limit normal (LLN) of the research institution;
- Enough organ function;
- Has at least one measurable lesion based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1;
- Life expectancy ≥3 months;
- Patients must be able to understand and willing to sign a written informed consent document.

2. Exclusion Criteria

- Fibrolamellar hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, cholangiocarcinoma etc;
- Tumor thrombus invasion at the main portal vein (Vp4), inferior vena cava or heart involvement;
- Subjects who have previously received immune checkpoint inhibitors (such as anti-PD-1/L1, CTLA-4, etc.);
- Subjects who have received liver local treatment (transcatheter chemoembolization, transcatheter embolization, hepatic artery perfusion, radiotherapy, radioembolization or ablation) within 4 weeks before administration;
- Subjects who need corticosteroids or immunosuppressive agents for systemic therapy;

- Any previous or current active autoimmune disease or history of autoimmune disease;
- History of hepatic encephalopathy or liver transplantation;
- History of interstitial lung disease or non-infectious pneumonia;
- History of allergic reactions to related drugs;
- Clinically obvious gastrointestinal abnormalities, which may affect the intake, transport or absorption of drugs (such as inability to swallow, chronic diarrhea, intestinal obstruction, etc.), or patients undergoing total gastrectomy;
- With serious systemic diseases such as heart disease and cerebrovascular disease, and the condition is unstable or uncontrollable;
- Subjects with clinically significant gastrointestinal bleeding or thrombosis or embolic events within 6 months;
- Untreated hepatitis infection: HBV DNA>2000IU/ml or10000 copies/ml, HCV RNA> 1000copy/ml, both HbsAg and anti-HCV body are positive;
- Evidence of active pulmonary tuberculosis (TB);
- Positive test of immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS);
- Pleural effusion, ascites and pericardial effusion with clinical symptoms or needing drainage.

3. Guidelines for dose adjustments

Lenvatinib dose adjustment was not allowed before the occurrence of DLT in the safety run-in period. For participants who had developed DLT, lenvatinib could be restarted at a reduced dose when the toxicity recovered to grade ≤1 and the investigators judged that the participants could benefit from continued treatment. The other participants were allowed to suspend, reduce, or permanently discontinue lenvatinib treatment according to their actual conditions. The lenvatinib dose adjustment principles were as follows: 1) if the initial dose was 12 mg once daily (QD), the first reduction was 8 mg QD, the second reduction was 4 mg QD, and the third reduction was 4 mg once every other day (QOD), 2) if the initial dose was 8 mg QD, the first reduction was 4 mg QD, and the second reduction was 4 mg QOD, and 3) lenvatinib was permanently discontinued if 4 mg QOD was not tolerated.

4. Definitions of endpoints

Objective response rate (ORR) was defined as the proportion of participants achieving a complete (CR) or partial response (PR). Duration of response (DOR) was defined as time from the first documented CR or PR to disease progression or death from any cause, whichever came first. Disease control rate (DCR) was defined as the proportion of participants achieving a CR, PR, or stable disease (SD). Time to response (TTR) was defined as the time from initiation of treatment to achievement of a CR or PR. Progression-free survival (PFS) was defined as the time from initiation of treatment to the first occurrence of disease progression or death from any cause, whichever came first. Overall survival (OS) was defined as the time from initiation of treatment to death from any cause.

Supplementary Table 1. Treatment-emergent adverse events occurring in ≥10% of the participants

Event, n (%)	KN046 + lenvatinib QD (n=55)
Platelet count decreased	26 (47.3)
Fatigue	22 (40.0)
Hypertension	22 (40.0)
Proteinuria	21 (38.2)
Elevated blood bilirubin	19 (34.5)
Elevated AST	18 (32.7)
Rash	18 (32.7)
Weight loss	16 (29.1)
White blood cell decreased	16 (29.1)
Infusion-related reactions	16 (29.1)
Loss of appetite	15 (27.3)
Hypokalemia	14 (25.5)
Elevated ALT	13 (23.6)
Fever	11 (20.0)
Joint pain	11 (20.0)
Hypoalbuminemia	10 (18.2)
Hyponatremia	10 (18.2)
Hypothyroidism	10 (18.2)
Neutrophil count decreased	9 (16.4)
Diarrhea	9 (16.4)
Abdominal pain	9 (16.4)
Pruritus	9 (16.4)
Hypochloremia	7 (12.7)
Elevated blood pressure	6 (10.9)
Nausea	6 (10.9)
Toothache	6 (10.9)
Gingival bleeding	6 (10.9)
Abdominal distension	6 (10.9)

Supplementary Table 2. Grade ≥3 treatment emergent adverse events occurring in >3% of the participants

Event, n (%)	KN046 + lenvatinib QD (n=55)
Hypertension	7 (12.7)
Elevated blood pressure	5 (9.1)
Platelet count decreased	3 (5.5)
Hyponatremia	3 (5.5)
Weight loss	2 (3.6)
Elevated aspartate aminotransferase	2 (3.6)
Gastrointestinal hemorrhage	2 (3.6)
Fatigue	2 (3.6)
Interstitial lung disease	2 (3.6)

Supplementary Table 3. Censoring information for progression-free survival (PFS)

Description of Events and Censoring	**PFS Status**	**Date of Death, Disease Progression, or Censoring**
Subject records disease progression [1]	Event	Date of disease progression
Subject dies before earliest record of disease progression	Event	Date of death
Subject without evaluation at baseline	Censoring	First administration date
Subject without assessment post-baseline	Censoring	First administration date
Subject with ⩾ 2 consecutive missing tumor assessments [2], followed by disease progression or death	Censoring	Last assessable tumor detection date before missing
Subject with pseudoprogression, followed by non-PD in subsequent efficacy assessment [3]	Censoring	Last assessable tumor detection date
Subject starts new antineoplastic treatment	Censoring	Last assessable tumor detection date before new treatment
No event occurred during the study	Censoring	Last assessable tumor detection date
Subject withdraws from study with no evidence of event	Censoring	Last assessable tumor detection date
Subject lost to follow-up	Censoring	Last assessable tumor detection date

Note: For assessable tumor detection date at each visit, the latest date among target lesion, non-target lesion, and new lesion imaging examination dates will be used (if the efficacy assessment

result for that visit is PD, the earliest date among the three will be used). "Assessable" refers to assessments that are not NE.

[1] Disease progression based on imRECIST should be confirmed. The event date is the earliest date among two consecutive disease progression dates.

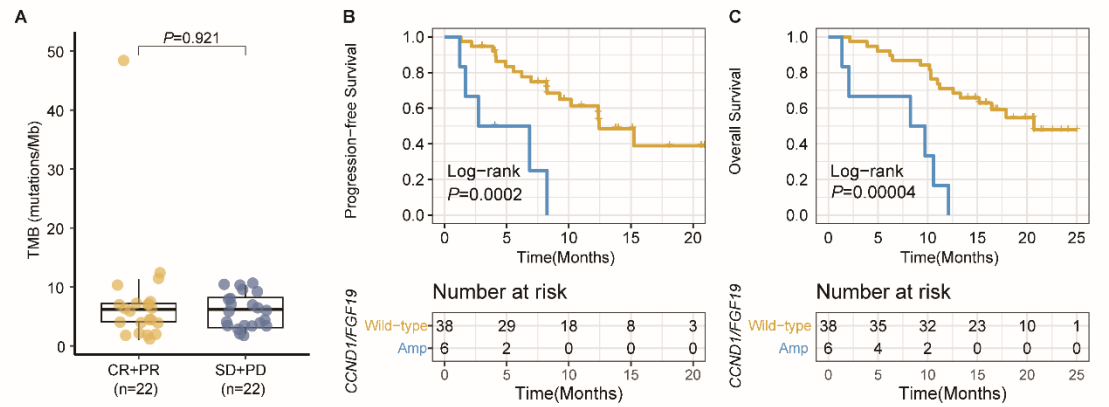
[2] The duration of consecutive missing ⩾ 2 disease assessments includes the duration of two tumor assessments + two time windows.

[3] For imRECIST only.

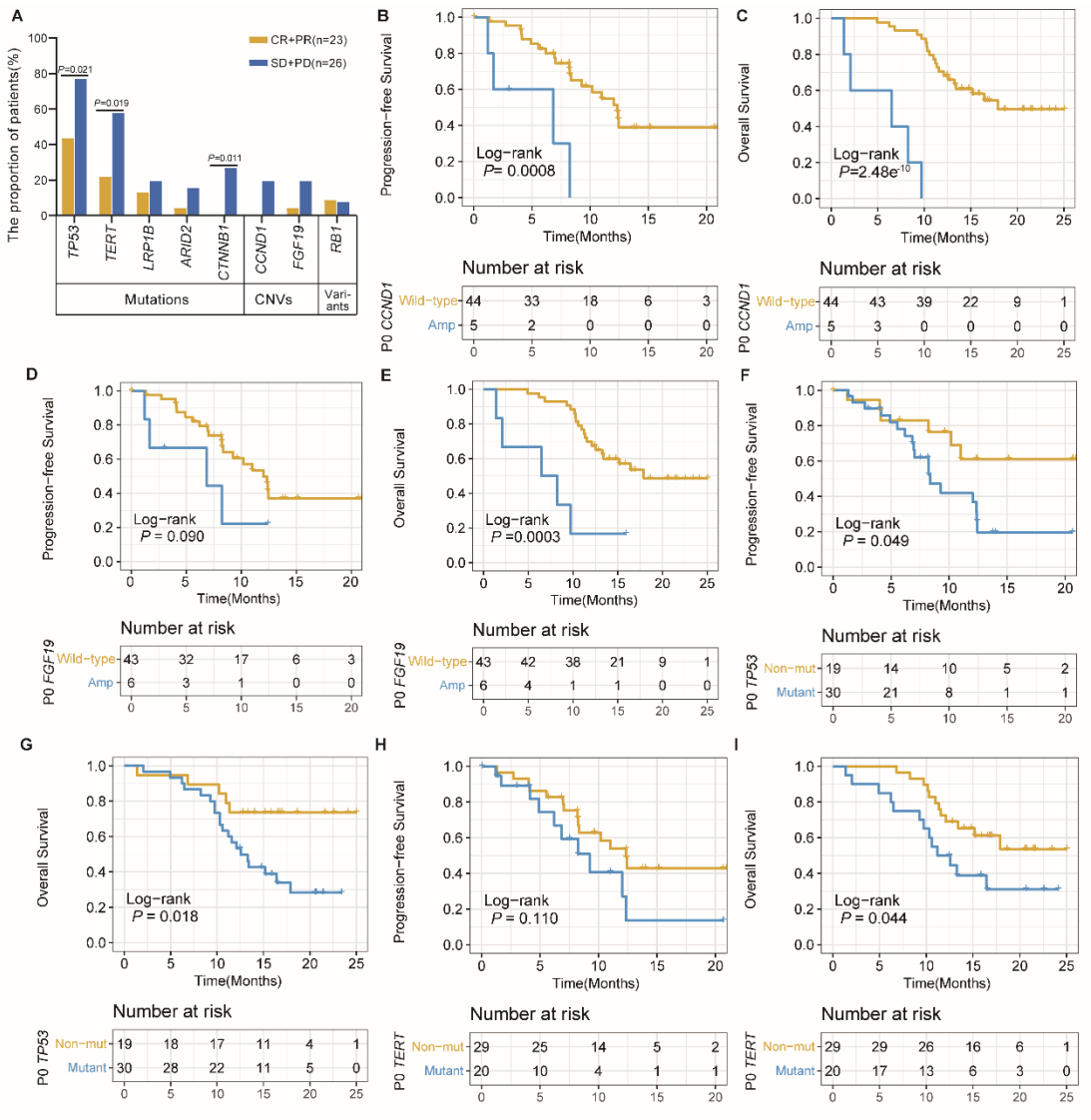
Supplementary Table 4. Censoring information for overall survival (OS)

Description of Events and Censoring	**OS Status**	**Date of Death or Censoring**
Death	Event	Date of death
No deaths in the study	Censoring	Last known survival date before data cutoff
Subject lost to follow-up is not confirmed dead	Censoring	Last confirmed survival date
Subject withdraws from study due to ICF withdrawal	Censoring	Last confirmed survival date
No deaths at the end of the study	Censoring	Last confirmed survival date

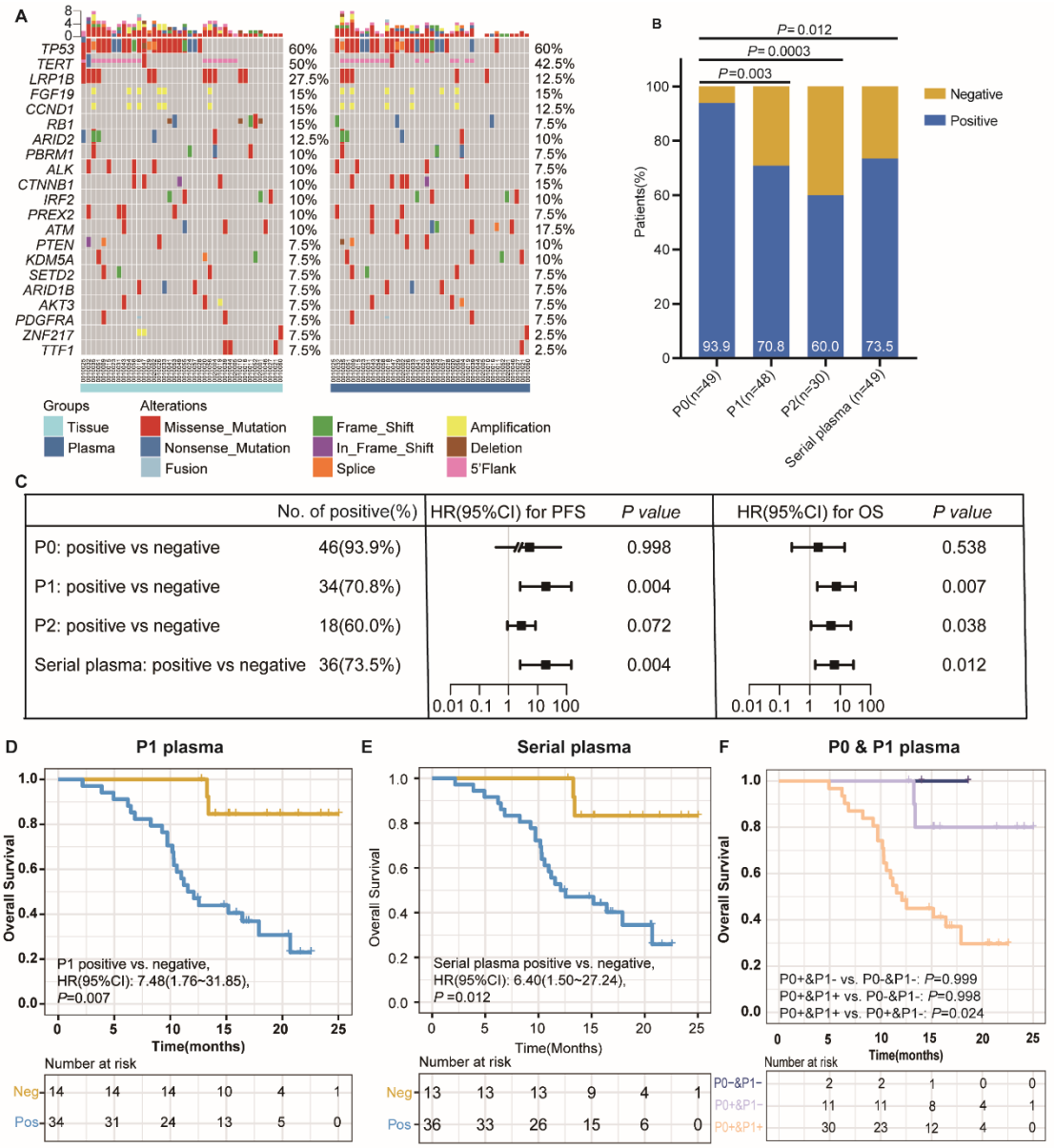
Note: The last confirmed survival date is defined as the latest date among the following: administration date, end of treatment date (only applicable to subjects who do not end treatment due to loss to follow-up or death), survival follow-up date, last known survival date, start/end date of AE, start/end date of CM, start/end date of non-drug treatment, all safety assessment dates, tumor assessment dates, end of study date (only applicable to subjects who do not end the study due to loss to follow-up or death).



Supplementary Figure 1. (A) The comparison of tumor mutation burden (TMB) between non-responders (patients with stable disease [SD] + progressive disease [PD]) and responders (patients with complete response [CR] + partial response [PR]) subgroups. Kaplan-Meier analysis of progression-free survival (PFS) (B) and overall survival (OS) (C) stratified by *CCND1* and *FGF19* CNV status in baseline tissue samples. The Kaplan-Meier survival curve was used to analyze PFS and OS. Source data are provided as a Source Data file.



Supplementary Figure 2 (A) A comparison of gene alterations in baseline plasma (P0) between the patients with complete response (CR) + partial response (PR) and stable disease (SD) + progressive disease (PD). (B-I) The Kaplan-Meier curves of PFS and OS stratified by CCND1 CNV status (B, C), FGF19 CNV status (D, E), TP53 mutation status (F, G), or TERT status (H, I) that was assessed by baseline plasma. The Kaplan-Meier survival curve was used to analyze progression-free survival (PFS) and overall survival (OS). Source data are provided as a Source Data file.



Supplementary Figure 3 (A) A comparison of the genetic variations between baseline tissue and plasma samples in 44 patients. (B) Circulating tumor DNA (ctDNA)-positive rate at different time points (P0-P2) and serial plasma. (C) The relationship of ctDNA status at different time points with progression-free survival (PFS) and overall survival (OS). (D) Kaplan–Meier analysis of OS stratified by ctDNA status at P1 (D), serial plasma (E) and P0+P1 (F). The Kaplan-Meier survival curve was used to analyze PFS and OS. Hazard ratio (HR) with 95% CIs were estimated by the Cox proportional

hazards regression analysis, and a two-sided P <0.05 was considered statistically significant. No adjustments were made for multiple comparisons. Source data are provided as a Source Data file.

Clinical Study Protocol

A Clinical Study to Evaluate the Safety and Efficacy of KN046 in Combination with Lenvatinib in Subjects with Advanced Hepatocellular Carcinoma

Protocol No.: KN046-IST-05

Version No.: 1.6

Version Date: 8-Jun-2022

Signature Page

I have read this clinical study protocol, Protocol No.: IST-05, Version No.: 1.6 (Version date: 8-Jun-2022). I agree to fulfill the relevant responsibilities in accordance with Chinese laws, the Declaration of Helsinki, the Good Clinical Practice (GCP) issued by National Medical Products Administration (NMPA), and this study protocol. This study can only be conducted after approval by the Ethics Committee (EC).

During the conduct of the study, I will strictly comply with the requirements of this protocol. If it is necessary to modify this protocol, the amended protocol may not be implemented until it is re-approved or agreed by the EC and filed in the EC, unless the amended protocol is necessary to protect the safety, rights and interests of the subjects.

I will keep this protocol and its related contents confidential.

Clinical Study Site: Beijing Cancer Hospital

Principal Investigator (Printed): Professor Baocai Xing

1 Study Background

1.1 Background of Hepatocellular Carcinoma

1.1.1 Epidemiology

Primary liver cancer (referred to as "liver cancer") is one of the most common tumors threatening human health. In 2018, there were 841,000 new cases of liver cancer patients worldwide. 782,000 patients died of liver cancer. The incidence of liver cancer ranks sixth, and the mortality rate ranks fourth. The incidence and mortality rates in males are 2-3 times higher than those in females. The distribution of liver cancer varies geographically, with higher incidence rates in North Africa, East Asia, and Southeast Asia than in other regions of the world [1]. Among them, patients with liver cancer in China account for more than 50% of liver cancer patients worldwide. According to epidemiological data, in 2015, there were 466,000 new cases of liver cancer in China and 422,000 deaths. The incidence and mortality rates in males are three times higher than those in females. Among Chinese males under the age of 60, the incidence and mortality rates of liver cancer rank first among malignant tumors [2]. Primary liver cancer mainly includes three different pathological types: hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and mixed HCC-ICC. Among them, HCC accounts for 75%-85% [1]. The main risk factors for hepatocellular carcinoma include chronic hepatitis C infection, chronic hepatitis B infection, excessive alcohol intake, obesity, smoking, type 2 diabetes, and aflatoxins in food. In China, chronic hepatitis B infection and aflatoxins in food are the main risk factors.

In early-stage hepatocellular carcinoma patients, cure can be achieved through treatments such as surgery, liver transplantation, and ablation. However, the onset of liver cancer is insidious. Most patients are already in the late stage of liver cancer at the time of initial diagnosis. According to the BRIDGE study, in China, only 33% of patients diagnosed for the first time can achieve radical cure of liver cancer through local treatments such as surgery. Among these 33% of liver cancer patients, most are in Barcelona Clinic Liver Cancer (BCLC) stages 0-A, and a few are in BCLC stage B. Over 60% of patients cannot achieve radical cure of liver cancer through local treatments such as surgery. These patients need to receive systemic treatment. Among these patients, 9% are in BCLC stage B, 55% are in stage C, and 2% are in stage D [3].

1.1.2 Current Treatment Status

Treatment methods for advanced primary hepatocellular carcinoma include systemic chemotherapy, targeted therapy, and immunotherapy, etc.

Systemic chemotherapy has very limited efficacy in advanced HCC. The FOLFOX4 regimen containing oxaliplatin is the only chemotherapy regimen approved in China for the treatment of advanced hepatocellular carcinoma.

Molecular targeted therapy drugs are mainly anti-angiogenic drugs. Among them, sorafenib and lenvatinib [4] are approved first-line molecular targeted drugs for the treatment of advanced HCC. Regorafenib, cabozantinib, ramucirumab, nivolumab, pembrolizumab, and camrelizumab have subsequently been approved by the FDA and NMPA for second-line treatment of advanced HCC. The approval of these drugs has provided more options for patients with advanced HCC.

1.2 KN046

KN046 is a recombinant humanized novel bispecific antibody. KN046 can simultaneously bind to PD-L1 and CTLA-4, thereby blocking the interaction between PD-L1 and PD1 as well as CTLA-4 and CD80/CD86. KN046 is expressed and produced by CHO cells. The wild-type IgG1 Fc in the molecule retains ADCC and CDC functions. CTLA-4 inhibitors act on initial T

cells in secondary lymphoid organs, mediating the depletion of regulatory T cells (Tregs) and thus producing an anti-tumor effect. PD-1/PD-L1 inhibitors can relieve inhibitory signaling pathways in the tumor microenvironment, thereby activating tumor-infiltrating CTLs. KN046 has a stronger binding affinity to PD-L1 than to CTLA-4. Therefore, KN046 can more effectively modulate the tumor microenvironment by targeting PD-L1. In non-clinical toxicology studies in cynomolgus monkeys, KN046 showed good tolerability.

1.2.1 Pharmacodynamics

In vitro study results show that KN046 has a higher affinity for human PD-L1 (24 times the affinity of KN046 for human CTLA-4). KN046 can target the tumor microenvironment with high PD-L1 expression, synergistically promoting T cell activation and proliferation, and persistently killing tumors. Compared with marketed drugs, KN046's affinity with human CTLA-4 and its blocking activity against CTLA4/B7 are comparable to ipilimumab. KN046's affinity with human PDL1 and its blocking activity against PD1/PD-L1 are comparable to durvalumab. In PBMCs from 4 healthy donors, under the stimulation of superantigen SEB, KN046 consistently showed a significant effect in promoting T cell activation. KN046's effect on T cell activation is significantly superior to the activation effect of two single-target control antibodies used alone or in combination on T cells. Additionally, for clinical cytokine release syndrome (CRS), KN046's direct stimulatory effect on unactivated human PBMCs was studied *in vitro*. The results showed that solid-phase KN046 could induce the release of low levels of IL-8, IL-1β, IL-6, and TNFa in two individuals studied. Soluble KN046 could induce the release of extremely low levels of IL-8, IL-1β, and IL-6.

The *in vivo* pharmacodynamics of KN046 were studied using the A375-PDL1/human PBMC xenograft mouse model and the CTLA4-PD-L1 humanized mouse/MC38-h PD-L1 allograft tumor model. The results showed that KN046 has a significant antitumor effect.

1.2.2 Pharmacokinetics/Pharmacodynamics and Immunogenicity

In cynomolgus monkeys, preclinical PK studies of KN046 were conducted. In cynomolgus monkeys, after a single intravenous administration, within the 1-10 mg/kg dose range, the C_{max} and AUC of KN046 increased proportionally with the dose, consistent with linear PK characteristics. The $T_{1/2}$ was 51-88.3 hours. The CL was 0.701-0.747 mL/h/kg. At different doses, cynomolgus monkeys all developed anti-drug antibodies (ADA) (positive rate of 83.3%-100%). In the single-dose study of KN046 in cynomolgus monkeys, the calculation of PK parameters may be affected by the content of ADA.

The PK study of KN046 via multiple intravenous administrations was conducted during the 4-week dosing toxicity study. In male and female cynomolgus monkeys, the AUC_{0-t} of KN046 increased with the dosing dose (from 10 mg/kg/dose to 100 mg/kg/dose). The increase in AUC_{0-t} was approximately proportional to the increase in doses. The differences in C_{max} and AUC_{0-t} between male and female cynomolgus monkeys were less than 2-fold. There were no significant gender differences in C_{max} and AUC_{0-t}. After 4 doses, the accumulation ratio (AR) of KN046 in cynomolgus monkeys was between 0.72 and 1.38. In all dose groups, the accumulation ratio of KN046 was less than 2. There was no significant accumulation of KN046. On day 22 of the dosing period, due to the influence of ADA, in some cynomolgus monkeys, AUC_{0-t} and $t_{1/2}$ decreased with the increase in the number of doses. The clearance (Cl) increased with the increase in the number of doses. In the low, medium, and high dose groups, the ADA positive rates were 50%, 40%, and 40%, respectively.

Following the relevant requirements in the guidelines for the safety evaluation of biopharmaceuticals in China and abroad, metabolism and excretion studies of KN046 were not implemented. KN046 is an Fc fusion protein. It is expected that *in vivo*, KN046 degrades into

peptides and amino acids. Then, KN046 is excreted or reused for the synthesis of proteins or peptides in the body.

Detailed PK information of KN046 can be found in the Investigator's Brochure (IB).

1.2.3 Toxicology

In non-human primates, single-dose and multiple-dose toxicity studies of KN046 were conducted.

Safety pharmacology: Separate safety pharmacology studies of KN046 were not conducted. The safety pharmacology studies of KN046 were conducted in the 4-week dosing toxicity study in cynomolgus monkeys. In the study, no significant changes related to administration were observed. The study showed that KN046 does not affect the cardiovascular system of cynomolgus monkeys.

Single-dose toxicity study: The toxicity after a single dose of KN046 was also observed in the 4-week multiple-dose toxicity study in cynomolgus monkeys. The results showed that the MTD of a single dose of KN046 was estimated to be more than 100 mg/kg.

Multiple-dose toxicity study: In the 4-week multiple-dose toxicology study in cynomolgus monkeys, 0 mg/kg (control group), 10 mg/kg, 30 mg/kg, and 100 mg/kg were administered intravenously to cynomolgus monkeys once a week. A total of 5 doses were administered. The recovery period was 6 weeks. Among them, in the 30 mg/kg group, one male monkey died during the 5th dose. Pathological observations were made on D18, D20, and/or D29. The cause is speculated to be the stimulation of an immunogenic response to KN046 (the highest ADA titer on day 29), rather than the direct effect of KN046. In the ≥ 30 mg/kg dose groups, the main changes related to KN046 were observed, including enlarged inguinal lymph nodes and reduced body weight and food consumption in one animal (100 mg/kg dose group). The main pathological changes included inflammatory responses, such as a slight increase in the count of unstained large cells, a mild to moderate increase in fibrinogen concentration, and a slight to mild increase in globulin concentration. In the histopathological examination, the adverse reactions observed included multi-organ vasculitis, mesangial proliferative glomerulonephritis and/or accompanying renal tubular degeneration/necrosis/regeneration, hypertrophy/proliferation of Kupffer cells, and infiltration of neutrophils/monocytes in the hepatic sinusoids and/or periportal areas, and degeneration/necrosis of cardiomyocytes (≥ 30 mg/kg dose groups). The NOAEL of KN046 was 10 mg/kg.

Immunogenicity: In the single-dose PK study via intravenous injection in cynomolgus monkeys, in three groups of animals (1.0 mg/kg, 3.0 mg/kg, or 10.0 mg/kg), ADA positivity was observed in all animals on Day 42 after administration. The number of positive animals was 17/18. Only in the 3.0 mg/kg group, one animal was ADA negative. In the multiple-dose study via intravenous injection in cynomolgus monkeys (10, 30, and 100 mg/kg weekly), the ADA positivity rate was 4/10 on Day 29 after administration. On Day 43, the ADA positivity rates were 4/10, 0/10, and 1/10, respectively.

Hemolysis studies showed that KN046 (26.3 mg/mL) did not cause hemolysis of rabbit erythrocytes.

The results of the tissue cross-reactivity study of KN046 showed that positive staining was detected only in human placenta and thymus, monkey thymus and tonsil lymphocytes. The results suggest that KN046 has strong binding specificity. KN046 does not cross-react with tissues outside the expected histological distribution.

Toxicology study results are detailed in the IB.

1.3 Rationale of Study

1.3.1 Theoretical Rationale for KN046 in Combination with Lenvatinib

In recent years, with the progress of molecular biology study, molecular-targeted therapy as a means of biological treatment has become a hot topic. Among them, studies on multi-target receptor tyrosine kinase inhibitors are very active. Sorafenib and lenvatinib are representatives of broad-spectrum TKIs. Targeted drugs designed for specific molecular targets of tumors have advantages such as strong specificity, rapid onset, high overall response rate (ORR), and less damage to normal tissues. However, due to drug resistance, the duration of response (DOR) in anti-tumor treatment is limited. Although immunotherapy has a slow onset, the DOR is long due to the production of memory cells. Targeted drugs cause tumor cell death, and the dead tumor cells release new antigens, which activate the immune system and enhance the immune response to the tumor. This provides the possibility for the combined effect of immune checkpoint inhibitors and targeted drugs to synergistically enhance anti-tumor activity.

The vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) axis is one of the important molecular pathways controlling angiogenesis and plays a significant role in the tumor microenvironment, including immune suppression. VEGFR2 is widely expressed in blood vessels, especially in the microvasculature of tumor tissues. In addition, VEGFR2 subgroups can be detected on the cell membrane surfaces of various immune cells such as dendritic cells, macrophages, and regulatory T cells (Tregs). The VEGFR2 subgroup is a key negative regulator in the tumor microenvironment, and VEGFR2 with high expression is involved in the regulation of immune suppression functions. VEGFR2+ Tregs play an important inhibitory role in the formation of the immune-suppressive microenvironment. Numerous reports have confirmed the synergistic effect of targeted therapy targeting VEGFR2 with immunotherapy [5, 6]. In T cells, inhibition of VEGFR2 activity can significantly reduce the infiltration of Tregs into tumor tissues. The ligand VEGF of VEGFR2 inhibits the maturation of DCs by activating NF-KB. NF-KB can affect the differentiation of monocytes into DCs. In addition, by increasing the production of the strong inhibitor IDO that inhibits T cell activation and inactivating STAT3, VEGF promotes an immune-suppressive phenotype. VEGF can inhibit the function of T cells, increase the recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), and hinder the differentiation and activation of dendritic cells (DCs). Studies have found that VEGF has an environment-dependent effect on T cell activation. The VEGF/VEGFR2 signaling pathway inhibits TCR-dependent activation in T cells, but does not inhibit TCR-dependent activation in CD47-deficient T cells. Since CD47 is widely expressed in human cells, VEGF is likely to inhibit the function of T cells in most cases. Since VEGF has an immune-suppressive effect on T cell function, it is biologically reasonable to intervene in VEGF/VEGFR to improve T cell function and enhance anti-tumor immunity. Some clinical and preclinical findings also support this hypothesis. Inhibitors targeting VEGFR2 can appropriately inhibit angiogenesis, promote vascular normalization, enhance the number and function of DCs, reduce Tregs in tumor tissues and circulation, reduce the proportion of MDSCs, increase the infiltration of CD4+ T cells and CD8+ T cells into tumors, and ultimately improve the tumor immune-suppressive microenvironment.

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that can inhibit the kinase activity of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Additionally, lenvatinib can also inhibit other RTKs related to angiogenesis and tumor development pathways, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, platelet-derived growth factor (PDGF) receptor PDGFRα, KIT, and RET. *In vitro*, lenvatinib combined with everolimus can inhibit the proliferation of human endothelial cells,

angiogenesis, and the VEGF signaling pathway. *In vivo*, the combination can reduce tumor volume in human renal cell carcinoma tumor-bearing mice. Compared to monotherapy, the combination therapy has greater anti-angiogenic and anti-tumor activity.

KN046 is a specific antibody against PD-L1 and CTLA-4. Theoretically, KN046 can specifically bind to CTLA-4 and PD-1, thereby blocking the immune-suppressive effects mediated by both pathways. KN046 can activate effector T cells, thereby exerting a tumoricidal effect. Lenvatinib is a multi-target tyrosine kinase (PTKs) inhibitor. Lenvatinib can selectively inhibit the activity of vascular endothelial growth factor receptors and inhibit the activity of other PTKs involved in tumor proliferation related to angiogenesis, thus exerting a dual inhibitory, multi-target blocking of anti-tumor effects. Theoretically, the combination of KN046 and lenvatinib will synergistically produce better anti-tumor effects through multiple pathways.

1.3.2 Clinical Study Progress of Similar Products in Combination Therapy for Hepatocellular Carcinoma

To further improve the efficacy of treatment for advanced HCC, various combination therapy models have been explored in domestic and international studies. Among them, immunotherapy combined with anti-angiogenic therapy is the most important direction of exploration. This treatment method has been validated for good efficacy in early clinical studies.

In a multicenter, open-label Phase Ib study of Pembrolizumab combined with Lenvatinib [7] conducted in subjects with advanced HCC who had not received systemic treatment, a total of 100 subjects were enrolled (6 subjects were receiving last-line treatment, and 94 subjects were receiving first-line treatment). In terms of efficacy, 67 subjects had evaluable efficacy. Based on mRECIST assessment (investigators), mRECIST assessment (independent radiological assessors) and RECIST 1.1 assessment (independent radiological assessors), the confirmed ORR was 41.8%, 46.3%, and 32.8%, respectively. DCR was 83.6%, 85.1%, and 85.1%, respectively. The median PFS was 9.7 months. In the combination therapy group, the ORR was significantly higher than in the Pembrolizumab monotherapy (17%) group and the Lenvatinib monotherapy (24.1% based on mRECIST assessment) group. In terms of safety, among the 67 subjects, the most common adverse events (AEs) were diarrhea (46%), decreased appetite (42%), and hypertension (44%). Treatment was discontinued in 10 subjects. No new AEs were found.

A Phase Ib study of Atezolizumab combined with Bevacizumab [8] was conducted in subjects with advanced HCC who had not received systemic treatment. In Arm A, 104 subjects were enrolled. The ORR was 32%. In Arm F, the efficacy and safety of Atezo+ bev combination therapy (N=60) were compared with Atezo monotherapy (N=59). The PFS was 5.6 and 3.4 m (HR 0.55, 80%CI, 0.40 – 0.74, P=0.0108) respectively. The proportion of Any-Gr TRAEs was 68% and 41%, respectively. The proportion of Grade 3-4 TRAEs was 20% and 5%, respectively.

A Phase III study comparing Atezolizumab combined with Bevacizumab treatment with Sorafenib monotherapy [10] was conducted in subjects with locally advanced unresectable HCC who had not previously received systemic treatment. In the study, subjects were randomized in a 2:1 ratio to the atezo 1200 mg+bev 15 mg Q3W group (N=336) and the sor 400 mg BID group (N=165). The primary endpoints were OS and PFS based on IRF-RECIST 1.1 assessment. Secondary endpoints were ORRs based on IRF-mRECIST and IRF-RECIST 1.1 assessment. The average follow-up period was 8.6 months. The OS was NE and 13.2 m (HR 0.58, 95% CI 0.42, 0.79) respectively. The PFS was 6.8 m and 4.3 m (HR 0.59, 95% CI 0.47, 0.76) respectively. The ORR was 27% and 12% (P< 0.0001) (IRF-RECIST 1.1), and 33% and 13% (P < 0.0001) (IRF- mRECIST) respectively.

A Phase Ib study of Axitinib combined with Avelumab [10] was conducted in subjects with locally advanced or metastatic HCC who had not previously received systemic treatment (VEGF Liver 100). As of August 1, 2018, a total of 22 subjects were enrolled. In the Axitinib combined with Avelumab study, safety was preliminarily controllable. The safety profile of combination therapy was consistent with that of monotherapy. In terms of efficacy, the ORR based on RECIST and mRECIST assessment was 12.6% (2.9-34.9) and 31.8% (13.9-54.9) respectively. Tumor shrinkage was observed in 68.2% and 72.7% of subjects, respectively. The median PFS was 5.5 months and 3.8 months, respectively. The PFS rate at Month 6 was 35.1% and 30.9%, respectively. Further follow-up is still ongoing.

A Phase I study of SHR-1210 (PD-1 antibody) combined with Apatinib [11] was conducted in subjects with HCC, gastric cancer, and gastroesophageal junction tumors who had failed standard treatment. As of February 27, 2018, a total of 18 subjects with liver cancer were enrolled. Sixteen subjects had evaluable efficacy. The results showed that in SHR-1210 combined with Apatinib treatment, the ORR of subjects with liver cancer who failed first-line treatment was 50%. The DCR was 93.8%. In studies of Apatinib monotherapy (N=70, first-line treatment) and SHR-1210 monotherapy (N=186, second-line treatment), the ORR in subjects with advanced liver cancer was 13% and 15%, respectively. Compared with monotherapy, immunotherapy combined with anti-angiogenic therapy significantly increased the ORR.

In summary, the study results of immunotherapy combined with anti-angiogenic therapy in subjects with advanced HCC all show that the ORR in the combination therapy group is significantly higher than that in the monotherapy group. The safety of the combined drugs is controllable. Therefore, in this study, KN046 combined with lenvatinib is designed to treat subjects with advanced hepatocellular carcinoma. In this study, the safety and efficacy of combination therapy in subjects with advanced hepatocellular carcinoma will be observed.

1.4 Benefit-risk Assessment

KN046 injection is a specific antibody against PD-L1 and CTLA-4. Theoretically, KN046 can specifically bind to CTLA-4 and PD-1, thereby blocking the immune-suppressive effects mediated by both pathways. KN046 can activate effector T cells and exert a tumoricidal effect. As of January 20, 2020, approximately 300 subjects have been enrolled. KN046 has good overall safety. The adverse reactions of KN046 are controllable. In Phase I studies in China and Australia, KN046 has shown good anti-tumor efficacy. The efficacy of lenvatinib, a first-line treatment drug for liver cancer, is confirmed. The main adverse reactions of lenvatinib do not significantly overlap with those of KN046. It can be considered that the risk of combination therapy of the two drugs is controllable.

The use of anti-PD-L1 and anti-CTLA-4 monoclonal antibody drugs can lead to autoimmune-related toxicity during treatment. Autoimmune-related toxicity should be closely monitored, and specific targeted treatment measures should be taken. Drug-related AEs include rash and pruritus (skin system), diarrhea and colitis (gastrointestinal system), hypophysitis, hepatitis, endocrine diseases, pneumonia, and renal insufficiency, etc. In this study, the principles for managing immune-related toxicity will be formulated with reference to ESMO and NCCN guidelines. Measures such as exclusion criteria, safety monitoring, treatment suspension regulations, treatment termination criteria, and management of immune-related toxicity will be used to reduce the potential risks to subjects.

2 Study Objectives and Endpoints

2.1 Objective

2.1.1 Primary Objective

To evaluate the safety and efficacy (ORR) of KN046 in combination with lenvatinib in subjects with advanced hepatocellular carcinoma.

2.1.2 Secondary Objective

To evaluate other anti-tumor activity of KN046 in combination with lenvatinib in subjects with advanced hepatocellular carcinoma.

2.1.3 Exploratory Objective

To analyze the relationship between potential immune-related biomarkers and anti-tumor efficacy of combination regimens

2.2 Study Endpoints

2.2.1 Primary Endpoint

1) Safety and tolerability, dose-limiting toxicity (DLT)

2) ORR by the investigator based on RECIST 1.1 criteria

2.2.2 Secondary Endpoints

1） ORR by the investigator based on mRECIST and imRECIST criteria

2） DOR, Disease Control Rate (DCR), Time to Response (TTR), and Progression-free Survival (PFS) by the investigator based on RECIST 1.1, mRECIST, and imRECIST criteria

3） Overall survival (OS) and 12-month survival (OS_{12})

2.2.3 Exploratory Endpoints

1） Relationship between antitumor activity and potential biomarkers (eg. ctDNA) and tumor response

3 Study Design

3.1 Overall Study Design

This study is a multicenter, open-label clinical study to investigate the safety and preliminary efficacy of KN046 in combination with lenvatinib in subjects with advanced hepatocellular carcinoma. The preset dose of KN046 is 5 mg/kg Q3W; the preset dose of lenvatinib is 12 mg QD (body weight [BW] ≥ 60 kg) or 8 mg QD (BW < 60 kg). In this study, during the safety introduction period, 6 subjects will be enrolled. These 6 subjects will receive KN046 5 mg/kg Q3W + lenvatinib 12 mg QD (BW ≥60 kg) or 8 mg QD (BW <60 kg). After all 6 subjects have completed the 28-day DLT observation period, the investigator will review the relevant safety data and decide whether to continue enrollment of the remaining subjects. If the subjects are intolerant (2 or more DLT events occur in the subjects), the subsequently enrolled subjects will receive KN046 5 mg/kg Q3W and lenvatinib (reduced dose) 8 mg QD (BW ≥ 60 kg) or 4 mg QD (BW < 60 kg). During the safety introduction period, subjects who discontinue treatment for reasons other than safety may be replaced.

In this study, the study periods include the screening period (D-28 - D-1), treatment period (until the subject develops disease progression, or until the subject develops intolerable toxicity, or until the subject withdraws ICF, or until the subject is lost to follow-up, or until the subject dies, or until the subject has been treated for at least 1 year, or until the subject has received an intervention other than that specified in this study protocol. At the end of the study, subjects may continue to receive KN046 or lenvatinib monotherapy or combination therapy if the investigator determines that the subject is still benefiting), the end of treatment visit (within 7 days after the last dose of KN046 and/or lenvatinib, whichever occurs later), safety follow-up (AEs within 30 days after the last dose of KN046 and/or lenvatinib, whichever occurs later, and all SAEs and drug-related AEs from 30 days to 90 days after the last dose of KN046 will be collected), and survival follow-up. Each subject will receive treatment according to the protocol until the subject experiences disease progression (as judged by the investigator based on mRECIST1.1), or the subject experiences an intolerable toxicity, or the subject withdraws the ICF, or the subject dies, or the subject receives an intervention other than that specified in this protocol, whichever occurs first. If the toxicity can be clearly attributed to one of the drugs in the combination, the subject may discontinue that drug and continue using the other drug.

In this study, during the safety introduction period, the first treatment cycle for the first 6 subjects is 28 days. On C1D1, KN046 will be administered. Lenvatinib will be administered once daily. Each remaining cycle is 21 days. On CnD1, KN046 will be administered. Lenvatinib will be administered once daily.

During the treatment period, if a subject experiences an intolerable AE, the subject may withhold or delay the administration of KN046. The subject may also reduce the dose of lenvatinib: 1) if the starting dose is 12 mg, the dose after the first reduction is 8 mg, the dose after the second reduction is 4 mg, and the dose after the third reduction is 4 mg (every other day); 2) if the starting dose is 8 mg, the dose after the first reduction is 4 mg, and the dose after the second reduction is 4 mg (every other day). If the subject cannot tolerate 4 mg every other day, the administration of lenvatinib will be discontinued.

During the study, tumor assessments will be conducted according to RECIST v1.1, imRECIST, and mRECIST. Starting from the first administration, assessments will be conducted every 6 weeks (±7 days) within the first year. Thereafter (starting with the second year), assessments will be performed every 12 weeks (± 7 days) until the subject experiences unacceptable toxicity, or the subject develops disease progression, or the subject withdraws the ICF, or the subject is

lost to follow-up, or the subject dies, or the study is prematurely terminated, whichever occurs first.

Subjects who prematurely discontinue study drug for reasons other than disease progression should continue to undergo tumor assessments at the frequency specified in this protocol until the subject develops disease progression, or the subject withdraws the ICF, or the subject starts a new anticancer treatment, or the subject is lost to follow-up, or the subject dies, or the study is prematurely terminated, whichever occurs first.

Subjects who withdraw from study drug treatment due to disease progression will be followed for survival every 2 months (60 ± 7 days) after disease progression using the end of treatment visit as the starting point. During survival follow-up, information on subsequent antitumor treatments and survival status of the subjects will be collected until withdrawal of the ICF by the subject, loss to follow-up of the subject, death of the subject, or early termination of the study (whichever occurs first).

During the study, for subjects who are still experiencing AEs at the end of the study or at the time of discontinuation of study treatment, follow-up will be continued until any of the following occurs:

- The AE resolves or improves to baseline level or better;
- The investigator confirms that the event is stable and no further improvement is expected;
- The subject dies;
- The subject is lost to follow-up or withdraws the ICF;
- The investigator confirms that the AE is unrelated to the study treatment;
- The subject starts a new antitumor treatment.

3.2 Dose Limiting Toxicity (DLT)

Within 28 days after the first administration of the study drug, any of the following AEs occurring in ≥ 2/6 subjects, unless the investigator judges that the AE is definitely unrelated to the study progression or caused by other external factors, will be considered as DLT, specifically as follows:

(1) Hematological toxicity:

- Grade 4 neutropenia lasting more than 7 days.
- Febrile neutropenia [absolute neutrophil count (ANC) < 1×10^9/L, with a single body temperature reaching 38.3℃ or a body temperature of 38℃ lasting for more than one hour].
- Grade 3 thrombocytopenia with severe uncontrollable bleeding events; Grade 4 thrombocytopenia lasting more than 3 days, requiring transfusion of blood products.
- Grade 4 anaemia (life-threatening).

(2) Non-hematological toxicity:

- Skin reactions: Grade 3 palmar-plantar syndrome or other skin adverse reactions. After appropriate interventions for the subject, the skin reaction persists for > 2 weeks, or the subject experiences skin reactions for the second time.

- Blood pressure: Grade 4 hypertension, or Grade 3 hypertension (subject's blood pressure remains ≥ 160/100 mmHg after 14 days (including 14 days) of antihypertensive drug treatment).
- Cardiac contractile function: the subject experiences a decrease in LVEF by > 10% for the first time, or an LVEF value < 40%.
- Gastrointestinal system: Grade 4 diarrhea; or despite active antidiarrheal treatment for the subject, Grade 3 diarrhea persists for > 24 hours; or regardless of duration, the subject experiences Grade 3 diarrhea twice. Despite adequate/maximum medical intervention and/or preventive measures, the subject experiences ≥ Grade 3 nausea and vomiting.
- Absolute QTcF > 500 msec (at two consecutive time points).
- Grade 3 or higher immune-related AEs (irAEs) (excluding hyperthyroidism or hypothyroidism controllable with hormone replacement therapy, infusion reactions, etc.);
- Other Grade 3 toxic effects (excluding laboratory test abnormalities that recover to Grade 2 (inclusive) or below within 3 days (asymptomatic and not requiring medical intervention)).
- Other Grade 4 or higher AEs.

In addition to the above events, DLT events also include any other toxicity reactions of any grade that the investigator considers to require the subject to withdraw from the study.

3.3 Definition of End of Study

The end of the study is defined as 1 year after the last administration to all subjects, or when all subjects have completed all visits, or when the investigator assesses that the study has reached the expected endpoint, whichever occurs first.

If there are still subjects under treatment at the end of the study, the investigator will comprehensively assess whether the subjects continue to benefit from the drug. If the investigator judges that the subjects still benefit, Alphamab will provide KN046 free of charge. The maximum duration of medication is 2 years. After the study ends, no further data on the subjects will be collected. The investigator only needs to report SAEs related to KN046 to Alphamab.

3.3.1 Early Termination of Study

The study may be terminated early in the following circumstances:

- New information suggests that the risk-benefit ratio of the study drug is unacceptable;
- From a medical and ethical perspective, the sponsor decides that it is no longer appropriate to continue the study and decides to terminate the study;
- The enrollment of subjects is poor, and the likelihood of completing the study within an acceptable time frame is low;
- The sponsor decides to terminate the development of the study drug.

If the study is terminated early, subjects should be visited as soon as possible. Subjects should complete the visit according to the requirements of the end of treatment visit. For the protection of the subjects, the investigator may be informed to conduct more visits.

4 Study Population

4.1 Inclusion Criteria

I01 Subjects can understand the ICF, voluntarily participate in the study, and sign the ICF;

I02 Subjects are ≥ 18 years old and ≤ 75 years old on the day of signing the ICF, male or female;

I03 Subjects with advanced hepatocellular carcinoma not suitable for surgical resection, diagnosed by histopathology and/or cytology examination according to the "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2019 Edition)";

I04 Subjects who have not previously received systemic first-line treatment (such as targeted therapy, immunotherapy, systemic chemotherapy);

I05 BCLC Stage B (not suitable for surgery and other local treatments) or C;

I06 Child-Pugh grade A or B (≤ 7 points) within 7 days before administration;

I07 Subjects should agree to provide previously stored tumor tissue samples or related pathological reports, and should agree to undergo tumor tissue biopsy (according to the investigator's assessment, subjects with typical space-occupying lesions diagnosed clinically, should collect a new sample of tumor lesion tissue by core needle biopsy during the screening period, if the subject agrees and it is convenient to obtain tumor tissue samples). The site for obtaining biopsy tissue should not have received prior local treatments such as radiotherapy. Subjects should not receive systemic antitumor treatment between the biopsy sampling and the first administration of the study drug;

I08 According to RECIST 1.1 criteria, subjects must have at least one measurable lesion at baseline;

Note: Lesions that have previously received local treatments (such as radiofrequency ablation, anhydrous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc.) should not be considered as measurable lesions unless there is clear progression.

I09 ECOG score 0 or 1;

I10 Cardiac function: left ventricular ejection fraction (LVEF) ≥ 50% or more than the lower limit of normal values in the study site;

I11 The subject's expected survival is more than 3 months;

I12 Within 7 days before the first administration, laboratory test values must meet the following criteria:

a) Hematology

- Neutrophils ≥ 1.5×10^9/L;
- Platelets ≥ 75×10^9/L;
- Hemoglobin ≥ 90 g/L;

Note: Subjects should not have received any blood component or colony-stimulating factor support treatment within two weeks before blood collection.

b) Renal function

- Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or creatinine clearance rate (Ccr) ≥ 50 mL/min. Ccr should be calculated using the Cockcroft-Gault formula:

Male:

$$\text{Clearance rate} = \frac{(140 - \text{Age}) \times \text{Weight（kg）}}{72 \times \text{Serum creatinine（mg/dL）}}$$

Female: Calculation result of male × 0.85.

- Urinalysis protein ≤ 1+; if urinalysis protein is ≥ 2+, then a 24-hour urine protein quantification of less than 1g is required;

c) Hepatic function

- Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤ 2.5 × ULN;
- Serum total bilirubin ≤ 2.0 × ULN;
- Serum albumin ≥ 28.0 g/L.

d) Coagulation function

- International standard ratio (INR) or prothrombin time (PT) ≤ 1.5 × ULN;
- Activated partial clotting time (aPTT) ≤ 1.5 × ULN.

I13 Female subjects of childbearing potential or male subjects with partners of childbearing potential agree to use effective contraceptive measures (annual failure rate below 1%) from 7 days before the first administration until 24 weeks after administration (see Appendix 4). Within 7 days before the first administration, female subjects of childbearing potential must have a negative serum pregnancy test;

I14 Subjects are able and willing to comply with the visits, treatment plans, laboratory tests, and other study-related procedures specified in the study protocol.

4.2 Exclusion Criteria

E01 Subjects with pathological types such as fibrolamellar hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, cholangiocellular carcinoma, and mixed hepatocellular carcinoma;

E02 Subjects with imaging findings of tumor thrombus invasion at the main trunk of the portal vein (Vp4), inferior vena cava (subjects with patent portal vein branches on the opposite side of the lesion may be allowed to enroll), or cardiac involvement;

E03 Subjects who have previously received immune checkpoint inhibitors (such as anti-PD-1/L1, CTLA-4, etc.);

E04 Subjects who have received local liver treatments (transcatheter chemoembolization, transcatheter embolization, hepatic artery infusion, radiotherapy, radioembolization, or ablation) within 4 weeks before administration;

Note: Subjects must show disease progression after local treatment to be eligible for enrollment. At the time of enrollment, it should be at least 3 months since the subject's transcatheter chemoembolization treatment.

E05 Subjects who have undergone major surgery within 4 weeks before starting administration or who are expected to undergo major surgery during the study period, or subjects with severe traumatic injuries, fractures, or ulcers, or subjects with long-term unhealed wounds or fractures;

E06 Subjects who have used immunomodulators or inhibitors within 2 weeks before administration, such as interleukin 2, interferons, and thymosin, anti-TNF-α drugs, etc.; subjects who have used NMPA-approved traditional Chinese medicine antitumor treatments within 2 weeks before administration; subjects who have undergone palliative radiotherapy within 2 weeks before administration;

E07 Subjects who need to use corticosteroids (> 10 mg/day prednisone, or equivalent dose of other corticosteroids) or immunosuppressants for systemic treatment within 2 weeks before administration; except for the following situations: adrenal replacement therapy, local skin, intraocular, intra-articular, nasal, and inhaled corticosteroids treatments, and short-term corticosteroids treatments to prevent allergies;

E08 Subjects with other malignant tumors within 5 years before the first administration, except for cured skin squamous cell carcinoma, basal cell carcinoma, non-muscle invasive bladder cancer, localized low-risk prostate cancer (defined as: subjects with stage ≤ T2a, Gleason score ≤ 6, and PSA ≤ 10 ng/mL at the time of prostate cancer diagnosis (if measured) who have undergone curative treatment and have no biochemical recurrence of prostate-specific antigen (PSA) may be enrolled in this study), *in situ* cervical/breast cancer;

E09 Subjects with a history of hepatic encephalopathy or current hepatic encephalopathy;

E10 Subjects with a history of interstitial lung disease (subjects with radiation pneumonitis not requiring steroid treatment may be enrolled) or a history of non-infectious pneumonia;

E11 Subjects with any active autoimmune disease or a history of autoimmune disease, including but not limited to: Crohn's disease, ulcerative colitis, systemic lupus erythematosus, sarcoidosis, Wegener's syndrome (granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis), autoimmune hepatitis, systemic sclerosis (scleroderma, etc.), Hashimoto's thyroiditis (exceptions see below), autoimmune vasculitis, autoimmune neuropathy (Guillain-Barre syndrome), etc. However, the following situations are excluded: controlled type I diabetes treated with insulin, stable hypothyroidism treated with hormone replacement therapy (including hypothyroidism caused by autoimmune thyroid disease), psoriasis, eczema, chronic simple lichen or vitiligo not requiring systemic treatment;

E12 Subjects who have received prior allogeneic stem cell or parenchymal organ transplantation;

E13 Subjects who have been vaccinated with any live vaccine within 4 weeks before enrollment;

E14 Subjects with a history of moderate to severe allergic reactions, hypersensitivity, or intolerance to antibody drugs;

E15 Subjects with clinically significant gastrointestinal abnormalities that may affect the intake, transport, or absorption of drugs (such as inability to swallow, chronic diarrhea, intestinal obstruction, etc.), or subjects who have undergone total gastrectomy;

E16 Subjects with hypertension that cannot be well controlled with medication (mean blood pressure of two measurements at least 1 hour apart > 140/90 mmHg), or subjects who have previously experienced hypertensive crises or hypertensive encephalopathy;

E17 Subjects with a history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes); subjects with QTcF >480ms (QTcF

is calculated using the Fridericia correction formula QTcF=QT/RR0.33); subjects with a history of congenital long QT syndrome;

E18 Subjects with any of the following diseases within 6 months before administration: myocardial infarction, severe or unstable angina, coronary artery bypass grafting, heart failure (New York Heart Association functional class III-IV), etc.;

E19 Subjects who have experienced thrombotic or embolic events within 6 months before administration, such as cerebrovascular accidents (including transient ischemic attacks), deep vein thrombosis, pulmonary embolism, etc., or who are receiving thrombolytic or anticoagulant treatment (such as warfarin or similar drugs), or who are receiving long-term treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), clopidogrel, or other drugs that affect platelet function;

Note: Prophylactic anticoagulant treatment for open venous infusion systems is allowed for subjects. As long as the subject meets the coagulation conditions in the inclusion criteria within 7 days before starting the study treatment, it is allowed. Subjects are allowed to use low molecular weight heparin treatment (e.g., enoxaparin 40 mg/day)

E20: Subjects who have experienced clinically significant bleeding symptoms or have a clear tendency to bleed within 6 months before administration, such as esophageal varices, gastrointestinal bleeding, hemorrhagic gastric ulcers, etc. (Subjects considered by the investigator to have portal hypertension with a high risk of bleeding should be excluded by endoscopic examination, e.g., severe varices); subjects with a history of melena or hematemesis within 2 months before administration; subjects who have experienced hemoptysis (daily expectoration of ≥ 2.5 mL of fresh blood) within 2 months before administration; subjects with positive fecal occult blood tests on two consecutive screenings; subjects whom the investigator considers at risk of visceral bleeding.

E21: Subjects judged by the investigator during the screening period to have uncontrollable, active infectious diseases, including but not limited to the following conditions:

a) Subjects with a history of active tuberculosis;

b) Subjects with congenital or acquired immunodeficiency, such as those infected with HIV or with a history of AIDS;

c) Subjects co-infected with HBV and HCV;

d) Subjects positive for HBsAg, requiring HBV DNA testing; for subjects with active hepatitis B, HBV DNA quantification should be < 2000 IU/mL or 10^4 copies/mL; subjects who have received antiviral treatment (such as entecavir, interferon treatment not allowed) for 14 days before administration and are willing to continue antiviral treatment during the study may be enrolled; subjects with HCV RNA positive (HCV RNA quantification > 10^3 copies/mL or the lower limit of local detection) who receive antiviral treatment according to local treatment guidelines and whose liver function meets the enrollment criteria may be enrolled; subjects with a history of HCV infection but with a negative PCR result for HCV RNA may be enrolled;

e) Subjects who have received systemic anti-infective treatment (intravenous or oral broad-spectrum antibiotics for more than one week) within 28 days prior to the first study drug administration.

E22: Subjects with clinically symptomatic or symptomatic treatment-requiring pleural/abdominal effusion or pericardial effusion (once a month or more frequently).

E23: Subjects who have experienced abdominal or tracheoesophageal fistulas, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to the start of study treatment.

E24: Subjects who, in the opinion of other investigators, will compromise the safety or compliance of this study drug (eg. psychiatric disorders, uncontrolled large serous effusions, etc.) and will not be suitable for this study.

4.3 Termination Criteria of Study

4.3.1 Early Termination of Study

The investigator has the right to terminate the study at any time, and reasons for early termination include but are not limited to:

1) Significant errors in the clinical study protocol are discovered during the study, making it difficult to evaluate the study drug;

2) The investigator requests termination of the study while ensuring the rights and safety of the subjects;

3) Health/regulatory authorities require termination of the study.

4.3.2 Early Termination of Study by the Subject (Dropout or Withdrawal)

Subjects have the right to withdraw from the study at any period. The investigator will terminate the subject's treatment at any period of the study for the following reasons:

1) Confirmed disease progression;
2) Death;
3) Intolerable AE;
4) The investigator judges that continuing treatment is not in the subject's best interest/risk ratio;
5) Poor compliance by the subject (including failure to take medication or attend visits as required; use of other medications that affect safety assessment; other behaviors that affect study outcomes);
6) Unintended pregnancy in the subject;
7) The subject's withdrawal of ICF;
8) The occurrence of concomitant diseases that do not allow the study to continue, or the subject requires treatment excluded by the study protocol;
9) The subject receives interventions outside those specified in the study protocol (see 5.2.2);
10) The subject starts other antitumor treatments before confirmed disease progression;
11) Loss to follow-up;
12) Any other reason confirmed by the investigator.

4.3.3 Management of Subjects Who Withdraw Early

If a subject withdraws early from the study drug treatment (withdraw from the study), the investigator should ascertain and record the reasons for withdrawal as much as possible. The subject will undergo all the assessments listed in the withdrawal visit. Upon withdrawal from the study, the subject will be asked whether they wish to continue with safety and long-term

follow-up. During long-term follow-up, survival data and subsequent antitumor treatment information for the subject will be collected.

5 Study Drugs and Subject Treatment

5.1 Study Drugs

KN046 and lenvatinib were study drugs in this study.

5.1.1 Dosage and Strength

The dosage form of KN046 is IV injection for single use, with the strength of 40 mg/1.6 mL/vial or 300 mg/12 mL/vial.

Lenvatinib is an oral capsule containing white to off-white granules with a strength of 4 mg/capsule.

5.1.2 Drug Preparation

KN046 is predetermined to be administered once every 3 weeks (Q3W) by intravenous infusion.

The dose volume of each group will be calculated based on body weight. For example, for a subject weighing 60 kg, the dosing will be 5.0 mg/kg * 60 kg = 300 mg, and the volume of administration will be 300 mg/40 mg * 1.6 mL = 12 mL or 300 mg/300 mg * 12 mL = 12 mL. Under aseptic conditions, 12 mL of KN046 injection solution should be drawn up and then added to 5% glucose injection solution. Before infusion, the solution should be gently mixed thoroughly. At the end of the drug infusion, an appropriate amount of sterile 5% glucose injection solution should be used to flush. The infusion time for the first six administrations should not be less than 120 min. If the subject tolerates the first six infusions well, the subsequent infusion time can be reduced to 90-120 minutes.

Before drug infusion, the solution should be visually inspected for particulate matter and discoloration. KN046 cannot be administered by intravenous bolus or rapid instillation.

5.1.3 Drug Use

On the day of or the day before each dosing cycle (the first treatment cycle for the first 6 subjects during the safety introduction period is 28 days, and each subsequent cycle is 21 days), the subject's weight will be measured. The dosing for KN046 and lenvatinib will be calculated. Lenvatinib will be administered once daily. At a fixed time (± 1 hour) on each dosing day, lenvatinib will be administered. On the day of combination therapy (Day 1 of each cycle), subjects should first take lenvatinib capsules orally. One hour later, KN046 injection solution should be administered via intravenous infusion.

Lenvatinib capsules should be swallowed whole. Alternatively, lenvatinib capsules (which should not be opened or crushed) can be mixed with a tablespoon of water or apple juice in a glass to form a suspension. The capsule should remain in the liquid for at least 10 minutes. The liquid should be stirred for at least 3 minutes to dissolve the capsule shell. Then the subject should swallow the suspension. After drinking, the same amount of water or apple juice (one tablespoon) should be added to the glass and stirred several times. Then, the subject should drink all the liquid in the glass (refer to the lenvatinib package insert). If a dose is missed and cannot be taken within 12 hours, it should not be made up. The subject should continue with the next dose at the regular dosing time.

During the safety introduction period, in the first cycle, for the first 6 subjects, the dosing of KN046 and lenvatinib should reach at least 75% of the planned dosing, otherwise a new subject will need to be enrolled.

Each subject will receive KN046/lenvatinib according to the protocol until the subject experiences disease progression based on mRECIST, or the subject experiences unacceptable toxicity, or the subject withdraws the ICF, or the subject is lost to follow-up, or the subject dies,

or the subject meets other conditions for discontinuation of KN046 treatment or withdrawal from the study. If the toxicity can be clearly attributed to one of the drugs in the combination, the subject may discontinue that drug and continue using the other drug.

5.1.4 Dose Modification of Study Drugs

■ **Dose Modification of KN046**

During the entire study period, dose adjustments of KN046 are not allowed, but KN046 may be temporarily suspended or delayed.

At any time, if a subject experiences a ≥ Grade 3 toxicity related to KN046 treatment (excluding laboratory abnormalities listed below that have no clinical significance or do not meet AE criteria), KN046 administration should be suspended until the treatment-related toxicity has resolved to ≤ Grade 1. In the table below, the guidelines for dose adjustments of KN046 are listed. Guidelines for dose modification of KN046 are listed in Table 2.

Table 3 Guidelines for Dose Modification of KN046

Toxicities	Grade	Suspension of administration	Criteria for resuming administration	Dose after resuming administration	Criteria for discontinuation
Hematologic toxicities	1、2	No	N/A	N/A	N/A
	3 *Except for grade 3 agranulocytosis alone (for grade 3 agranulocytosis alone, suspension of administration is not required.)*	Yes	Toxicity resolves to ≤ Grade 1 within 12 weeks of last dose	Original dose	Toxicity does not resolve to ≤ Grade 1 within 12 weeks of last dose *Permanent discontinuation may be considered if toxicity meets the criteria for SAEs*
	4	Yes	N/A	N/A	Permanent discontinuation
Non-hematologic toxicities Note: The following toxicities will be treated as Grade 1 toxicities • Alopecia of any grade • Grade 2 asthenia • Laboratory abnormalities that are not clinically significant or do not meet the criteria for AEs	1	No	N/A	N/A	N/A
	2	If toxicity persists, consideration should be given to suspending administration.	Toxicity resolves to ≤ Grade 1 within 12 weeks of last dose	Original dose	Toxicity does not resolve to ≤ Grade 1 within 12 weeks of last dose
	3	Yes	Toxicity resolves to ≤ Grade 1 within 12 weeks of last dose	Original dose	Toxicity does not resolve to ≤ Grade 1 within 12 weeks of last dose *Permanent discontinuation may be considered if toxicity meets the criteria for SAEs*
	4	Yes	N/A	N/A	Permanent discontinuation

In rare cases, resumption of KN046 administration is allowed when treatment-related toxicity persists at Grade 2, for example, in medical conditions with appropriate alternative treatments

such as treatment-related hypothyroidism, Type 1 diabetes, etc. In these instances, after the subject has received alternative treatment and their symptoms are controlled, the investigator must confirm that the subject can restart KN046 treatment.

For treatment-related toxicities requiring corticosteroid intervention, subjects may restart KN046 treatment once the dose of corticosteroids has been tapered to ≤ 10 mg/day of prednisone (or an equivalent dose of another corticosteroid). If the dose of corticosteroids cannot be reduced to ≤ 10 mg/day of prednisone (or an equivalent dose of another corticosteroid) within 12 weeks after the last administration, the investigator should carefully decide whether to restart KN046 treatment.

After resuming KN046 treatment, if the same type of treatment-related toxicity reoccurs and reaches the criteria for suspension treatment, the subject should permanently discontinue KN046 treatment. If the subject experiences an infusion reaction that meets the criteria for suspension treatment again (excluding Grade 3/4 infusion reactions), the investigator will carefully decide whether to permanently discontinue KN046 treatment (Section 6.2.3.1).

If a subject develops Grade 3 immune-related elevation of liver enzymes, the investigator should carefully decide whether the subject can continue KN046 treatment.

In certain situations, when a subject experiences KN046 treatment-related toxicity, the investigator should also consider permanently discontinuing KN046 treatment for the protection of the subject's safety. These situations include, but are not limited to:

- Grade 3 immune-related pneumonia;
- Recurrence of Grade 2 immune-related pneumonia lasting more than 4 weeks after active treatment;
- Grade 2 immune-related central nervous system toxicity lasting more than 4 weeks after active treatment;
- Grade 3 immune-related colitis;
- Grade 3 immune-related uveitis;
- Grade 3 immune-related hepatitis with ALT/AST ≥ 5 × ULN and/or total bilirubin ≥ 3 × ULN;
- Grade 3 immune-related nephritis and renal insufficiency;
- Grade 2 immune-related myocarditis.

■ **Dose Modification of Lenvatinib**

During the safety introduction period, dose modifications are not permitted for the first six subjects during the DLT observation period. For subjects who have experienced DLTs, a reduced dose of lenvatinib may be administered to continue treatment if the investigator deems it beneficial for the subject to continue treatment after the drug has been discontinued and the toxicity has been reduced or returned to ≤ Grade 1 or baseline level.

For the remaining enrolled subjects and those who have passed the DLT observation period, drug suspension will be allowed based on the subject's condition. After the toxicity has been reduced, subjects will continue dosing at the original dose, or continue dosing at a reduced dose, or discontinue dosing.

Before dose modification (suspension, reduction) of lenvatinib, adverse reactions such as nausea, vomiting, and diarrhea should be actively treated. Gastrointestinal toxicities should be

actively managed to reduce the risk of renal impairment or renal failure (refer to the precautions in the drug's prescribing information).

It may be necessary to manage certain adverse reactions by suspending administration, dose modification, or discontinuing lenvatinib treatment. For mild to moderate adverse reactions (e.g., Grade 1 or 2), treatment is generally not suspended unless the subject remains intolerant after active treatment. For severe (e.g., Grade 3) or intolerable adverse reactions, treatment should be suspended until the adverse reaction improves to Grade 0-1 or baseline. In the following table, the guidelines for dose modification in subjects experiencing adverse reactions after using lenvatinib are listed. Refer to the instructions for details.

Table 4 Dose Modification Principles for Adverse Drug Reactions of Lenvatinib

Adverse Reaction	Severity	Action(s)	Dose Reduction and Resumption of Lenvatinib
Hypertension	Grade 3 (despite best antihypertensive treatment)	Suspension	Resolved to Grade 0, 1, or 2
	Grade 4	Discontinuation	Treatment should not be resumed
Proteinuria	≥ 2 g/24 h	Suspension	Resolved to less than 2 g/24 h
Syndrome nephrotic	——	Discontinuation	Treatment should not be resumed
Renal insufficiency or renal failure	Grade 3	Suspension	Resolved to Grade 0-1 or baseline
	Grade 4*	Discontinuation	Treatment should not be resumed
Cardiac dysfunction	Grade 3	Suspension	Resolved to Grade 0-1 or baseline
	Grade 4	Discontinuation	Treatment should not be resumed
Posterior reversible encephalopathy syndrome (PRES) /Reversible posterior leukoencephalopathy syndrome (RPLS)	Any grade	Suspension	If adverse reactions are resolved to Grade 0-1, treatment should be resumed at a reduced dose.
Hepatotoxicity	Grade 3	Suspension	Resolved to Grade 0-1 or baseline
	Grade 4*	Discontinuation	Treatment should not be resumed
Arterial thromboembolism	All grades	Discontinuation	Treatment should not be resumed
Haemorrhage	Grade 3	Suspension	Resolved to Grade 0-1 or baseline
	Grade 4	Discontinuation	Treatment should not be resumed
	Grade 3	Suspension	Resolved to Grade 0-1 or baseline

Gastrointestinal perforation or gastrointestinal fistula	Grade 4	Discontinuation	Treatment should not be resumed
Prolonged QT interval	> 500 ms	Suspension	Resolved to ≤ 480 ms or baseline
Diarrhea	Grade 3	Suspension	Resolved to Grade 0-1 or baseline
	Grade 4 (despite medical management)	Discontinuation	Treatment should not be resumed

*When the adverse reaction is a Grade 4 laboratory abnormality, if the investigator judges that the adverse reaction is not life-threatening, it can be managed as a Grade 3 adverse reaction.

The principles for dose reduction of lenvatinib are as follows: 1) if the starting dose is 12 mg, the dose after the first reduction is 8 mg, the dose after the second reduction is 4 mg, and the dose after the third reduction is 4 mg (every other day); 2) if the starting dose is 8 mg, the dose after the first reduction is 4 mg, and the dose after the second reduction is 4 mg (every other day). If the subject cannot tolerate 4 mg every other day, the administration of lenvatinib will be discontinued.

Table 5 Guidelines for Dose Modification of Lenvatinib

Starting dose		Weight ≥ 60 kg 12 mg (3 capsules (4 mg), oral, QD)	Weight < 60 kg 8 mg (2 capsules (4 mg) oral, QD)
Persistent and intolerable Grade 2 or 3 adverse reactions [a]			
Adverse Reaction	Modification	Modified dose [b] (Weight ≥ 60 kg)	Modified dose [b] (Weight < 60 kg)
First occurrence [c]	Administration should be suspended until adverse reactions are resolved to Grade 0-1 or baseline [d]	8 mg (2 capsules (4 mg)) Oral, QD	4 mg (1 capsule (4 mg)) oral, QD
Second occurrence (same reaction or new reaction)	Administration should be suspended until adverse reactions are resolved to Grade 0-1 or baseline [d]	4 mg 1 capsule (4 mg) Oral, QD	4 mg (1 capsule (4 mg)) oral, every other day
Third occurrence (same reaction or new reaction)	Administration should be suspended until adverse reactions are resolved to Grade 0-1 or baseline [d]	4 mg 1 capsule (4 mg) Oral, every other day	Discontinuation
Life-threatening adverse reactions (Grade 4): discontinuation [e]			
a Before suspension or dose reduction of the study drug, adverse reactions such as nausea, vomiting, and diarrhea should be actively treated. b Based on the previous dose level, the dose will be gradually reduced in the sequence of 12 mg QD, 8 mg QD, 4 mg QD, or 4 mg every other day. c If the subject experiences hematological adverse reactions or proteinuria for the first time, dose modification is not required. d If the subject experiences hematological adverse reactions or proteinuria, treatment can be resumed when the event has resolved to Grade 2. e When the adverse reaction is a Grade 4 laboratory abnormality, if the investigator judges that the adverse reaction is not life-threatening, it can be managed as a Grade 3 adverse reaction.			

Adverse reactions will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events.

5.1.5 Treatment Assignment

After the subject signs the ICF, a subject number will be assigned. When subjects receive KN046 and lenvatinib, a treatment assignment number will be assigned to the subject. Subject numbers and treatment assignment numbers should be compiled in ascending order by date. Once determined, subject numbers and treatment assignment numbers cannot be reassigned to other subjects.

5.1.6 Packaging and Labeling of Drugs

KN046 will be aseptically filled into neutral borosilicate colorless glass vials. The vials will be sealed with a halogenated butyl rubber stopper and an aluminum-plastic composite cap. Each vial will be packaged in a cardboard box.

The vial label will mainly contain the following information: protocol number, drug content and strength, batch number, expiration date, storage conditions, etc. The label content will comply with current regulatory requirements.

Lenvatinib is a commercially available drug. Lenvatinib will be packaged in double aluminum blister packs. The shelf life of lenvatinib is 24 months.

5.1.7 Storage and Transportation of Drugs

In accordance with relevant regulations and the sponsor's provisions, study drugs should be distributed to the study site upon receipt of the demand order. The use of the drug should be carried out according to the following procedures. Study drugs can only be used after the subject is enrolled in the study. Only authorized personnel at the study site can supply or administer the study drug. To ensure the safety of the subjects and that the subjects receive the drug infusion according to the protocol, subjects should return to the study site for medication each time KN046 is used. Subjects should not carry or use the drug themselves. At each visit, subjects should confirm the quantity of lenvatinib used with the investigator. The study drug KN046 should be stored in a secure area. Only the investigator and authorized personnel at the study site can enter this area. The storage area should meet the storage requirements of the study drug at 2-8°C. Lenvatinib capsules should be stored at no more than 30°C.

5.1.8 Quantity Management of Drug

The investigator or authorized drug administrator should be responsible for the accountability, dispensing, recording, and maintenance of study drugs. According to relevant regulatory requirements, the investigator or designated personnel at the study site should record the quantity of drugs throughout the study. The records include the quantity of study drugs received from the sponsor and the quantity supplied to the subjects. After the study is completed, the unused drugs will be registered. Unused drugs will be recovered or destroyed on-site or at an independent site with the written consent of the sponsor.

5.1.9 Assessment of Compliance

Subject compliance with treatment/medication and the study protocol refers to the subject's willingness to adhere to various examinations, sampling, etc., as specified in the study protocol. Based on the decision of the principal investigator, subjects may be withdrawn from the study for non-compliance with visit arrangements or study drug use requirements.

5.1.10 Occupational Safety

Under normal preparation and administration conditions, KN046 does not pose an occupational safety risk to the staff at the study site.

5.2 Concomitant Medications and Non-drug Therapies

5.2.1 Permitted Medications

The investigator may provide subjects with concomitant medications or treatments according to medical standards, considering the needs of the subject's disease treatment. All concomitant medication situations will be recorded in the eCRF, including drug treatments (such as prescription drugs, over-the-counter drugs, herbal supplements, intravenous medications, and liquid medications) and important non-drug treatments (including physical therapy and blood transfusions). Concomitant medications from 28 days before the first administration to the 90-day safety follow-up period, medication modifications during the study, and treatments received for KN046-related SAEs after the 90-day safety follow-up period should all be recorded in the eCRF. The recorded content should include the dosage, regimen, route, indications, and start and end times of concomitant medication.

In this study, the use of bone palliative radiotherapy (e.g., local radiotherapy to relieve bone pain or to prevent the risk of fractures caused by osteolytic lesions) is allowed. However, it is required that the lesions in the area of bone palliative radiotherapy are not selected as target lesions, and the palliative radiotherapy is not for the purpose of treating the tumor. The

occurrence of disease progression in subjects should be judged according to RECIST 1.1 standards, not based on the need for bone palliative radiotherapy.

5.2.2 Prohibited Medications and Procedures

During the study, medications that should not be used in combination include:

- Other antitumor drugs (e.g., cytotoxic drugs, curative radiotherapy or radiotherapy intended to treat tumors, immunotherapy, antitumor cytokine therapy);
- Systemic steroids (except for the treatment of immune-related adverse reactions, prophylactic medications used before contrast-enhanced CT scans due to allergy to contrast agents, replacement therapy at physiological doses, and topical steroids [topical, nasal, ocular, inhaled]);
- Immunosuppressants;
- Traditional Chinese medicines with antitumor indications approved by the NMPA;
- Other investigational drugs;
- Plant medicines that can stimulate the immune system (e.g., mistletoe extracts).

Caution should be exercised when using drugs known to have a narrow therapeutic index that are substrates of CYP3A4, such as astemizole, terfenadine, sildenafil, pimozide, quinidine, bepridil, or ergot alkaloids (ergotamine, dihydroergotamine).

If the subject needs to use prohibited concomitant medications or procedures during the study, the subject should discontinue the study drug treatment. If the subject uses traditional Chinese medicine with antitumor indications approved by the NMPA, the investigator should make a comprehensive evaluation based on the specific situation of the subject and then decide whether to stop the study drug treatment. The investigator can also contact the sponsor to discuss whether it is necessary to stop the study drug treatment.

5.2.3 Special Precautions

■ **Lenvatinib**

Before starting treatment with lenvatinib, the subject's blood pressure (BP) should be well controlled. If the subject is known to have hypertension, they should receive a stable dose of antihypertensive treatment for at least one week before starting treatment with lenvatinib. Early detection and effective management of hypertension are important to reduce the suspension and reduction of lenvatinib administration. Once hypertension is diagnosed, the subject should start antihypertensive medication as soon as possible. The antihypertensive treatment plan should be individualized based on the subject's clinical condition. The subject should follow standard care. For subjects with previously normal blood pressure, monotherapy with an antihypertensive should be initiated upon observation of elevated blood pressure. For subjects already receiving antihypertensive therapy, the dose of the current medication may be increased, or one or more different types of antihypertensive drugs may be added, Recommendations for hypertension management are shown in the table below.

Table 6 Recommendations for Hypertension Management

Blood Pressure (BP) Level	Suggested Measures
140 mmHg ≤ systolic blood pressure < 160 mmHg or 90 mmHg ≤ diastolic blood pressure < 100 mmHg	Lenvatinib treatment should be continued with the initiation of antihypertensive therapy (if not previously administered), or lenvatinib treatment should be continued with an increase in the dose of

	the current antihypertensive medication or the addition of another antihypertensive therapy.
Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg after optimal antihypertensive therapy	1. Lenvatinib administration should be suspended. 2. If systolic blood pressure is ≤ 150 mmHg and diastolic blood pressure is ≤ 95 mmHg, and the subject has been on a stable dose of antihypertensive treatment for over 48 hours, then dose reduction should be applied, and lenvatinib treatment should be resumed.
Life-threatening hypertension (malignant hypertension, neurological dysfunction, or hypertensive crisis)	Urgent interventions are required. Lenvatinib treatment should be discontinued and appropriate therapy should be administered.

■ KN046

Subjects should receive KN046 infusion in a medical institution equipped with resuscitation equipment and emergency medications. After each infusion, subjects should be observed in the hospital for at least 2 hours. Regardless of when the subject receives KN046 infusion treatment, it should be ensured that the subject's infusion-related reactions or severe hypersensitivity reactions can be urgently treated according to local treatment guidelines. To ensure timely treatment of potential allergic reactions in subjects, corresponding rescue medications, such as dexamethasone 10 mg, adrenaline 1:1000 dilution or alternative drugs, and auxiliary ventilation equipment, should be readily available at the study site.

When the subject experiences a ≥ Grade 2 hypersensitivity reaction, inflammatory reaction, or allergic reaction, KN046 infusion should be immediately stopped.

Symptoms of infusion-related reactions can manifest as fever, chills, shivering, sweating, and headache. Once the subject experiences an infusion-related reaction, it can be managed according to the table below.

Table 7 Handling of Infusion-related Reactions Caused by KN046

NCI-CTCAE 5.0 Grade	Dose Modification of KN046
Grade 1 - Mild Mild transient reaction; infusion interruption are not required; intervention are not required.	• The infusion rate of KN046 should be reduced to half of the original rate, and the patient's condition should be closely monitored for any deterioration. • Prior to subsequent administrations, in addition to the routine prophylactic medications specified in the protocol, it is recommended to use additional prophylactic medication such as dexamethasone 10 mg p.o. The investigator may decide at their discretion whether to add extra prophylactic medications.
Grade 2 - Moderate Treatment or infusion should be interrupted and symptomatic treatment should be administered promptly (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, anesthetics, intravenous fluids).	• KN046 infusion should be suspended, and symptomatic treatment should be given. Once the infusion-related reaction subsides, the infusion can be resumed at half the previous rate. Close monitoring for any deterioration in the condition should be maintained • Prior to subsequent administrations, in addition to the routine prophylactic medications specified in the protocol, it is recommended to use additional prophylactic medication such as dexamethasone 10 mg p.o. The investigator may decide at their discretion whether to add extra prophylactic medications.
Grade 3: Prolonged symptoms (e.g., not rapidly relieved after symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	• The infusion of KN046 should be stopped immediately, and symptomatic treatment should be provided. Subsequently, the investigator and the sponsor's medical personnel should discuss and evaluate. If the anticipated treatment benefit outweighs the acceptable risks, treatment with KN046 may be cautiously resumed after obtaining the subject's informed consent and adequate prophylactic administration. • Prior to subsequent administrations, in addition to the routine prophylactic medications specified in the protocol, it is recommended to use additional prophylactic medication such as dexamethasone 10 mg p.o. The investigator may decide at their discretion whether to add extra prophylactic medications.
Grade 4; life-threatening consequences; urgent intervention indicated	• KN046 should be permanently discontinued.

Note: 1. After prophylactic medication is administered, if the subject experiences a Grade ≥ 3 infusion-related reaction again, it is recommended to discontinue KN046 treatment; however, if the investigator assesses that the subject may still benefit from KN046 treatment, medication can be continued after communication between the investigator and the sponsor's Clinical Research Associate (CRA); 2. The recommended prophylactic medication regimen for KN046 is as follows: diphenhydramine 25-50 mg i.m. or p.o. at an equivalent dose, cimetidine 400 mg i.v., and acetaminophen tablets 500-1000mg p.o., with the above medications to be administered 30-60 minutes before KN046 administration; 3. If the subject has previously experienced an infusion-related reaction, the investigator may consider adding prophylactic medications such as promethazine and calcium gluconate at their discretion. The investigator may also decide, based on medical judgment, whether to include steroids (such as 25 mg of hydrocortisone or an equivalent dose of a similar drug) in the prophylactic medication regimen.

Once the infusion rate of KN046 is reduced by 50% due to an infusion-related reaction, this rate should be maintained for all subsequent infusions. If the subject experiences an infusion reaction, the details of drug preparation and infusion should be recorded.

Severe hypersensitivity reactions can manifest as airway injury, decreased oxygen saturation (below 90%), confusion, somnolence, hypotension, pale/cold skin, cyanosis.

When the subject experiences a severe hypersensitivity reaction, they should be monitored immediately, and adrenaline and steroids should be injected immediately (methylprednisolone 1-2 mg/kg i.v., every 6 hours, or other equivalent steroids). The ICU should be notified. If necessary, the subject should be referred to the ICU. Specific management principles can be found in the full version of the Emergency Treatment of Anaphylactic Reactions: Guidelines for Healthcare Providers (UK) established by the Resuscitation Council Working Group at https://www.resus.org.uk/anaphylaxis/emergency-treatment-of-anaphylactic-reactions/
(Reference: Emergency Treatment of Anaphylactic Reactions: Guidelines for Healthcare Providers, 2008).

If the investigator judges that continuing administration is more beneficial than the risks to the subject, KN046 treatment should be allowed to continue. In all subsequent administration cycles, prophylactic administration should be given to the subject 30-60 minutes before administration. Examples of the prophylactic medication regimen are as follows: cetirizine 10 mg p.o., famotidine 20-40 mg p.o. (or i.v. at an equivalent dose), acetaminophen 650 mg p.o. (or i.v. at an equivalent dose). If the subject's hypersensitivity reaction manifests as bronchospasm symptoms, montelukast 10 mg p.o. should be part of the prophylactic medication regimen.

6 Study Procedures and Evaluations

6.1 Study Visit Schedule

The study visit schedule for this study is detailed in the study flow chart.

6.1.1 Screening Period

- All subjects should provide a written signed ICF before starting any study assessments and examinations;
- Demographic information: Date of birth, sex, race/ethnicity;
- History of alcohol consumption and smoking;
- Past medical and treatment history: All past medical and treatment histories related to the study, excluding the indication for this study, that started before the subject signed the ICF, should be collected;
- Past oncology history and treatment history: Dates of cancer diagnosis, start/end dates of previous treatment regimens, best treatment assessment, date of disease progression; radiotherapy history: start/end dates, sites of radiotherapy. Past significant procedures (such as gastroscopy, biopsy, etc., diagnostic or therapeutic invasive procedures) should be recorded in the electronic Case Report Form (eCRF), including start and end dates, names, and sites of the procedures;
- Collection of tumor tissue samples: All subjects should provide tumor tissue samples for tumor biomarker testing at the central laboratory (fresh tumor tissue samples from biopsies prior to enrollment are preferred) before enrollment;
- Physical examination: head, eyes, ears, nose, throat, neck, heart, chest (including lungs), abdomen, limbs, skin, lymph nodes, nervous system, and general condition of the subject;
- Measurement of height and weight;
- Vital signs: body temperature, respiration, blood pressure, and heart rate;
- ECOG score: it is recommended that the same investigator should evaluate ECOG throughout the study, as detailed in Appendix IV;
- Hematology: Red blood cell count, hemoglobin, hematocrit, white blood cell count and differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils), and platelet count;
- Blood chemistry: Total protein, albumin, globulin, blood glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, urea, creatinine, ALP, lactate dehydrogenase, creatine kinase, total bilirubin, direct bilirubin, indirect bilirubin, AST, ALT, calcium, phosphorus, magnesium, potassium, sodium, chloride, serum amylase, uric acid;
- AFP；
- Urinalysis: specific gravity, pH, glucose, protein, casts, ketones, and blood cells; if urine protein is ++ or higher for two consecutive tests, or if the investigator deems the result abnormal and clinically significant, a 24-hour urine protein quantification should be performed;
- Routine stool examination: stool color and shape, red blood cells, white blood cells, and occult blood;
- Coagulation function tests: aPTT, PT, TT, INR;

- Blood pregnancy test: female subjects of childbearing potential only;
- Echocardiography: Particular attention should be paid to the evaluation of left ventricular ejection function;
- 12-ECG;
- Virological testing: Hepatitis B in two-half pairs [hepatitis B virus surface antibody (HBsAb), HBsAg, hepatitis B virus e antigen (HBeAg), hepatitis B virus e antibody (HBeAb), and HBcAb], HCV antibody, HDV antigen, HIV antibody;
- Thyroid function assessment: thyroid-stimulating hormone (TSH), serum free triiodothyronine (FT3), serum free thyroxine (FT4);
- Tumor assessment: During the screening period, tumor assessment should be performed within 3 weeks (21 days) before enrollment, and chest, abdominal, and pelvic CT or MRI scans should be performed; if clinically indicated, any other known or suspected disease sites should be examined using appropriate methods, such as head MRI, bone scan, or neck CT scan; for tumor imaging examinations performed for routine diagnosis and treatment before the subject signes the ICF, if the imaging examination is performed within 3 weeks (28 days) before enrollment and at the study site, it is not necessary to repeat it; the same imaging method should be used for baseline and subsequent assessments, and the assessments should preferably be performed by the same investigator;
- Child-Pugh score: should be completed within 7 days before dosing on C1D1;
- Determination of tumor staging: According to the Barcelona liver cancer staging, HCC subjects should complete this determination within 7 days before dosing on C1D1;
- Inclusion and exclusion criteria should be reviewed to assess the eligibility of the subject for enrollment;
- Collection of concomitant medications/concomitant treatments: All drug treatments received by the subject from the signing of the ICF to before the first dosing should be recorded in the eCRF. The record should include the generic name and daily dose of the drug, the reason for using the drug, and the start and end dates;
- AE collection: AEs occurring after the signing of the ICF and before the first dosing should be recorded on the past medical history page of the eCRF.

If a subject fails screening due to abnormal laboratory tests, the subject is allowed to undergo laboratory testing once more. If the subject does not meet the eligibility inclusion/exclusion criteria during the screening period, the subject is deemed to have failed screening and cannot receive the study drug. For subjects who fail screening, the following information should be recorded on the eCRF:

- Informed consent page;
- Reason for screening failure;
- Demographic information;
- AEs;
- Inclusion/exclusion criteria page.

6.1.2 Treatment Period

Treatment period: From the first administration of the study drug in C1D1 until the subject experiences disease progression (based on RECIST1.1 criteria), or the subject experiences

intolerable toxicity, or the subject withdraws the ICF, or the subject is lost to follow-up, or the subject dies, or the last subject completes one year of treatment, or the investigator assesses that the study objectives have been achieved, or the subject receives interventions outside the study protocol, or the subject needs to withdraw from the study.

During the DLT observation period, subjects should be followed up once a week for safety assessment. If the subject exhibits suspicious symptoms or signs or abnormal related test values, the investigator may increase the frequency of examinations based on clinical practice.

During the treatment period after the DLT observation period, the subject should have one visit before each administration of KN046. The visit window is 3 days before to 3 days after (±3 days) the scheduled visit date.

During the treatment period, the evaluations implemented are detailed in Table 1. The evaluations should follow the provisions in Table 1.

6.1.3 End of Treatment Visit (EOT)

Subjects who discontinue KN046 and/or lenvatinib treatment for any reason should have an EOT visit. The EOT visit should be conducted within 7 days of the subject's decision to discontinue KN046 and/or lenvatinib treatment, or before the subject starts a new antitumor treatment (if applicable), whichever occurs first. The EOT visit can also be conducted on the same day that the subject decides to discontinue KN046 treatment, that is, the EOT visit and the last pre-treatment assessment are conducted on the same day. In this case, it is not necessary to repeat the same examination items as the EOT. Subjects who need to end treatment due to AEs that lead to a drug suspension for more than 12 weeks should only have the EOT examination and do not need to repeat the examination in the 30-day safety follow-up.

On the eCRF page for the EOT visit, the following should be included: the date of the decision to discontinue KN046 treatment, the date of the last KN046 treatment, and any of the following reasons:

- AEs;
- Protocol deviations;
- Withdrawal of informed consent;
- Lost to follow-up;
- Death (should be noted it is caused by "study indication" or "other" reasons);
- Disease progression judged according to RECIST 1.1 criteria;
- End of treatment according to the protocol;
- Other reasons.

If the subject withdraws the ICF, it should be clearly noted whether the subject is willing to continue follow-up after the end of treatment.

See Table 1 for the specific assessments at the EOT visit.

6.1.4 30-Day and 90-Day Safety Visits

A safety follow-up will be conducted 30 ± 7 days after the last dose of lenvatinib and/or KN046 (whichever occurs later). Within 30 to 90 days after the last use of KN046, all SAEs and AEs related to KN046 (TRAE) should be collected.

After the EOT visit, AEs should be recorded until the 30-day safety follow-up visit. Thereafter, all SAEs and non-SAEs related to treatment (including immune-related AEs) should be recorded until the 90-day safety follow-up. The investigator needs to continue monitoring the ongoing SAEs after the 30-day safety follow-up until the SAE stabilizes or the outcome is understood by the investigator.

During the safety follow-up period, subsequent antitumor treatments, tumor imaging evaluations, etc., should also be collected. Please refer to Table 1 for the content of the visits during the safety follow-up period.

6.1.5 Long-term Follow-up

If the subject experiences an SAE related to KN046 treatment (SAE), regardless of when it occurs or how long it has been since KN046 was discontinued, the SAE should be recorded. According to local regulations, the SAE should be reported to the drug regulatory authorities.

After the EOT visit, the subject's survival status information and subsequent antitumor treatments should be collected every 2 months (± 7 days). Survival follow-up will continue until one year after all subjects have discontinued KN046 treatment, or until the last subject completes the last study-related telephone contact or visit, or the subject withdraws from the study or is lost to follow-up (i.e., the investigator is unable to contact the subject), or all subjects die or withdraw from the study early, or the investigator assesses that the study objectives have been achieved (such as completing the primary study endpoint assessment), whichever occurs first.

Each subject will be followed up until the subject dies, or the subject is lost to follow-up, or the entire study ends. For subjects who do not experience disease progression (based on the current RECIST 1.1) after the EOT visit, tumor assessments should continue for the subjects.

Please refer to Table 1 for the content of the long-term follow-up visits.

6.2 Study Evaluations

6.2.1 Demographics and Other Baseline Characteristics

The study evaluations described in this section should be completed during the screening period.

6.2.1.1 Demographic data

During the screening period, the following data should be collected:

- Date of birth;
- Gender;
- Ethnicity;
- Height, etc.

6.2.1.2 Tumor diagnosis

During the screening period, each subject's tumor disease information should be confirmed and recorded, including:

- Detailed tumor history determined at diagnosis according to the Barcelona classification standard, including histopathological type, grade, and stage;
- All previous antitumor treatments (including surgery, radiotherapy, chemotherapy, immunotherapy);
- Any other diseases treated with chemotherapy, radiotherapy, or immunotherapy;

- Current tumor symptoms and signs, as well as current and/or previous adverse reactions of antitumor treatment;
- Current tumor status.

6.2.1.3 Medical history

During the screening period, each subject's complete medical history should be collected and recorded. It should be confirmed whether the subject meets the enrollment criteria. The complete medical history should at least include the following information:

- Prior non-tumor diseases and concomitant therapies;
- Prior tumor diseases and concomitant therapies;
- Medications (including botanicals) and procedures received within 28 days prior to screening;
- Family history of tumor;
- History of alcohol consumption.

6.2.1.4 Other baseline evaluations

Additional baseline evaluations include oncology evaluations, vital signs, full physical examination, ECOG score, laboratory tests, 12-lead ECG, biomarker tests, evaluation of inclusion/exclusion criteria, and other relevant tests required by the protocol (Table 1).

Please refer to Section 6.2.2 for Oncological Assessment at Baseline. Please refer to Section 6.2.3 for Safety Evaluation at Baseline. Please refer to Section 6.2.5 for Biomarker Tests. Please refer to Sections 4.1 and 4.2 for Evaluation of Inclusion/Exclusion Criteria.

6.2.2 Efficacy Evaluation

In this study, the investigator will evaluate based on RECIST 1.1 (Appendix 1). The results of the investigator's evaluation will be used to guide clinical decisions (such as termination of treatment) as well as analyses of efficacy endpoints and exploratory endpoints. Refer to the imaging manual for detailed oncology evaluation.

6.2.2.1 Computed Tomography (CT), MRI, FDG PET/CT, and Evaluation at Baseline

All subjects will undergo neck/chest/abdominal/pelvic CT scans or MRI (if MRI is used, chest CT should be performed). If CT/MRI imaging is insufficient to assess tumor burden, other established evaluation methods may be added. Enhanced CT scans are recommended. If the subject is allergic to contrast agents, enhanced MRI may be considered.

CT scans or MRI with a 5 mm slice thickness and continuous reconstruction algorithm are preferred. When using a continuous reconstruction algorithm, the slice thickness of CT/MRI scans should not exceed 8mm. All scans performed at baseline and other imaging (other supportive imaging) used in clinical applications should be repeated in subsequent visits. In summary, the imaging method should be consistent with the method used to detect lesions at baseline. In subsequent tumor assessment visits, the same imaging equipment should be preferred.

If clinically indicated, appropriate methods may be used to examine any other known or suspected disease sites, such as head MRI, bone scan, or neck CT scan. During the screening period, for brain CT/MRI, imaging examinations completed within 42 days before the first dose are acceptable. For bone scans, imaging examinations completed within 90 days before the first dose are acceptable. For tumor imaging examinations performed for routine diagnosis and

treatment before the subject signs the ICF, if the imaging examination is performed within 28 days before enrollment and at the study site, it is not necessary to repeat it.

6.2.2.2 Subsequent oncology evaluation

The frequency of subsequent oncological assessments is once every 6 weeks (±7 days) during the first year (54 weeks). After the first year, the assessment will be performed once every 12 weeks (±7 days) until the subject experiences disease progression (imaging), the subject starts a new antitumor treatment, the subject withdraws the ICF, the subject is lost to follow-up, the subject dies, whichever occurs first. For subjects who terminate treatment due to unacceptable toxicity or clinical progression, imaging follow-up should continue for tumor assessment until the subject experiences imaging progression.

All target lesions or non-target lesions identified at baseline should be evaluated in subsequent follow-ups and should be recorded on the corresponding eCRF pages. The evaluation method should be consistent with the method used at baseline. If possible, the same radiologist should perform all oncological assessments for the subject. For new lesions that were not found at baseline but appeared later, they may be measurable or non-measurable lesions. The lesion should be evaluated/measured. The lesion should be recorded on the new lesion eCRF page.

6.2.3 Safety Evaluation

Safety monitoring will be performed for each subject in this study, including hematology, blood chemistry, coagulation, urinalysis, stool routine, 12-lead ECG, physical examination, vital signs, height, weight, ECOG score, endocrinology examination, etc. Detailed tests and frequencies are presented in Table 1.

6.2.3.1 Physical examination

Full physical examination: general condition, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, limbs, blood vessels, nervous system, and vital signs.

The full physical examination will be conducted during the following visits:

- Screening period;
- EOT visit.

Symptom-directed physical examination: general condition, vital signs, and abnormal findings from the physical examination.

Symptom-directed physical examination will be conducted during the following visits:

- Days 1, 8, 15, 22, 28 of the DLT observation period;
- Before each dosing cycle;
- 30, 90-day safety follow-up.

The physical examination should be recorded in the source documents of the study site. For physical examination abnormalities that existed before the subject signs the ICF, they should be recorded on the corresponding past medical history/current medical history of eCRF page. For new or worsening physical examination abnormalities that occur after the subject signs the ICF, they should be recorded as AEs on the corresponding eCRF page.

6.2.3.2 Vital signs

Vital sign examinations include respiration, heart rate, blood pressure, and body temperature. Vital sign examinations will be conducted during the following visits:

- Screening period;
- Days 1, 8, 15, 22, 28 of the DLT observation period;
- Before each dosing cycle;
- EOT visit;
- 30, 90-day safety follow-up.

If the time for measuring vital signs coincides with the time for safety laboratory blood collection, vital signs should be measured first.

6.2.3.3 Height and weight

Height will be measured during the screening period.

Weight measurements will be conducted during the following visits:

- Screening period;
- Days 1, 8, 15, 22, 28 of the DLT observation period;
- Before dosing on the first day of each treatment cycle;
- EOT visit;
- 30, 90-day safety follow-up.

The weight measured before each administration of KN046 will be used to calculate the dosing of KN046.

6.2.3.4 ECOG score

The ECOG score will be conducted during the following visits:

- Screening period;
- Days 1, 8, 15, 22, 28 of the DLT observation period;
- Before each dosing cycle;
- EOT visit;
- 30, 90-day safety follow-up.

The ECOG scoring method is shown in Appendix 4.

6.2.3.5 Laboratory tests

Laboratory tests for safety evaluation will be conducted at local laboratories. The normal value ranges of the local laboratory will be adopted. The examination content includes: hematology, serum biochemistry, coagulation function, urinalysis, fecal routine, electrocardiogram, echocardiography, thyroid function tests, and urine pregnancy/serum pregnancy tests, etc. The tests will be conducted according to the visit flow chart.

Before shipping the study drug, the study site should provide the sponsor with a list of normal ranges for the study site's laboratory. If the normal ranges of the laboratory change during the study, these changes should be provided to the CRO designated by the sponsor.

Blood samples should be collected before the administration of KN046. All routine laboratory tests will be conducted at the local laboratory of the study site. Test results that are of significant clinical importance for the treatment decision of the subject (such as hematology, blood biochemistry, endocrine tests) should be known before the administration of KN046 and should

be evaluated. The result report should be kept as part of the subject's medical records or original documents and should be recorded in the eCRF.

6.2.4 Biomarker Evaluation

Formalin-fixed, paraffin-embedded (FFPE) tissue blocks containing tumor tissue obtained from biopsies within the last 2 years from non-irradiated areas, or unstained tumor slides prepared within one week, should be submitted for ctDNA analysis during the screening period. Biomarker samples should be collected, processed, standardized, stored, and transported according to the laboratory manual and materials provided by the central laboratory.

If one or more biomarker evaluations indicate a lack of utility based on newly emerging data, the analysis may be terminated. Based on new scientific evidence, the sponsor may request additional material from previously collected tumor samples for retrospective analysis during or after the study. In such cases, this analysis will only be used for research related to the study drug or disease.

Tissue collection: Samples should be collected during the screening period. Archived specimens (biopsy or surgical) tissue (blocks or slides) should have been obtained within the last 2 years prior to the screening period. Samples obtained through endoscopic biopsy, needle aspiration biopsy, excisional biopsy, core needle biopsy, and surgery are acceptable. Samples from fine needle aspiration biopsies are not acceptable.

Sample provision: Priority 1: FFPE tissue blocks containing tumor; Priority 2: If the entire FFPE block containing tumor cannot be provided, then slides from this block should be provided. Slides should be freshly cut (within one week) and 4-5 μm thick. Approximately 10-15 slides are preferred.

Tissue processing: Tumor tissue should be fixed in 10% neutral buffered formalin, embedded in paraffin, and then routinely processed for histological evaluation. Formalin substitutes are not suitable as fixatives.

Sample and tissue bank: Biomarker samples may be stored until after the study ends. Biomarker samples may be analyzed together with samples from other studies. Biomarkers will be analyzed for their relationship with the efficacy of the study drug or the disease, as well as the potential development of diagnostic kits.

Peripheral blood biomarker evaluation: During the screening period, peripheral blood samples will be collected from each subject for the correction of TMB. Additionally, blood samples will be collected at the time of the first tumor assessment, the second tumor assessment, and upon tumor progression for analysis.

7 Evaluation and Recording of Adverse Events

7.1 Definition of Adverse Events

7.1.1 Adverse Event

AE refers to an adverse medical event that occurs in a subject receiving a certain drug. This event does not necessarily have a causal relationship with the treatment. Therefore, AE may be discomfort or signs (including abnormal laboratory results), symptoms, or diseases temporarily associated with the use of drugs in terms of timing, regardless of whether there is a causal relationship with the drug use.

For surgical or diagnostic procedures, the condition/disease that leads to the procedure should be considered as AE, not the procedure itself. Scheduled examinations and surgeries (including endoscopic examinations, appendectomies) prior to enrollment, hospitalizations due to convenience or social reasons, daily fluctuations in symptoms or diseases that existed before the start of the study rather than worsening, and clinical symptoms that manifest in the expected progression of the disease under study (unless the investigator judges it to be related to the study drug) will not be considered as AE.

7.1.2 Serious Adverse Event

SAE refers to an adverse medical event that occurs at any dose and can lead to the following outcomes:

- Events leading to death;
- Life-threatening events;

  Note: The term "life-threatening" in the definition refers to the risk of death at the time of the event, not the assumption that the event could lead to death if it were more severe.
- Events requiring hospitalization or prolonging current hospitalization;
  - Hospitalizations due to social reasons or convenience (such as insurance, accommodation inconvenience for out-of-town patients, etc.) that are not related to the treatment of AE should not be reported as SAE;
- Events leading to permanent or serious disability/incapacity;
- Events leading to congenital anomalies/birth defects;
- Other medically significant events.

  Note: For certain important medical events that do not lead to death, are not life-threatening, or do not require hospitalization, these events may be judged as SAE based on the investigator's medical judgment if they could harm the subject or may require medical or surgical intervention to prevent any of the above SAE conditions from occurring. Examples of such events include allergic bronchospasm (requiring intensified treatment in the emergency room or at home), hematological diseases or seizures that do not require hospitalization, or the occurrence of drug dependence or drug abuse.

7.1.3 Adverse Reactions of Special Interest for Lenvatinib

Adverse reactions of special interest for lenvatinib include:

- Hypertension

- Proteinuria
- Renal failure and renal insufficiency
- Cardiac dysfunction
- Posterior reversible encephalopathy syndrome (PRES)/Reversible posterior leukoencephalopathy syndrome (RPLS)
- Hepatotoxicity
- Arterial thromboembolism
- Haemorrhage
- Gastrointestinal perforation and gastrointestinal fistula formation
- Non-gastrointestinal fistula
- Prolonged QT interval
- Diarrhea
- Impaired thyrotropin suppression/Thyroid dysfunction
- Wound healing complications
- Embryo-fetal toxicity

For potential adverse reactions of lenvatinib, existing risk factors should be controlled. These adverse reactions should be closely monitored during treatment. These adverse reactions should be treated symptomatically in a timely manner.

7.1.4 Immune-related Advers Reactions

KN046 can block the PD-L1 and CTLA-4 dual pathways, which may cause delayed autoimmune-related reactions or inflammatory responses. irAE may affect any organ, such as the gastrointestinal tract, endocrine system, skin, liver, lungs, nervous system, cardiovascular system, musculoskeletal system, and hematological system, etc. For suspected irAEs:

- The subject should be evaluated to identify other possible causes, such as infection, tumor, metabolic or other factors.
- If there is a lack of a clear cause, for all inflammatory reaction events, the possibility of irAE should be considered. For events of Grade 3-4 or above, tissue biopsy for differential diagnosis may be considered.
- For less severe irAE, symptomatic or local treatment may be considered.
- For severe irAE or persistent mild irAE, systemic corticosteroid treatment should be considered.
- If corticosteroids are difficult to treat, more potent immunosuppressants may be considered.

See Appendix 3 for details.

7.2 Recording and Reporting of Adverse Events

In this study, any adverse medical events that occur after the subject signs the ICF and during the study process should be recorded until 30 days after the last administration or the subject starts a new antitumor treatment, whichever occurs first. For SAE and TRAE, data should be collected until 90 days after the last administration. For SAE suspected to be related to KN046, regardless of when it occurs or how long after KN046 discontinuation, the SAE should be recorded and reported.

The investigator should grade the severity/intensity of each AE. The investigator should grade the severity/intensity of each AE. If the severity/intensity of a particular AE is not graded in the guidelines, the investigator may grade it from 1 to 5, based on their best medical judgment:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Deaths related to AE.

Each AE report should include a description of the event, duration (dates/times of occurrence and resolution. If the timing of AE occurrence relative to administration needs to be evaluated, "administration time" should also be recorded), severity, relationship to the study drug, other potential causes leading to AE, treatments given or other measures taken (including delay or discontinuation of the study drug), and outcome. In addition, serious events should be identified and the corresponding severity criteria should be recorded.

For deaths, the primary cause of death (the event leading to death) should be recorded and reported as SAE. "Fatal" should be recorded as the outcome of the event. Death should not be recorded as SAE alone. Only when the cause of death is unknown (e.g., sudden death, unexplained death), can death itself be reported as SAE.

If symptoms or signs related to the study indication in the subject worsen, the event should be recorded as AE in the CRF. Disease progression confirmed by imaging assessment or other means and its related symptoms/signs (meeting RECIST1.1 criteria) are efficacy endpoints and should not be recorded as AE. If these symptoms/signs lead to serious outcomes, they also do not need to be reported as SAE.

On the eCRF, diagnoses should be recorded as much as possible rather than individual symptoms and signs (e.g., liver failure should be recorded, not jaundice, elevated transaminases with flapping tremor). However, if symptoms and signs cannot be attributed to a single diagnosis at the time of reporting, each individual event should be recorded as AE or SAE on the eCRF. If a diagnosis is later established, the diagnosis should be reported as follow-up information.

The investigator should assess the causality of each AE or SAE to KN046 based on clinical condition:

- **Not related**: AE or SAE is not suspected to have a reasonable relationship with KN046. There are reasonable other causes that can explain the event more than KN046.
- **Related**: AE or SAE is suspected to have a reasonable relationship with KN046. AE is medically (pharmacologically/clinically) attributed to KN046.

For AE records, integrity, accuracy, and consistency of data should be ensured. For specific filling instructions, see the "eCRF Filling Guide".

7.2.1 Recording and Reporting of Serious Adverse Events

For any new SAE (of any grade) that occurs during the reporting period, the investigator should complete the "Serious Adverse Event Report" within 24 hours of becoming aware of it. The investigator should send the report via email to the pharmacovigilance department of Jiangsu Alphamab Biopharmaceuticals Co., Ltd.: drugsafety@alphamabonc.com. If there is any new information about a previously reported SAE, the reporting procedure and time limit are the same as for the initial report.

For all written reports, the SAE report form should be completed by the investigator according to specific filling instructions. In addition, the investigator should fill out the AE section of the eCRF. Relevant pages of the eCRF (such as medical history, concomitant medication) can also be provided. In any case, the information provided in the SAE report form should be consistent with the event data recorded in the corresponding section of the eCRF. If the pharmacovigilance personnel request follow-up information about the SAE (such as additional information, outcome and final evaluation, specific records (as appropriate)) or have questions about the SAE report, the investigator should respond promptly. The response time requirement is the same as for the initial SAE report. This allows the pharmacovigilance personnel to quickly evaluate the event. This allows Jiangsu Alphamab Biopharmaceuticals Co., Ltd. to meet the strict timing requirements for reporting safety events through rapid reporting as stipulated by the regulatory authorities. Usually, the CRA responsible for the study site should make the follow-up request. However, in exceptional cases, the pharmacovigilance department of Jiangsu Alphamab Biopharmaceuticals Co., Ltd. may also contact the investigator directly to clarify or discuss specific key events.

In addition to reporting all SAEs to the pharmacovigilance department of Jiangsu Alphamab Biopharmaceuticals Co., Ltd., the investigator should also report to the regulatory authorities and EC in a timely manner according to regulatory requirements.

7.2.1.1 Follow-up of Serious Adverse Events

Once a subject experiences an SAE, the investigator should follow up on the subject's SAE (clinical symptoms/signs, abnormal laboratory tests or other) until the SAE returns to normal, returns to baseline level, or the subject's clinical outcome stabilizes. Therefore, follow-up of the SAE may continue after the end of the study. Jiangsu Alphamab Biopharmaceuticals Co., Ltd. may also request follow-up results of the SAE after the end of the study.

7.2.2 Recording and Reporting of Laboratory Abnormalities and Other Abnormalities

If abnormal laboratory test results and other abnormal study findings (such as ECG) are determined to be clinically significant, such as having related clinical symptoms and signs, causing treatment interruption, requiring medical intervention or changing concomitant treatment, etc., they should be recorded as AE. For abnormal laboratory test results that are determined to be clinically insignificant, there is no need to record them as AE. If a clinically significant laboratory abnormality or an abnormal vital sign is a sign of a disease or syndrome (e.g., ALP and bilirubin increased to > 5× ULN as a result of cholecystitis), only the diagnosis (i.e., cholecystitis) is recorded in the Adverse Event Form of the eCRF. Medical issues identified must be reported as AEs, with values above or below the normal range indicated (e.g., "blood potassium increased" should be recorded rather than "blood potassium abnormal"); if there are corresponding standard clinical terms for the laboratory test abnormalities or vital sign abnormalities, clinical terms should be recorded in the eCRF, e.g., blood potassium increased to 7.0 mEg/L should be recorded as "hyperkalemia".

7.2.2.1 Abnormal liver function

When the following situations occur, the investigator should report this as AE. The investigator should record the most appropriate diagnosis or laboratory abnormal value on the Adverse Event Form of the eCRF (when the diagnosis cannot be established). The investigator should report to the pharmacovigilance department of Jiangsu Alphamab Biopharmaceuticals Co., Ltd. within 24 hours of becoming aware of the event, regardless of whether it is an SAE:

- Subjects with treatment-emergent increased ALT or AST greater than 3 times the baseline value, or with increased transaminases at baseline are found to have increased ALT or AST greater than 2 times the baseline value with increased total bilirubin greater than 2 times the ULN (35% for direct bilirubin);
- ALT or AST elevation during treatment exceeds 3 times the baseline value combined with clinical jaundice.

7.2.3 Pregnancy and Intrauterine Exposure

To ensure the safety of the subjects, the investigator should report to the pharmacovigilance department of Jiangsu Alphamab Biopharmaceuticals Co., Ltd. within 24 hours of becoming aware of pregnancy events that occur during the treatment with the study drug or within 6 months after discontinuation of the drug for the subject or their spouse. Pregnant subjects should be followed up to determine the outcome of the pregnancy, including spontaneous abortion or voluntary termination of pregnancy. Detailed information related to the birth of the baby and whether there are birth defects, congenital anomalies, or maternal inherited and/or newborn complications should be recorded.

Pregnancy events should be recorded on the clinical study pregnancy form. Pregnancy events should be reported by the investigator to the pharmacovigilance department of Jiangsu Alphamab Biopharmaceuticals Co., Ltd. Follow-up information on pregnancy should be recorded on the same form. The relationship between the study drug and the outcome of the pregnancy should be assessed. All SAEs that occur during pregnancy should be recorded and reported on the SAE report form. For male subjects receiving the study drug, information on the pregnancy outcome of their female partners should be collected. When reporting these pregnancy outcome information, informed consent should be obtained from the mother.

Adverse pregnancy outcomes such as spontaneous miscarriage, fetal death, fetal malformation, stillbirth, birth defects, or congenital anomalies, etc., should be reported as SAE.

7.2.4 Overdose, Medication Error and Abuse

Drug overdose: The administered dose exceeds the dose specified in the protocol by 20%.

If a subject experiences an overdose of KN046, medication errors, abuse, or misuse during the study, whether or not there are related AEs, the investigator should report to the pharmacovigilance department of Jiangsu Alphamab Biopharmaceuticals Co., Ltd. within 24 hours of becoming aware of the situation. If the above situation leads to an SAE, the investigator should report the SAE.

8 Data Analysis and Statistics

8.1 Statistical Methods

All data for all subjects in the study will be listed based on the SS. Unless otherwise noted, all data will be evaluated based on actual observations and missing data will be not estimated.

Descriptive statistics will be used to summarize the study results. Statistical measures for continuous variables may include mean, median, range, and standard deviation/variability. For qualitative variables, counts and percentages will be summarized. The uncertainty of the estimates will be evaluated with confidence intervals (CI). Specific analysis methods will be described in the Statistical Analysis Plan (SAP).

8.2 Sample Size

In this study, approximately 53 subjects are planned. Among them, 6 subjects are planned to be enrolled during the safety introduction period.

The calculation of sample size will be based on the binomial exact test. The hypothesis test is as follows:

H_0： $P \leq P_0$

H_1： $P > P_0$

P_0 is the historical experience value. P_0=20%. The assumed ORR =40%. A one-sided test will be used, α=0.025, and power = 85%. It is expected to enroll 53 subjects.

8.3 Analysis Sets

The following analysis datasets will be used for statistical analysis and data reporting.

8.3.1 Safety Set

The SS includes subjects who have been enrolled and have used the study drug at least once and have at least one safety assessment. Safety information will be summarized according to the actual treatment received by the subjects.

For subjects who fail screening, they will only be listed and not summarized or analyzed.

8.3.2 Efficacy Analysis Set

The Efficacy Analysis Set (EAS) includes all subjects who have received the study drug at least once and have at least one post-baseline tumor imaging evaluation. EAS will be mainly used for efficacy analysis of tumor assessment efficacy endpoints.

8.4 Demographics and Other Baseline Characteristics

In the study report, the demographic and other baseline data of each subject will be listed, including age, gender, height, weight, ECOG score, etc. Descriptive statistics (for continuous data) or frequency tables (for categorical data) will be used to summarize the above data.

8.5 Study Endpoints

8.5.1 Primary Endpoint:

- Safety and tolerability, dose-limiting toxicity (DLT);
- ORR by the investigator based on RECIST 1.1 criteria;

8.5.2 Secondary Endpoints:

- ORR by the investigator based on mRECIST and imRECIST criteria;

- DOR, DCR, TTR, and PFS by the investigator based on RECIST 1.1, mRECIST, and imRECIST criteria;
- OS and OS_{12};

8.5.3 Exploratory Endpoints:

- Correlation between antitumor activity and potential biomarkers (eg. ctDNA).

8.6 Efficacy Analysis

OS, PFS, and TTR will be analyzed based on SS and the remaining efficacy analyses will be based on the EAS.

8.6.1 Analysis of Primary Efficacy Endpoint

ORR based on RECIST 1.1 criteria: The number and percentage of subjects with CR or PR will be calculated. The ORR for the study group and the corresponding confidence intervals will be calculated using the Clopper-Pearson method, and a binomial exact test will be used for hypothesis test of the study group.

8.6.2 Analysis of Secondary Efficacy Endpoints

(1) ORR based on mRECIST and imRECIST criteria: The number and percentage of subjects with CR or PR based on BOR will be calculated. The ORR for the study group and the corresponding confidence intervals will be calculated using the Clopper-Pearson method. A binomial exact test will be used for hypothesis test of the study group.

(2) DCR based on RECIST 1.1, mRECIST, and imRECIST criteria: The number and percentage of subjects with CR, PR, or SD (i.e., CR+PR+SD) based on BOR will be calculated. The percentage of DCR and its 95% confidence interval will be calculated using the Clopper-Pearson method.

(3) PFS based on RECIST 1.1, mRECIST, and imRECIST criteria: The number of events, number of censored subjects, and percentages will be summarized. PFS will be summarized. The Kaplan-Meier method will be used to plot the survival curves for PFS, and the Brookmeyer-Crowley method will be used to calculate the 95% confidence interval for the median time. The Greenwood method will be used to estimate the survival rates and confidence intervals at 3, 6, 9, and 12 months.

(4) DOR based on RECIST 1.1, mRECIST, and imRECIST criteria: The number of events, number of censored subjects, and percentages will be summarized. DOR will be summarized. The Kaplan-Meier method will be used to plot the survival curves for DOR. The Brookmeyer-Crowley method will be used to calculate the 95% confidence interval for the median time. The Greenwood method will be used to estimate the DOR rates and confidence intervals at 3, 6, 9, and 12 months. The follow-up times for DOR will be listed.

(5) TTR based on RECIST 1.1, mRECIST, and imRECIST criteria: The statistical analysis method will be the same as for PFS.

(6) OS: The number of events, number of censored subjects, and percentages will be summarized. OS will be summarized. The Kaplan-Meier method will be used to plot the survival curves for OS. The Brookmeyer-Crowley method will be used to calculate the 95% confidence interval for the median time. The Greenwood method will be used to estimate the survival rates and confidence intervals at 3, 6, 9, 12, 18, and 24 months.

(7) The sum of diameters of target lesions in subjects will be described. The percentage change in the sum of diameters of target lesions post- baseline from baseline and the best percentage change for each subject will be calculated. Spider plots will be drawn to show the percentage

change over time in the sum of diameters of target lesions after administration from baseline. Waterfall plots will be drawn to show the best percentage change in the sum of diameters of target lesions from baseline. In the waterfall plots, different BORs will be distinguished by different colors.

Percentage change in the sum of diameters of target lesions after administration from baseline (%):

$$\frac{100 \times (\text{sum of diameters of target lesions after administration} - \text{sum of diameters of target lesions at baseline})}{\text{sum of diameters of target lesions at baseline}}$$

8.6.3 Exploratory Analysis

Based on BAS, circulating tumor DNA (ctDNA) for each quantitative test will be described by visit. Statistical indicators include mean, standard deviation, median, quartiles, maximum, minimum, geometric mean, and coefficient of variation, and their changes from baseline. The AUC (Area Under Curve) value of ROC (receiver operating characteristic) will be used to assess the correlation between ctDNA and ORR, DCR (RECIST v1.1).

For PFS based on RECIST 1.1, mRECIST, and imRECIST criteria, for patients undergoing surgery, the censored time is not the date of the last tumor assessment before surgery, but the time of continued follow-up until disease progression or death. For surgical patients, disease progression is defined as the detection of recurrence or metastatic lesions.

8.7 Safety Endpoints

Safety analyses will be performed based on the SS. All clinical and/or statistical safety indicators will be evaluated for safety and tolerability. In the safety analysis, the incidence of AEs, TEAEs, irAEs, TRAEs, as well as changes in vital signs, ECG, weight, ECOG performance status, and laboratory values will be analyzed. The treatment period is defined as from the first administration to the end of the safety follow-up, or until the day before the subject starts a new anti-tumor treatment, whichever occurs first. DLTs will be categorized and summarized by hematology and non-hematology. MedDRA medical terminology will be used for description.

8.7.1 Adverse Event

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded according to the NCI-CTCAE Version 5.0 Toxicity Rating Scale. AEs will be summarized by preferred term (PT) and system organ class (SOC). The severity of AEs and their relationship to the study drug will be described.

Analysis of AEs will include, but is not limited to:

- SAEs;
- TEAEs;
- TRAEs;
- irAEs;
- AEs leading to treatment discontinuation;
- AEs leading to death.

8.7.2 Tolerability

In this study, the tolerability of the study drug in subjects will be assessed by the number of subjects with dose interruptions, delays, and discontinuations. The reasons for dose

interruptions, delays, and discontinuations will be listed. Descriptive statistical analysis will be conducted on the frequency of subjects with dose interruptions, delays, and discontinuations.

8.7.3 Laboratory Abnormalities

Laboratory results will be graded according to NCI-CTCAE Version 5.0. Parameters that cannot be graded will be classified as decreased/normal/increased according to the normal range of laboratory tests.

Test values for each laboratory test (e.g., hematology, serum chemistry, etc.) will be listed by laboratory parameter, subject, and dose level. Then, the frequency of significant laboratory abnormalities (judged as Grade 3 or 4 by NCI-CTCAE 5.0) will be described by parameters, number of treatment cycles, and treatment cohorts. The frequency of all laboratory abnormalities will be described by parameters, worst grade (according to NCI-CTCAE 5.0), and treatment cohorts.

The obvious laboratory abnormalities (Grade 3 or 4 laboratory test abnormalities judged by the NCI-CTCAE Version 5.0) will be listed. For the parameters that can be categorized using the CTCAE Version 5.0, laboratory data can be summarized by changes in grade as listed in the tables. For parameters that cannot be categorized by CTCAE 5.0, they will be divided into decreased/normal/increased based on the normal range, and the data will be listed and the frequency of laboratory abnormalities will be statistically described.

8.7.4 Other Safety Data (Physical Examination, ECG and Vital Signs)

All ECG parameters will be listed, including the QT interval corrected by the Fridericia method (QTc interval) for each subject. Descriptive statistical analysis will be conducted according to treatment cohorts and assessment times. Additionally, descriptive statistical analysis will be conducted on changes from baseline for each parameter.

Blood pressure, pulse, respiratory rate, temperature, and weight for all subjects will be listed. Additionally, changes in values from baseline will be statistically described.

All abnormal physical examination results will be listed.

1. Introduction

In this statistical analysis plan (SAP), the planned analysis and reporting contents of safety evaluation, efficacy evaluation in the protocol (A Clinical Study to Evaluate the Safety and Efficacy of KN046 in Combination with Lenvatinib in Subjects with Advanced Hepatocellular Carcinoma) are described. The primary reference documents for this SAP are:

- Protocol: V1.6/8-Jun-2022.
- eCRF: V3.0/7-Sep-2021.

2. Study Objectives

2.1 Primary Objective

To evaluate the safety and efficacy (objective response rate, ORR) of KN046 in combination with lenvatinib in subjects with advanced hepatocellular carcinoma.

2.2 Secondary Objective

To evaluate other anti-tumor activity of KN046 in combination with lenvatinib in subjects with advanced hepatocellular carcinoma.

2.3 Exploratory Objectives

To analyze the relationship between potential immune-related biomarkers and anti-tumor efficacy of combination regimens.

3. Study Plan

3.1 Overall Design

This study is a multicenter, open-label clinical study to investigate the safety and preliminary efficacy of KN046 in combination with lenvatinib in subjects with advanced hepatocellular carcinoma. The preset dose of KN046 is 5 mg/kg Q3W; the preset dose of lenvatinib is 12 mg QD (body weight [BW] ≥ 60 kg) or 8 mg QD (BW < 60 kg). In this study, during the safety introduction period, 6 subjects will be enrolled. These 6 subjects will receive KN046 5 mg/kg Q3W + lenvatinib 12 mg QD (BW ≥60 kg) or 8 mg QD (BW <60 kg). After all 6 subjects have completed the 28-day dose-limiting toxicity (DLT) observation period, the investigator will review the relevant safety data and decide whether to continue enrollment of about 24 subjects. If the subjects are intolerant (2 or more DLT events occur in the subjects), the subsequently enrolled subjects will receive KN046 5 mg/kg Q3W and lenvatinib (reduced dose) 8 mg QD (BW ≥ 60 kg) or 4 mg QD (BW < 60 kg). During the safety introduction period, subjects who discontinue treatment for reasons other than safety may be replaced.

In this study, the study periods include the screening period (D-28 - D-1), treatment period (until the subject develops disease progression, or until the subject develops intolerable toxicity, or until the subject withdraws the informed consent form (ICF), or until the subject is lost to follow-up, or until the subject dies, or until the subject has been treated for at least 2 year, or until the sponsor assesses that the expected outcomes of the study have been achieved, or until the subject has received an intervention other than that specified in this study protocol. At the end of the study, subjects may continue to receive KN046 or lenvatinib monotherapy or combination therapy if the investigator determines that the subject is still benefiting), the end of treatment visit (within 7 days after the last dose of KN046 and/or lenvatinib, whichever occurs later), safety follow-up (AEs within 30 days after the last dose of KN046 and/or

lenvatinib, whichever occurs later, and all SAEs and drug-related AEs from 30 days to 90 days after the last dose of KN046 will be collected), and survival follow-up. Each subject will receive treatment according to the protocol until the subject experiences disease progression (as judged by the investigator based on RECIST 1.1), or the subject experiences an intolerable toxicity, or the subject withdraws the ICF, or the subject dies, or the subject has completed 2 years of treatment, or the subject receives an intervention other than that specified in this protocol, whichever occurs first. If the toxicity can be clearly attributed to one of the drugs in the combination, the subject may discontinue that drug and continue using the other drug.

In this study, during the safety introduction period, the first treatment cycle for the first 6 subjects is 28 days. On C1D1, KN046 will be administered. Lenvatinib will be administered once daily. Each remaining cycle is 21 days. On CnD1, KN046 will be administered. Lenvatinib will be administered once daily.

During the treatment period, if a subject experiences an intolerable AE, the subject may withhold or delay the administration of KN046. The subject may also reduce the dose of lenvatinib: 1) if the starting dose is 12 mg, the dose after the first reduction is 8 mg, the dose after the second reduction is 4 mg, and the dose after the third reduction is 4 mg (every other day); 2) if the starting dose is 8 mg, the dose after the first reduction is 4 mg, and the dose after the second reduction is 4 mg (every other day). If the subject cannot tolerate 4 mg every other day, the administration of lenvatinib will be discontinued.

During the study, tumor assessments will be conducted according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), the modified immune-related Response Criteria in Solid Tumors (imRECIST), and the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Starting from the first administration, assessments will be conducted every 6 weeks (±7 days) within the first year (54 weeks). Thereafter (starting with the second year), assessments will be performed every 12 weeks (± 7 days) until the subject experiences unacceptable toxicity, or the subject develops disease progression, or the subject withdraws the ICF, or the subject is lost to follow-up, or the subject dies, or the study is prematurely terminated, whichever occurs first.

Subjects who prematurely discontinue study drug for reasons other than disease progression should continue to undergo tumor assessments at the frequency specified in this protocol until the subject develops disease progression, or the subject withdraws the ICF, or the subject starts a new anticancer treatment, or the subject is lost to follow-up, or the subject dies, or the study is prematurely terminated, whichever occurs first.

Subjects who withdraw from study drug treatment due to disease progression will be followed for survival every 2 months (60 ± 7 days) after disease progression using the end of treatment visit as the starting point. During survival follow-up, information on subsequent antitumor treatments and survival status of the subjects will be collected until withdrawal of the ICF by the subject, loss to follow-up of the subject, death of the subject, or early termination of the study (whichever occurs first).

During the study, for subjects who are still experiencing AEs at the end of the study or at the time of discontinuation of study treatment, follow-up will be continued until any of the following occurs:

- The AE resolves or improves to baseline level or better;
- The investigator confirms that the event is stable and no further improvement is

expected;

- The subject dies;
- The subject is lost to follow-up or withdraws the ICF;
- The investigator confirms that the AE is unrelated to the study treatment;
- The subject starts a new antitumor treatment.

3.2 Interim Analysis

No interim analysis will be performed in this study.

3.3 Randomization and Blinding

In this study, blinding will not be used, nor will randomization be conducted.

3.4 Sample Size Estimation

In this study, approximately 53 subjects are planned. Among them, 6 subjects are planned to be enrolled during the safety introduction period.

The calculation of sample size will be based on the binomial exact test. The hypothesis test is as follows:

H_0： $P \leq P_0$

H_1： $P > P_0$

P_0 is the historical experience value. P_0=20%. The assumed ORR is 40%. A one-sided test will be used, α=0.025, and Power = 85%. At least 53 subjects are required to have sufficient power to reject the null hypothesis.

3.5 Study Endpoints

Primary Endpoints:

- Safety and tolerability, dose-limiting toxicity (DLT);
- ORR by the investigator based on RECIST 1.1 criteria;

Secondary Endpoints:

- ORR by the investigator based on mRECIST and imRECIST criteria;
- Duration of Response (DOR), Disease Control Rate (DCR), Time to Response (TTR), and Progression-free Survival (PFS) by the investigator based on RECIST 1.1, mRECIST, and imRECIST criteria;
- Overall survival (OS) and 12-month survival (OS_{12});

Exploratory Endpoint:

- Correlation between antitumor activity and potential biomarkers (eg.ctDNA).

3.6 Evaluation Endpoints

3.6.1 Efficacy Endpoints

Investigators will evaluate the efficacy of subjects at each visit based on RECIST 1.1, mRECIST, and imRECIST criteria, respectively. Investigators will assess the status of target lesions, non-target lesions, and new lesions.

Best Overall Response (BOR) is defined as the best response from the start of treatment with the study drug until the end of the study. The sequence of BOR evaluation is as follows: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and UNK. UNK specifically includes the following data situations:

- The subject has no tumor assessment at baseline.
- The subject dies within 7 (=6+1) weeks after the first administration of the study drug and has no tumor assessment post-baseline;
- All assessments post-baseline are NE;
- Within 7 (=6+1) weeks after the first administration of the study drug, the subject starts a new anti-tumor treatment in the same tumor assessment, and there is no tumor assessment post-baseline;
- SD does not meet the specified time criteria (only tumor assessments within 5 weeks after randomization (< 35 days));
- Tumor assessment after 13 (=12+1) weeks of the first administration of the study drug is PD, and all tumor assessments within 13 weeks are "NE";
- For other reasons, the subject has no tumor assessment post-baseline.

Tumor response evaluated after the start of new anti-tumor treatment will not be included in the BOR assessment. In this study, BOR will be assessed separately based on RECIST 1.1 (see Appendix 1), mRECIST criteria (see Appendix 2), and imRECIST criteria (see Appendix 3). The following efficacy endpoints will be calculated:

Primary Efficacy Endpoint:

- ORR according to RECIST 1.1 criteria: The proportion of subjects with confirmed CR or PR based on BOR from the first administration of the study drug until the end of the study. For the definition of confirmed CR or PR, please see Appendix 4.

Secondary Efficacy Endpoints:

- ORR based on mRECIST and imRECIST criteria (see Appendix 5).
- DCR based on RECIST 1.1, mRECIST, and imRECIST criteria: The proportion of subjects with confirmed CR/PR or SD based on BOR from the first administration of the study drug until the end of the study. When BOR is SD, it should be at least 6 (-1) weeks from the first administration of the drug. If the minimum time criteria are not met, even if BOR is SD, SD is not acceptable.
- TTR based on RECIST 1.1, mRECIST, and imRECIST criteria: The time from the first administration of the study drug to the first recorded confirmed response (based on RECIST 1.1, mRECIST criteria, imRECIST criteria, tumor assessment as CR or PR, whichever comes first).
- DOR: Only subjects with confirmed response (CR or PR) will be evaluated for DOR.
  - Based on RECIST 1.1, mRECIST criteria: DOR is defined as the time from the first confirmed response (tumor assessment as CR or PR, whichever comes first) to the first recorded disease progression or death due to any cause (whichever comes first).
  - Based on imRECIST criteria: DOR is defined as the time from the first

confirmed response (tumor assessment as CR or PR, whichever comes first) to the first confirmed disease progression or death due to any cause (whichever comes first).

- PFS based on RECIST 1.1, mRECIST, and imRECIST criteria: The time from the first administration of the study drug to the recorded or confirmed disease progression (based on RECIST 1.1, mRECIST criteria, the first disease progression should be recorded; based on imRECIST criteria, confirmed disease progression should be recorded) or death due to any cause (whichever comes first).
- The best percentage change in the sum diameters of target lesions from baseline.
- OS: The time from the first administration of the study drug to death due to any cause.
- OS_{12}: The proportion of subjects survival within 12 months after the first administration of the study drug.
- Potential biomarkers (such as ctDNA) will be tested. The possible correlation between biomarkers and anti-tumor activity will be analyzed.

3.6.2 Safety and Tolerability Endpoints

Safety and tolerability endpoints include DLT, AE, clinical laboratory tests (hematology, blood biochemistry, coagulation function, urinalysis, stool routine, 12-lead ECG, echocardiography, thyroid function tests, urine pregnancy/blood serum pregnancy tests), virology serology tests, physical examinations, vital signs, ECOG performance status scores.

4. Statistical Analysis Methods

4.1 General Principles

Statistical analysis will be performed using SAS 9.4 (or later versions) statistical software. For quantitative data, arithmetic mean, standard deviation, median, upper quartile, lower quartile, maximum, and minimum values will be used for statistical description. For count data or ordinal data, the number and percentages will be used for statistical description.

In the analysis of exposure to the study drug and efficacy, the analysis will be conducted by the initial dose level of lenvatinib. In other analyses, the analysis will be conducted by the initial dose level of lenvatinib and the total.

In this study, baseline is defined as the last non-empty assessment before the first administration of the study drug.

For statistical analysis data, the following provisions will be used (unless otherwise specified):

- The decimal places for arithmetic means, medians, and quartiles will be one more than that of the original data but will not exceed four. If the decimal places exceed four, four decimal places will be retained;
- For maximum and minimum values, the original data will be retained, but the decimal places will not exceed four. If the decimal places exceed four, four decimal places will be retained;
- The decimal places for standard deviation will be two more than that of the original data but will not exceed four. If the decimal places exceed four, four decimal places will be retained;

- For percentages, one decimal place will be retained; when the frequency is 0, the percentage will not be displayed;
- For the confidence interval, two decimal places will be retained.
- In addition to the above rules, the number of decimal places may be adjusted in line with the actual significance of the data results.

4.2 Statistical Analysis Population

Safety Analysis Set (SAS): All subjects who have received at least one administration of the study drug and have at least one safety assessment. SAS will be the default analysis set for all analyses.

Efficacy Analysis Set (EAS): All subjects who have received at least one administration of the study drug and have a tumor imaging evaluation at baseline. EAS will be primarily used for efficacy analyses related to tumor assessment endpoints.

Dose-Limiting Toxicity Analysis Set (DLTS): All subjects who undergo the DLT induction period. During the first cycle, the dose of KN046 and lenvatinib should reach at least 75% of the planned dose. Subjects who are replaced during the DLT observation period will not be included in the DLT analysis set.

Demographic and baseline characteristics, safety analysis, study drug exposure, concomitant therapy, and efficacy evaluations (TTR, PFS, DOR, and OS) will be analyzed based on SAS. Tumor assessment efficacy analyses (ORR and DCR, etc.) will be based on EAS for analysis.

4.3 Subject Disposition

In this study, the number of subjects screened, subjects who fails screening, subjects not enrolled (if any, further classified by reason), subjects enrolled, subjects treated, and subjects in each analysis dataset (SAS, EAS, DLTS) will be summarized. The number and percentage of subjects undergoing treatment before the data cutoff, subjects who ends treatment (if any, further classified by reason), and subjects who ends the study (if any, further classified by reason) will be described. In the percentage calculation, the number of all enrolled subjects will be used as the denominator. Lists of subjects who fails screening, subjects who are successfully screened but not enrolled, subjects included in the analysis set, subjects not included in the analysis set, subjects who ends treatment before the data cutoff, and subjects who ends the study will be provided.

4.4 Protocol Deviation

Based on SAS, the number and percentage of subjects with significant protocol deviations will be summarized. A list of subjects with protocol deviations will be provided. Significant protocol deviations and deviations affecting the inclusion of subjects in the statistical analysis population will be identified.

4.5 Demographics and Baseline Characteristics

For demographic and baseline characteristics, data will be summarized based on the type of data (quantitative data, count data, or ordinal data) based on the statistical information provided in section 4.1, based on SAS. Demographic and baseline characteristics include:

- General demographic and baseline characteristics: age (groups include < 65 years or ≥ 65 years), gender, race, ethnicity, hepatitis B/hepatitis C status, height, weight, BMI [(kg/m^2) = weight (kg)/height (m^2), rounded to one decimal place], total diameter of

target lesions at baseline-RECIST, total diameter of target lesions at baseline-mRECIST. Age, height, weight, BMI, and total diameter of target lesions at baseline are quantitative data. Arithmetic mean, standard deviation, median, quartiles, maximum, and minimum values will be described. For other count data, the number and percentage of subjects will be described. In the percentage calculation, the number of subjects included in SAS will be used as the denominator.

- Tumor diagnosis: tumor duration (tumor duration (months) = (date of informed consent signature - date of first diagnosis + 1) / 30.4375, results will be rounded to one decimal place. For missing handling of the first diagnosis date, please refer to Section 5), histological grade, pathological type, BCLC stage at screening, presence of cirrhosis at screening, presence of major vascular invasion at screening, extrahepatic metastasis at screening, Child-Pugh classification at screening. For count data, the number and percentage of subjects will be described. In the percentage calculation, the number of subjects included in SAS will be used as the denominator.
- Previous tumor treatment history: drug treatment history, surgical treatment history, radiation treatment history, interventional treatment history, other treatment history. The number and percentage of subjects with a history of tumor treatment will be described. For drug treatment history, the World Health Organization Drug Dictionary (WHODrug September 2020 or later version) will be used for coding. The number and percentage of subjects with at least one previous tumor drug treatment will be summarized by ATC4 category and Preferred Drug Name (PN). In the percentage calculation, the number of subjects included in SAS will be used as the denominator.
- Previous habits: smoking status, drinking status. The number and percentage of subjects will be described by category. For percentages, the number of subjects included in SAS will be used as the denominator.
- A list of demographic and baseline characteristics data for subjects will be provided.

4.6 Past Medical History/Current Medical History and Surgical History

Past medical/surgical history includes past medical or current medical history and surgical history other than the indication for this study. For past medical or current medical history and surgical history, MedDRA (version 23.0 or later) will be used for coding. The number and percentage of subjects with past medical or current medical history and surgical history will be summarized. If the percentage is not zero, the number and percentage of subjects with at least one past/current medical history will be further summarized by System Organ Class (SOC) and Preferred Term (PT) and by group. For percentages, the number of subjects included in SAS will be used as the denominator.

4.7 Prior and Concomitant Therapies

Prior/concomitant therapies include both drug and non-drug treatments. Prior medication/therapy refers to any non-study drug (including anti-tumor and non-anti-tumor drugs)/therapy that has been discontinued within 28 days prior to the first administration of the study drug.

Concomitant medication/therapy refers to any non-study drug/therapy used at least once from the administration of the study drug until 30 days after the last administration. If the start/end dates of prior/concomitant therapies are completely or partially missing and the dates cannot be

determined, they will be imputed according to the missing data rules (Section 5). Based on the imputation, it will be determined whether the treatment is considered prior/concomitant. If the dates still cannot be determined after imputation, the treatment will be considered concomitant.

For prior/concomitant medications, the World Health Organization Drug Dictionary (WHODrug September 2020 or later version) will be used for coding. Based on SAS, by therapeutic classification (ATC2) and PN, the number and percentage of subjects with at least one prior/concomitant non-oncology medication will be summarized. In the calculation of percentages, the denominator will be the number of subjects included in SAS. A list of subjects with prior/concomitant medication will be provided.

A list of subjects with concomitant non-drug treatments and subsequent antineoplastic treatments will be provided.

4.8 Drug Exposure

Based on SAS, by group, descriptive statistics will be provided for the cumulative dose, planned dose, relative dose intensity, duration of exposure (weeks), and number of cycles of exposure of KN046 and lenvatinib. Arithmetic means, standard deviations, medians, quartiles, maximum, and minimum values will be described. For relative dose intensity, further categorization into < 80%, 80% - 120%, > 120% will be made, and the number and percentage of subjects will be described.

Based on SAS, by group, the number of infusion delays, infusion interruptions for KN046, and the number of dose modifications for lenvatinib (e.g., 1 time, 2 times, 3 times, etc.) will be summarized. The number and percentage of subjects will be calculated.

- The duration of exposure to KN046 (weeks, one decimal place) = (date of death + 1, data cutoff date + 1, or last administration date of KN046 + 21, whichever comes first - first administration date)/7;
- The duration of exposure to lenvatinib (weeks, one decimal place) = (date of death/data cutoff date/last administration date of lenvatinib, whichever comes first - first administration date +1)/7;
- The number of cycles of exposure to KN046/lenvatinib (to one decimal place): duration of exposure to KN046/lenvatinib (weeks)/3;
  - Subjects in the DLT introduction period = [duration of exposure to KN046/lenvatinib (weeks) -1]/3;
  - For the number of exposure cycles, subjects will be further categorized as having received at least 1/2/4/6/8/12/16 cycles of treatment. The number and percentage of subjects will be described;
- The actual cumulative dose of KN046 (mg/kg) = the total of the actual unit doses received from the first administration date to the last administration date;
- The planned cumulative dose of KN046 (mg/kg) = the total of the planned unit doses from the first administration date to the last administration date;
- The actual cumulative dose of lenvatinib (mg) = the total of the actual doses received from the first administration date to the last administration date;
- The planned cumulative dose of lenvatinib (mg) = the total of the planned doses from the first administration date to the last administration date;

For actual/planned cumulative doses, calculations will be based on the body weight value before the current administration.

- The relative dose intensity (%) of KN046/lenvatinib = actual cumulative dose/planned cumulative dose * 100%.

4.9 Efficacy Evaluation

For OS, PFS, DoR, and TTR, analyses will be based on SAS. Other efficacy analyses will be based on EAS.

4.9.1 Analysis of Primary Efficacy Endpoint

ORR based on RECIST 1.1 criteria: Based on BOR, the number and percentage of subjects with CR or PR will be calculated. The Clopper-Pearson method will be used to calculate the ORR of the study group and the corresponding confidence intervals. A binomial exact test will be used for hypothesis testing of the study group.

The hypothesis test is as follows:

H_0： $P \leq P_0$ H_1： $P > P_0$

P_0 is the historical experience value, P_0=20%. A one-sided test will be used, with a Type I error α=0.025.

4.9.2 Analysis of Secondary Efficacy Endpoints

(1) ORR based on mRECIST and imRECIST criteria, respectively: Based on BOR, the number and percentage of subjects with CR or PR will be calculated. The Clopper-Pearson method will be used to calculate the ORR of the study group and the corresponding confidence intervals.

(2) DCR based on RECIST 1.1, mRECIST, and imRECIST criteria, respectively: Based on BOR, the number and percentage of subjects with CR, PR, or SD (i.e., CR + PR + SD) will be calculated. The Clopper-Pearson method will be used to calculate the percentage of DCR with a 95% confidence interval.

(3) PFS based on RECIST 1.1, mRECIST, and imRECIST criteria, respectively: The number of events, number of censored events, and percentage will be counted. PFS will be summarized. The Kaplan-Meier method will be used to plot the survival curve for PFS. The Brookmeyer-Crowley method will be used to calculate the median time with a 95% confidence interval. The Greenwood method will be used to estimate the survival rates and confidence intervals at 3, 6, 9, and 12 months. PFS (months) = (date of death, disease progression, or censoring - first administration date +1)/30.4375.

Description of Events and Censoring	**PFS Status**	**Date of Death, Disease Progression, or Censoring**
Subject records disease progression [1]	Event	Date of disease progression
Subject dies before earliest record of disease progression	Event	Date of death
Subject without evaluation at baseline	Censoring	First administration date
Subject without assessment post-baseline	Censoring	First administration date
Subject with ≥ 2 consecutive missing tumor assessments [2], followed by disease progression or death	Censoring	Last assessable tumor detection date before missing
Subject with pseudoprogression,	Censoring	Last assessable tumor detection date

Description of Events and Censoring	PFS Status	Date of Death, Disease Progression, or Censoring
followed by non-PD in subsequent efficacy assessment [3]		
Subject starts new antineoplastic treatment	Censoring	Last assessable tumor detection date before new treatment
No event occurred during the study	Censoring	Last assessable tumor detection date
Subject withdraws from study with no evidence of event	Censoring	Last assessable tumor detection date
Subject lost to follow-up	Censoring	Last assessable tumor detection date

Note: For assessable tumor detection date at each visit, the latest date among target lesion, non-target lesion, and new lesion imaging examination dates will be used (if the efficacy assessment result for that visit is PD, the earliest date among the three will be used). "Assessable" refers to assessments that are not NE.

[1] Disease progression based on imRECIST should be confirmed. The event date is the earliest date among two consecutive disease progression dates.

[2] The duration of consecutive missing ≥ 2 disease assessments includes the duration of two tumor assessments + two time windows.

[3] For imRECIST only.

(4) DOR based on RECIST 1.1, mRECIST, and imRECIST criteria, respectively: The number of events, number of censored events, and percentage will be counted. DOR will be summarized. The Kaplan-Meier method will be used to plot the survival curve for DOR. The Brookmeyer-Crowley method will be used to calculate the median time with a 95% confidence interval. The Greenwood method will be used to estimate the DOR rates and confidence intervals at 3, 6, 9, and 12 months. The follow-up time for DOR will be listed. DOR (months) = (date of death, disease progression, or censoring - first confirmed response date +1)/30.4375. The censoring rules for DoR refer to the censoring rules under PFS.

(5) TTR based on RECIST 1.1, mRECIST, and imRECIST criteria, respectively: The statistical analysis method is the same as for PFS. TTR (months) = (first date of disease response - first administration date +1)/30.4375.

(6) OS: The number of events, number of censored events, and percentage will be counted. OS will be summarized. The Kaplan-Meier method will be used to plot the survival curve for OS. The Brookmeyer-Crowley method will be used to calculate the median time with a 95% confidence interval. The Greenwood method will be used to estimate the survival rates and confidence intervals at 3, 6, 9, 12, 18, and 24 months. OS (months) = (date of death, or censoring - first administration date +1)/30.4375. Data processing is as follows:

Description of Events and Censoring	Status	Date of Death or Censoring
Death	Event	Date of death
No deaths in the study	Censoring	Last known survival date before data cutoff
Subject lost to follow-up is not confirmed dead	Censoring	Last confirmed survival date
Subject withdraws from study due to ICF withdrawal	Censoring	Last confirmed survival date
No deaths at the end of the study	Censoring	Last confirmed survival date

Note: The last confirmed survival date is defined as the latest date among the following: administration date, end of treatment date (only applicable to subjects who do not end treatment due to loss to follow-up or death), survival follow-up date, last known survival date, start/end date of AE, start/end date of CM, start/end date of non-drug treatment, all safety assessment dates, tumor assessment dates, end of study date (only applicable to subjects who do not end the study due to loss to follow-up or death).
Note: refer to Section 5 for handling missing dates of death.

(7) A description of the total diameter of target lesions in subjects will be provided. The

percentage change in the sum of diameters of target lesions post- baseline from baseline and the best percentage change for each subject will be calculated. Spider plots will be drawn to show the percentage change over time in the sum of diameters of target lesions after administration from baseline. Waterfall plots will be drawn to show the best percentage change in the sum of diameters of target lesions from baseline. A swimmer plot of overall efficacy assessment and treatment time will be plotted.

Percentage change in the sum of diameters of target lesions after treatment from baseline (%):

$$\frac{100 \times (\text{sum of diameters of target lesions after administration - sum of diameters of target lesions at baseline})}{\text{Sum of diameters of target lesions at baseline}}$$

4.10 Safety Evaluation

4.10.1 Dose-limiting Toxicity

By SOC and PT, by group, the number and incidence of subjects with DLT will be summarized. In the calculation of incidence, the denominator will be the number of subjects included in DLTS.

A list of DLT data will be provided.

4.10.2 Adverse Event

AE refers to an adverse medical event that occurs in a subject receiving a certain drug. This event does not necessarily have a causal relationship with the treatment.

For the evaluation of AEs, the evaluation of treatment-emergent adverse events (TEAEs) will be the main focus. TEAEs are defined as follows:

- All TEAEs: New or increased CTCAE grade AEs from the first administration of the study drug until 30 days after the last administration of KN046/lenvatinib;
- Treatment-related adverse events (TRAEs) related to any study drug: AEs recorded as "related" in the CRF. If this data is missing, the AE will also be considered related to the study drug;
- KN046-related TEAEs: For TEAEs related to KN046, they will be summarized within 90 days after the last use of KN046;
- Lenvatinib-related TEAEs: For TEAEs related to lenvatinib, they will be summarized within 30 days after the use of lenvatinib;
- Serious Adverse Events (SAEs): For SAEs, they will be summarized up to the later time point of 90 days after the last KN046 administration and 30 days after the last lenvatinib administration;
- Immune-related AEs (irAEs): For irAEs, they will be summarized within 90 days after the last use of KN046.

If the start or end date of the AE is missing or partially missing, the data will first be imputed according to the rules (Section 5). After imputation, it will be determined whether the AE is a TEAE. If it is still not possible to determine after imputation, the AE will be considered a TEAE.

Toxicity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Using MedDRA (version 23.0 or later), AEs will be coded. Coded AEs will be summarized:

- A list of AEs will be provided. TEAEs, ≥ Grade 3 TEAEs based on CTCAE, serious TEAEs (SAEs), ≥ Grade 3 SAEs based on CTCAE, TEAEs leading to dose reduction of lenvatinib, TEAEs leading to suspension of KN046/lenvatinib, TEAEs leading to suspension of both KN046 and lenvatinib, TEAEs leading to permanent discontinuation of KN046/lenvatinib, and TEAEs leading to death will be summarized;
- TEAEs related to any study drug (KN046/lenvatinib), ≥ Grade 3 TEAEs based on CTCAE related to KN046/lenvatinib, SAEs related to KN046/lenvatinib, ≥ Grade 3 SAEs based on CTCAE related to KN046/lenvatinib, TEAEs leading to dose reduction related to lenvatinib, TEAEs leading to suspension of KN046/lenvatinib, TEAEs leading to suspension of both KN046 and lenvatinib , TEAEs leading to permanent discontinuation related to KN046/lenvatinib, and TEAEs leading to death related to KN046/lenvatinib will be summarized;
- irAEs, ≥ Grade 3 irAEs based on CTCAE, irAEs leading to suspension of the study drug, irAEs leading to permanent discontinuation of the study drug, and irAEs leading to death will be summarized;
- In the above summaries, if the incidence of AEs under the corresponding situation is not 0, then by SOC and PT, the number and incidence of subjects with TEAEs, TRAEs, irAEs will be summarized;
- Further, by SOC, PT, and highest CTCAE grade, the number and incidence of all TEAEs will be summarized;
- Further, by PT, the number of subjects and incidence of TEAEs with an incidence of 10% or more, ≥ Grade 3 TEAEs, irAEs, TRAEs, SAEs based on CTCAE will be summarized;
- A bar chart of TEAEs with an incidence of x% or more will be plotted by PT.
- Lists of data for AEs, SAEs, and AEs leading to death will be provided.

4.10.3 Laboratory Tests

For laboratory tests including stool routine, urine routine, and thyroid function data, the number and percentage of subjects with the worst post-administration results compared to baseline results will be cross-tabulated. Quantitative data will be statistically described. The arithmetic means, standard deviations, medians, quartiles, maximum, and minimum values, etc., of post-administration test values (including values at each routine visit after administration) and their changes from baseline will be described. For laboratory test data, data should be uniformly converted to standardized units before descriptive analysis is performed. For original data that is below the quantification limit (BLQ) or above the quantification limit (ULQ), during descriptive statistical analysis, it will be summarized according to the lower limit of quantification (LLOQ) or upper limit of quantification (ULOQ).

By visit, laboratory test results (based on CTCAE grading) will be categorized and summarized (applicable indicators). For measurements that cannot be classified according to CTCAE grading (e.g., normal test results), they will be classified as Grade 0. Changes in laboratory test results before and after treatment (based on CTCAE grading) will be cross-tabulated. The number and percentage of subjects will be listed according to the highest grade of CTCAE after baseline. In the calculation of percentages, the denominator will be the number of subjects included in SAS.

Lists of laboratory test results for subjects at baseline and visits post-administration will be provided. A list of serum virology test results for subjects will be provided.

4.10.4 12-lead ECG

A cross-tabulation of the overall assessment of the 12-lead ECG (in order: normal, abnormal without clinical significance, abnormal with clinical significance) will be performed. The number and percentage of subjects with post-administration results compared to baseline results will be summarized. The number and percentage of subjects with QTcF prolongation (> 450 to ≤ 480 ms, > 480 to ≤ 500 ms, > 500 ms) after administration will be listed. In the calculation of percentages, the denominator will be the number of subjects included in SAS.

Lists of 12-lead ECG examination data for subjects at baseline and visits post-administration will be provided.

4.10.5 Vital Signs and Weight

Vital sign data (systolic blood pressure, diastolic blood pressure, body temperature, pulse, respiration) and body weight for subjects will be statistically described. By post-administration visit, the measured values and their changes from baseline will be described in terms of arithmetic means, standard deviations, medians, quartiles, maximum, and minimum values, etc.

Lists of vital signs and weight data for subjects at baseline and visits post-administration will be provided.

4.10.6 Physical Examination and Symptom-Directed Physical Examination

Lists of physical examination results for subjects at baseline and at the end of treatment visits will be provided. Data from symptom-directed physical examinations after each administration visit will be listed.

4.10.7 ECOG Score

The number and percentage of subjects with the worst results post-baseline (including planned and unplanned visits) compared to results at baseline will be cross-tabulated. In the calculation of percentages, the denominator will be the number of subjects included in SAS.

Lists of ECOG score data for subjects at baseline and visits post-administration will be provided.

4.10.8 Echocardiographic examination

An overall assessment of echocardiography will be analyzed. The worst results post-administration will be compared with results at baseline, and the number and percentage of subjects will be calculated in the form of a cross-table. In the calculation of percentages, the denominator will be the number of subjects included in SAS.

A statistical description of the left ventricular ejection fraction will be provided. The arithmetic mean, standard deviation, median, quartiles, maximum, and minimum values of measurements post-administration (including those at each routine visit) and their changes from baseline will be described.

Data of echocardiographic examinations for subjects will be listed by visit.

4.10.9 Pregnancy Test

Data of the pregnancy test of female subjects will be listed.

5. Handling of Missing Values and Outliers

(1) Date of first diagnosis

- If the year is missing (or completely missing), no imputation will be made;
- If only the day is missing, it will be imputed as the 1st of the month;
- If both month and day are missing, they will be imputed as January 1st.

If the imputed date is after the date of ICF signing, it will be imputed as the date of ICF signing - 1.

(2) Missing start date of AE

- If the year and month are known, and they are not the same as the year and month of the first dose, the day will be imputed as the 1st of that month.
- If the year and month are known, and they are the same as the year and month of the first dose, the start date of AE will be set as the first dosing date.
- If only the year is known, and it is the same as the year of the first dose, the start date of AE will be set as the first dosing date.
- If the year, month, and day are all missing, the first dosing date will be used as the start date.
- If the end date of AE is not missing and the imputed start date of AE is after the end date of AE, the start date of AE will be imputed as the end date of AE.

(3) Missing end date of AE

- If only the day is missing, it will be imputed as the last day of the month, the data cut-off date, or the date of death, whichever is earlier.
- If the month or year is missing, no imputation will be made.

(4) Missing end date of prior/concomitant medication:

- If the year and month are known, the last day of the month will be used for imputation.
- If only the year is known, December 31st will be used for imputation.
- If the year, month, and day are all missing, and the year of the start date is known, December 31st of year of the start date will be used for imputation.
- If the start date is not missing and the imputed end date is before the start date, the start date will be used as the end date.
- No imputation will be made in other cases.

(5) Missing date of death

- If the year, month, and day are all missing, "last known survival date + 1" will be used for imputation;
- If only the day is missing, or both month and day are missing, the latest of the following dates will be used for imputation:
  - Last known survival date + 1
  - If only the day is missing, the 1st of the known year and month will be used for imputation; if both month and day are missing, or only the month is missing,

January 1st of the known year will be used for imputation.

(6) Missing start date of subsequent antineoplastic therapy

- Two reference dates should first be obtained: (1) the date of disease progression (only applicable to RECIST and mRECIST) + 1, the date of the last assessable tumor measurement (only applicable to imRECIST) + 1, the date of the last dose + 1, the date of the end of treatment imaging examination + 1, whichever occurs later; (2) the end date of subsequent antineoplastic therapy;
- If only the day is missing:
  - If the year is the same as the year of the earlier of (1) and (2):
    a. And if the month is before the month of the earlier of (1) and (2), the last day of that month, the date of death, and the data cut-off date, whichever is earlier, will be used for imputation;
    b. And if the month is the same as the month of the earlier of (1) and (2), the date of the earlier of (1) and (2) will be used for imputation;
    c. And if the month is after the month of the earlier of (1) and (2), the 1st of that month and the data cut-off date, whichever is earlier, will be used for imputation;
  - If the year is before the year of the earlier of (1) and (2), the last day of that month, the date of death, and the data cut-off date, whichever is earlier, will be used for imputation;
  - If the year is after the year of the earlier of (1) and (2), the 1st of that month and the data cut-off date, whichever is earlier, will be used for imputation;
- If both month and day are missing:
  - If the year is before the year of the earlier of (1) and (2), December 31st and the data cut-off date, whichever is earlier, will be used for imputation;
  - If the year is the same as the year of the earlier of (1) and (2), the date of the earlier of (1) and (2) will be used for imputation;
  - If the year is after the year of the earlier of (1) and (2), January 1st of that year and the data cut-off date, whichever is earlier, will be used for imputation;
- If completely missing, the date of the earlier of (1) and (2) will be used for imputation.

The above imputation rules will only be used when exact dates are needed for calculations and analyses. In lists, the actual data entered in the database will still be presented.

In this study, outliers will not be identified or handled (except as specifically stated).