Supplementary Information for

Osimertinib with or without savolitinib as first-line treatment for MET-aberrant, EGFR-mutant NSCLC: randomized phase 2 trial (FLOWERS)

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Supplementary Figures 1 to 5
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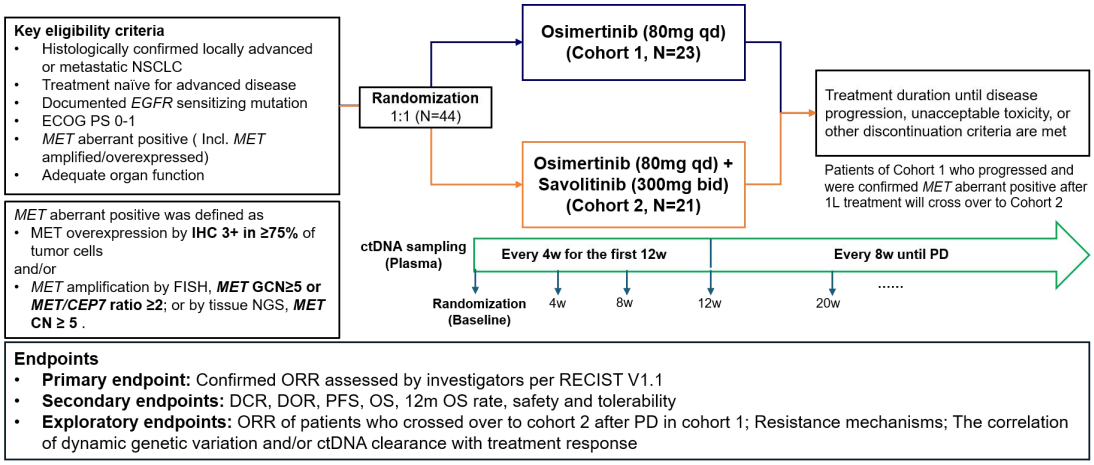
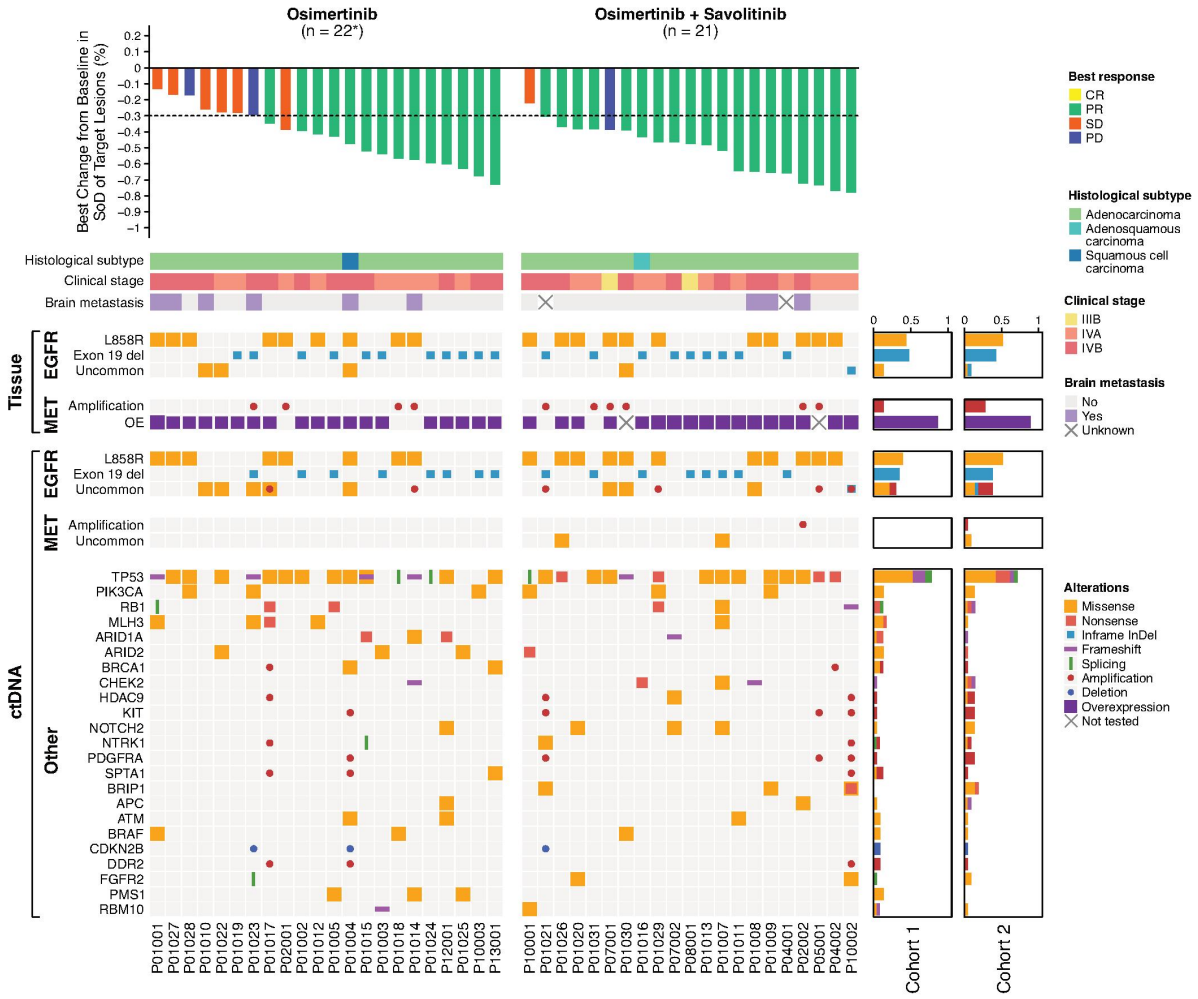
Other Supplementary Information for this manuscript include the following:

Supplementary Note 1: Study Protocol
Supplementary Note 2: Statistical Analysis Plan
Supplementary Note 3: CONSORT 2010 Checklist



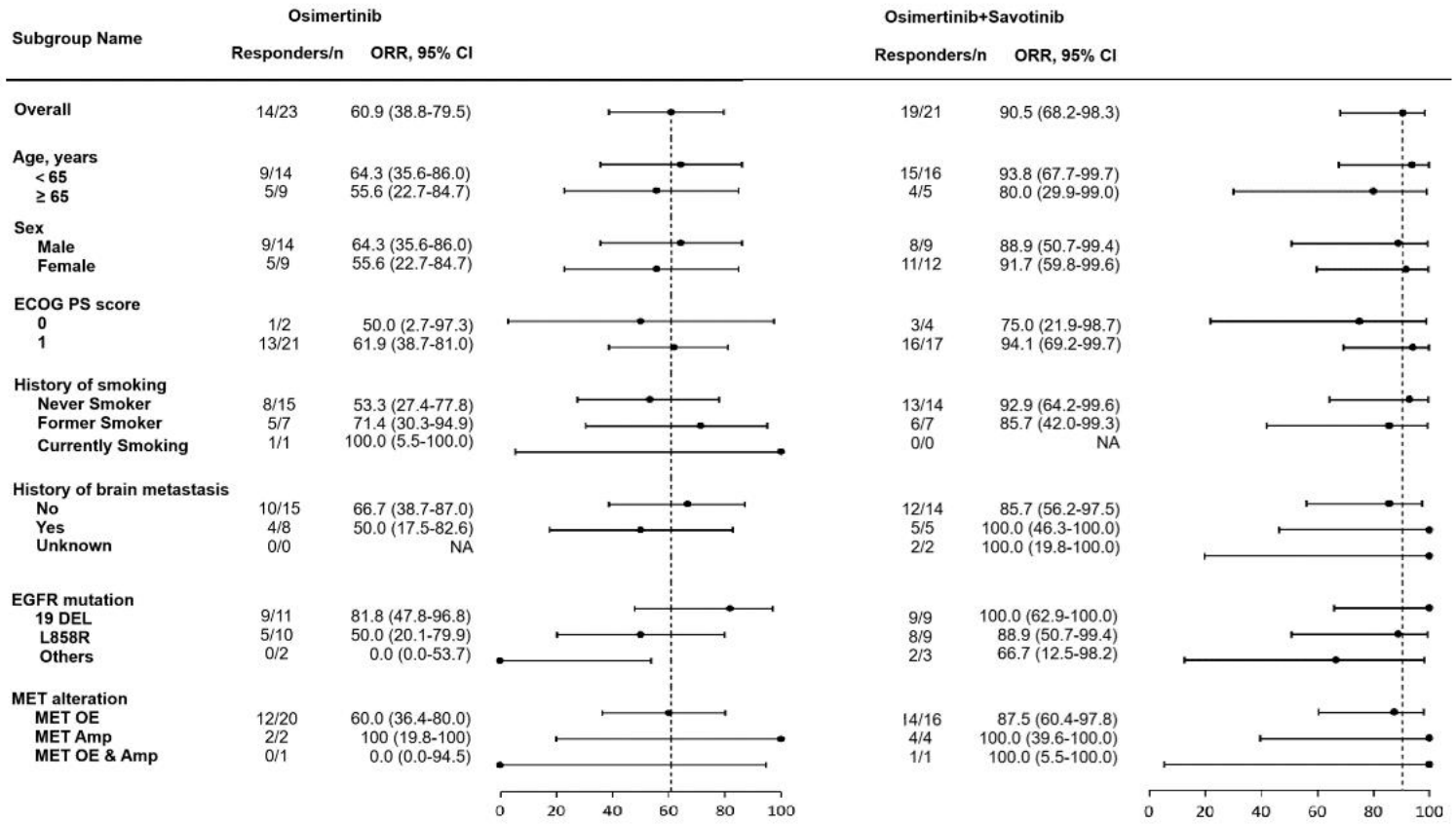
Supplementary Figure 1. Study Design.

IHC assay: MET (SP44) (Roche); FISH probe (Abbott); NGS (GENETRON). NSCLC, non-small cell lung cancer; ORR, Overall response rate; DCR, Disease control rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. PD, Progressive disease; IHC, immunohistochemistry; GCN, gene copy number; CN, copy number.



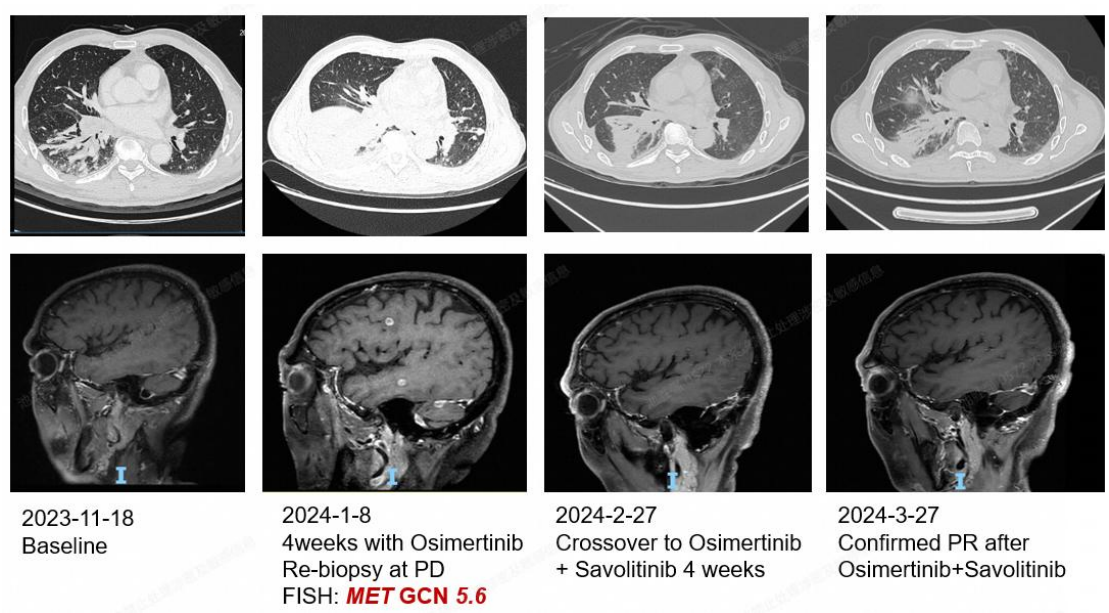
Supplementary Figure 2. Baseline molecular profiles and response to treatment.

Plasma samples from 22 patients in Cohort 1 and 21 patients in Cohort 2 were analyzed by the Onco Sonar assay. Variants present in ≥5% of patients are presented, including missense, nonsense, inframe insertions/deletions (InDels), frameshift mutations, splicing alterations, amplifications, and deletions. Uncommon EGFR variants identified in tumor tissues included G719X, S768I, E709X, and exon 19 insertion (without amplification data). Additional uncommon EGFR variants uniquely detected in ctDNA included L62R, L703F, P1059L, and amplification. Uncommon MET variants identified in ctDNA included D822N and M1049I. OE, overexpression. *One patient did not complete target lesion assessment after baseline.



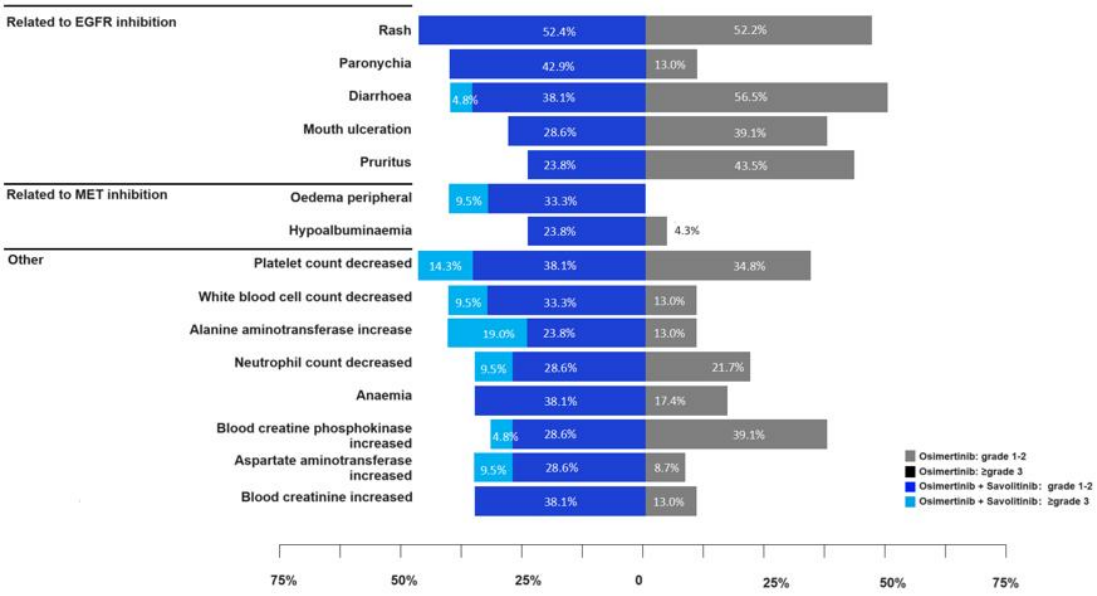
Supplementary Figure 3. ORR subgroup analysis.

ORR, objective response rate; CI, confidence interval; NE, not evaluate.



Supplementary Figure 4. Radiographic response in a patient with primary resistance on osimertinib achieving response to combination therapy.

A typical case involves a patient diagnosed with adenocarcinoma of the right lower lung lobe (cT4N3M1c, Stage IVB). IHC revealed MET OE (3+, 95%) and PD-L1 expression at 80%. FISH demonstrated an MET GCN of 5·2, whereas tissue NGS revealed the presence of an EGFR exon 19 deletion (19 del) and a MET CN of 3·4. The patient commenced treatment with osimertinib on December 13, 2023, but experienced disease progression within the first four weeks. Following the study protocol, this patient transitioned to combination therapy on January 29, 2024, and achieved durable PR by the data cutoff. IHC, immunohistochemistry; OE, overexpression; PD-L1, programmed death-ligand 1; FISH, Fluorescence in situ hybridization; NGS, next-generation sequencing; GCN, gene copy number; CN, copy number; PR, partial response.



Supplementary Figure 5. Most common TRAEs (≥20%) by preferred term.

Treatment-related safety profiles of osimertinib monotherapy (N = 23) and osimertinib plus savolitinib (N = 21) were consistent with prior reports, most TRAEs were Grade 1-2. No fatal AE was observed in both cohorts. TRAEs, Treatment related adverse events; AE, adverse event.

Supplementary Table 1. The specific scoring criteria of MET overexpression in different trials.

Trials	Scoring criteria of MET overexpression
INSIGHT[1-2]	IHC ⩾50% 2+ or 3+
TATTON[3-4]	IHC ⩾50% 3+
SAVANNAH[5]	IHC ⩾50% 3+/90% 3+
FLOWERS	IHC ⩾75% 3+

[1] Liam, C.K., et al. Randomized Trial of Tepotinib Plus Gefitinib versus Chemotherapy in EGFR-Mutant NSCLC with EGFR Inhibitor Resistance Due to MET Amplification: INSIGHT Final Analysis. Clinical cancer research: an official journal of the American Association for Cancer Research 29, 1879-1886 (2023).
[2] Wu Y-L, Cheng Y, Zhou J, et al. Tepotinib plus gefitinib in patients with EGFR-mutant non-small-cell lung cancer with MET overexpression or MET amplification and acquired resistance to previous EGFR inhibitor (INSIGHT study): an open-label, phase 1b/2, multicentre, randomised trial. The Lancet Respiratory Medicine 2020;8(11):1132-1143.
[3] Sequist LV, Han JY, Ahn MJ, et al. Osimertinib plus savolitinib in patients with EGFR mutation-positive, MET-amplified, non-small-cell lung cancer after progression on EGFR tyrosine kinase inhibitors: interim results from a multicentre, open-label, phase 1b study. Lancet Oncol 2020;21(3):373-386.
[4] Hartmaier RJ, Markovets AA, Ahn MJ, et al. Osimertinib + Savolitinib to Overcome Acquired MET-Mediated Resistance in Epidermal Growth Factor Receptor–Mutated, MET-Amplified Non–Small Cell Lung Cancer: TATTON. Cancer Discov 2023;13(1):98-113.
[5] Ahn MJ, Kim TM, Bonanno L, et al. SAVANNAH: Savolitinib (savo) + osimertinib (osi) in patients (pts) with EGFRm advanced NSCLC and METoverexpression (OverExp) and/or amplification (Amp) following progressive disease (PD) on osi. J Thorac Oncol 2025; 20(3): S4-S5.

Supplementary Table 2. MET alteration testing results.

MET alteration testing	Cohort 1 (N, %)		Cohort 2 (N, %)		Total (N, %)	
	Positive	**Negative**	**Positive**	**Negative**	**Positive**	**Negative**
FISH (N=5)	2 (40.0%)	0	3 (60.0%)	0	5 (100.0%)	0
Tissue NGS (N=34)	0	17 (50.0%)	2 (5.9%)	15 (44.1%)	2 (5.9%)	32 (94.1%)
IHC (N=42)	22 (52.4%)	1 (2.4%)	17 (40.5%)	2 (4.8%)	39 (92.9%)	3 (7.1%)

Supplementary Table 3. Grade ≥3 Treatment-Related Adverse Events (TRAEs).

Grade ≥3 TRAE, N (%)	Cohort 1 (N=23)	Cohort 2 (N=21)	Total (N=44)
Total	**2 (8.7)**	**12 (57.1)**	**14 (31.8)**
Electrocardiogram QT prolonged	1 (4.3)	0 (0.0)	1 (2.3)
Chest discomfort	1 (4.3)	0 (0.0)	1 (2.3)
Alanine aminotransferase increase	0 (0.0)	4 (19.0)	4 (9.1)
Platelet count decreased	0 (0.0)	3 (14.3)	3 (6.8)
White blood cell count decreased	0 (0.0)	2 (9.5)	2 (4.5)
Hepatic function abnormal	0 (0.0)	2 (9.5)	2 (4.5)
Aspartate aminotransferase increased	0 (0.0)	2 (9.5)	2 (4.5)
Peripheral edema	0 (0.0)	2 (9.5)	2 (4.5)
Neutrophil count decreased	0 (0.0)	2 (9.5)	2 (4.5)
Pyrexia	0 (0.0)	1 (4.8)	1 (2.3)
Diarrhea	0 (0.0)	1 (4.8)	1 (2.3)
Anaphylactic shock	0 (0.0)	1 (4.8)	1 (2.3)
Pain	0 (0.0)	1 (4.8)	1 (2.3)
Blood creatine phosphokinase increased	0 (0.0)	1 (4.8)	1 (2.3)
Drug eruption	0 (0.0)	1 (4.8)	1 (2.3)

Cohort 1, osimertinib monotherapy. Cohort 2, a combination of osimertinib and savolitinib therapy.

Supplementary Table 4. Incidence of treatment-related adverse events (TRAEs) during the treatment period classified by preferred terms in Osimertinib monotherapy group.

Any TRAE[1]	Osimertinib monotherapy (N=23)		
	Grade 1-2, N(%)	Grade ≥3, N(%)	Total, N(%)
Total	23 (100.0)	2 (8.7)	23 (100.0)
Diarrhea	13 (56.5)	0 (0.0)	13 (56.5)
Rash	12 (52.2)	0 (0.0)	12 (52.2)
Pruritus	10 (43.5)	0 (0.0)	10 (43.5)
Mouth ulceration	9 (39.1)	0 (0.0)	9 (39.1)
Blood creatine phosphokinase increased	9 (39.1)	0 (0.0)	9 (39.1)
Platelet count decreased	8 (34.8)	0 (0.0)	8 (34.8)
Neutrophil count decreased	5 (21.7)	0 (0.0)	5 (21.7)
Bilirubin conjugated increased	4 (17.4)	0 (0.0)	4 (17.4)
Skin fissures	4 (17.4)	0 (0.0)	4 (17.4)
Anaemia	4 (17.4)	0 (0.0)	4 (17.4)
White blood cell count decreased	3 (13.0)	0 (0.0)	3 (13.0)
Alanine aminotransferase increase	3 (13.0)	0 (0.0)	3 (13.0)
Proteinuria	3 (13.0)	0 (0.0)	3 (13.0)
Paronychia	3 (13.0)	0 (0.0)	3 (13.0)
Blood creatinine increased	3 (13.0)	0 (0.0)	3 (13.0)
Dry skin	3 (13.0)	0 (0.0)	3 (13.0)
Electrocardiogram QT prolonged	2 (8.7)	1 (4.3)	3 (13.0)
Sinus bradycardia	2 (8.7)	0 (0.0)	2 (8.7)
Hypermagnesemia	2 (8.7)	0 (0.0)	2 (8.7)
Hyperglycaemia	2 (8.7)	0 (0.0)	2 (8.7)
Decreased appetite	2 (8.7)	0 (0.0)	2 (8.7)
Aspartate aminotransferase increased	2 (8.7)	0 (0.0)	2 (8.7)
Alopecia	2 (8.7)	0 (0.0)	2 (8.7)
Back pain	1 (4.3)	0 (0.0)	1 (4.3)
Nasal dryness	1 (4.3)	0 (0.0)	1 (4.3)
Epistaxis	1 (4.3)	0 (0.0)	1 (4.3)
Bile acids increased	1 (4.3)	0 (0.0)	1 (4.3)
Hypoalbuminaemia	1 (4.3)	0 (0.0)	1 (4.3)
Hypocalcaemia	1 (4.3)	0 (0.0)	1 (4.3)
Hyponatraemia	1 (4.3)	0 (0.0)	1 (4.3)
Amylase increased	1 (4.3)	0 (0.0)	1 (4.3)
Nausea	1 (4.3)	0 (0.0)	1 (4.3)
Mitral valve disease mixed	1 (4.3)	0 (0.0)	1 (4.3)
Pulmonary arterial hypertension	1 (4.3)	0 (0.0)	1 (4.3)
Abdominal discomfort	1 (4.3)	0 (0.0)	1 (4.3)
Abdominal pain	1 (4.3)	0 (0.0)	1 (4.3)
Anal haemorrhage	1 (4.3)	0 (0.0)	1 (4.3)
Hyperuricaemia	1 (4.3)	0 (0.0)	1 (4.3)
Red blood cell count decreased	1 (4.3)	0 (0.0)	1 (4.3)
Muscle spasms	1 (4.3)	0 (0.0)	1 (4.3)
Myalgia	1 (4.3)	0 (0.0)	1 (4.3)
Conjunctivitis	1 (4.3)	0 (0.0)	1 (4.3)
Stomatitis	1 (4.3)	0 (0.0)	1 (4.3)
White blood cells urine positive	1 (4.3)	0 (0.0)	1 (4.3)
Urine ketone body present	1 (4.3)	0 (0.0)	1 (4.3)
Vomiting	1 (4.3)	0 (0.0)	1 (4.3)

Any TRAE[1]	Osimertinib monotherapy (N=23)		
	Grade 1-2, N(%)	Grade ≥3, N(%)	Total, N(%)
Tricuspid valve incompetence	1 (4.3)	0 (0.0)	1 (4.3)
Eczema	1 (4.3)	0 (0.0)	1 (4.3)
Ventricular extrasystoles	1 (4.3)	0 (0.0)	1 (4.3)
Weight decreased	1 (4.3)	0 (0.0)	1 (4.3)
Gastroesophageal reflux disease	1 (4.3)	0 (0.0)	1 (4.3)
Chest discomfort	0 (0.0)	1 (4.3)	1 (4.3)
Asthenia	1 (4.3)	0 (0.0)	1 (4.3)
Blood bilirubin increased	1 (4.3)	0 (0.0)	1 (4.3)
Haematuria	1 (4.3)	0 (0.0)	1 (4.3)
Gingival bleeding	1 (4.3)	0 (0.0)	1 (4.3)
Eye pain	1 (4.3)	0 (0.0)	1 (4.3)
Throat irritation	1 (4.3)	0 (0.0)	1 (4.3)
Lipase increased	1 (4.3)	0 (0.0)	1 (4.3)
Aortic valve incompetence	1 (4.3)	0 (0.0)	1 (4.3)

[1] AEs related to the study drug will include those categorized as "definitely related," "related," "very likely related," "likely related," or "possibly related." If the data is missing or unknown, the AE will be considered related to the study drug. If multiple AEs are reported by a patient under the same SOC (System Organ Class) or PT (Preferred Term), the patient will be counted only once in that SOC or PT category.

Supplementary Table 5. Incidence of treatment-related adverse events (TRAE) during the treatment period classified by preferred terms in Osimertinib plus Savolitinib group.

Any TRAE[1]	Osimertinib plus Savolitinib group (N=21)		
	Grade 1-2, N(%)	Grade ≥3, N(%)	Total, N(%)
Total	21 (100.0)	12 (57.1)	21 (100.0)
Rash	11 (52.4)	0 (0.0)	11 (52.4)
Platelet count decreased	8 (38.1)	3 (14.3)	11 (52.4)
Diarrhea	8 (38.1)	1 (4.8)	9 (42.9)
White blood cell count decreased	7 (33.3)	2 (9.5)	9 (42.9)
Alanine aminotransferase increase	5 (23.8)	4 (19.0)	9 (42.9)
Paronychia	9 (42.9)	0 (0.0)	9 (42.9)
Peripheral edema	7 (33.3)	2 (9.5)	9 (42.9)
Neutrophil count decreased	6 (28.6)	2 (9.5)	8 (38.1)
Anaemia	8 (38.1)	0 (0.0)	8 (38.1)
Blood creatinine increased	8 (38.1)	0 (0.0)	8 (38.1)
Aspartate aminotransferase increase	6 (28.6)	2 (9.5)	8 (38.1)
Blood creatine phosphokinase increased	6 (28.6)	1 (4.8)	7 (33.3)
Mouth ulceration	6 (28.6)	0 (0.0)	6 (28.6)
Pruritus	5 (23.8)	0 (0.0)	5 (23.8)
Hypoalbuminaemia	5 (23.8)	0 (0.0)	5 (23.8)
Bilirubin conjugated increased	4 (19.0)	0 (0.0)	4 (19.0)
Vomiting	4 (19.0)	0 (0.0)	4 (19.0)
Gamma-glutamyltransferase increased	4 (19.0)	0 (0.0)	4 (19.0)
Face edema	4 (19.0)	0 (0.0)	4 (19.0)
Skin fissures	3 (14.3)	0 (0.0)	3 (14.3)
Dry skin	3 (14.3)	0 (0.0)	3 (14.3)
Amylase increased	3 (14.3)	0 (0.0)	3 (14.3)
Nausea	3 (14.3)	0 (0.0)	3 (14.3)
Asthenia	3 (14.3)	0 (0.0)	3 (14.3)
Lymphocyte count decreased	3 (14.3)	0 (0.0)	3 (14.3)
Blood alkaline phosphatase increased	3 (14.3)	0 (0.0)	3 (14.3)
Mouth haemorrhage	3 (14.3)	0 (0.0)	3 (14.3)
Pyrexia	2 (9.5)	1 (4.8)	3 (14.3)
Proteinuria	2 (9.5)	0 (0.0)	2 (9.5)
Electrocardiogram QT prolonged	2 (9.5)	0 (0.0)	2 (9.5)
Sinus bradycardia	2 (9.5)	0 (0.0)	2 (9.5)
Decreased appetite	2 (9.5)	0 (0.0)	2 (9.5)
Alopecia	2 (9.5)	0 (0.0)	2 (9.5)
Hypocalcaemia	2 (9.5)	0 (0.0)	2 (9.5)
Hyponatraemia	2 (9.5)	0 (0.0)	2 (9.5)
Abdominal pain	2 (9.5)	0 (0.0)	2 (9.5)
Myalgia	2 (9.5)	0 (0.0)	2 (9.5)
Stomatitis	2 (9.5)	0 (0.0)	2 (9.5)
Pain in extremity	2 (9.5)	0 (0.0)	2 (9.5)
Hypokalaemia	2 (9.5)	0 (0.0)	2 (9.5)
Blood bilirubin unconjugated increase	2 (9.5)	0 (0.0)	2 (9.5)
Blood urea increased	2 (9.5)	0 (0.0)	2 (9.5)
Arrhythmia	2 (9.5)	0 (0.0)	2 (9.5)
Weight increased	2 (9.5)	0 (0.0)	2 (9.5)
Hepatic function abnormal	0 (0.0)	2 (9.5)	2 (9.5)

Any TRAE[1]	Osimertinib plus Savolitinib group (N=21)		
	Grade 1-2, N(%)	Grade ≥3, N(%)	Total, N(%)
Muscle spasms	1 (4.8)	0 (0.0)	1 (4.8)
Ventricular extrasystoles	1 (4.8)	0 (0.0)	1 (4.8)
Blood bilirubin increased	1 (4.8)	0 (0.0)	1 (4.8)
Haematuria	1 (4.8)	0 (0.0)	1 (4.8)
Drug eruption	0 (0.0)	1 (4.8)	1 (4.8)
Bundle branch block right	1 (4.8)	0 (0.0)	1 (4.8)
Onychoclasis	1 (4.8)	0 (0.0)	1 (4.8)
Alpha hydroxybutyrate dehydrogenase increased	1 (4.8)	0 (0.0)	1 (4.8)
Eructation	1 (4.8)	0 (0.0)	1 (4.8)
Hypersensitivity	1 (4.8)	0 (0.0)	1 (4.8)
Dermatitis acneiform	1 (4.8)	0 (0.0)	1 (4.8)
Sacral pain	1 (4.8)	0 (0.0)	1 (4.8)
Rash pustular	1 (4.8)	0 (0.0)	1 (4.8)
Blood lactate dehydrogenase increased	1 (4.8)	0 (0.0)	1 (4.8)
Musculoskeletal chest pain	1 (4.8)	0 (0.0)	1 (4.8)
Gastrointestinal sounds abnormal	1 (4.8)	0 (0.0)	1 (4.8)
Venous thrombosis limb	1 (4.8)	0 (0.0)	1 (4.8)
Diabetes mellitus	1 (4.8)	0 (0.0)	1 (4.8)
Pain	0 (0.0)	1 (4.8)	1 (4.8)
Abdominal distension	1 (4.8)	0 (0.0)	1 (4.8)
Hypertriglyceridaemia	1 (4.8)	0 (0.0)	1 (4.8)
Arthralgia	1 (4.8)	0 (0.0)	1 (4.8)
Anaphylactic shock	0 (0.0)	1 (4.8)	1 (4.8)
Perineal swelling	1 (4.8)	0 (0.0)	1 (4.8)
Interstitial lung disease	1 (4.8)	0 (0.0)	1 (4.8)
Atrial fibrillation	1 (4.8)	0 (0.0)	1 (4.8)
Back pain	1 (4.8)	0 (0.0)	1 (4.8)
Epistaxis	1 (4.8)	0 (0.0)	1 (4.8)
Bile acids increased	1 (4.8)	0 (0.0)	1 (4.8)

[1] AEs related to the study drug will include those categorized as "definitely related," "related," "very likely related," "likely related," or "possibly related." If the data is missing or unknown, the AE will be considered related to the study drug. If multiple AEs are reported by a patient under the same SOC (System Organ Class) or PT (Preferred Term), the patient will be counted only once in that SOC or PT category.

Supplementary Table 6. The names of all the institutional review boards.

Investigator Name	Institution	Institutional Review Board Name
Jin-Ji Yang	Guangdong Provincial People's Hospital	Institutional Review Board of Guangdong Provincial People's Hospital
Wei-Neng Feng	The First People's Hospital Foshan	Institutional Review Board of the First People's Hospital Foshan
Juan Li	Sichuan Cancer Hospital & Institute	Institutional Review Board for Medical Research and New Medical Technologies of Sichuan Cancer Hospital
Jun Zhao	Beijing Cancer Hospital	Institutional Review Board of Beijing Cancer Hospital
Yun Jia	Dongguan People`s Hospital	Institutional Review Board of Dongguan People's Hospital
Ke-Jing Tang	The First Affiliated Hospital of Sun Yat-Sen University	Institutional Ethics Committee for Clinical Research and Animal Trials of the First Affiliated Hospital of Sun Yat-sen University
Yong-sheng Li	Chongqing University Cancer Hospital	Institutional Review Board of Chongqing University Cancer Hospital
Cheng-Zhi Zhou	The First Affiliated Hospital of Guangzhou Medical University	Institutional Review Board of the First Affiliated Hospital of Guangzhou Medical University
Yun Fan	Zhejiang Cancer Hospital	Institutional Review Board of Zhejiang Cancer Hospital
Xiaolong Cao	The Affiliated Panyu Central Hospital of Guangzhou Medical University	Institutional Review Board of Panyu District Central Hospital, Guangzhou

Clinical Study Protocol	
Study Intervention	Savolitinib+Osimertinib
Study Code	CTONG 2008 (ESR 20-20862)
Version	V 3.0
Date	15 June 2021

A prospective, pilot study of first line osimertinib with or without savolitinib in *de novo MET* positive, *EGFR*-mutant NSCLCs (FLOWERS)

Sponsor Name: Guangdong Association of Clinical Trials (GACT)

Legal Registered Address: Suite 5502, China International Center, 33 Zhongshan San Road, Yuexiu District, Guangzhou, P.R.China.

Protocol Number: Version 3.0

Study Intervention: osimertinib and savolitinib

Study Phase: Phase II

Short Title: osimertinib with or without savolitinib as 1L in *de novo* MET+, EGFR+ NSCLC

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A prospective, pilot study of first-line osimertinib with or without savolitinib in *de novo* MET positive, *EGFR*-mutant NSCLCs (FLOWERS)

Short Title: Osimertinib with or without savolitinib as 1L in *de novo EGFR*m+/*MET*+ NSCLC

Rationale:

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (EGFR-TKIs) are the established first-line therapy in patients with advanced non-small-cell lung cancer (NSCLC) possessing activating mutations in EGFR (*EGFR*m). *EGFR*-mutant NSCLC is a set of heterogeneous disease rather than a single-oncogene-driven disease (Blakely, Watkins et al. 2017), among which *EGFR*m NSCLC with *de novo MET* amplification is a very important subgroup. Hepatocyte growth factor receptor (HGF)/mesothelial-epithelial transition (MET) pathway activation has been implicated as an oncogenic driver in *EGFR*m NSCLC and can mediate primary and secondary resistance to EGFR TKIs.

De novo MET amplification was reported to be concomitant in about 2~26% *EGFR*m NSCLC (Wang, Cheng et al. 2018, Yu, Suzawa et al. 2018, Lai, Lim et al. 2019, Wang, Diao et al. 2019). Moreover, *de novo MET* amplification negatively affects the response and survival of patients who receive first-line treatment with EGFR TKI monotherapy. A study explored the clinical relevance of *MET* cope number gain (GCN) in the setting of treatment-naïve *EGFR*m NSCLC and suboptimal response to EGFR TKI was observed in patients with coexisting *MET* amplification (median time-to-treatment failure, mTTF was 5.0 months vs 13.1 months for *MET* amplification vs *MET*-low) (Lai, Lim et al. 2019). Yu HA, et al., reported similar results that shorter time to progression on EGFR TKI was associated with amplification of *MET* (median time-to-progression, mTTP was 5 months vs 11months for MET amplification vs MET negative, HR 3.7, p=0.019) (Yu, Suzawa et al. 2018).

EGFR and HGF/MET signalling pathways are both activated in this patient population, using EGFR TKI alone is not effective enough to treat *de novo MET*-amplified, *EGFR*-mutant advanced NSCLC and more effective solution is needed for such patients. Gainor JF, et al., reported dramatic response to combination erlotinib and crizotinib in a patient with advanced, *EGFR*m NSCLC harbouring *de novo MET* amplification after primary resistance to erlotinib (Gainor, Niederst et al. 2016), which indicate that the combination of EGFR TKI and MET TKI may be the solution for these EGFR TKI monotherapy refractory patients.

Osimertinib (TAGRISSO™, AZD9291) is a potent and specific irreversible dual inhibitor of both the sensitising *EGFR* mutations and the *T790M* resistance mutation (Reck, Popat et al. 2014, Masters, Temin et al. 2015). Savolitinib (AZD6094, HMPL-504) is a potent and highly selective MET kinase inhibitor (Jia, Dai et al. 2014). Osimertinib in combination with

savolitinib may improve efficacy and prevent *MET*-driven primary resistance in patients with *de novo* MET positive, *EGFR*m NSCLC.

Objectives and Endpoints

Primary objective(s)	**Outcome measure**
To explore the objective response of osimertinib plus savolitinib or osimertinib monotherapy as first-line therapy in *de novo* MET positive, *EGFR*m NSCLC	ORR (Investigator assessment as defined by RECIST 1.1)
Secondary objective(s)	**Outcome measure**
To explore the survivals of osimertinib plus savolitinib or osimertinib monotherapy as first-line therapy in *de novo* MET positive, *EGFR*m NSCLC	PFS, DoR, DCR, percentage change from baseline in tumor size, OS, 12m OS rate by Investigator assessment
Subgroup analysis of the efficacy of osimertinib plus savolitinib or osimertinib monotherapy as first-line therapy in patient population identified by different testing platforms	ORR, PFS, DoR, DCR, percentage change from baseline in tumor size, OS, 12m OS rate by Investigator assessment
Safety objective(s)	**Outcome measure**
To evaluate the safety and tolerability of osimertinib and savolitinib in patients with *de novo* MET positive, *EGFR*m NSCLC	AE, SAE, non-serious ADR, AESI, Laboratory test Vital signs Physical examination
Exploratory objective(s)	**Outcome measure**
To assess the efficacy of osimertinib plus savolitinib as second-line therapy in *de novo* MET positive, *EGFR*m NSCLC patients progressed on first- line osimertinib monotherapy	ORR (Investigator assessment as defined by RECIST 1.1) of osimertinib plus savolitinib in patients progress on first line osimertinib monotherapy
To explore potential molecular resistance mechanism by plasma biomarker analysis at disease progression.	Genetic alteration changes at disease progression
To collect longitudinal plasma samples for the exploration of the correlation of genetic variation and/or ctDNA clearance with treatment response	Longitudinal changes of genetic variation and/or ctDNA clearance compared with treatment response.

Overall Design

Disclosure Statement: This is a prospective, pilot, two-arm, randomized, multicenter study exploring the efficacy and safety of osimertinib with or without savolitinib as first-line therapy in patients with *de novo* MET positive, *EGFR*-mutant advanced NSCLC.

Participant Population:

The target population of interest in this study is participants with *de novo* MET positive ,

EGFR-mutant, have not received any systemic anti-cancer therapy at first-line, histologically or cytologically confirmed locally advanced or metastatic NSCLC.

Number of Participants:

Approximately 44 eligible patients will be enrolled to randomly assigned to study interventions so that approximately 40 evaluable participants complete the study, based on assumption of 10% participants not complete the study.

All patients must have measurable disease (using computer tomography/magnetic resonance imaging) as defined by RECIST 1.1 guidelines, with Eastern Cooperative Oncology Group (ECOG)/ World Health Organization (WHO) performance status of 0 to 1 and adequate liver function test at Screening.

Eligible patients will be those with histologically or cytologically confirmed diagnosis of *EGFR*m NSCLC that is locally advanced or metastatic and have not received any systemic anti-cancer therapy at first-line. Patients must have confirmation of MET+ tumor by IHC, FISH, or central NGS testing. In patients confirmed as MET+, MET+ is defined as a) high expression of MET (by IHC, 3+ in ⩾75% of tumor cells) and/or b) increased *MET* gene copy number (by FISH, *MET* gene copy ⩾5 or MET / CEP7 ratio ⩾2; or by tissue NGS, ⩾20% tumour cells, ⩾200x sequencing depth of coverage and CN ≥5). Patients must not have received prior or current treatment with savolitinib or any other MET inhibitors.

Study Period:

The first patient is estimated to be enrolled in Q3, 2021.The enrolment period is about 12 months and the follow-up will be ended when 80% maturity of PFS achieved, which is estimated to be about 40 months after last subject in (LSI).

Intervention Groups and Duration:

All eligible patients will be randomized to receive treatment with osimertinib (80 mg daily) or osimertinib (80 mg daily) in combination with savolitinib (300 mg BID) in this study. Treatment will continue until either objective disease progression, unacceptable toxicity occurs, consent is withdrawn or other discontinuation criterion is met.

Patients who progress on first-line treatment of osimertinib monotherapy will have the opportunity to receive second-line treatment of osimertinib plus savolitinib after confirmation of MET status at disease progression.

Follow-up of participants post discontinuation of study intervention:

After study intervention discontinuation, all participants will undergo an end-of-treatment visit (within 14 days of discontinuation) and will be followed up for safety assessments 30 days after their last dose of study interventional medication (ie, the safety follow-up visit).

Participants who have discontinued study interventional medication in the absence of RECIST 1.1-defined confirmed by investigator assessment radiological progression will be followed up with tumor assessments according to the Schedule of Activities (SoA) until RECIST 1.1-defined PD or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

In addition, all participants will be followed up for survival status after study medication discontinuation every 12 weeks (±7 days) until death, withdrawal of consent, or the end of the study, ie, at the time of final analysis. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. In addition to the survival status, the assessment of anti-cancer and surgical treatments are also required.

See Section 6.7 for a description of assessments after final analysis.

Statistical methods

The efficacy analysis will be conducted per FAS set, which will be specified in Section 9.2.4.

All statistical procedures will be conducted using SAS version 9.4 or later version. Summary statistics will be provided for most if not all analysis. For continuous variables, this will include the number of observations, mean, median, standard deviation, minimum and maximum. For categorical variables, this will include frequency counts and percentages at each category.

There will be two analyses for this study. The data cut-off (DCO) date for primary analysis for ORR will be 12 weeks after last subject in (LSI). The second analysis DCO for PFS/OS will be at the point when 80% data maturity of PFS events (32 PFS events, 16 PFS events in each cohort) is achieved, which is estimated to be 40 months after LSI, with an enrollment period of 12 months and assumption of 18 months for median PFS in cohort 2 .

There will be no statistical comparison between osimertinib plus savolitinib arm and osimertinib monotherapy arm.

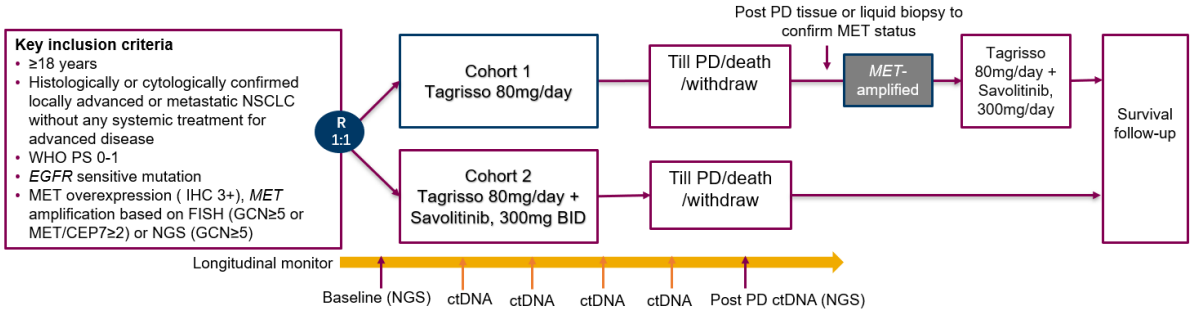
The primary outcome, ORR is defined as the number (%) of subjects with at least one visit response of confirmed CR or PR, based on Investigator assessment according to RECIST 1.1. A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging, preferably at the next regularly scheduled imaging visit and not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visits. Therefore, data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who have taken the assigned treatment but discontinue the

treatment without progression, receive a subsequent anti-cancer therapy and then respond will not be included as responders in the ORR. The results of ORR will be presented in percentage with its 95% confidence interval estimate using Clopper-pearson method. DCR will be analyzed in the same way and 12 month OS rate will be estimated using Kaplan-Meier method.

The analysis of secondary endpoint, PFS, based on Investigator assessment (according to RECIST 1.1) will occur when at least 32 progression events, 16 events in each arm have been observed in the patients (approximately 80% PFS maturity). Kaplan-Meier method will be used to estimate the median PFS and its 95% confidence interval. A KM curve will be provided as well. Above analysis methods will apply on overall population and subgroups identified by different diagnostic platforms if applicable. DoR and OS will be analyzed in the same way.

1.2 Schema

Figure 1 study design



1.3 Schedule of Activities

The procedures for this study are presented in below Table 1.

Table 1 Schedule of Activities

Visit	Screening (up to 28 Days Before Day 1)	Intervention Period [Weeks]				Post-intervention Follow-up Period			Details in CSP Section or Appendix
		Week 1	Week 4	Week 8	Week 4n	End-of-Treatment Visit（Within 14 days of the final dose)	Safety Follow-up (30 + 7 Days After Last Dose)[a]	Survival Follow-up (q12w ±7 days)	
Informed consent: main study [b]	X								Sections 5.1 and 3
Inclusion and exclusion criteria	X								Section 5.1 and 5.2
Randomisation	X								
Biomarker diagnosis									
Tumor harbours EGFRm (exon 19 deletion and/or L858R)[c]	X								
MET status: IHC, FISH or NGS [d]	X								
Routine clinical procedure									
Demography	X								Section 5.1
Full physical examination	X	Every visit							Section 8.2.1
Height	X								Section 8.2.1
Weight	X	Every visit				X			Section 8.2.1
Medical history and comorbid conditions	X	X [e]							Sections 5.1 and 5.2
WHO/ECOG performance status	X	X [e]	X	X	X	X	X		Section 8.2.6.2
Concomitant medication and procedures	X	At every visit and may be conducted by phone if not tied to a clinic visit				X	X		Section 6.5
Routine safety measurements									
Adverse events	X	Every visit							Sections 8

Visit	Screening (up to 28 Days Before Day 1)	Intervention Period [Weeks]				Post-intervention Follow-up Period			Details in CSP Section or Appendix
		Week 1	Week 4	Week 8	Week 4n	End-of-Treatment Visit (Within 14 days of the final dose)	Safety Follow-up (30 + 7 Days After Last Dose)[a]	Survival Follow-up (q12w ±7 days)	
Serum/urine pregnancy test (WOCBP only)	X	As clinically indicated.							Sections 8.2.4
Clinical safety laboratory assessment [m](renal function tests, clinical chemistry, haematology, urinalysis)	X	Every visit				X	X[f]		Section 8.2.4
Liver function tests	X	Weekly for the first 9 weeks, then Day 1 of every subsequent cycle				X	X[f]		Section 8.2.4
12-lead ECG	X	Every visit				X	X[f]		Section 8.2.3
MUGA/ECHO	X	Every 16 weeks (±2 weeks) relative to first dose [k]				X	X[f]		Section 8.2.3
Vital signs	X	Every visit				X	X		Section 8.2.2
Ophthalmic assessment [l]									
Study treatment administration									
Dose with osimertinib		X (daily dosing)							Sections 6
Dose with savolitinib		X (daily dosing)							Sections 6
Efficacy measurements									
Tumor imaging (RECIST Version 1.1) [g]	X	First efficacy assessment at Week 4, then every 8 weeks (±7 days) until objective disease progression							
Biomarker analyses									
Liquid biopsy [h]	X	Collect blood sample when conducting efficacy assessment (±7 days)				X, conduct after PD			
Tissue biopsy [i]	X					X, conduct after PD			
Survival follow up									

Visit	Screening (up to 28 Days Before Day 1)	Intervention Period [Weeks]				Post-intervention Follow-up Period			Details in CSP Section or Appendix
		Week 1	Week 4	Week 8	Week 4n	End-of-Treatment Visit (Within 14 days of the final dose)	Safety Follow-up (30 + 7 Days After Last Dose)[a]	Survival Follow-up (q12w ±7 days)	
Survival status[j]								Q12W	Section 8.1.3
Subsequent anti-cancer treatment								Q12W	Section 8.1.3

[a] As a minimum, telephone contact should be made with the patient 30 days following the discontinuation of both IPs to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy, if appropriate).

[b] Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations.

[c] EGFRm status is an inclusion criterion and part of disease diagnosis; prospective central testing is not mandatory.

[d] Testing for MET+ tumor by IHC, FISH or NGS must be performed on tumor tissue collected before any systemic treatment of advanced NSCLC. Local IHC, FISH and tissue NGS testing are acceptable, and central FISH and/or central tissue NGS confirmation are highly suggested if tissue sample available after local testing.

[e] If screening assessments have been performed within 7 days prior to starting study intervention, they do not have to be repeated at Cycle 1 Day 1 if the participant's condition has not changed.

[f] A 30 day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy to confirm reversibility of the abnormality.

[g] A visit response of CR or PR must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed. Patients who discontinue study drug for reasons other than investigator-confirmed disease progression will continue RECIST 1.1 tumor assessments every 8 weeks (relative to the first dose of treatment) until objective disease progression. At the same time points ECOG/WHO performance status, vital signs, ECGs, plasma samples for ctDNA and serum sample for circulating proteins will be collected. SAEs considered related to study treatment and/or study procedures will be collected throughout progression follow-up.

[h] Plasma samples will be collected at baseline, every tumor assessment visit and after progression of first line treatment if available for central lab ctDNA NGS testing for the biomarker analysis and resistance profile exploration. Please note that the sample collection during intervention period is optional.

[i] Tissue samples will be collected at baseline and after first line treatment if available for central lab NGS testing for the biomarker analysis and resistance profile exploration. Patients who progress on first-line therapy of osimertinib monotherapy will have MET status re-confirmation before receive a second-line therapy of osimertinib plus savolitinib. Tissue biopsy (based on IHC, FISH and/or NGS) is the preferred way to do a secondary MET status confirmation, but liquid biopsy (NGS) is also acceptable when tissue re-biopsy is not available.

[j] Patients will be contacted for survival follow-up every 12 weeks. Patients should be contacted in the week after data cut-off for each study analysis to establish survival status.

[k] In studies where osimertinib is being administered in accordance with the approved indication, assessment of cardiac function for changes in cardiac contractility must adhere to the 'Special warnings and special precautions for use' in the current approved TAGRISSO core data sheet.

[l] Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

[m] Serum electrolyte include Mg^{2+}, Ca^{2+}, K^{+}, etc. and blood creatine phosphokinase (CPK) will be evaluated in laboratory assessments. Electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) must be corrected to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment.

Note: All assessments on treatment days are to be performed prior to study intervention administration, unless otherwise indicated. Data collection following study analysis until the end of the study is described in Section 8.

AE=adverse event; C=cycle; CSP=Clinical Study Protocol; CTCAE=Common Terminology Criteria for Adverse Events; CV=cardiovascular; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; E/D=Early Study Intervention/Discontinuation; EoT=End of Treatment; ICF=informed consent form; IV=intravenous; MUGA=multigated acquisition; PFS2=time to second progression or death; qXXw=every X weeks; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SoC=standard of care; WHO=World Health Organisation; WOCBP=women of childbearing potential.

2 INTRODUCTION

Lung cancer has been the most common cancer in China for several decades, and by 2015, there were an estimated over 780,000 new cases. It was also the most common cause of death from cancer, with over 631,000 deaths (19.4% of the total) (Chen, Zheng et al. 2016). Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of NSCLC patients already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of early stage NSCLC patients who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters and Le Chevalier 2005). Patients presenting with unselected advanced NSCLC have a median overall survival (OS) of 10 to 12 months (Bonomi 2010).

In current clinical practice, therapeutic decisions for patients with advanced NSCLC are informed by the molecular subtypes of the tumour (Reck, Popat et al. 2014, Soria, Wu et al. 2015). Epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase rearrangement are the most well-known genetic alterations in NSCLC, and the EGFR-mutant rate is most commonly mutant alteration in Asian NSCLC patients, about 50% in non-squamous NSCLC (Shi, Au et al. 2014). Treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) demonstrates superior efficacy, compared with chemotherapy, for patients with *EGFR*-mutant advanced non–small cell lung cancer (NSCLC) and thus EGFR-tyrosine kinase inhibitors (EGFR-TKIs) are the established first-line therapy in patients with NSCLC possessing activating mutations in EGFR (*EGFR*m) (Reck, Popat et al. 2014, Masters, Temin et al. 2015). However, approximately 20% to 30% of patients who receive such treatment do not response and exhibit de novo resistance to therapy with EGFR TKIs (Hong, Gao et al. 2018).

However, the current view that *EGFR*m NSCLC is a single-oncogene-driven disease is now challenged. Blakely CM, *et al.*, identified critical co-occurring oncogenic events present in most (92.9%; 1,043/1,122) advanced-stage EGFR-mutant lung cancers patients through genomic analysis of 1,122 EGFR-mutant lung cancer samples (Blakely, Watkins et al. 2017). Similar results were reported by Wang, *et al.*, in BENEFIT trial that 66% (118/179) of the enrolled *EGFR*m NSCLC patients had concurrent *EGFR* sensitising mutations and tumor-suppressor gene mutations, including 12% (21/179) patients who also harboured other driver oncogenic mutations (Wang, Cheng et al. 2018). These data support the emerging view that EGFR-mutant NSCLC is a set of heterogeneous disease rather than a single-oncogene-driven disease.

In addition, although EGFR TKIs are the established first line treatment in patients with *EGFR*m advanced NSCLC, genetic co-alterations negatively affect the response and survival of patients who receive first-line treatment with EGFR TKIs monotherapy. The subgroup

analysis of BENEFIT trial revealed distinct median progression-free survival (PFS) and overall survival (OS) of first-line gefitinib treatment in patients with *EGFR* mutations only group and patients with mutations of *EGFR* plus oncogenes (include *MET* amplification) (median PFS, 13.2 months vs 4.7 months, HR 2.66, 1.58–4.49; p=0.0003; median OS, 32.0 months vs 21.7 months) (Wang, Cheng et al. 2018, Duan, Xu et al. 2020). Zhang Li, *et al.*, also reported that concomitant mutations was significantly associated with reduced objective response rate (ORR, 44%vs 77%; P = 0.01), shorter duration of progression-free survival (6.20 months vs 18.77 months;HR,3.51;P < 0.001), and shorter duration of overall survival (22.70 months (95% CI, 18.01-22.30 months) vs not reached; HR, 4.65 [95%CI, 1.92-11.28]; P < .001) (Hong, Gao et al. 2018). A reduced ORR of EGFR TKI in *EGFR*m NSCLC patients with concomitant genetic mutations (include *MET* amplification) was also reported by Wang F, et al. (ORR, *EGFR*m + co-mutations vs *EGFR*m only: 60.5% vs 34.2%) (Wang, Diao et al. 2019). These data indicate that patients with baseline co-mutations might require more effective therapy due to limited survival benefit of EGFR-TKI monotherapy.

With a deeper understanding of the heterogeneity nature of *EGFR*m NSCLC and the co-mutations in *EGFR*m NSCLC, researchers began to pay attention to one of the important subgroups, *EGFR*m NSCLC with *de novo MET* amplification. MET (hepatocyte growth factor receptor) pathway activation has been implicated as an oncogenic driver in *EGFR*m NSCLC and can mediate primary and secondary resistance to EGFR TKI. *De novo MET* amplification was reported to be concomitant in about 2~26% *EGFR*m NSCLC (Wang, Cheng et al. 2018, Yu, Suzawa et al. 2018, Lai, Lim et al. 2019, Wang, Diao et al. 2019). The prevalence of *de novo MET* amplification in *EGFR*m NSCLC differs across different studies due to different detection methods and different definitions of MET positive. Lai G, *et al.*, reported 52 (26%) of 200 patients in the metastatic *EGFR*m NSCLC were MET-high at diagnosis (46 polysomy and 6 focal amplification), defined as CNG ≥ 5, with an additional criterion of MET/centromeric portion of chromosome 7 ratio (MET/CEP7) ≥ 2 for amplification by fluorescence in situ hybridization (FISH) (Lai, Lim et al. 2019). While Wang F and her colleagues only find 4.7% (8/169) *EGFR*m NSCLC with *de novo MET* amplification when adopting similar definition of MET amplification based on FISH (Wang, Diao et al. 2019). In another study using ctDNA NGS as the detection method, *MET* amplification was detected in 4% (7/179) treatment naïve *EGFR*m NSCLC patients (Wang, Cheng et al. 2018). Though the prevalence of *de novo MET* amplification in *EGFR*m NSCLC is still under debate, given the importance of this population and its relatively considerable incidence, especially in Asian NSCLC patients almost half of whom are *EGFR*-mutant, it is worth further exploration.

Moreover, similar to the results found in *EGFR*m NSCLC patients with genetic co-alterations, *de novo MET* amplification negatively affect the response and survival of patients who receive first-line treatment with EGFR TKIs monotherapy. A study explored the clinical relevance of *MET* cope number gain (GCN) in the setting of treatment-naïve *EGFR*m NSCLC and suboptimal response to EGFR TKI was observed in patients with coexisting *MET* amplification (median time-to-treatment failure, mTTF was 5.0 months vs 13.1 months for *MET* amplification vs *MET*-low) (Lai, Lim et al. 2019). Yu HA, *et al.*, reported similar results that shorter time to progression on EGFR TKI was associated with amplification of *MET*

(median time-to-progression, mTTP was 5 months vs 11months for *MET* amplification vs *MET* negative, HR 3.7, p=0.019) (Yu, Suzawa et al. 2018). Wang F, et al., also found that *de novo MET* FISH + (HR = 2.83,95% CI = 1.37–5.86) were independent predictors for PFS in patients with EGFR-TKI treatment after adjustment for multiple factors (Wang, Diao et al. 2019).

EGFR and HGF/MET signaling pathways are both activated in this patient population, thus EGFR TKI monotherapy can only block the EGFR signaling pathway while leaving the by-pass HGF/MET signaling pathway still activated and may result in primary resistance of EGFR TKI. More effective solution is needed for patients with *de novo MET*-amplified, *EGFR*-mutant advanced NSCLC.

Although lack of perspective data of the combination of EGFR TKI and MET inhibitor in this patient population, there are some preliminary data can show some clues. Gainor JF, *et al.*, reported dramatic response to combination of erlotinib and crizotinib in a patient with advanced, *EGFR*m NSCLC harboring *de novo MET* amplification after primary resistance to erlotinib (Gainor, Niederst et al. 2016), which indicate that the combination of EGFR TKI and MET TKI may be the solution for these EGFR TKI monotherapy refractory patients.

Osimertinib (TAGRISSO™, AZD9291) is a potent and specific irreversible dual inhibitor of both the sensitising EGFR mutations and the T790M resistance mutation, and is now the recommended first line therapy in patients with NSCLC known to have activating mutations in *EGFR* (EGFRm+) (Reck, Popat et al. 2014, Masters, Temin et al. 2015). Savolitinib (AZD6094, HMPL-504) is a potent and highly selective MET kinase inhibitor (Jia, Dai et al. 2014) which has demonstrated anti-tumour activity in MET driven cancers (Choueiri, Halabi et al. 2017). Based on the TATTON data, adopting osimertinib plus savolitinib in patients with similar molecular features, *EGFR*-mutant and *MET* amplification, the combination therapy showed promising anti-tumor activity with manageable safety profile in later lines [cohort D (osimertinib 80mg plus savolitinib 300mg daily), ORR 64%, median PFS 9.1 months] (Sequist, Han et al. 2020), which also inspire us that osimertinib in combination with savolitinib may improve efficacy and prevent *MET* driven primary resistance in patients with *de novo MET*-amplified, *EGFR*m NSCLC.

2.1 Study Rationale

The efficacy of EGFR TKI monotherapy is insufficient in *EGFR*-mutant NSCLC patients with *de novo* MET positive, and a combination of MET TKI, savolitinib with third generation EGFR TKI, osimertinib may be a potential better solution for this patient population. The FLOWERS study will investigate the efficacy of osimertinib with or without savolitinib as first line therapy in patients with *de novo* MET positive, *EGFR*-mutant, locally advanced or metastatic NSCLC.

The rationale for the design of the study is presented in Section 4.2

2.2 Background

Refer to Section 2.

A detailed description of the chemistry, pharmacology, efficacy, and safety of osimertinib and savolitinib is provided in the Investigator's Brochures.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of osimertinib and savolitinib may be found in the Investigator's Brochures.

2.3.1 Risk Assessment

2.3.1.1 Osimertinib

In the pivotal osimertinib clinical development programme to date (n=1479 patients), these patients received osimertinib at a dose of 80 mg daily in three randomised Phase 3 studies (ADAURA, adjuvant; FLAURA, first-line; AURA3, second-line only), two single-arm Phase 2 studies (AURA Part II; AURA2, second-line or greater) and one Phase 1 study (AURA Part 1, first-line or greater). The majority of adverse drug reactions (ADRs) were Grade 1 or 2 in severity. The most commonly reported ADRs were diarrhoea (47%) and rash (45%). The incidence of CTCAE Grade 3 and Grade 4 adverse reactions with osimertinib was 8.5% and 0.1%, respectively. In patients treated with osimertinib 80 mg once daily, dose reductions due to adverse reactions occurred in 3.2% of the patients. Discontinuation due to adverse reactions occurred in 4.6% of patients.

2.3.1.2 Savolitinib

The adverse events of nausea, vomiting, oedema peripheral/oedema, fatigue, pyrexia and QTc prolongation are expected events (identified risks) for savolitinib treatment. Hypersensitivity (including anaphylaxis and Stevens-Johnson syndrome) and hepatotoxicity are important identified risks for savolitinib.

The potential risks of savolitinib are testicular toxicity, drug-drug interaction, renal tubular basophilia and urothelial hyperplasia and female reproductive organ atrophy and embryofoetal developmental toxicity.

In general, savolitinib is well tolerated when close attention to monitoring and management of risks are appropriately followed.

Liver Function Tests

Drug-induced liver injury (DILI) has been identified as a risk for patients receiving savolitinib

and requires specific monitoring. Frequent monitoring of liver function tests will take place as outlined in the study plan. The hepatotoxicity management algorithm included in the protocol clearly defines and limits the patients who can be re-challenged to those with lower grade abnormalities with rapid resolution. As stated in the eligibility criteria and risk mitigation sections, patients with abnormal baseline liver function tests will be excluded from the study ..

Pyrexia and Hypersensitivity

Pyrexia and hypersensitivity have been identified as a risk for patients receiving savolitinib. Pyrexia was followed in some cases by drug induced liver injury (see above) or an association of symptoms suggestive of hypersensitivity such as but not limited to allergic rash, cytopenias, myalgia/arthralgia and one case of SJS. Patients who experience pyrexia with or without an association of the above symptoms after initiation of savolitinib treatment must follow the toxicity management guidelines.

QTc prolongation

The QTc interval prolongation potential of savolitinib 600mg was assessed in a thorough QT study in healthy volunteers. Analysis of the data concluded that is a positive study as the upper bound of the two-sided 90%CI for the mean ΔQTcF is up to 13.6 and 14 msec at 4 and 5 hours, respectively. Regular ECG assessments will be done throughout the study according to the study plan. Patients who present ECG abnormalities with or without symptoms during treatment with savolitinib must follow the QTc prolongation toxicity management guidelines.

2.3.2 Benefit Assessment

As state in Section 2, *EGFR*-mutant NSCLC is a set of heterogeneous disease, among which *EGFR*m NSCLC with *de novo MET* amplification is a very important subgroup. *De novo MET* positive negatively affects the response and survival of patients who receive first-line treatment with EGFR TKI monotherapy, with mTTF about 5 months. EGFR and HGF/MET signaling pathways are both activated in this patient population, using EGFR TKI alone is not effective enough to treat *de novo* MET positive, *EGFR*-mutant advanced NSCLC. Although lack of perspective data of the combination of EGFR TKI and MET inhibitor in this patient population, preliminary data showed that combination of erlotinib and crizotinib overcame primary resistance to EGFR TKI monotherapy in a patient with *de novo MET*-amplified, *EGFR*m NSCLC. And osimertinib plus savolitinib showed promising anti-tumor activity with manageable safety profile in patients with similar molecular features in later line setting (TATTON study, ORR 62-67%, mPFS 9-11 months).

Although there can be no certainty of clinical benefit to patients, the positive efficacy data for osimertinib plus savolitinib from TATTON, supported by preliminary data of EGFR TKI plus MET inhibitor in this patient population, provide support for the hypothesis that osimertinib in

combination with savolitinib may improve efficacy and prevent MET driven primary resistance in patients with *de novo* MET positive, *EGFR*m NSCLC.

In this study, patients will receive osimertinib and/or savolitinib for free.

2.3.3 Overall Benefit: Risk Conclusion

Based on the above evidence review of the potential benefits and risks, the potential risks in association with osimertinib and savolitinib are manageable with close safety monitoring as specified in SoA and safety mitigation plans (Section 8.5). This study can reduce patients' financial burden, and may bring clinical benefits to these patients at the same time. The benefit/risk assessment for this study appears to be acceptable.

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

Primary objective(s)	**Outcome measure**
To explore the objective response of osimertinib plus savolitinib or osimertinib monotherapy as first-line therapy in *de novo* MET positive, *EGFR*m NSCLC	ORR (Investigator assessment as defined by RECIST 1.1)
Secondary objective(s)	**Outcome measure**
To explore the survivals of osimertinib plus savolitinib or osimertinib monotherapy as first-line therapy in *de novo* MET positive, *EGFR*m NSCLC	PFS, DoR, DCR, percentage change from baseline in tumor size, OS, 12m OS rate by Investigator assessment
Subgroup analysis of the efficacy of osimertinib plus savolitinib or osimertinib monotherapy as first-line therapy in patient population identified by different testing platforms	ORR, PFS, DoR, DCR, percentage change from baseline in tumor size, OS, 12m OS rate by Investigator assessment
Safety objective(s)	**Outcome measure**
To evaluate the safety and tolerability of osimertinib and savolitinib in patients with *de novo* MET positive, *EGFR*m NSCLC	AE, SAE, non-serious ADR, AESI, Laboratory test Vital signs Physical examination
Exploratory objective(s)	**Outcome measure**
To assess the efficacy of osimertinib plus savolitinib as second line therapy in *de novo* MET positive, *EGFR*m NSCLC patients progressed on first line osimertinib monotherapy	ORR (Investigator assessment as defined by RECIST 1.1) of osimertinib plus savolitinib in patients progress on first line osimertinib monotherapy
To explore potential molecular resistance mechanism by plasma biomarker analysis at disease progression.	Genetic alteration changes at disease progression
To collect longitudinal plasma samples for the exploration of the correlation of genetic variation and/or ctDNA clearance with treatment response	Longitudinal changes of genetic variation and/or ctDNA clearance compared with treatment response.

4 STUDY DESIGN

4.1 Overall Design

This is a phase II, pilot, randomized, open-label, two arm, multicenter, interventional study assessing the efficacy and safety of osimertinib with or without savolitinib as first line treatment in Chinese patients with *de novo* MET positive, *EGFR*-mutant locally advanced or metastatic NSCLC.

Approximately 44 participants will be randomized to receive osimertinib with or without savolitinib in this study to ensure that approximately 40 evaluable participants complete the study, based on assumption of 10% participants not complete the study.

Participants will be randomised in a 1:1 ratio to 1 of the following intervention groups.

- Cohort 1: osimertinib, 80mg, daily, P.O.
- Cohort 2: osimertinib 80mg daily, P.O. and savolitinib 300mg BID, P.O.

This study consists of the following phases.

Screening: Prospective testing of tumor tissue to determine MET positivity by IHC,FISH or NGS results using tumor tissue should be performed. In patients confirmed as MET positive (MET +), MET+ is defined as a) high expression of MET (by IHC, 3+ in ≥75% of tumor cells) and/or b) increased MET gene copy number (by FISH, *MET* gene copy ⩾5 or *MET* / CEP7 ratio ≥2; or by tissue NGS, ⩾20% tumour cells, ⩾200x sequencing depth of coverage and CN ≥5). Local IHC, FISH and pre-existing local NGS results are acceptable. When tissue sample is available, central FISH and central NGS confirmation is highly suggested if the MET testing is done at local laboratories. Patients determined to be MET+ will undergo screening during 28 days prior to first administration of study medication to confirm eligibility after screening Informed Consent Form signed.

Treatment period:

All enrolled patients will be randomised in a 1:1 ratio to 1 of the following intervention groups.

- Cohort 1: osimertinib, 80mg, daily, P.O.
- Cohort 2: osimertinib 80mg daily, P.O. and savolitinib 300mg BID, P.O.

Patients will continue to receive study medication in 28-day cycles until objective disease progression, unacceptable toxicity occurs, consent is withdrawn or another discontinuation criteria is met (Section 7).

Plasma samples will be collected longitudinally at baseline, every treatment visit till progression of first line treatment if available for future biomarker analysis and resistance profile exploration.

Patients in Cohort 2 can continue on savolitinib monotherapy (if osimertinib was stopped earlier) or osimertinib monotherapy (if savolitinib was stopped earlier) until objective disease progression or meet any of the discontinuation criteria.

Patients in Cohort 1 should have a MET status confirmation based on IHC, FISH or NGS after progression on first line treatment of osimertinib monotherapy. The definition of MET positivity is the same as above description. Tissue biopsy is the preferred way to do the MET status confirmation, but liquid biopsy (NGS) is also acceptable when tissue re-biopsy is not available. Patients confirmed as MET positive after progression will have the opportunity to receive osimertinib 80mg daily, P.O. in combination with savolitinib 300mg BID, P.O. as second line treatment in 28-day cycles until objective disease progression, unacceptable toxicity occurs, consent is withdrawn or another discontinuation criteria is met (Section 7). Patients who permanently discontinue osimertinib due to any reason other than disease progression, who withdraw informed consent or with any other reasons judged by the investigator to prevent the subject to receive the combination therapy will not be eligible to receive the combination of osimertinib and savolitinib as second line treatment.

The primary analysis for objective response rate (ORR) will be carried out at 12 weeks after last subject in (LSI). The final analysis for PFS/OS will be performed 80% maturity of PFS achieved (36 PFS events, at least 16 PFS events in each cohort) which is estimated to be about 40 months after LSI (12-month enrolment).

Treatment follow-up: End of Treatment (EoT) visit will be scheduled within 14 days after last administration of all study medication. Participants who have discontinued study intervention(s) in the absence of RECIST 1.1-defined confirmed by investigator assessment radiological progression will be followed up with tumor assessments according to the Schedule of Activities (SoA) until RECIST 1.1-defined PD or death regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

Safety follow-up:

After study intervention discontinuation, all participants will be followed up for safety assessments 30 days after their last dose of study intervention (ie, the safety follow-up visit).

For patients who continue to receive treatment beyond the time of the final analysis, investigators are responsible for reporting AE to EC/IRC as per China regulations. The investigators are encouraged to report AEs related to savolitinib and/or osimertinib to AZ spontaneously. Additionally as stated in Section 8.3.2 (Follow-up of AEs and SAEs), any SAE or non-serious AE that is ongoing at the time of the final data cut-off, must be followed up by

the investigator for as long as medically indicated.

Survival follow-up:

All participants will be followed up for survival status after study medication discontinuation every 12 weeks (±7 days) until death, withdrawal of consent, or the end of the study, ie, at the time of final analysis. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. In addition to the survival status, the assessment of anti-cancer and surgical treatments are also required.

See Section 6.7 for a description of assessments following final analysis.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

4.2 Scientific Rationale for Study Design

Refer to Sections 2 and 2.1.

4.2.1 Rationale for study design

Retrospective analyses have demonstrated insufficient anti-tumor activities of EGFR TKI monotherapy in patients with *de novo* MET positive, *EGFR*-mutant advanced NSCLC, but limited data of osimertinib monotherapy in this patient population. Combination of EGFR TKI and MET inhibitor can block both the EGFR signalling pathway and MET/HGF signalling pathway at the same time and may be a better solution in this patient population. There is no prospective data of neither a combination of EGFR TKI and MET inhibitor nor current SoC, osimertinib monotherapy as first-line treatment in patients with *de novo* MET positive, *EGFR*-mutant advanced NSCLC.

This phase II study is designed to explore the preliminary efficacy of osimertinib with or without savolitinib as first line treatment by assessment of ORR in patients with *de novo* MET positive, *EGFR*-mutant advanced NSCLC.

This study is designed to find early signal that whether the combination of osimertinib and savolitinib have trend of better efficacy over osimertinib monotherapy in this patient population, so that there will no statistical comparison between the two cohorts and the efficacy of the two cohorts will be independently evaluated. A minimal sample size of 20 evaluable patients will be ensured to fulfil the primary analysis of ORR in each cohort.

FISH and IHC are the current well used and validated methods to detect *MET* amplification/ overexpression in clinical trials. The definitions of MET positivity based on IHC and FISH as

a) high expression of MET (by IHC, 3+ in ⩾75% of tumor cells) and/or b) increased MET gene copy number (by FISH, *MET* gene copy ⩾5 or *MET* / CEP7 ratio ⩾2, by NGS, ⩾20% tumour cells, ⩾200x sequencing depth of coverage and CN ≥5) are adopted in TATTON and SAVANNAH trials, which will also be used in this study. Tissue NGS can also used to detect *MET* amplification and is the most commonly used detection method of *MET* amplification in China clinical practice currently. While the clinical validation data of NGS is limited in this treatment scenario. Thus NGS will also be adopted in this study to generate the clinical validation data. The inclusion criteria adopted in this study are that patients with MET positivity identified by any of the three detection methods, IHC, FISH or tissue NGS, will be included to ensure that all eligible patients can be enrolled in.

4.2.2 Rationale for endpoints

ORR, PFS, DCR, duration of response (DoR) and percentage change from baseline in tumor size assessed by RECIST 1.1 using investigator assessment and OS are standard measures of clinical activity and are used to assess efficacy in solid tumor clinical studies.

Without prospective data of neither a combination of EGFR TKI and MET inhibitor nor current SoC, osimertinib monotherapy as first-line treatment in patients with *de novo* MET positive, *EGFR*-mutant advanced NSCLC, this phase II, pilot study is designed to explore the preliminary efficacy of osimertinib with or without savolitinib as first line treatment in this patient population, which justifies the choice of ORR as the primary endpoint.

Standard safety parameters will be used to assess the safety and tolerability of study interventions. To evaluate the safety and tolerability of savolitinib in combination with osimertinib, the proportion of patients discontinuing due to any AE and the proportion of patients discontinuing due to AE of hypersensitivity/anaphylaxis may be assessed.

The TATTON data indicate encouraging anti-tumor activity of osimertinib plus savolitinib in patients with *MET*-driven, *EGFR*m NSCLC progressed on prior osimertinib treatment, which clues the adoption of osimertinib plus savolitinib as second line therapy in cohort 1 patients who progress on first line treatment of osimertinib monotherapy after MET status confirmation, and the efficacy of osimertinib plus savolitinib in second line will be assessed by ORR as the exploratory endpoint in this study if applicable. Resistance profile of first line treatments and translational analysis of the correlation of genetic variation and/or ctDNA clearance with treatment response will also be explored in this study if applicable.

4.3 Justification for Dose

The recommended daily dose of osimertinib (80 mg od) adopted in this study is the approved dose for first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations.

Preclinical PK-PD modelling suggests that greater target engagement with near complete inhibition of the MET for the duration of the dosing interval may optimize efficacy of savolitinib. If the near complete inhibition is maintained for a higher proportion of patients, it is hypothesized that it could increase the response in this combination.

Based on the interim analysis and preclinical PK-PD analyses from ongoing SAVANNAH study, it is considered that evaluation of savolitinib 300 mg bid (where near complete target inhibition is likely for all patients) in combination with osimertinib (80 mg od) is warranted. Evaluation of 300 mg BID may help to better understand the impact of dose/dosing regimen and exposure on efficacy and safety of savolitinib in this combination treatment. Whilst savolitinib 300 mg bid has not been previously tested in combination with osimertinib, savolitinib bid has been tested as monotherapy in approximately 80 patients, with 6 patients receiving 600 mg bid, and 62 patients receiving 500 mg bid, with no observed dose limiting toxicities.

Based on SAVANNAH IA1 results for Savolitinib; overall ORR for 600mg dose regimen of [38.5% (5/13)] compared to [18.2% (6/33)] for the 300mg dose regimen. Hence the introduction of a new dose regimen of 300mg BID based on Savolitinib short half-life of 3 hours to provide sustained greater concentration, in effect maintain max. target inhibition.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA (including survival follow-up).

The study may be stopped if, in the judgment of sponsor, study participants are placed at undue risk because of clinically significant findings.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA or 80% of subjects progress on first line therapy (32 PFS events, 16 PFS events in each cohort) or at least three years of follow-up after LSI, whichever comes earlier.

See Section 6.7 for details on participant management following the final analysis as well as following study completion.

5 STUDY POPULATION

The target population of interest in this study is participants with *de novo* MET positive, *EGFR*-mutant locally advanced or metastatic NSCLC.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known

as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be enrolled on the study. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements will be referred as screen failures, for detailed description please refer to Section 5.4.

In this protocol, "Enrolled" patients are defined as those who sign informed consent for the main study and are confirmed as eligible for the study.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed consent

1 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2 Provision of signed and dated, written ICF prior to any mandatory study specific procedures, sampling, and analyses.

Age

3 Participant must be ≥18 years at the time of signing the ICF. All genders are permitted.

Type of Participant and Disease Characteristics

4 Histologically or cytologically confirmed locally advanced or metastatic *EGFR*m+ NSCLC harbouring an EGFR mutation known to be associated with EGFR-TKI sensitivity.

5 Has not received any systemic treatment of advanced NSCLC.

- Prior adjuvant/neo-adjuvant therapy completed > 6 months before screening is allowed.

6 MET amplification/high expression as determined by FISH, IHC or NGS testing on tumor tissue collected before any systemic treatment in first line.

- MET high expression by IHC, 3+ in ≥75% of tumor cells
- increased MET gene copy number by FISH, *MET* gene copy ≥5 or *MET* / CEP7 ratio ≥2; or by tissue NGS, ≥20% tumour cells, ≥200x sequencing depth of coverage and CN ≥5.
- Local IHC, FISH and pre-existing local NGS results are acceptable, central FISH and central NGS confirmation is highly suggested if tissue sample available.

7 WHO or Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 with no deterioration over the previous 2 weeks prior to baseline or day of first dosing and a minimum life expectancy of 12 weeks.

8 At least 1 lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and is suitable for accurate repeated measurements.

9 Adequate haematological function defined as:

- Haemoglobin ≥8.5 g/dL (no transfusion in the past 2 weeks).
- Absolute neutrophil count ≥1.5×10^9/L.
- Platelet count ≥100,000/μL (no transfusion in the past 10 days)

10 Adequate liver function defined as:

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN) with total bilirubin (TBL) ≤ ULN
- OR TBL >ULN to ≤1.5x ULN with ALT and AST ≤ ULN

11 Adequate renal function defined as a creatinine <1.5 times the institutional ULN OR a glomerular filtration rate ≥50 mL/min, as assessed using the standard methodology at the investigating centre (eg, Cockcroft-Gault, Modification of Diet in Renal Disease or Chronic Kidney Disease-Epidemiology Collaboration formulae, ethylenediaminetetraacetic acid clearance or 24-hour urine collection). Confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN.

12 Adequate coagulation parameters, defined as:

- International Normalisation Ratio (INR) <1.5 x ULN and activated partial thromboplastin time <1.5 x ULN unless patients are receiving therapeutic anti-coagulation which affects these parameters.

13 Patients with known tumor thrombus or deep vein thrombosis are eligible if clinically stable on low molecular weight heparin (LMWH) for ≥2 weeks.

14 Ability to swallow and retain oral medications.

15 Willingness and ability to comply with study and follow-up procedures.

Reproduction

16 Females must be using highly effective contraceptive measures (see Section 5.3.2), and have a negative pregnancy test (serum) for women of childbearing potential, or must have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:

- Post-menopausal is defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.
- Women under the age of 50 years would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle stimulating hormone levels in the post-menopausal range for the institution.
- Women with documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

- Further information is available in Appendix F (Contraception Requirements).

17 Male patients with a female partner of childbearing potential should be willing to use barrier contraception during the study and for 6 months following discontinuation of study drug. Patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 As judged by the investigator, active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (eg, ulcerative disease, uncontrolled nausea, vomiting, diarrhoea Grade ≥2, malabsorption syndrome or previous significant bowel resection).

2 Any of the following cardiac diseases currently or within the last 6 months:
- Unstable angina pectoris
- Congestive heart failure (New York Heart Association [NYHA] ≥Grade 2)
- Acute myocardial infarction
- Stroke or transient ischemic attack
- Uncontrolled hypertension (BP ≥150/95 mmHg despite medical therapy).
- Mean resting correct QT interval (QTcF) >470 msec for women and >450 msec for men at Screening, obtained from 3 ECGs using the screening clinic ECG machine derived QTcF value.
- Any factors that may increase the risk of QTcF prolongation or risk of arrhythmic events such as heart failure, electrolyte abnormalities (including: Serum/plasma potassium < LLN; Serum/plasma magnesium < LLN; Serum/plasma calcium < LLN), congenital or familial long QT syndrome, family history of unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medication known to prolong the QT interval and cause Torsade de Pointes.

- Any clinically important abnormalities in rhythm, conduction or morphology of resting ECGs, eg, complete left bundle branch block, third degree heart block, second degree heart block, P-R interval >250 msec.
- Acute coronary syndrome

3 Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy.

4 Major surgical procedures ≤28 days of beginning study drug or minor surgical procedures ≤7 days. No waiting is required following port-a-cath placement.

5 As judged by the investigator, any evidence of severe or uncontrolled systemic diseases, including renal transplant, active bleeding diatheses or uncontrolled hypertension, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol.

6 Active hepatitis B (HBV) (positive HBV surface antigen [HBsAg] result) or hepatitis C (HCV). Viral testing is not required for assessment of eligibility for the study. Patients with a past or resolved HBV or HCV infection are eligible if:

- Negative for HBsAg and positive for hepatitis B core antibody [anti-HBc] or
- Positive for HBsAg, but for >6 months have had normal transaminases and HBV DNA levels between 0 to 2000 IU/mL (inactive carrier state) and willing to start and maintain antiviral treatment for at least the duration of the study.
- HBV DNA levels >2000 IU/mL but on prophylactic antiviral treatment for the past 3 months and will maintain the antiviral treatment during the study.
- Patients with positive HCV antibody are eligible only if the polymerase chain reaction is negative for HCV ribonucleic acid.

7 Presence of other active cancers, or history of treatment for invasive cancer, within the last 5 years. Patients with Stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (ie, non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.

8 Unresolved toxicities from any prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment/randomization with the exception of alopecia

9 Spinal cord compression or brain metastases unless asymptomatic, stable, and not requiring steroids for at least 2 weeks prior to start of study intervention. Subjects with leptomeningeal metastases are ineligible.

10 Past medical history of ILD/pneumonitis, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.

11 Known serious active infection including, but not limited to, tuberculosis, or human immunodeficiency virus (positive human immunodeficiency virus 1/2 antibodies). Testing is not required for assessment of eligibility for the study..

12 Known history of liver fibrosis/cirrhosis.

13 Known contraindications to osimertinib administration.

14 Known hypersensitivity to the active or inactive excipients of osimertinib or savolitinib or drugs with a similar chemical structure or class.

Prior/Concomitant Therapy

15 Prior exposure to HGF/MET inhibitors, e.g., foretinib, crizotinib, cabozantinib, merestinib, onartuzumab, capmatinib, tepotinib, etc..

16 Prior exposure to EGFR TKI.

17 Patients currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be strong inducers of CYP3A4, strong inhibitors of CYP1A2, within 2 weeks of the first dose of study treatment (3 weeks for St John's Wort) will be excluded. All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4 during the study and for 3 months later the last dose intake.

Prior/Concurrent Clinical Study Experience

18 Participation in another clinical study with a study interventional medication administered within five half-lives of the compound or 3 months, whichever is greater or investigational medicinal device administered in the last 30 days prior to randomisation/first dose of study intervention or concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

Other Exclusions

19 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

20 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.

21 For women only-Currently breastfeeding.

22 Previous enrolment in the present study.

23 Without civil capacity or with restricted civil capacity.

24 Any other reasons judged by the leading investigator to prevent the subject from participating in this study

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Osimertinib should be taken with water, with or without food. Savolitinib should be taken within 15 minutes after the start of a meal. Osimertinib and savolitinib can be taken together.

5.3.2 Pregnancy and contraception

Women of childbearing potential

Females of childbearing potential should use reliable methods of contraception from the time of screening until 6 weeks after discontinuing study treatment. Acceptable methods of contraception include full abstinence, tubal ligation, combined oral, transdermal or intra-vaginal hormonal contraceptives, medroxyprogesterone injections, copper-banded intra-uterine devices, hormone impregnated intra-uterine systems and vasectomised partners. All methods of contraception (with the exception of total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse.

Males

Male patients must use a condom during sexual intercourse with a female partner of childbearing potential during the study and for 24 weeks after discontinuing study treatment. If the partner is not of childbearing potential, male patients should use a condom during the trial and for 5 elimination half-lives afterwards (48 hours after last dose of savolitinib) with all sexual partners.

Male patients should refrain from donating sperm from the start of dosing until 24 weeks after discontinuing study treatment.

5.3.3 Other lifestyle restrictions

For patients on treatment of savolitinib, during the study therapy and for 4 weeks after the last dose of study treatment patients should be advised to avoid prolonged exposure to the sun, wear protective clothing, a hat and seek shade from the sun as far as possible; in addition SP30+ sunscreen should be used. Exposure to other sources of ultraviolet light including sun beds and tanning booths, etc, should be avoided.

Patients should not donate blood or blood products during the study.

If medically feasible, patients taking regular medication, with the exception of strong inducers of CYP3A4, should be maintained on their regular medication throughout the study period. Patients taking concomitant medications whose disposition is dependent upon BCRP and/or P-glycoprotein (Pgp) with a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst

receiving osimertinib. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Appendix G “Concomitant Medications”).

Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.

Patients who have received prior treatment with immune-oncology (IO) therapies should be closely monitored for an appropriate period of time after the last dose of the IO treatment, in accordance with the respective IO label, as immune mediated adverse reactions with the IO therapy may occur at any time during or after discontinuation of therapy. The stop date of the prior IO drug therapy should be captured in the case report forms.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSOR) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse event (AE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a single time. Rescreened participants should be assigned the same participant number (ie, E-code) as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

These participants should have the reason for study withdrawal recorded in the electronic Case Report Form (eCRF).

Participant enrolment and randomisation is described in Section 6.3.

6 STUDY INTERVENTION

Study treatment is defined as any IP(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to osimertinib and/or savolitinib.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Dose modifications are described in Section 6.6.

Table 3 Investigational Products

ARM Name	Cohort 1	Cohort 2	
Intervention Name	Osimertinib	Osimertinib	Savolitinib
Type	Drug	Drug	Drug
Dose Formulation	80 mg osimertinib QD (1 ×80 mg tablet once daily) 40 mg osimertinib tablets are available if a dose reduction is required	80 mg osimertinib QD (1 ×80 mg tablet once daily) 40 mg osimertinib tablets are available if a dose reduction is required	300 mg savolitinib BID (3 ×100 mg tablets twice daily)
Route of Administration	Oral	Oral	Oral
Use	Osimertinib will be administered once daily with or without food except. Doses should be taken approximately 24 hours apart at the same time point each day. Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the scheduled dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their study drug, they should not make up for this dose, but should take the dose at the next scheduled time.	Osimertinib will be administered once daily with or without food except. Doses should be taken approximately 24 hours apart at the same time point each day. Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the scheduled dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their study drug, they should not make up for this dose, but should take the dose at the next scheduled time.	Savolitinib will be taken twice a day within 15 minutes after the start of a meal. Doses should be taken approximately 12 hours apart at the same time point each day. Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 6 hours, it is acceptable to take the dose. If it is more than 6 hours after the scheduled dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their study drug, they should not make up for this dose, but should take the dose at the next scheduled time.
IMP and NIMP	NIMP	NIMP	IMP
Sourcing	Provided centrally by the Sponsor or locally by the study site.	Provided centrally by the Sponsor or locally by the study site.	Provided centrally by the Sponsor or locally by the study site.

Packaging and Labelling	Study treatment will be provided in HDPE bottles with child resistant closures. Each package will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Study treatment will be provided in HDPE bottles with child resistant closures. Each package will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Study treatment will be provided in HDPE bottles with child resistant closures. Each package will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.
Provider	AstraZeneca	AstraZeneca	Hutchison Whampoa

Duration of Treatment

Participants will continue to receive study medication in 28-day cycles until objective disease progression, unacceptable toxicity occurs, consent is withdrawn or another discontinuation criteria is met (Section 7).

Participants in the cohort 1 group will receive osimertinib 80mg daily plus savolitinib 300mg BID as second line therapy until subsequent disease progression after RECIST 1.1-defined radiological progression on first line treatment of osimertinib after MET status confirmation.

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.3 Measures to Minimise Bias: Randomisation

Participant Enrolment and Randomisation

This is two arm, open label study. Once the subjects meet all the inclusion criteria and do not meet any exclusion criteria, the investigator or his representative will use the Guangdong Clinical Trial Association (CTONG) Randomized Grouping Program Software(CTONG RGPS) for research treatment allocation. Minimization of dynamic randomization method is used with smoking status (yes, no) and EGFR mutation status (19 exon, 21 exon, other mutations) setting as covariate factors. Randomization is implemented to ensure objective

allocation to cohort 1 (osimertinib monotherapy) and cohort 2 (osimertinib plus savolitinib) to avoid any influence of subject characteristics on treatment decisions.

Study using CTONG RGPS	All participants will be centrally assigned to randomised study intervention using the CTONG RGPS. Before the study is initiated, please refer to the CTONG Randomization Grouping Procedure User Guide. Study intervention will be dispensed at the study visits summarised in SoA. Returned study intervention should not be re-dispensed to the participants.

If a participant withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn participants will not be replaced.

Investigators should keep a record (ie, the participant screening log) of participants who entered screening.

At screening (Days -28 to -1), the investigators or suitably trained delegate will:

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the participant.
- Screening begins after the informed consent form signed and the date recorded, participants will be identified to CTONG RGPS. Obtain a unique 5-digit enrolment number (E-code), through the CTONG RGPS in the following format (NNXXX, NN being the centre number, and XXX being the participant enrolment code at the centre). For example, 01001, please note: 01 for a centre, participant enrolment code is consecutive. This number is the participant's unique identifier and is used to identify the participant on the eCRFs. And the numbers should be assigned in consecutive order. All screened subjects are assigned an electronic code, regardless of whether they are subsequently randomized to study treatment.
- Determine participant eligibility (see Sections 5.1 and 5.2).
- Obtain sample of eligible patients and send for centralised MET FISH and/or tissue NGS testing.

At randomisation, once the participant is confirmed to be eligible, the investigator or suitably trained delegate will:

- Assign a randomised treatment group via the CTONG RGPS. Randomisation codes will be assigned strictly sequentially within each stratum and country as participants become eligible for randomisation. The system will randomise the eligible participant to 1 of the two treatment groups.

Participants will begin treatment on Day 1. Participants must not be randomised and treated unless all eligibility criteria have been met.

Procedures for Handling Incorrectly Enrolled or Randomised Participants

Participants who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Participants who are enrolled but subsequently found not to meet all the eligibility criteria must not be randomised or started on study intervention and must be withdrawn from the study.

Where a participant does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the investigator should inform the sponsor immediately, and a discussion should occur between the sponsor and the investigator regarding whether to continue or discontinue the participant from treatment. The sponsor must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant.

Methods for Assigning Treatment Groups

The block randomisation method will be used for this study. The actual treatment given to participants will be determined by the randomisation scheme in the CTONG RGPS. The randomisation scheme will be produced by a computer software programme that incorporates a standard procedure for generating randomisation numbers. One randomisation list will be produced for each of the randomisation strata. .

Methods for Ensuring Blinding

This is an open-label study, not applicable.

6.4 Study Intervention Compliance

The study medication should only be used as directed in this protocol. Details of treatment with study medication for each patient will be recorded in the appropriate sections in the eCRF.

Compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets/capsules, etc. during the site visits and documented in the source documents and eCRF.

A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, dose reductions and/or dose discontinuations will also be recorded in the eCRF.

Patients should return all unused medication and empty containers to the investigator.

The study personnel at the investigational site will account for all drugs dispensed and for appropriate destruction. Certificates of delivery and destruction should be signed.

It is the investigator/institution's responsibility to establish a system for handling study treatments, including IPs, so as to ensure that:

- Deliveries of such products from AstraZeneca or its representative are correctly received by a responsible person.
- Such deliveries are recorded.
- Study treatments are handled and stored safely and properly as stated on the label.
- Study treatments are only dispensed to study patients in accordance with the protocol.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed, the quantity and date of dispensing and unused study treatment returned to the investigator. This record is in addition to any drug accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist, and copies retained in the investigator site file.

6.5 Concomitant Therapy

Any concomitant treatment, procedure, or other medication considered necessary by the investigator for the participant's safety and wellbeing, or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving within 4 weeks prior to the first dose of study intervention, during the study and until the 28-day follow-up period following the last dose of study intervention must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Medication other than that described in Table 5, including denosumab, corticosteroids and/or bisphosphonates for the treatment of bone metastases, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

Table 5 Prohibited medications

Prohibited medication/class of drug:	
Herbal preparations/medications	These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (three weeks for St John's wort).
Strong CYP3A4 inducer or strong CYP1A2 inhibitors	Strong inducer of CYP3A4 and strong inhibitors of CYP1A2 must not be taken within 2 weeks of the first dose of study treatment, during the study and for 3 months after the last dose of osimertinib.

The use of medications listed in Table 6 is restricted, these medications are permitted with caution and careful monitoring of patients.

Table 6 Restricted medications

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed)**
Paracetamol	The administration of acetaminophen (paracetamol) to a patient is restricted to 3 g per day or the maximum dose approved locally (if less than 3 g/day) during the study.
Sensitive CYP2C8 substrates	Those drugs defined as sensitive CYP2C8 substrates (almost exclusively metabolised by CYP2C8, such as repaglinide and rosiglitazone) should be used with caution.
Drugs affected by P-glycoprotein	Drugs that are known to be affected by P-glycoprotein such as digoxin, quinidine, loperamide, ritonavir and saquinavir should be used with caution.
Metformin	Use with caution, monitor patients for the effect of increased metformin exposure.
Adefovir, lamivudine and tenofovir	Use with caution, monitor patients for the effect of increased exposure.

Table 6 Restricted medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed)
Drugs whose disposition is dependent upon the Breast Cancer Resistance Protein	Patients taking concomitant medications whose disposition is dependent upon the Breast Cancer Resistance Protein and with a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib. Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to Breast Cancer Resistance Protein-mediated increase in exposure). If the patient experiences any potentially relevant adverse events suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.
Drugs prolonging QT interval	The concomitant administration of drugs known to prolong QT interval is restricted unless considered essential due to patient management, in which case, patients should be closely monitored with more frequent ECGs. Additional guidance on drugs known to prolong QT interval is provided in Appendix G. The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with osimertinib: Aclarubicin, anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine, terlipressin, cilostazol, cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, sotalol, roxithromycin, sevoflurane, sparfloxacin, thioridazine, Azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine, donepezil, terodiline, levomethadyl, methadone, pimozide, arsenic trioxide, ibogaine, pentamidine, astemizole, probucol, vandetanib, amiodarone, chloroquine. See Appendix G.

Table 6 Restricted medications

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed)**
Drugs that may possibly prolong QT interval	Patients receiving drugs that prolong QT interval or may increase the risk of TdP from other TdP risk categories can be enrolled, notwithstanding other exclusions and restrictions, if these drugs are considered essential for patient management and the patient has been stable on therapy. Close monitoring of ECGs and electrolytes is recommended. See Appendix G.

Table 6 Restricted medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed)
Drugs prolonging QT interval	The following drugs are known to prolong QT interval or induce Torsades de Pointes and required wash-out periods prior to savolitinib initiation: Minimum 2 days' withdrawal period on medication prior to savolitinib start: anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine, terlipressin. Minimum 7 days' withdrawal period on medication prior to savolitinib start: cilostazol, Cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine. Minimum 14 days' withdrawal period on medication prior to savolitinib start: azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine. Minimum 3 weeks' withdrawal period on medication prior to savolitinib start: donepezil, terodiline. Minimum 4 weeks' withdrawal period on medication prior to savolitinib start: levomethadyl, methadone, pimozide. Minimum 6 weeks' withdrawal period on medication prior to savolitinib start: arsenic trioxide*, ibogaine. Minimum 8 weeks' withdrawal period on medication prior to savolitinib start: pentamidine. Minimum 4 months' withdrawal period on medication prior to savolitinib start: astemizole, probucol, vandetanib. Minimum 1 year's withdrawal period on medication prior to savolitinib start: amiodarone, chloroquine.

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

Guidance on medicines to avoid, medications that require close monitoring, and washout periods is provided in Appendix G.

Rescue Medicine

The study site will not supply specify type rescue medication. The study will be conducted at

clinical research centres where researchers were trained in basic or emergency life support. If an allergic reaction occurs, the research centre can provide relevant equipment and drugs (epinephrine and prednisolone, etc.)

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 Dose Modification

Dose modifications of one or both agents are decided by the investigator (following discussion with AstraZeneca when needed) based on the type of AEs and the known adverse drug reactions for each drug. In case a dose reduction is necessary, the study treatments will be administered as follows:

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of study drug, as appropriate unless symptoms are associated with hypersensitivity (see Section 8.4.2).

Dose reductions or holds are allowed as clinically indicated by the treating physician per local practice and in line with Table 8. No dose re-escalations are allowed. Guidance on dose level reduction is presented in the table below.

Table 7 Dose reduction for osimertinib to manage adverse events

Starting osimertinib dose	**80 mg**
Reduced dose -1	40 mg

Table 8 Dose reduction for savolitinib to manage adverse events

Starting savolitinib dose	**300 mg bid**
Reduced dose -1	200 mg bid
Reduced dose -2	100 mg bid

Note: Only 2 dose reductions of savolitinib are permitted.

For guidance on dose modifications for management of AEs for osimertinib and savolitinib, see Section 8.4..

6.7 Intervention after the End of the Study

After the PFS analysis, the clinical study database will be locked. Patients receiving study treatment at the time of the final data cut can continue to receive study treatment (either combination or monotherapy) which follow local clinical practice until disease progression occurs again, unacceptable toxicity occurs or death.

Patients who remain on study treatment after the final analysis will be monitored according to routine clinical practice as defined by the investigator.

The investigators are encouraged to report AEs related to savolitinib and/or osimertinib to AZ spontaneously.

Osimertinib and savolitinib are only free for subjects during study period, once the study is completed, even if the Investigator judges that the patient can still benefit from the study treatment, osimertinib and savolitinib cannot be provided free of charge for patients.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention(s). The investigator should instruct the participant to contact the site before or at the time if study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

Participants who have permanently discontinued from further receipt of study intervention(s) will need to be discontinued from the IVRS. All study intervention(s) should be returned by the participant at their next on-site study visit or unscheduled visit.

Participants may be discontinued from study intervention(s) in the following situations:

- RECIST 1.1-defined radiological progression (refer to Section 8.1.1 and Appendix E).
- Investigator determination that the participant is no longer benefiting from study intervention.
- An AE that, in the opinion of the investigator, contraindicates further dosing.
- Any AE that meets criteria for discontinuation defined in the dose modification guidelines for management of study intervention-related toxicities (see Section 6.6).
- Any AE of grade ≥3 that does not resolve to grade ≤ 2 after 3 weeks of withholding osimertinib.
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment. A participant who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.2).

- Severe non-compliance with the CSP as judged by the investigator.
- Pregnancy or intent to become pregnant.
- Specific stopping criteria ie, ILD, acute anaphylaxis or QTcF interval prolongation with signs/symptoms of serious arrhythmia.

Note that discontinuation from study intervention(s) is NOT the same thing as a withdrawal from the study.

Continuing on monotherapy.

If a participant discontinues treatment with one of the combination agents due to toxicity, they may continue with osimertinib or savolitinib in monotherapy as long as they are continuing to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria.

Participants who have discontinued study intervention(s) prior to objective RECIST 1.1-defined radiological progression, regardless of whether or not they have commenced subsequent anticancer therapy, will be followed up with tumor assessments as indicated in the SoA until RECIST 1.1-defined PD or death, unless they have withdrawn all consent to study-related assessments.

See the SoA for data to be collected at the time of intervention discontinuation (ie, the end-of-treatment visit) and follow-up and for any further evaluations that need to be completed.

7.1.1 Rechallenge

See guidance in Appendix H for circumstances under which a patient whose study treatment was temporarily interrupted due to an AE can restart treatment.

7.1.2 Follow-up of Participants Post Discontinuation of Study Intervention

All participants who discontinue the study intervention will be followed up for safety assessments 30 days after their last dose of study intervention. Additional assessments to be performed at the time of the 30-day safety follow-up are detailed in the SoA.

Discontinuation of study treatment(s), for any reason, does not impact on the patient´s participation in the study. The patient should continue attending subsequent study visits and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to

modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.1.3 Follow-up for Survival

Participants will be followed up for survival status as indicated in the SoA until withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the participant or the participant's family, or by contact with the participant's current physician.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options to ensure the collection of endpoints and safety information including new AEs and follow-up on any ongoing AEs and concomitant medications (eg, telephone contact at 30 days (±7 days) after study intervention is discontinued, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she is still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits for three times of continuous and is unable to be contacted by the study site.

Participants who decline to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up."

Investigators should document attempts to re-establish contact with missing participants throughout the study period. If contact with a missing participant is re-established, the participant should not be considered lost to follow-up and evaluations should resume according to the protocol.

The following actions must be taken if a participant fails to return to the clinic for a required

study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study the patient should be considered to be lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA. Data collection following study analysis until the end of the study is described below.

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

8.1.1 CT and MRI scans tumor assessments (RECIST 1.1)

RECIST 1.1 guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumor response criteria are presented in Appendix E of this Clinical Study Protocol.

Baseline tumor assessments should include CT/MRI of chest and abdomen (including liver and adrenal glands) and should be performed within 28 days before treatment start, and ideally as close as possible to the start of study treatment.

Follow-up assessments should be performed at Week 4 (±7 days) after the start of treatment, and then every 8 weeks(±7 days) until objective disease progression as defined by RECIST 1.1 even if a patient discontinues treatment prior to progression (unless they withdraw consent). Any other regions suspected, or with known metastasis at baseline, will be assessed by imaging and recorded at baseline. The same imaging modality and the same assessment should be performed at baseline and at all subsequent assessments.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled visit ±1 week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients will be evaluated until objective radiological disease progression by RECIST as per the SoA (Appendix E).

Categorization of objective tumor response at each visit will be based on the RECIST 1.1 guidelines for response: complete response (CR), partial response (PR), stable disease (SD) and progression of disease (PD). For ORR, a visit response of CR or PR must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed.

TL progression will be calculated in comparison to when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

If repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression.

All CT/MRI scans and all imaging assessments performed for RECIST 1.1 tumor assessment will be reviewed at site. Duplicates must be available at the site in readiness to be sent for

retrospective independent central RECIST 1.1 review, if deemed appropriate.

8.1.2 Overall Survival

Assessments for survival will be conducted every 12 weeks following objective PD or treatment discontinuation till End of Study. Survival information may be obtained via telephone contact with the participant, participant's family, by contact with the participant's current physician, or local death registries as described in Section 7.2.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

A physical examination will be performed and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.

Physical examination will be performed at timelines as specified in the SoA; investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.3.5 for details.

8.2.2 Vital Signs

Vital signs (blood pressure [BP], pulse, temperature and respiration rate) will be evaluated according to the SoA (Table 1). Weight will be assessed on Day 1 of each cycle for the first 6 cycles then every 8 weeks after; height will be assessed at screening only.

- Temperature, pulse rate and BP will be assessed.
- Blood pressure and heart rate will be measured preferably using a semi-automatic BP recording device with an appropriate cuff size after 10 minutes rest on a bed. Blood pressure and pulse will be measured as per study plan and as clinically indicated thereafter.
- Vital sign measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).
- Measurements will be taken in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic BP, and pulse.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.5.

8.2.3 Electrocardiograms

ECGs will be collected centrally.

- 12-lead ECG will be obtained as outlined in the SoA (Table 1) using an ECG machine that automatically calculates the heart rate and measures RR, P-R, QRS, QT, and QTcF intervals.

- Triplicate ECGs will be obtained after the patient has been rested in a semi-supine position for at least 5 minutes. The 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes. ECGs will be recorded at 25 mm/sec.

- All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal/not clinically significantly abnormal. If there is a clinically significant abnormal finding during the treatment period, the investigator will record it as an AE on the eCRF, according to standard AE collection and reporting processes. A 28 day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality. The original ECG traces must be stored in the patient medical record as source data.

- QTcF evaluation will be done based on triplicate 12 lead ECGs during the screening period, every week in the first cycle, every cycle thereafter, C3D1 (pre-dose, 1, 3, 4 and 6 hours post dose) and at the end of treatment as indicated in the study plan. A 30-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

Situations in which ECG results should be reported as AEs are described in Section 8.3.5.

8.2.4 Echocardiogram/MUGA

An Echocardiogram or MUGA scan to assess LVEF will be performed at screening (prior to first dose of osimertinib) and at least every 16 weeks throughout the treatment period. The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans. The patients should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

8.2.5 Clinical Safety Laboratory Assessments

See Table 9 for the list of clinical safety laboratory tests to be performed and the SoA (Table 1) for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the SoA.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following laboratory variables will be measured.

Table 9 Laboratory Safety Variables

Haematology/Haemostasis (Whole Blood)	Clinical Chemistry (Serum or Plasma)
Haemoglobin	Creatinine
Leukocyte count	Bilirubin, total
Leukocyte differential count (absolute count)	Alkaline phosphatase
Platelet count	AST
Absolute neutrophil count	ALT
Absolute lymphocyte count	Albumin
Total white blood cell count	Potassium *
Total red blood cell count	Calcium, total
Haematocrit	Sodium *
	Magnesium *
	Blood creatine phosphokinase (CPK)
	Amylase
Urinalysis	Gamma-glutamyl transferase
Haemoglobin/Erythrocytes/Blood	Glucose
Protein/Albumin	Lactate dehydrogenase
Glucose	Protein, total
Ketones	Urea nitrogen/blood urea nitrogen
Leukocyte esterase	Coagulation variables (aPTT, PTT, and INR)

*: In light of the potential for QT changes associated with osimertinib, electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) must be corrected to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment
ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; INR=international normalised ratio; PTT=partial thromboplastin time.

The investigator should assess the available results with regard to clinically relevant abnormalities in documentation. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.5.

All participants with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study intervention must be followed and have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.2.6 Other Safety Assessments

8.2.6.1 Pregnancy assessments

A pregnancy test on urine or blood sample will be performed for pre-menopausal women of childbearing potential, at the study screening visit, and prior to the first dose of study drug on Cycle 1 Day 1, Day 1 of every cycle and at treatment discontinuation. Tests will be performed by the institutional laboratory. If results are positive, the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated and if positive, the patient will be discontinued from study treatment immediately.

8.2.6.2 WHO/ECOG Performance Status

WHO/ECOG performance status will be assessed at the times specified in the SoA based on the following:

4 Fully active; able to carry out all usual activities without restrictions.

5 Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work).

6 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.

7 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.

8 Completely disabled; unable to carry out any self-care and totally confined to bed or chair.

9 Dead.

Any significant change from baseline or screening must be reported as an AE.

8.3 Adverse Events and Serious Adverse Events

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, recording, and reporting events that meet the definition of an AE.

Definition of adverse drug reactions (ADR)

An Adverse Drug Reaction (ADR) is an Adverse Event suspected to be causally related to the investigational products.

An ADR is a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure.

Adverse Events (AEs) for malignant tumours

Adverse Events (AEs) for new malignant tumours (i.e., it is not the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumour under study) reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history, and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy For studies in Early Stage and Late Stage Immuno-Oncology and Oncology Studies:

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (i.e., it is not the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of

existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of signature of the ICF, throughout the treatment period and until the last follow-up period for safety is completed. The safety follow-up period is defined as 30 days after the last dose of Savolitinib and/or Osimertinib for patients discontinued treatment for disease progression. If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, the safety follow-up period will be defined as the time of confirmed PD. If the time period for the two conditions overlaps, the longer time period will be selected. If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported to AZ as an AE or SAE as applicable. In the survival follow-up period, AEs related to AZ products will be reported spontaneously without recording in CRF. Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.3.12.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

Adverse event variables

The following variables will be collected for each AE;

- AE (verbatim).
- The date when the AE started and stopped.
- CTCAE grade.
- Whether the AE is serious or not (Appendix B).
- Investigator causality rating against the study intervention(s) (yes or no).
- Action taken with regard to study intervention(s).
- AE caused participant’s withdrawal from study (yes or no).
- Administration of treatment for the AE.
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE.

- Date investigator became aware of SAE.
- Seriousness criteria.
- Date of hospitalisation.
- Date of discharge.
- Probable cause of death.
- Date of death.
- Autopsy performed.
- Causality assessment in relation to study procedure(s).
- Causality assessment to other medication.

The grading scales found in the National Cancer Institute CTCAE will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention and each AE, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: "Have you/the child had any health problems since the previous visit/you were last asked?", or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and

there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests, vital signs, physical examinations and ECGs will be summarised in the Clinical Study Report (CSR).

Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs and ECG should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or study intervention interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to PD, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Elevated liver biochemistries (Hy’s Law criteria)

During the course of the study the investigator will remain vigilant for increases in liver biochemistry.

Investigator will follow, assess and record abnormal liver biochemistry results according to HL principle. Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3×ULN together with TBL ≥2×ULN will be reported as SAEs.

Please refer to Appendix I for further instruction on cases of increases in liver biochemistry and evaluation of HL. Please note that not all the processes in the Appendix I are applicable in this study, the Investigators don’t need to follow the unapplicable ones

8.3.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the study intervention is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as PD and not an AE. Events, which are unequivocally due to PD, should not be reported as an AE during the study.

8.3.8 Disease Under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of advanced NSCLC. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study intervention.

8.3.9 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New primary cancers are those that are not the primary reason for the administration of study intervention and are identified after the participant's inclusion in this study. They do not include metastases of the original cancer.

8.3.10 Deaths

All deaths that occur during the study intervention period, or within the protocol-defined follow-up period after the administration of the last dose of study intervention, must be reported as follows:

- Death clearly resulting from PD should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to PD under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined follow-up period after the administration of the last dose of study intervention should be documented in the Statement of Death page. If the

death occurred as a result of an event that started after the defined follow-up period and the event is considered to be due to a late-onset toxicity to study intervention, then it should also be reported as an SAE.

8.3.11 Adverse Events of Special Interest

AESIs are events of scientific and medical interest specific to the further understanding of osimertinib with or without savolitinib safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF.

AESI of Savolitinib includes:

- Hepatic Disorders
- Pyrexia
- Hypersensitivity (Including SJS and Anaphylaxis)
- QTc Prolongation

AESI of Osimertinib includes:

- ILD/Pneumonitis
- QTc prolongation
- Changes in cardiac contractility
- Haematological events
- Erythema Multiforme and Stevens-Johnson syndrome

8.3.12 Safety Data Collection Following the Final Data Cut-off of the Study

For participants continuing to receive study treatment after the final DCO, safety data will not be collected for the purpose of this study. In addition, it is recommended that investigators monitor the participant's safety laboratory results periodically during treatment with study treatment in order to manage AEs, consistent with the dose modification guidelines for management of study intervention-related toxicities (see Section 6.6).

8.3.13 Reporting of Adverse Events

Note: The content of this part may need to be revised because the update of Pharmacovigilance agreement between AstraZeneca and HMPL.

The investigators are responsible for informing the EC and the Regulatory Authority of the adverse events as per China regulations.

The investigators are also responsible for reporting all SAEs within 24 hours after awareness to Sponsor and reporting non-serious ADRs related to investigational products to Sponsor within 5 calendar days after awareness. Investigators should report AESIs which is also a SAE within 24 hours and within 5 calendar days for AESIs of non-serious ADRs (AESIs of Savolitinib and Osimertinib).

For all SAEs, non-serious ADRs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Sponsor of any follow-up information on a previously reported SAE/ non-serious ADR within the same timeframe as initial reports of when he or she becomes aware of it.

Contact information of Sponsor:

E-mail: kary@chinactong.com

8.3.14 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study drug.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.14.1 Maternal Exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the study intervention should be discontinued immediately and the pregnancy reported to AstraZeneca.

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy,

normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

8.3.14.2 Paternal Exposure

Non-sterilised male participants who intend to be sexually active with a female partner of childbearing potential should refrain from fathering a child or donating or banking sperm for the duration of the study (from the time of screening) and for 6 months after the last dose of study intervention.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose of study intervention until 6 months after the last dose of study intervention should be followed up and documented in the medical record and provided to the AstraZeneca Patient Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca.

8.4 Management of IP-related toxicities

8.4.1 Management of osimertinib-related toxicities

Potential osimertinib-related toxicities during the course of the study can be managed by interruption of the dose of osimertinib or dose reductions (see Appendix H Section H 1). Repeat dose interruptions are allowed as required. If a patient experiences a CTCAE Grade 3 (CTCAE version 5.0) and/or unacceptable toxicity, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. If the toxicity resolves or reverts to ≤CTCAE Grade 2 after 3 weeks of onset, treatment with osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg) using the rules in Appendix H Section H 1 and with discussion and agreement with the AstraZeneca Study Team Physician as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose modification. If the toxicity does not resolve to ≤CTCAE Grade 2 after 3 weeks, then the patient should be withdrawn from the study and observed until resolution of the toxicity. Osimertinib can be dose reduced to 40 mg od: if the reduced dose of 40 mg od is not tolerable, no further dose reduction is allowed and study treatment should be discontinued. Once a dose is reduced escalation is not permitted.

Dose modifications are permitted in the management of IP-related toxicities as described in Table 10 with further information being provided in Appendix H Section H 1.

Table 10 Osimertinib dose adjustment information for adverse reactions

Target organ	Adverse reaction[a]	Dose modification
Pulmonary	ILD/pneumonitis	Permanently discontinue osimertinib
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is less than 481 msec or recovery to baseline if baseline is more than 481 msec within 3 weeks of onset, then restart at a reduced dose (40 mg) or at 80 mg (at the discretion of the investigator to allow for situations where causality in relation to osimertinib may be difficult to determine.)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Other	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0 to 2 after withholding of osimertinib for up to 3 weeks	Osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0 to 2 after withholding for up to 3 weeks	Permanently discontinue osimertinib

[a] The intensity of the clinical adverse events graded by the National Cancer Institute CTCAE Version 5.0.
CTCAE Common Terminology Criteria for Adverse Events; ECG Electrocardiogram; ILD Interstitial lung disease; QTcF corrected QT interval using Fridericia's formulas.

8.4.2 Management of savolitinib related toxicities

Potential savolitinib related toxicities during the course of the study can be managed as medically indicated and with interruption of the dose of savolitinib or dose reductions as appropriate, **unless symptoms are associated with hypersensitivity** (see Appendix H Section H 2). Repeat dose interruptions are allowed as required, taking into consideration the additional precautions for restart of savolitinib as illustrated in Appendix H. For each patient the savolitinib dose can be reduced a maximum of 2 times (Table 8). No dose reescalations are allowed.

Dose modification guidelines for savolitinib related toxicities are shown in Table 11. Appropriate and optimal treatment of the toxicity is assumed prior to considering dose modifications.

Table 11 Dose modifications for savolitinib-related toxicities

NCI CTCAE v5.0 toxicity grade	Action
Grade 0, 1 or 2	None
Grade 3[a]	Hold dosing and follow algorithm below

Table 11 Dose modifications for savolitinib-related toxicities

NCI CTCAE v5.0 toxicity grade	Action
• Grade 3 toxicity for ≤7 days and resolves to ≤Grade 2 or baseline within 14 days of onset. • Grade 3 toxicity for >7 days.	• Resume dosing at same dose or 1 reduced dose level (maximum of 2 dose reductions) as clinically appropriate[b] • Discontinue study drug
Grade 4 • Expected to be manageable/reversible with dose reduction • Not expected to be manageable/reversible with dose reduction	• Hold dose and consult with study medical monitor • Discontinue study drug
Recurrence of Grade 3 • Grade 3 toxicity for ≤7 days • Grade 3 toxicity for >7 days.	• Resume dosing at same dose or 1 reduced dose level (maximum of 2 dose reductions) as clinically appropriate[b] • Discontinue study drug
Recurrence of Grade 4	Discontinue study drug

[a] Despite appropriate supportive care
[b] Resumption of savolitinib must follow the specific restart guidelines if the event is a constellation of pyrexia, skin reactions, myalgia, arthralgia, or hypersensitivity, as per Appendix H.

CTCAE Common Terminology Criteria for Adverse Events; ECG Electrocardiogram; NCI National Cancer Institute; QTcF corrected QT interval using Fridericia's formulas.

8.4.3 Management of overlapping toxicities between osimertinib and savolitinib

QTc prolongation

QT prolongation is a recognised toxicity of osimertinib and savolitinib; management of this toxicity is summarised in Table 12.

Table 12. Management of QTc prolongation

CTCAE Grade	Instructions for osimertinib	Instructions for savolitinib	Further investigation required
CTCAE Grade 1 or Grade 2	No action required	No action required	Review concomitant treatments and co-morbidities for risks of QT prolongation or risk for TdP[a]
CTCAE Grade 3	(QTc interval >500 msec or >60 msec change from baseline on at least 2 separate ECGs)	Withhold savolitinib until QTcF interval is <481 msec. If the QTcF resolves to <481 msec in 21 days,	Review concomitant treatments and co-morbidities for risks of QT

	Withhold osimertinib until QTcF interval is <481 msec within 21 days of onset, then restart osimertinib at a reduced dose of 40 mg or 80 mg at the discretion of the investigator.	restart savolitinib at a reduced dose.	prolongation or risk for TdP[a] Consult with cardiologist to validate ECG finding. Ensure cardiac surveillance and take actions in accordance with clinical standards. Regular ECGs performed until resolution to QTcF <481 msec.
	If the QTcF does not resolve to <481 msec in 21 days, discontinue osimertinib.	If the QTcF does not resolve to <481 msec in 21 days, discontinue savolitinib.	Consult with a cardiologist for further management as clinically indicated.
CTCAE Grade 4 (Torsades de pointes; polymorphic ventricular tachycardia; signs and symptoms of serious arrhythmia)	Discontinue osimertinib	Discontinue savolitinib	Consult with a cardiologist for further management as clinically indicated.

Note: One overall evaluation per timepoint should be performed, based on an average of the triplicate readings.
[a] For guidance regarding potential interactions with concomitant medications known to prolong the QT interval, see Table 6 and Appendix G.

CTCAE Common Terminology Criteria for Adverse Events; ECG electrocardiogram; QTcF QT interval calculated using Fridericia's correction; TdP torsades de pointes.

In light of the potential for QT changes associated with osimertinib, electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) must be corrected to within normal ranges prior to first dose and electrolyte levels monitored during study treatment. The QTc interval prolongation potential of savolitinib 600 mg was assessed in a thorough QT study in healthy volunteers. Analysis of the data showed that it was a positive study, as the upper bounds of the 2-sided 90% CI for the mean ΔΔQTcF were up to 13.6 msec and 14 msec, at 4 hours and 5 hours, respectively. QTcF will be assessed frequently on triplicate electrocardiogram (ECG) assessments performed at regular intervals throughout the study according to the SoA (See Table 1).

Erythema multiforme and Stevens-Johnson syndrome
Case reports of EM and SJS have been uncommonly and rarely reported, respectively, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM and SJS. If signs and symptoms suggestive of EM develop,close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interruptedor discontinued immediately.

A case of SJS has been reported in temporal association with savolitinib. Patients who show symptoms or signs suggesting emerging SJS while on study treatment (eg, progressive skin rash often with blisters or mucosal lesions), must discontinue savolitinib immediately and receive appropriate treatment. If emerging SJS is suspected, rechallenge with savolitinib must be avoided.

8.5 Safety mitigation plans

To better mitigate the risk of administration of osimertinib (80 mg qd) plus savolitinib (300 mg bid) in Chinese patients, the study team will take below actions to ensure the wellbeing of patients:

- A full safety assessment will be conducted every 4 weeks according to the SoA. Liver function tests will be performed every week for the first 9 weeks and management of the overlapping toxicities between osimertinib and savolitinib is demonstrated in Section 8.4.3.
- Investigator can add ad hoc safety assessment as medical indicated.
- After FSI, the safety data/events, especially hepatic disorders and hypersensitivity if any, will be summarized on the monthly study meeting for investigators' review and discussion.
- When all of the first enrolled 6 patients have at least 6 weeks follow up, the safety data/events of the 6 patients will be summarized and a safety review meeting involving all investigators and study physician and PV physician from AstraZeneca will be held to determine whether there is any major safety risk or not. If any major safety risk is identified, it is possible to suspend enrolment in an emergency, export all safety data for analysis, and share the analysis results to AstraZeneca global team. According to the discussion and also suggestions from AstraZeneca PV physicians, it will be decided whether to restart the enrolment; the protocol may be amended to ensure the safety of the enrolled patients if necessary.
- If the safety analysis of SAVANNAH reveals certain critical safety signals or major safety risks, the protocol may be amended accordingly if necessary.

8.6 Human Biological Samples

Instructions for the collection, handling, storage and shipping of biological samples will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality.

Samples will be stored for a maximum of 15 years from the end of the study (as defined in the

protocol) in line with consent and local requirements, after which they will be destroyed/repatriated.

- Samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (is earlier), unless consented for future analyses.
  - Samples collected will be stored and disposed of according to local laws and regulations. Additional analyses may be conducted on the anonymised, pooled samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining sample aliquots will be retained at sponsor or its designee for a maximum of 15 years from the end of the study (as defined in the protocol) or according to local laws and regulations. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

For further details on Handling of Human Biological Samples, see Appendix C.

8.7 Human Biological Sample Biomarkers

8.7.1 Collection of Mandatory Samples for Biomarker Analysis

Participant consent to the study includes participation in the mandatory biomarker assessment components of the study. The following samples for biomarker research are required and will be collected from all patients in this study as specified in the SoA (Table 1):

- Tumor biopsy tissue, taken before any systemic treatment of advanced NSCLC will be required at screening to assess eligibility. MET status by IHC, FISH or tissue NGS will be determined at local laboratories or a central laboratory. Local IHC, FISH and pre-existing local NGS results are acceptable. When tissue sample is available, central FISH and central NGS confirmation is highly suggested if the MET testing is done at local laboratories. Additional analyses of predictive biomarkers may also be performed. Tumor sample requirements for biomarker testing will be defined in the supporting Central Laboratory Manual. Provision of tumor biopsy tissue is mandated for patients enrolled using a local NGS result.
- Peripheral blood samples will be collected from eligible subjects prior to study treatment for central laboratory ctDNA NGS testing. The requirements for peripheral blood samples will be defined in the Central Laboratory Manual
- After RECIST 1.1 defined objective radiological progression determined by investigator, both tissue and peripheral blood samples will be collected for central laboratory NGS testing to explore the mechanism of treatment resistance prior to subsequent antitumor

therapy. It is strongly recommended that a second biopsy be performed after progression. If a second biopsy is not available, a peripheral blood sample is required. A MET status re-confirmation in cohort 1 patients who progress on first-line therapy of osimertinib monotherapy before receive a second-line therapy of osimertinib plus savolitinib is also required. Tissue biopsy (based on IHC, FISH and/or NGS) is the preferred way to do a secondary MET status confirmation, but liquid biopsy (NGS) is also acceptable when tissue re-biopsy is not available.

Sampling should be undertaken by experienced physicians in appropriate medical facilities in accordance with standard clinical practice for subjects with advanced NSCLC.

Patients will only undergo biopsy when the risks are considered medically acceptable by their caring physicians. Where possible, high-risk sites (such as brain, pancreas etc) should be avoided.

For further details on Handling of Human Biological Samples, including storage, re-use and destruction, refer to Appendix C and the Laboratory Manual.

8.7.2 Collection of Optional Biomarker Samples

Collection of optional samples for biomarker assessment is also part of this study as specified in the SoA (Table 1):

- Blood samples for circulating DNA will also be collected from enrolled patients during study treatment till objective radiological progression to monitor dynamic changes in molecular biomarkers, including, but not limited to, MET gene copy number and EGFR mutations, etc., to evaluate their association with the observed clinical responses and prognosis.

Please note that the collection of these samples is optional and informed consent of the optional biomarker sample collection is required before the collection of samples. Dynamic and continuous collection of peripheral blood samples at every tumor assessment (RECIST 1.1) visit is recommended, but the actual collection of peripheral blood samples will be based on the willingness of the subjects and the judgment of the investigator.

For further details on Handling of Human Biological Samples, including storage, re-use and destruction, refer to Appendix C and the Laboratory Manual.

8.7.3 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the last patient's last visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by sponsor or its representatives.

A comprehensive SAP will be prepared before first subject in (FSI) with final amendments completed prior to database lock.

9.1 Statistical Hypotheses

There is no hypothesis testing planned for this study, as all analyses will be descriptive primarily.

9.2 Sample Size Determination

The study is sized to characterise the ORR benefit of osimertinib monotherapy or osimertinib plus savolitinib as first line therapy in participants with *de novo MET*-amplified, *EGFR*-mutant advanced NSCLC. Because of the exploratory purpose of this study, no statistic comparison will be conducted between the two cohorts.

All analyses will be primarily descriptive unless otherwise specified.

Approximately 44 participants will be randomly assigned to study intervention and to achieve 40 participants complete the study (20 participants complete the study in each cohort). Assuming the true ORR of osimertinib monotherapy and osimertinib in combination with savolitinib would be 44% and 65% respectively, then a sample size of 20 could provide the 95% confidence interval estimate as [22.3%, 67.6%] and [40.8%, 84.6%] respectively, using Clopper-Pearson's exact method and assuming a 10% drop-out rate.

Randomly assigned/assigned	Estimated 44 participants
Participants complete the study	Estimated 40 participants

9.3 Populations for Analyses

The following populations are defined:

Table 13 Populations for Analysis

Population/Analysis Set	Description
FAS	All participants who are randomised in the study and take at least one dose of study treatment. Participants who were randomised but did subsequently receive the other study intervention are included in the analysis in the treatment group to which they actually took.

9.4 Statistical Analyses

The SAP will be prepared before first subject in (FSI) with final amendments completed prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

There will be two analyses for this study. The data cut-off (DCO) date for primary analysis for ORR will occur when all patients have had the opportunity to complete two efficacy assessments, which is estimated to be 12 weeks after last subject in (LSI). The second analysis DCO for PFS/OS will be at the point when 80% data maturity of PFS events (32 PFS events, 16 PFS events in each cohort) is achieved, which is estimated to be 40 months after LSI, with an enrollment period of 12 months and assumption of 18 months for median PFS in cohort 2 .

Descriptive statistics will be used for all variables. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total.

All analyses will be conducted based on FAS unless specified otherwise.

Subgroup analyses might be conducted for each cohort if applicable, for subjects identified by different diagnostic platforms (confirmed by IHC, FISH, tissue NGS and ctDNA NGS).

Additional subgroup analyses of efficacy and safety may be performed and will be specified in the SAP.

9.4.2 Efficacy

9.4.2.1 Calculation or Derivation of Tumor Response Variables

Investigator RECIST 1.1-based assessments

From the investigators review of the imaging scans, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST Version 1.1. It will be used to determine the endpoints PFS, ORR, DCR, DoR and tumor size change.

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a participant discontinues study intervention or receives another anticancer therapy.

At each tumor assessment, participants will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, PD, or NE depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to the

first dose of study intervention. The tumor response endpoints (PFS, ORR, best observed response, and duration of response [DoR]) will then be derived from the scan dates and overall visit responses.

Please refer to Appendix E for the definitions of CR, PR, SD and PD.

9.4.2.2 Analysis of the primary variables

Objective Response Rate

The primary outcome, ORR is defined as the number (%) of subjects with at least one visit response of confirmed CR or PR in the evaluable for response population set, based on Investigator assessment according to RECIST 1.1.

Patients who discontinue treatment without progression, receive a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) and then respond will not be included as responders in the ORR.

ORR and its 95% CI (Clopper-Pearson) will be summarized by treatment arm and presented in form of percentage with 95% confidence interval estimation provided.

9.4.2.3 Analysis of the secondary variables

Disease Control Rate

The DCR is defined as the number (%) of subjects with at least one visit response of confirmed CR, PR and SD in the evaluable for response population set, based on Investigator assessment according to RECIST 1.1.

Patients who discontinue treatment without progression, receive a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) and then respond will not be included as responders in the DCR.

DCR and its 95% CI (Clopper-Pearson) will be summarized by treatment arm and presented in form of percentage with 95% confidence interval estimation provided.

Percentage change from baseline in tumor size

Absolute change and percentage change from baseline in TL's tumor size at 12 weeks will be based on RECIST TLs measurements taken at baseline and at Week 12. Tumor size is the sum of the longest diameters of the TLs. Baseline for RECIST is defined as the last evaluable assessment prior to the start of treatment.

The percentage change in TL tumor size at Week 12 will be obtained for each patient taking the difference between the sum of the TLs at Week 12 and the sum of the TLs at baseline divided by the sum of the TLs at baseline times 100 (ie, [Week 12-baseline]/baseline×100).

The absolute change in TL tumor size at Week 12 will be obtained for each patient by the difference between the sum of the TL at Week 12 and the sum of the TL at baseline.

Handling of missing data will be described in the SAP.

The percentage change at Week 12 in TL tumor size from baseline will be summarized using descriptive statistics. Best percentage change will also be summarized.

Waterfall plots showing the percentage change at Week 12 and the best percentage change from baseline in sum of the diameters of TLs will be produced. Spider plots showing the actual change and the percentage change from baseline in tumor size for each patient over time may be produced.

Duration of response

The DoR will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression (ie, date of PFS event or censoring–date of first response+1). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of CR or PR.

The DoR will be summarized and analyzed for FAS.

If a patient does not progress following a response, then their DoR will use the respective PFS censoring time.

If there are sufficient numbers of responders, and sufficient numbers of responses that have progressed by the point of the analysis, Kaplan-Meier plots of DoR in the responding patients will be produced and appropriate descriptive summary statistics will be presented (n, number of responses that have progressed, median, quartile, minimum and maximum DoR).

Progression-free survival

PFS is defined as the time from the first dose of study intervention until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at Day 1 unless they die within 2 visits of baseline: in such a case, the death date will be used as the event date.

The PFS time will always be derived based on scan/assessment dates, not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

The PFS will be summarized and analyzed for FAS. Summaries of PFS (n, events, medians, quartiles, proportion progression free at 3, 6, 9 and 12 months and corresponding 95% CIs) and Kaplan-Meier plots will be provided.

Overall survival

OS is defined as the time from the start of treatment until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Patients will be contacted for survival follow-up every 12 weeks. Patients should be contacted in the week after data cut-off for each analysis to establish survival status.

Summaries of OS (n, events, medians, quartiles, proportion alive at 6, 12, 24 and 36 months and corresponding 95% CIs) and a Kaplan-Meier plot will be provided.

Subgroup analysis for subjects identified by different diagnostic platforms

The ORR, DCR, DoR, percentage change from baseline in tumor size, PFS and OS will also be summarized, as described in Section 9.4.2.2 and Section 9.4.2.3 for subjects with MET positivity identified by IHC, central FISH, central tissue NGS and blood NGS, if applicable.

9.4.2.4 Exploratory Endpoint(s)

Efficacy of osimertinib plus savolitinib as second line treatment in cohort 1 patients who progress on first line osimertinib monotherapy

The ORR among patient who receive osimertinib plus savolitinib as second line treatment after disease progression in cohort 1 will be summarized and analyzed if applicable. Other efficacy variables, such as DoR and PFS2, will also be summarized and analyzed if applicable.

9.4.3 Safety

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs, ECG data and ECOG performance status. All safety analyses will be performed on the FAS

Set. Additional analysis of key safety data may also be produced for some subgroup populations. These will be defined in the SAP.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs. AEs will be graded according to the National Cancer Institute CTCAE (Version 5.0).

The number of patients experiencing each AE will be summarised by the MedDRA system organ class and preferred term. The number and percentage of patients with AEs in different categories (eg, causally related, CTCAE Grade ≥3 etc) will be summarised, and events in each category will be further summarised by MedDRA system organ class and preferred term. SAEs will be summarised separately if a sufficient number occur.

Any AE occurring before the first dose of study drug will be included in the data listings but will not be included in the summary tables of AEs. AE summary tables will include only treatment-emergent adverse events. AEs will be defined as treatment emergent if they have an onset, or worsen (by investigator report of a change in intensity), during the study treatment period (defined from date of first dose of any study treatment to date of last dose of any study treatment) or safety follow-up period (30 days [±7 days] after last dose of study treatment). Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

Discontinuation of savolitinib and/or osimertinib rate due to AEs will be summarised for the first 6 weeks and at any time.

Examples of these could be marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. Tables and figures for potential Hy's Law cases will be produced.

Any AE occurring within the defined 30 day follow-up period after discontinuation of study drug will be included in the AE summaries. AEs occurring after the 30 day follow-up period after discontinuation of study drug or after starting subsequent anti-cancer therapy will not included in the summaries of this study.

Duration of exposure will be summarised. The number and percentage of patients with at least 1 dose interruption/dose delay and at least 1 dose reduction will also be summarised separately for the first 6 weeks and at any time.

Hematology, clinical chemistry, coagulation, urinalysis, vital signs and ECG data will be listed individually by patient and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated.

Details of any deaths will be listed for all patients.

9.4.4 Other Analyses

Biomarker exploratory analyses will be conducted if applicable, and may be described in a separate analysis plan. The results of this biomarker assessment will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

ctDNA clearance at Week 4/8/12 and longitudinal ctDNA monitoring

The percentage change in EGFR mutation and/or MET GCN ctDNA allele frequencies at Week 4/8/12 will be obtained, taking EGFR sensitising mutations and/or MET GCN in ctDNA at baseline as reference (ie, [Week 4/8/12-baseline]/baseline×100). Patients with undetectable EGFR mutations and/or MET GCN at baseline ctDNA will be excluded from this analysis.

The absolute change in ctDNA at Week 4/8/12 will be obtained for each patient by the difference between the EGFR mutation and/or MET GCN ctDNA allele frequencies at Week 4/8/12 and at baseline.

Patients with detectable EGFR mutations and/or MET GCN at baseline and available data at 4/8/12-weeks will also be categorized into the following groups: (1)EGFR ctDNA clearance: defined by a 100% percent change in EGFR mutations in ctDNA (ie, undetectable at Week 4/8/12); (2) EGFR ctDNA non-clearance: defined by a percent change in EGFR mutations in ctDNA less than 100% (ie, detectable at Week 4/8/12); (3) MET ctDNA clearance defined by a 100% percent change in MET GCN in ctDNA(ie, undetectable at Week 4/8/12) and (4) MET ctDNA non-clearance defined by a percent change in MET GCN in ctDNA less than 100% (ie, detectable at Week 4/8/12). Patients with undetectable EGFR mutations and/or MET GCN at baseline will be categorized as “uninformative.”

The percentage change and absolute change at Week 4/8/12 in ctDNA from baseline will be summarised using descriptive statistics. Descriptive summaries showing the actual change and the percentage change from baseline in tumour size for each patient over time may be produced. Summary statistics of the categorized ctDNA groups will also be produced.

Waterfall plots showing the percentage change at Week 4/8/12 will be produced. Spider plots showing the actual change and the percentage change from baseline in tumour size for each patient over time may be produced.

Longitudinal EGFR mutation, MET GCN and/or other alterations ctDNA allele frequencies will be followed and described if applicable.

Exploratory objectives will include but are not limited to exploring other variables in ctDNA changes such as: other concomitant alterations (including but not limited to MET amplifications and combining multiple alterations), modelling other ctDNA signals (including but not limited to: percentage change, specific allele thresholds), and correlations to all clinical efficacy endpoints (PFS, OS, and ORR).

Resistance profile exploration

Blood samples will also be collected after disease progression of first line treatment to explore mechanisms of resistance and biomarkers of clinical efficacy.

9.5 Interim Analyses

There is no planned interim analysis in this study currently.

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Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable IHC GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [IB or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason

during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, IHC guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

A 3 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 4 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 5 Data Quality Assurance

- All participant data relating to the study will be recorded on the CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, IHC GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years from the end of the study (as defined in the protocol) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 6 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 7 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any Contract Research Organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 8 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a participant or clinical study participant administered a study intervention and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the study intervention.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-participant hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the "Important Medical Event" criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **Non-Serious** AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as Non-Serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (ie, it is *not* the tumor for which entry into the study is a criterion and that is being treated by the study intervention under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, RIHCter's transformation of B cell chronic lymphocytic leukaemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

Life threatening

"Life-threatening" means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity rating scale:

The grading scales found in the revised National Cancer Institute CTCAE latest version will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Causality of "related" is made if following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as "not related".

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- occurred.
- was identified and intercepted before the participant received the drug.
- did not occur, but circumstances were recognised that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, for example, wrong route or wrong site of administration.
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature.
- Wrong participant received the medication (excluding IVRS/IWRS).

- Wrong drug administered to participant (excluding IVRS errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS- including those which lead to one of the above listed events that would otherwise have been a medication error.
- Participant accidentally missed drug dose(s) eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose).
- Participant failed to return unused medication or empty packaging.
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product.

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

B 5 Overdose

A maximum tolerated dose has not been established for osimertinib or savolitinib, therefore an overdose is any dose which exceeds the daily dose that is defined in this clinical study protocol.

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.12. For other overdoses, reporting must occur within 30 days.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

The sponsor or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the sponsor assigned biobanks or other sample archive facilities and will be tracked by the appropriate sponsor Team during for the remainder of the sample life cycle.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent specifically to the subsequent use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, sponsor is not obliged to destroy the results of this research. The participant will be presented with the option to opt out of the subsequent use of the donated samples during the withdrawal process. If the participant decides to opt out, then the donated samples will be disposed of. If the participant withdraws consent without opting out for the subsequent use of the donated samples, then the samples will be used as per protocol.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to Sponsor or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and Sponsor are informed about the sample disposal.

Sponsor ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- Sponsor intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study intervention continues but no longer than 15 years from the end of the study (as defined in the protocol) or other period as per local requirements.

D 2 Genetic Research Plan and Procedures

Selection of genetic research population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the CSP and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Transfusion of non-leukocyte depleted blood or blood component within 120 days of genetic sample collection.

Withdrawal of consent for genetic research

Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not

prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main CSP.

Collection of samples for genetic research

The blood sample for this genetic research will be obtained from the participants at baseline, every visit till disease progression. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE.

Coding and storage of DNA samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples may be stored for a maximum of 15 years from the end of the study (as defined in the protocol), after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the sponsor genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person.
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at sponsor or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date the consent form for the study and the addendum for the Genomics Initiative component of the study. Copies of signed and dated consent form must be given to the participant and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant data protection

- Sponsor will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at sponsor's organization and/or designated organisations to analyse the samples.
- Sponsor and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods

The number of participants that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

Appendix E Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al 2009). Investigator assessments will use the RECIST 1.1 guidelines described in this appendix.

Imaging modalities and acquisition specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of TLs, NTLs and NLs is provided in Table .

Table 13 Summary of Imaging Modalities for Tumor Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT MRI	CT MRI Plain X-ray Chest X-ray	CT MRI Plain X-ray Chest X-ray Bone scan (Scintigraphy) ^{18}F-fluoro-deoxyglucose-PET/CT

CT=computed tomography; PET/CT=positron emission tomography/CT; MRI=magnetic resonance imaging.

Computed Tomography and Magnetic Resonance Imaging

CT with IV contrast is the preferred imaging modality (although MRI with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumor assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumor assessor (eg, radiologist), and method of tumor assessment (eg, RECIST 1.1) are used consistently for each participant throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumor assessment schedule as closely as possible (refer to the SoA), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artefacts (eg, heart, major blood vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal

resolutions; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

The most critical CT and MRI image acquisition parameters for optimal tumor evaluation are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest-abdomen (-pelvis). Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual participants. Because a lesion later identified in a body part not scanned at baseline would be considered as a NL representing PD, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumor burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these time points are specified in the SoA. Examples include the following:

- IV contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) (-pelvis).
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including the entire liver and both adrenal glands) (-pelvis).
- IV contrast-enhanced CT or MRI of the head and neck.
- IV contrast-enhanced MRI (preferred) or CT of the brain.

For chest-abdomen (-pelvis) imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when participants have sensitivity to IV contrast or have compromised renal function:

1 Chest-abdomen (-pelvis) CT with IV CT contrast (most preferred).
2 Chest CT without IV-contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study.
3 Chest-abdomen (-pelvis) CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the participant has compromised renal function.

4 Chest-abdomen (-pelvis) MRI with IV MRI contrast, if CT cannot be performed at any time during the study.

b. IV contrast administration: Optimal visualisation and measurement of metastases in solid tumors require consistent administration (dose and rate) of IV contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumor lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given participant. Oral contrast is recommended to help visualise and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) slices with ≤5 mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses >5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

Chest X-ray

Chest X-ray assessment will not be used for the assessment of TLs. Chest X-ray can, however, be used to assess NTLs and to identify the presence of NLs. However, there is preference that a higher resolution modality, such as CT, be used to confirm the presence of NLs.

Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTLs and followed by the same method per baseline assessment (CT, MRI, or X-ray).

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. NLs may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at

that time point.

^{18}F-Fluoro-deoxyglucose-PET/CT

^{18}F-fluoro-deoxyglucose positron emission tomography(PET)/CT scans may be used as a method for identifying new extrahepatic lesions (but not intrahepatic lesions) for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[1] not present on baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the ^{18}F-fluoro-deoxyglucose-PET scan. The PET portion of the PET/CT introduces additional data that may bias an investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

At present, low-dose or attenuation correction CT portions of a combined ^{18}F-fluoro-deoxyglucose-PET/CT scan are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumor assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an investigator if it is not routinely or serially performed.

Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of the true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Other tumor assessments

Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

1 A positive ^{18}F-fluoro-deoxyglucose-PET scan lesion should be reported only when an uptake (eg, standard uptake value) greater than twice that of the surrounding tissue or liver is observed.

Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Histology and cytology

Histology or tumor markers on tumor biopsy samples will not be used as part of the tumor response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment as per RECIST 1.1.

Furthermore, an overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if an effusion remains present radiologically.

Measurability of tumor lesions at baseline

RECIST 1.1 measurable lesions at baseline

A tumor lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis[2] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. Please see additional RECIST 1.1 guidance below on measurability of intrahepatic hepatocellular carcinoma lesions and porta hepatis lymph nodes.

Non-measurable lesions at baseline

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component).
  - Leptomeningeal disease.
  - Ascites, pleural effusion, or pericardial effusion.
  - Inflammatory breast disease.
  - Lymphangitic involvement of skin or lung.
- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline).[3]
- Previously irradiated lesions.[4]

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[2] The short axis is defined as the longest in-plane axis perpendicular to the long axis.

[3] Lymph nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

[4] Localised post-radiation changes that affect lesion size may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

- Brain metastasis.

Special considerations regarding lesion measurability at baseline

- Bone lesions:
  - Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability.
  - Blastic lesions are considered non-measurable.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same participant, these should be selected over cystic lesions as TLs.

RECIST 1.1 TL selection at baseline

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TLs at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented, as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases for TL assessment at baseline

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.
- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- Tumor lesions selected for newly acquired screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a NL.

RECIST 1.1 NTL selection at baseline

All other lesions, including non-measurable lesions and surplus measurable lesions, not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of tumor response and progression

RECIST 1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimetres. The sum of the diameters for all TLs at each follow-up visit will be compared with the baseline sum of diameters (for response or SD) or to the smallest prior (nadir) sum of diameters (for progression).

Special cases for TL assessment at follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs

are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion. The choice of "Too large to measure" in the CRF will trigger an overall visit response of PD.
- When a TL has had any intervention (eg, definitive radiotherapy, embolisation, surgery, transarterial chemoembolisation, etc) during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 CRF for the current imaging visit and all subsequent visits. If a TL has been completely removed (surgery) or disappears, the longest diameter should be recorded as 0 mm.

Table 14 RECIST 1.1 Evaluation of Target Lesions

CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm.
PR	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
SD	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
PD	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir). This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
NE	Only relevant if any of the TLs at follow-up were not assessed or NE (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
Not applicable	Only relevant if no TLs present at baseline.

CR=complete response; NE=not evaluable; PD=progression of disease; PR=partial response; SD=stable disease; TL=target lesion.

RECIST 1.1 NTL assessment at follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator.

To achieve "unequivocal progression" on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs,

the overall tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest "increase" in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PD of target disease will therefore be extremely rare.

Table 15 RECIST 1.1 Evaluation of Non-Target Lesions

CR	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of 1 or more NTLs.
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
NE	Only relevant when 1 or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For participants without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable	Only relevant if no NTLs present at baseline.

CR=complete response; NE=not evaluable; NTL=non-target lesion; PD=progression of disease; TL=target lesion.

RECIST 1.1 NL identification at follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the CRF. The presence of 1 or more NLs is assessed as progression. The finding of a NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. If a NL is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously (pre-existing) NL has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a NL and will indicate PD.

RECIST 1.1 evaluation of overall visit response at follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs uses the algorithm shown in Table .

Table 16 RECIST 1.1 Overall Visit Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Visit Response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE or NA	No	PR
SD	Non PD or NE or NA	No	SD
NA	Non-CR/Non-PD	No	SD (non-CR/non-PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
NA	NA	No	NED
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Non-CR/Non-PD for overall response if only NTL (no TLs) are present at baseline.

Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.

CR=complete response; NA=not applicable (only relevant if there were no TLs at baseline or NTLs at baseline), NE=not evaluable; NED=no evidence of diseases (only relevant if there were neither target lesions nor non-target lesions at baseline); NTL=non-target lesion; PD=progression of disease; PR=partial response; SD=stable disease; TL=target lesion.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For participants with TLs (at baseline): CR, PR, SD, PD, or NE.
- For participants with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE.
- For participants with no disease at baseline: no evidence of disease (available as an option in the eCRF), PD, or NE.

Evaluation of scans subsequent to RECIST 1.1-defined progression

A follow-up scan is requested at least 4 weeks after a RECIST 1.1-defined radiological progression and no longer than the next regularly scheduled imaging visit. The follow-up scans provide additional information to the investigator for participant management and further treatment decisions, and since the published RECIST 1.1 criteria (Eisenhauer et al 2009) do not provide guidance on how to assess scans acquired after RECIST 1.1-defined PD, supplemental instructions for investigators on how to evaluate these follow-up scans are provided below. An immediate prior RECIST 1.1-defined radiologic PD would be considered confirmed if *any* of the following criteria are met in the subsequent follow-up scan:

- ≥20% increase and at least a 5 mm increase in the sum of diameters of TLs compared with the nadir sum of diameters at 2 consecutive visits, and a further increase of ≥5 mm in the sum of diameters at the follow-up scan time point compared with the immediate prior time point.
- significant progression (worsening) of NTLs at the follow-up scan time point compared with the immediate prior time point.
- significant progression (worsening) of previously NLs (pre-existing NLs) at the follow-up scan time point compared with the immediate prior time point.
- additional brand-new unequivocal lesions at the follow-up scan time point.

Central imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an sponsor-appointed imaging Contract Research Organisation (iCRO) for quality control, storage, and for BICR. Digital copies of all original scans should be stored at the investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. A BICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to investigators, and results of investigator tumor assessments will not be shared with the central reviewers.

The management of participants will be based in part upon the results of the tumor assessments conducted by the investigator. Further details of the BICR will be documented in an Independent Review Charter.

References

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix F Contraception Requirements

Contraception requirements for this study are as follows.

F 1Female Participants

Women not of childbearing potential are defined as those who are surgically sterile (ie, bilateral saLSIngectomy, bilateral oophorectomy, or complete hysterectomy) or who are post-menopausal.

Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy, or had radiation-induced menopause with last menses >1 year ago, or had chemotherapy-induced menopause with last menses >1 year ago.

Women of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a nonsterilised male partner must use at least 1 highly effective method of contraception (Table). They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and continue to use it throughout the total duration of the drug treatment and the drug washout period (6 weeks after the last dose of study intervention).

Non-sterilised male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant. Female participants should refrain from breastfeeding throughout this period.

F 2Male Participants with a Female Partner of Childbearing Potential

Non-sterilised male participants (including males sterilised by a method other than bilateral orchidectomy, eg, vasectomy) who intend to be sexually active with a female partner of childbearing potential must be using an acceptable method of contraception such as male

condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening throughout the total duration of the study and the drug washout period (6 months after the last dose of study intervention) to prevent pregnancy in a partner.

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male participants should refrain from sperm donation or banking throughout this period.

Vasectomised (ie, sterile) males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study.

Even if the female partner is pregnant, male participants should still use a condom plus spermicide (where approved), as indicated above during the clinical study, if there is a concern about damaging the developing foetus from drug in ejaculate.

Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period (Table).

F 3Highly Effective Methods of Contraception

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in Table . Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 17 Highly Effective Methods of Contraception (<1% Failure Rate)

Non-Hormonal Methods	Hormonal Methods
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) • Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • Tubal occlusion • Intrauterine device (provided coils are copper-banded)	• Injection: Medroxyprogesterone injection (eg, Depo-Provera®)[a] • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a] • Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Combined pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Mini pill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[a] Hormonal methods not prone to drug-drug interactions.

Appendix G Concomitant Medications

G 1 Guidance Regarding Potential Interactions with Concomitant Medications

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

1. Drugs Inducing CYP3A4 Metabolism That AstraZeneca Strongly Recommend Are Not Combined With Osimertinib

Osimertinib is metabolised by CYP3A4 and CYP3A5 enzymes.

A drug-drug interaction study of osimertinib evaluated in patients showed that there is potential for osimertinib being a victim when co-administered with strong inducers of CYP3A4 (osimertinib concentrations are decreased when co-dosed with rifampicin).

The following potent inducers of CYP3A4 must not be used during this study for any patient receiving osimertinib.

Table 18 Drugs inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to osimertinib start
Carbamazepine, phenobarbital, phenytoin Rifampicin, rifabutin, rifapentin St John's Wort	3 weeks
Phenobarbitone	5 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

G 2 Drugs inhibiting CYP1A2 metabolism that AstraZeneca strongly recommend are not combined with savolitinib

Table 20 Drugs inhibiting CYP1A2

Contraindicated drugs	Withdrawal period prior to savolitinib start
Ciprofloxacin, Enoxacin, Clinafloxacin Fluvoxamine	2 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly inhibit CYP1A2 activity. Appropriate medical judgment is

required. Please contact AstraZeneca with any queries you have on this issue.

Savolitinib is a weak inhibitor of OATP1B1, OATP1B3 and BCRP.

G 3 Medicines whose exposures may be affected by osimertinib that AstraZeneca considers may be allowed with caution

Osimertinib may increase the concentration of sensitive BCRP and Pgp substrates (concentration of the sensitive BCRP substrate, rosuvastatin and sensitive Pgp substrate, fexofenadine, are increased)..

Table 21 Exposure, pharmacological action and toxicity may be increased or decreased by osimertinib

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine Doxorubicin Daunorubicin Topotecan Dabigatran Aliskiren Digoxin	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with osimertinib.

G 4 Drugs that may prolong QT interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics website: https://www.crediblemeds.org. The website categorises drugs based on the risk of inducing Torsades de Pointes (TdP).

During screening, the drugs that patients are currently receiving (prescription and non-prescription) should be checked against the Arizona Center website In addition, drugs intended for use following study treatment initiation should be checked against the website.

G 4.1 Drugs with a known risk of Torsades de Pointes (TdP)

Drugs in this category are known to prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended.

G 4.1.1 Before commencing study treatment

Drugs in the category of known risk of TdP must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table 22.

G 4.1.2 During study treatment

It is recommended that drugs in the category of known risk of TdP are not co-administered with study treatment (osimertinib) and for a period of two weeks after discontinuing study treatment, however if it is considered essential for patient management to co-administer these drugs with study treatment (osimertinib) close monitoring of ECGs and electrolytes is recommended.

The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such investigators are recommended to search the CredibleMeds® website (https://www.crediblemeds.org/) to provide the most up to date information.

Table 22 Drugs with a known risk of Torsades de Pointes (TdP) [a]

Contraindicated drug	Withdrawal period prior to osimertinib start [b]
Aclarubicin, anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine, terlipressin.	2 days
Cilostazol, cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, sotalol, roxithromycin, sevoflurane, sparfloxacin, thioridazine	7 days
Azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide [c], ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, probucol, vandetanib	4 months
Amiodarone, chloroquine	1 year

a This list should be checked against the full and most current list presented in the CredibleMeds® website (https://www.crediblemeds.org/).

b Values determined from comprehensive review (internal to AZ) of each compounds PK half-life and determination of the washout period.

c Estimated value as pharmacokinetics of arsenic trioxide has not been studied.

Other TdP risk Categories

Patients receiving drugs that prolong QT interval or may increase the risk of TdP from other TdP risk categories can be enrolled, notwithstanding other exclusions and restrictions, if these drugs are considered essential for patient management and the patient has been stable on therapy. Close monitoring of ECGs and electrolytes is recommended.

Patients with **congenital long QT syndrome (CLQTS) are excluded** from this study.

Guidance regardless of TdP risk category
Following study treatment initiation if it is considered essential for patient management to give drugs known to prolong QTc interval, **regardless of TdP risk category**, close monitoring of ECGs and electrolytes is recommended.

G 5 References

The Arizona Center for Education and Research on Therapeutics website
Available at URL: https://www.crediblemeds.org.

Appendix H Dose Modifications for the Management of Adverse Events

H 1 Osimertinib dose modification and guidance

Osimertinib management should be in accordance with the local label in the first instance.

If a patient experiences a CTCAE Grade 3 and/or unacceptable toxicity dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines.

If a toxicity resolves or reverts to ≤CTCAE Grade 2 within 3 weeks of onset, treatment with osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg) using the rules below for dose modifications (Table 24) and with discussion and agreement with the AstraZeneca Study Team Physician as needed. There will be no individual modifications to dose regimen in response to toxicity, only potential dose reduction or dose interruption.

If the toxicity does not resolve to ≤CTCAE Grade 2 after 3 weeks, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

Table 24 Dose reduction for osimertinib to manage adverse events

	Starting osimertinib dose 80 mg
Reduced dose -1	40 mg

On resolution of toxicity within 3 weeks:

If an AE subsequently requires dose interruption, osimertinib may restart at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the investigator.

H 1.1 ILD/Pneumonitis-like toxicity

If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is recommended, and the Sponsor study team should be informed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema or pulmonary haemorrhage. The results of full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters) will be captured by eCRF. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued

H 1.2 QTcF prolongation

In light of the potential for QT changes associated with osimertinib, and in accordance with good clinical practice, it is recommended that correction of clinically significant electrolyte abnormalities to within normal ranges takes place prior to first dose and during study treatment.

Patients with QTcF prolongation to >500 msec should have study treatment interrupted and regular ECGs performed until resolution to <481 msec, or recovery to baseline if baseline QTcF is ≥ 481 msec and then restarted at a reduced dose of 40 mg or at the same dose 80mg at the discretion of the Investigator. If the toxicity does not resolve to ≤Grade 1 within 21 days the patient will be permanently withdrawn from study treatment.

H 1.3 Keratitis

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

H 1.4 Erythema Multiforme and Stevens-Johnson syndrome

Case reports of Erythema multiforme (EM) and Stevens-Johnson syndrome (SJS) have been uncommonly and rarely reported, respectively, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM and SJS. If signs and symptoms suggestive of EM develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted or discontinued immediately.

H 1.5 Changes in cardiac contractility

Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. In patients with cardiac risk factors and those with conditions that can affect left ventricular ejection fraction (LVEF), cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

H 1.6 Permanent discontinuation due to toxicity

Patients experiencing ILD or QTcF prolongation with signs/symptoms of serious arrhythmia will not be permitted to restart study treatment.

H 2 Savolitinib dose modification and guidance

H 2.1 Savolitinib dose modification and guidance

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of savolitinib, as appropriate unless due to suspected hypersensitivity (See section I 2.4).

Dose reductions or holds are allowed as clinically indicated by the treating physician and in line with Table 25. For each patient, a maximum of 2 dose reductions of savolitinib will be allowed. No dose re-escalations are allowed. Guidance on dose level reduction is presented in Table 25.

Table 25 Dose reduction for savolitinib to manage adverse events

Starting savolitinib dose	**300mg bid**
Reduced dose -1	200 mg bid
Reduced dose -2	100 mg bid

Note: Only 2 dose reductions of savolitinib are permitted.

H 2.2 Hepatoxicity management guideline

- Promptly evaluate patients with elevated LFTs during study treatment for alternative etiologies and potential Hy's law criteria, and discontinue potential contributing concomitant medications or alternative causal agents, as well as anti-coagulants, if appropriate.
- Ensure a PK sample is collected as soon as feasible when the patient is diagnosed with abnormal LFTs necessitating drug discontinuation.
- If a patient discontinues due to LFT abnormality, LFT monitoring should continue until resolved to Grade 1 or baseline or an apparent plateau has been reached.

H 2.2.1 Dose modification due to drug-related hepatotoxicity

- Discontinue drug if:
  - ALT or AST >8 × ULN with total bilirubin elevation above baseline or ULN, or
  - ALT or AST >5 × ULN for >2 weeks with total bilirubin elevation above baseline or ULN, or
  - ALT or AST >3 × ULN and (TBL >2 × ULN or INR>1.5 if not on anticoagulants that elevate the INR), or
  - AST or ALT >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia >5%

- Withhold dosing if ALT or AST >5x ULN for > 2 weeks or 8 ×ULN without total bilirubin elevation above baseline or ULN, repeat LFT testing twice a week for 1 week:
  - If improved to Grade 1 or baseline in 1 week, resume at reduced dose with LFT testing twice a week for 6 weeks
  - If not, discontinue
- Withhold dosing if ALT or AST >3 ×ULN and concurrent total bilirubin 1.5 ×ULN, repeat LFT testing twice a week for 1 week:
  - If both ALT/AST and total bilirubin improved to Grade 1 or baseline in 1 week, resume at reduced dose with LFT testing twice a week for 6 weeks
  - If not, discontinue
- Continue dosing if ALT or AST >3 ×ULN without total bilirubin elevation above baseline or ULN, repeat LFT testing every week
  - If ALT or AST trending upward, withhold dosing and repeat LFT twice a week for 1 week
  - If improve to Grade 1 or baseline in 1 week, resume at same dose with LFT testing every week for 6 weeks
  - If improve to Grade 1 or baseline in 2 weeks, resume at reduced dose with LFT testing every week for 6 weeks
  - If not, discontinue
- Discontinue for recurrent ALT or AST >5 ×ULN
- Discontinue for recurrent ALT or AST >3 ×ULN and total bilirubin >1.5 ×ULN
- Withhold dosing for recurrent ALT or AST >3 ×ULN without total bilirubin elevation above baseline or ULN, repeat LFT testing twice a week for 1 week
  - If improve to Grade 1 or baseline in 1 week, resume at reduced dose with LFT testing every week for 6 weeks; if not, discontinue

H 2.3 Guidance for management of savolitinib specific toxicities

Dermatologic: A case of Stevens-Johnson syndrome (SJS) has been reported in temporal association with savolitinib. Patients who show symptoms or signs suggesting emerging SJS while on study treatment (eg, progressive skin rash often with blisters or mucosal lesions), must discontinue savolitinib immediately and receive appropriate treatment. If emerging SJS is suspected, re-challenge with savolitinib must be avoided.

Hypersensitivity: Hypersensitivity, which may manifest as a constellation of symptoms such as but not limited to pyrexia, allergic skin reaction, increased liver enzymes, cytopenia, or myalgia and/or arthralgia has been reported after savolitinib dosing. These reactions have occurred within days to weeks after the first dose but the majority of reactions have occurred in the first six weeks of therapy. Patients with suspected savolitinib-related hypersensitivity

(excluding confirmed infective aetiology), may be managed with corticosteroids, antihistamines and antipyretics (doses and duration of treatment according to local practice at the discretion of the investigator). Dose interruption with savolitinib should be avoided, if possible. Some patients who experienced the initial hypersensitivity reaction also reported severe acute hypersensitivity reactions, including anaphylaxis, upon restarting savolitinib treatment following a short period of interruption. **If patients do need dose interruption, restarting savolitinib must be done under controlled conditions as per below.**

If the patient experiences an acute hypersensitivity or anaphylactic reaction, immediate intervention must be instituted and treatment with savolitinib should be permanently discontinued.

Restarting savolitinib: acute hypersensitivity including anaphylaxis has been observed in a number of patients mostly upon savolitinib restart. If interruption of savolitinib occurs in the first 6 weeks of study treatment due to savolitinib-related general toxicities, or specific hypersensitivity toxicities occur at any time, dosing with savolitinib may be resumed but at a reduced dose, only after consultation with and approval from the study physician and with the following management:

- Treatment:
  - Pre-treatment with systemic corticosteroids must be started **at least** 24 hours before the restart of savolitinib;
  - Pre-treatment with antipyretics and antihistamines on the day of restart of savolitinib;
  - Doses of antihistamines, corticosteroids and antipyretics should be according to labelling instructions/product information.
  - These medications must be continued daily until discontinuation of savolitinib, but doses of steroids may subsequently be tapered according to local practice
- Intense medical monitoring (restart at the institution);
  - The restart of savolitinib must be performed in the hospital/institution where the clinical study is carried out with medical equipment readily available for resuscitation and management of anaphylaxis
  - Vital status recording (blood pressure, temperature, respiratory rate, heart rate, etc.) before administration of study drug, every 15 mins after savolitinib dosing for the 1st hour, every 30 mins for the next hour and hourly for a total of at least 4 hours and
  - Patient must be observed in the clinic for 24 hours before discharge.
  - Should the symptoms recur, or an acute anaphylactic reaction occurs, immediate intervention must be instituted for appropriate management of event and savolitinib must be permanently discontinued.

Any recommendations regarding hypersensitivity management or pre-treatment should be used as guidelines only. Final decisions concerning management of individual patients reside with the investigator or the treating physician.

QTC prolongation:

Table 27 Dose modifications for savolitinib-related QTc prolongation

NCI CTCAE Toxicity Grade	Action
Grade 0, 1, or 2	None
Grade 3 • Patients with QTcF prolongation to >500 msec on at least 2 separate ECGs	Hold dosing and follow algorithm below: • Consult with cardiologist to validate ECG finding. Ensure cardiac surveillance and take actions in accordance with clinical standards. Regular ECGs performed until resolution to QTcF <481 msec and then restart drug at one reduced dose level
• If the toxicity does not resolve to QTcF <481 msec within 21 days	• Discontinue study drug and consult with a cardiologist for further management as clinically indicated
Grade 4 • QTcF ≥501 or >60 msecs change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	• Discontinue study drug and consult with a cardiologist for further management as clinically indicated

CTCAE Common Terminology Criteria for Adverse Events; ECG Electrocardiogram; NCI National Cancer Institute; QTcF corrected QT interval using Fridericia's formulas.

Appendix I Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Delete appendix if not applicable for the clinical study.

I 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the study intervention.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

I 2 Definitions

PHL

Aspartate aminotransferase or ALT ≥3×ULN **together with** TBL ≥2×ULN at any point during the study following the start of study intervention irrespective of an increase in alkaline phosphatase.

HL

AST or ALT ≥3×ULN **together with** TBL ≥2×ULN, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline

phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

I 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 ×ULN.
- AST ≥3 ×ULN.
- TBL ≥2 ×ULN.

Central laboratories being used

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the investigator will:

- Notify the AstraZeneca representative.
- Request a repeat of the test (new blood draw) by the central laboratory without delay.
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result.

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the participant meets PHL criteria (see Section I 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

Local laboratories being used

The investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative.

- Determine whether the participant meets PHL criteria (see Section I 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

I 4 Follow-up

I 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

I 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention (See Section I 6).
- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criterion "Important medical event" and causality assessment "yes/related" according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting study intervention, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study physician.
  - Complete the 3 Liver eCRF Modules as information becomes available.

#A "significant" change in the participant's condition refers to a clinically relevant change in

any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

I 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the study physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study intervention, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the study intervention:

- Send updated SAE (report term "Hy's Law") according to AstraZeneca standard processes.
  - The "Medically Important" serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information

necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now "Hy's Law case") ensuring causality assessment is related to study intervention and seriousness criterion is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

I 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Intervention

This section is applicable to participants with liver metastases who meet PHL criteria on study intervention, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on-study intervention occurrence of PHL criteria being met the investigator will determine if there has been a **significant change** in the participant's condition compared with the last visit where PHL criteria were met.

- If there is no significant change no action is required.
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section I 4.2.

I 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study intervention and has already met PHL criteria at a previous on study intervention visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease or did the participant meet PHL criteria prior to starting study intervention and at their

first on-study intervention visit as described in Section I 6 of this Appendix?

If **No**: follow the process described in Section I 4.2 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the participant's condition compared with when PHL criteria were previously met.

- If there is no significant change no action is required.
- If there is a significant change follow the process described in Section I 4.2 for reporting PHL as an SAE.

I 8 References

Aithal et al 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89(6):806-15.

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Appendix J Abbreviations

Abbreviation or Special Term	Explanation
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
BICR	Blinded Independent Central Review
CD	cluster of differentiation
CI	confidence interval
CL	clearance
ClinRO	clinician-reported outcome
C_{max}	maximum observed concentration
CMC	Chemistry, Manufacturing and Controls
COA	clinical outcome assessment
CR	complete response
CRF	Case report form
CrCL	calculated creatinine clearance
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DCO	data cutoff
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DoR	duration of response
DSUR	Development Safety Update Report
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form

Abbreviation or Special Term	Explanation
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	formalin fixed and paraffin embedded
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HL	Hy's Law
HR	hazard ratio
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
IHC	International Council for Harmonisation
iCRO	imaging Contract Research Organisation
IDFU	Investigational Directions for Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
International co-ordinating investigator	If a study is conducted in several countries the international co-ordinating investigator is the investigator co-ordinating the investigators and/or activities internationally.
IND	Investigational New Drug
IO	immuno-oncology
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	Intent to treat
IV	intravenous
IVD	in vitro diagnostic
IVRS	interactive voice response system
MRI	magnetic resonance imaging
MTP	multiple testing procedure
MUGA	multigated acquisition
NE	not evaluable

Abbreviation or Special Term	Explanation
NIMP	non-investigational medicinal product
NL	new lesion
NSCLC	non-small cell lung cancer
NTL	non-target lesion
ORR	objective response rate
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
PFS2	time to second progression or death
PHL	Potential Hy's Law
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PSSR	Project Specific Safety Requirements
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SoC	Standard of care
SOP	Standard Operating Procedure
T½	half-life
TA	Therapeutic Area
TBL	total bilirubin
TdP	Torsades de Pointes
TKI	tyrosine kinase inhibitor
TL	target lesion
TOC	Table of Contents
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHO	World Health Organisation

Appendix K Authorship and Publication

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. Authorship should be in line with International Committee of Medical Journal Editors authorship requirements and follow Good Publication Practice (GPP3).

The results of this study should be published or presented at scientific meetings. The Sponsor agrees to submit all manuscripts or abstracts to AZ before at least 30 days prior to submission. This allows AZ to protect proprietary information and to provide comments.

- The Sponsor and the Principal Investigator shall include the following acknowledgement in all publications and presentations relating to the Study, the Study Data, or the Developed Technologies, as well as in any financial disclosure information relating to the Study: "This research was conducted with support from AstraZeneca SA." A copy of any publications and presentations relating to the Study shall be provided to the Company on publication or presentation, and the Company will be granted such rights or licenses as may be required to enable it to make copies of and distribute the publication or presentation as it considers necessary.

At the request of the Company, the Sponsor and/or Principal Investigator:

- Shall not include in or shall remove from any proposed publication any Confidential Information; and

- Shall withhold publication, submission, for publication, or presentation for a period of ninety (90) days from the date on which the Company receives the material to allow the Company to take such measures as the Company considers necessary to preserve its proprietary rights and/or protect its Confidential Information

PROTOCAL AMENDMENT SUMMARY

ESR-20-20862_FLOWERS

Version 1.0, 12 Sep 2020

Version 2.0, 16 April 2021
Description of Change: • Savolitinib dose change from 300mg qd to 300mg bid, and corresponding descriptions. • Shorten the visit window during treatment to every 4 weeks (refer to SoA) to better monitor the safety, according to the sponsor. • Specify the mandatory and optional samples collection in Section 8.6. • Updates in safety management.
Version 3.0, 15 June 2021
Description of Change: • Updates in Reporting of Adverse Events contact information. • Randomisation system change from the Interactive Voice Response System (IVRS) to Guangdong Association of Clinical Trials/Chinese Thoracic Oncology Group (CTONG) Randomized Grouping Program Software.

STATISTICAL ANALYSIS PLAN

TITLE: Osimertinib with or without savolitinib as first-line treatment for MET-aberrant, EGFR-mutant NSCLC (FLOWERS; CTONG2008): a randomized, multicenter, open-label, non-comparative, phase 2 trial

SPONSOR: Guangdong Association of Clinical Trials/Chinese Thoracic Oncology Group

VERSION NUMBER: 1.0

PROTOCOL VERSION: 3.0

STUDY DRUG: Osimertinib, Savolitinib

STATISTICAL ANALYSIS INSTITUTION: Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University

DATA FINAL: 2024/05/28

CONTENTS

LIST OF ABBREVIATIONS

MET	mesenchymal-epithelial transition
OE	overexpression
EGFR	epidermal growth factor receptor
NSCLC	non-small cell lung cancer
NGS	next-generation sequencing
ORR	objective response rate
CR	complete response
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
IHC	immunohistochemistry
FISH	fluorescence in situ hybridization
PFS	progression-free survival
DoR	duration of response
DCR	disease control rate
SD	stable disease
TL	target lesion
OS	overall survival
AEs	adverse events
MedDRA	Medical Dictionary for Regulatory Activities thesaurus terms
CTCAE	Common Terminology Criteria for Adverse Events
FAS	full analysis set
DCO	data cutoff date
LSI	last subject enrollment
CIs	confidential intervals
OR	odds ratio

1. STUDY DESIGN

This randomized, open-label, phase II clinical study is designed to explore the efficacy and safety of osimertinib in combination with savolitinib or osimertinib monotherapy as first-line therapy in pts with *de novo MET* amp and/or MET OE, *EGFR*-mutant, locally advanced or metastatic non-small cell lung cancer (NSCLC).

2. POPULATION

Patients with advanced NSCLC who harbored primary MET expansion or overexpression, EGFR mutations, had not received any first-line systemic anti-tumor therapy, and had local progression or metastasis confirmed by histology or cytology.

3. STUDY OBJECTIVES

3.1 Primary study objective

- To explore the objective response of osimertinib alone or in combination with savolitinib as first-line treatment for patients with primary MET-positive EGFR mutated advanced non-small cell lung cancer.

3.2 Secondary study objectives

- To explore the efficacy of osimertinib alone or in combination with savolitinib as first-line treatment for primary MET-positive EGFR-mutated NSCLC.
- To perform a subgroup analysis of the efficacy of osimertinib alone or in combination with savolitinib in first-line treatment in patient populations identified by different testing platforms.

3.3 Safety assessment

- To explore the safety and tolerability of osimertinib and savolitinib in patients with primary MET-positive EGFR mutated NSCLC.

3.4 Exploratory assessment

- To explore the efficacy of osimertinib combined with savolitinib in the second-line after resistance to first line osimertinib monotherapy.
- To explore the molecular resistance mechanisms of disease progression through NGS detection.
- To explore the association of genetic variants and/or ctDNA clearance with treatment response by serially collecting plasma samples for genetic testing.

4. STUDY ENDPOINT

4.1 Primary endpoint

- The objective response rate (ORR) was defined as the number (%) of subjects with at least one visit response of **confirmed** CR or PR in the evaluable for response population set, based on Investigator assessment according to RECIST 1.1.

Already receiving assigned treatment but discontinuing treatment without progression, receiving subsequent anticancer treatment (please note that in this analysis Radiotherapy is not considered subsequent anticancer therapy) and patients who subsequently respond will not be considered responders for inclusion ORR is in progress.

4.2 Secondary endpoints

4.2.1 Investigator assessed for the overall population and subgroup population.

Subgroup population refers to IHC, central laboratory FISH, central laboratory tissue NGS, and blood NGS defined as MET-positive subjects.

Endpoints	Definitions
Progression-Free Survival (PFS)	• PFS was defined as the date from the first dose of study intervention to objective

	disease progression or death (death from any cause in the absence of progression), regardless of whether the patient discontinued treatment before progression or received another anticancer treatment. Patients who had not progressed or died at the time of analysis participants will be censored on the date of their last evaluable RECIST assessment. • However, if a patient progresses or dies after more than 2 missed visits, the patient will be treated as the last evaluable RECIST evaluation date is censored. If the patient does not have an evaluable visit or does not have baseline data, the patient will be censored on Day 1., unless the patient dies within 2 visits after baseline, in which case the date of death will be used as the event date. • PFS times are always based on the scan/assessment date, not the visit date. RECIST assessments/scans for a visit may occur on different days. The following rules will apply: (1) The date of progression will be determined based on the earliest date of the examination/assessment in which progression was found.

	(2) When the PFS was censored, it was censored on the latest date assessed at a visit.
Duration Of Response (DoR)	• DoR was defined from the date of first documented response until the date of documented progression or the absence of disease progression the date of death. The endpoint of sustained response should be the PFS endpoint used was consistent with the date of progression or death from any cause. Initial response time will be defined as the first visit the most recent date the response was a CR or PR. • DoR will be summarized and analyzed based on treatment group. • If a patient does not progress after response, their DoR will use their respective PFS censoring time.
Disease Control Rate (DCR)	DCR was defined as the number (%) of subjects with at least one visit response of **confirmed** CR, PR and SD in the evaluable for response population set, based on Investigator assessment according to RECIST 1.1.. • Already receiving assigned treatment but discontinuing treatment without progression, receiving subsequent anticancer treatment (please note that in this analysis Radiotherapy is not

	considered subsequent anticancer therapy), and patients who subsequently respond will not be considered responders.
Percentage change in tumor size from baseline	• Absolute and percentage changes from baseline in target lesion (TL) size at Week 12 will be based on baseline and Week 12 RECIST standard target lesion measurements were calculated. Tumor size was the sum of the longest diameters of all target lesions. • Baseline assessment refers to the last evaluable tumor assessment before the start of treatment. • Calculation of percent change in TL tumor size at week 12 for each patient: sum of TL at week 12 minus Sum of TL at baseline, divided by the sum of baseline TL multiplied by 100 (i.e. [Week 12 - Baseline] / Baseline × 100). • The absolute change in TL tumor size at week 12 for each patient will be obtained by subtracting the baseline TL sum from the week 12 TL sum.
Overall Survival (OS)	OS was defined from the onset of study intervention to death from any cause. Any patient known not to have died at the time of analysis will be based on the last recorded date of known patient survival was censored.

The 12-month overall survival rate	12-month overall survival was defined as the percentage of people still alive following 12 months after the date of the first dose of study intervention.

4.3 Safety endpoints

- Adverse Event (AE)

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms (MedDRA), and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, selected adverse events, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. All safety analyzes will be performed for treatment arm on the FAS set. It may also be critical for some subgroups of people. For example, perform subgroup analysis on MET different diagnostic platforms (IHC overexpression vs. FISH amplification vs. NGS copy number increase).

4.4 Exploratory endpoints

- The ORR of osimertinib combined with savolitinib in the second-line after resistance to first-line osimertinib monotherapy.
- Genetic abnormalities after disease progression.
- Genetic variants and/or changes in ctDNA clearance correlate with efficacy relevance.

5. SAMPLE SIZE

This study plans to enroll 44 subjects and receive intervention treatment according to random allocation, and 40 subjects will complete the study (20 subjects in each cohort will complete the study). Assuming that the ORRs of osimertinib alone or in combination with savolitinib are 44% and 65% respectively, then the 95% confidence intervals provided by 20 subjects are expected to be [22.3%, 67.6%] and [40.8%, 84.6%] respectively with using Clopper-Pearson method and assuming a 10% drop-out rate.

6. ANALYSIS TIMING

There were two analyzes planned in this study. The data cutoff date (DCO) for the ORR preliminary analysis will occur when all patients have had the opportunity to complete two efficacy assessments, which is expected to be 12 weeks after last subject enrollment (LSI). DCO for PFS/OS analysis will be estimated at 40 months after LSI when PFS reaches 80% data maturity (32 PFS events, 16 PFS events per cohort), assuming an enrollment period of 12 months and Cohort 2 median PFS was 18 months.

7. MISSING DATA

A 10% drop-out rate was included in the sample size calculation. Complete case analysis will be used as primary analysis for an outcome if the proportion of missing data is below 10% (at least 40 evaluable patients).

If less than 40 evaluable patients remain, missing data patterns will be studied to assess the likelihood of data being missing (completely) at random. Imputation may be done by "multiple imputation" or "last observation carried forward". The method to handle missing data will be ultimately chosen based on the robustness of the analysis results for the available cases ($n < 40$). The imputation method with the smallest confidence interval and point estimates closest to the results of the complete case analysis of available cases will be considered the most robust one. If robustness is lacking due to changes in the direction of differences between treatment groups,

worst- and best-case imputation cases are constructed. The handling of missing data will be reported extensively and transparently in the supplementary material in the final results section.

8. ANALYSIS POPULATION

Full analysis set (FAS): All subjects randomized to receive at least one dose of study treatment. Subjects who were randomized but subsequently received another study intervention were included in the analysis of the treatment group they actually received. Unless otherwise stated, all analyzes will be performed on the FAS set.

9. ANALYSIS OF STUDY CONDUCT

- The database will be cleaned and locked before analysis. No interim analysis will be performed. Analyzes will be performed using R software (version 4.3.2).
- Study enrollment, study treatment administration, reasons for discontinuation from study treatment, and reasons for study termination will be summarized by treatment arm for the FAS population. Major protocol deviations, including major deviations of inclusion/exclusion criteria, will be reported and summarized by treatment arm.
- Demographics and baseline prognostic characteristics will be summarized between both treatment arms Descriptive baseline summaries of continuous data will present the group mean, standard deviation, median, minimum, and maximum. Descriptive baseline summaries of discrete data will present the category counts as frequencies and percentages.
- The ORR, DCR and their 95% CIs will be summarized descriptively by treatment group and reported using percentages and 95% CIs estimated with use of the Clopper-Pearson method. The weighted logistic regression was used for response outcomes to estimate odds ratios (OR) with 95% CIs.
- Kaplan-Meier methodology will be used to estimate the median PFS and the Kaplan-Meier curve will be constructed for each treatment arm. The number of

patients, number of events, median and quartile PFS, progression-free survival rate and its 95% CI at 3, 6, 9, and 12 months will be reported by treatment arm.

- The methodology used for PFS will be applied for DoR. If there are sufficient numbers of responders and progression events, we will report Kaplan-Meier plots of DoR and summarize the descriptive number of patients per treatment group, number of progressions, median, quartiles, minimum and sum of DoR maximum.
- The methodology used for PFS will be applied for OS. The number of patients, number of events, median and quartile OS, overall survival rate and its 95% CI at 6, 12, 24, and 36 months will be reported by treatment arm.
- The percent change in TL tumor size from baseline at week 12 will be summarized descriptively for each treatment group. The best percentage changes will also be summarized. Waterfall plots will be used to display the percent change in TL tumor size at week 12 compared to baseline and the percent change from optimal compared to baseline. Spider plots will be used to display actual and percent change over time in tumor size for each patient compared to baseline.
- The number of patients who experienced each AE will be summarized by MedDRA system organ class and preferred term. The number and percentage of patients who experienced AEs in different categories (e.g., causally related, CTCAE grade ≥3, etc.) will be summarized and events in each category will be further summarized using MedDRA system organ classes and preferred terms. If a sufficient number of SAEs occur, they will be summarized separately. Length of exposure to the study intervention, rates of discontinuation of sarvotinib and/or osimertinib due to AEs, number and proportion of patients with at least one interruption/delay and dose reduction may also be summarized by treatment group.
- Exploratory analysis will determine whether it is feasible based on the actual situation. This part of the analysis can be described in a separate analysis plan.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Page 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Page 3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Page 4-6
	2b	Specific objectives or hypotheses	Page 6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Page 13-14
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Supplementary information note 2: page 125
Participants	4a	Eligibility criteria for participants	Page 13-14
	4b	Settings and locations where the data were collected	Page 13-14
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Page 14
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Page 16
	6b	Any changes to trial outcomes after the trial commenced, with reasons	No changes.
Sample size	7a	How sample size was determined	Page 16
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Page 15-16
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Page 14
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Supplementary information note 2: page 35-36

Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Supplementary information note 2: page 36-37
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Supplementary information note 2: page 36-37
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Page 16-17
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Page 16-17
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Page 6
	13b	For each group, losses and exclusions after randomisation, together with reasons	Page 6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Page 6
	14b	Why the trial ended or was stopped	Not ended.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Page 23
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Page 6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Page 7-9
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Page 8
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Page 9
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Page 12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Page 9-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Page 9-13

Other information			
Registration	23	Registration number and name of trial registry	Page 13
Protocol	24	Where the full trial protocol can be accessed, if available	Page 13
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Page 21

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.