Janssen Research & Development

Statistical Analysis Plan

A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Protocol 73841937NSC3003; Phase 3

JNJ-61186372 (amivantamab) and JNJ-73841937 (lazertinib)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

FIGURES

VERSION HISTORY

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	11 February 2021	Not Applicable	Initial release

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables and statistical methods for the Phase 3, multicenter, randomized study to compare the efficacy and safety of combining amivantamab (JNJ-61186372) and lazertinib (JNJ-73841937) versus single-agent osimertinib as first-line treatment in participants with epidermal growth factor receptor (EGFR)-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The SAP is to be interpreted in conjunction with the protocol. This SAP covers the planned analysis for the clinical study report (CSR).

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of the amivantamab and lazertinib combination, compared with osimertinib, in participants with EGFR mutation (Exon 19del or Exon 21 L858R substitution) positive, locally advanced or metastatic NSCLC	• Progression-Free-Survival (PFS) according to RECIST v1.1 by blinded independent central review
Secondary	
To further assess the clinical benefit achieved using the amivantamab and lazertinib combination compared with osimertinib in participants with EGFR mutation positive, locally advanced or metastatic NSCLC	• Overall survival • Objective response rate • Duration of response • PFS after first subsequent therapy • Time to symptomatic progression • Intracranial PFS
To evaluate the safety and tolerability of the amivantamab and lazertinib combination compared with osimertinib	• Incidence (%) of severity of adverse events and clinical laboratory abnormalities, assessment of vital signs, and physical examination abnormalities
To evaluate pharmacokinetics or immunogenicity for amivantamab and pharmacokinetics for lazertinib and assess their relationship to selected endpoints (including but not limited to efficacy, safety, and/or patient-reported outcomes)	• Serum amivantamab and lazertinib concentrations, and anti-amivantamab antibodies
To assess health-related quality of life and disease-related symptoms in participants treated with the amivantamab and lazertinib combination compared with osimertinib	• NSCLC-SAQ • EORTC-QLQ-C30
To assess the efficacy of the amivantamab and lazertinib combination, compared with lazertinib monotherapy, in participants with EGFR mutation positive, locally advanced or metastatic NSCLC	• PFS • Overall survival
Exploratory	
To further assess the clinical benefit achieved using the amivantamab and lazertinib combination compared with osimertinib in participants with EGFR mutation positive, locally advanced or metastatic NSCLC	• Disease control rate • Time to treatment discontinuation • Time to subsequent therapy
To assess the intracranial activity of the amivantamab and lazertinib combination compared with osimertinib.	• Intracranial objective response rate • Intracranial duration of response • Time to intracranial disease progression
To further assess health-related quality of life in participants treated with the amivantamab and lazertinib combination compared with osimertinib	• EQ-5D-5L
To explore genetic biomarkers predictive of improved outcome in participants treated with amivantamab in combination with lazertinib, compared with lazertinib and osimertinib monotherapies.	• Characterization of tumor genetics by NGS of ctDNA and genetic analysis of tumor biopsy material at baseline, and at progression • Characterization of circulating EGFR mutation levels by ddPCR of ctDNA at baseline, on therapy, and at progression
To explore mechanisms of resistance to amivantamab and lazertinib and amivantamab/lazertinib combination therapy	• Characterization of tumor protein markers by immunohistochemistry (eg, EGFR, MET) at baseline and at progression • Characterization of changes in tumor genetics, relative to baseline, by NGS of ctDNA and genetic analysis of tumor biopsy material at progression

ctDNA=circulating tumor deoxyribonucleic acid; ddPCR=digital droplet polymerase chain reaction; EGFR=epidermal growth factor receptor; EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L=EuroQol five-dimensional descriptive system (5-level version); MET=mesenchymal-epithelial transition; NGS=next-generation sequencing; NSCLC=non-small cell lung cancer; NSCLC-SAQ=Non-Small Cell Lung Cancer – Symptom Assessment Questionnaire; RECIST=Response Evaluation Criteria in Solid Tumors.

1.2. Study Design

This randomized, multicenter, Phase 3 study will compare the efficacy and safety of combining amivantamab and lazertinib (Arm A) versus single-agent osimertinib (Arm B) as first-line treatment in participants with EGFR-mutated locally advanced or metastatic non-small cell lung cancer not amenable to curative therapy. Combining amivantamab and lazertinib may lead to improved treatment outcomes through synergistic anti-EGFR activity, prevention of EGFR- or MET-based resistance to a third-generation EGFR TKI, and potential recruitment of Fc-bearing immune cells in the anti-tumor response. The contribution of amivantamab to the activity of the combination will be assessed by comparing the efficacy observed in the amivantamab and lazertinib combination arm (Arm A) with that in a lazertinib monotherapy arm (Arm C).

The study will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. Participants must complete screening procedures within 28 days before randomization. To be randomized, all participants must have been previously diagnosed with NSCLC, characterized by Exon 19del or Exon 21 L858R substitution EGFR mutations.

The Treatment Phase for a participant will begin on Cycle 1 Day 1 and continue as 28-day cycles until the End of Treatment visit, approximately 30 days after discontinuation of study treatment. Participants who discontinue study treatment for any reason will be followed for survival and symptomatic progression in the Follow-up Phase. The Follow-up Phase starts after the End of Treatment Visit and continues until the end of study, death, lost to follow-up, or withdrawal of consent, whichever comes first.

Approximately 1000 eligible participants will be randomly assigned to study treatment in a 2:2:1 ratio (Arm A, B, and C respectively). Randomization will be stratified by mutation type (Exon 19del vs Exon 21 L858R), race (Asian vs non-Asian), and history of brain metastasis (present vs absent).

Study Treatment Groups and Duration

- **Arm A**: Approximately 400 participants will be assigned to open-label treatment with the combination of amivantamab (1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg by intravenous [IV] infusion, once weekly for the first 4 weeks and then once every 2 weeks) and lazertinib (240 mg orally, once daily).

- **Arm B**: Approximately 400 participants will receive double-blind treatment with single-agent osimertinib (80 mg orally, once daily).

- **Arm C**: Approximately 200 participants will receive double-blind treatment with single-agent lazertinib (240 mg orally, once daily).

Study treatments may be withheld and the dosages may be subsequently modified to manage treatment-related toxicity.

Study treatment should continue until one of the following criteria applies: documented radiographic disease progression using Response Evaluation Criteria in Solid Tumors (RECIST)

v1.1 (Exception: Continuation of study treatment after disease progression may be allowed in accordance with local practice, after consultation with the Medical Monitor, if the investigator believes the participant is deriving clinical benefit); withdrawal of consent; the investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study treatment; the participant becomes pregnant; or noncompliance with study treatment or procedure requirements.

Tumor response will be assessed by blinded independent central review (BICR) according to RECIST v1.1. Baseline disease assessments, including brain magnetic resonance imaging (MRI) will be performed no more than 28 days prior to randomization. Repeat imaging will occur at regular intervals, as defined in the Schedule of Activities (SoA) (see study protocol Section 1.3), until disease progression.

Safety will be assessed by physical examinations, laboratory tests, vital signs, electrocardiograms, left ventricular ejection fraction (echocardiogram or multigated acquisition), Eastern Cooperative Oncology Group (ECOG) performance status, monitoring of adverse events, and concomitant medication usage.

Health-related quality of life in participants will be assessed by patient-reported outcomes (PROs) measures including EuroQol five-dimensional descriptive system (EQ-5D-5L), European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30), and Non-Small Cell Lung Cancer - Symptom Assessment Questionnaire (NSCLC-SAQ).

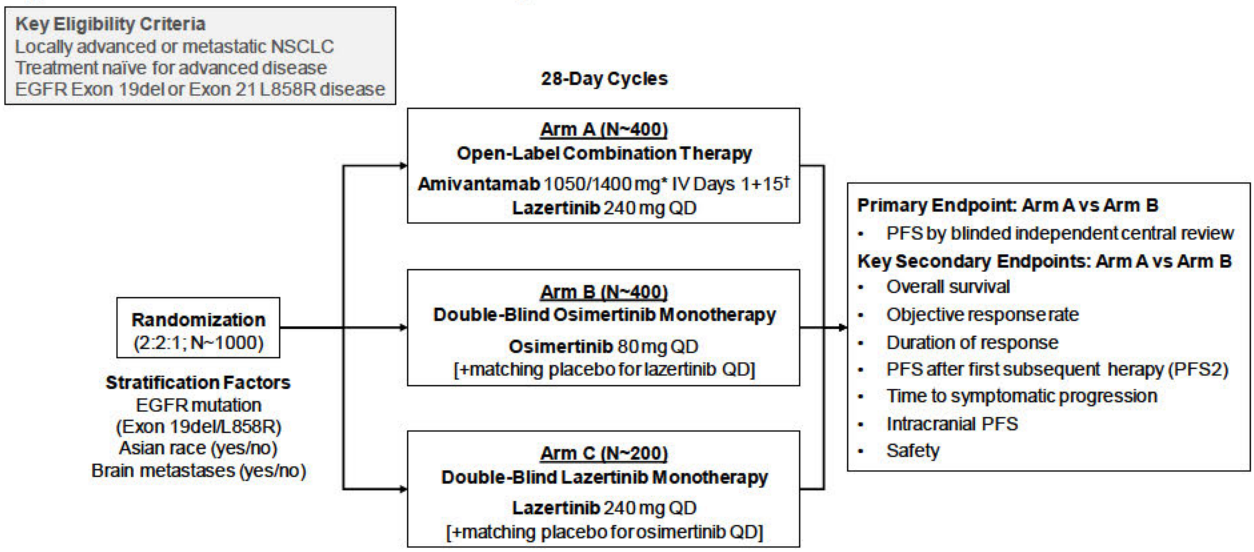
All study evaluations will be conducted according to the SoA in study protocol.

The primary endpoint of the study is progression-free-survival (PFS). Analysis of the primary endpoint will be performed after approximately 450 PFS events from Arms A and B combined have occurred.

There are two interim analyses for PFS planned to test futility and early efficacy. An Independent Data Monitoring Committee (IDMC) will be established to review data at 2 interim analyses prior to the final analysis of the primary endpoint. The futility analysis will occur when approximately 120 (27%) PFS events (from Arms A and B combined) been observed. The second interim analysis will be performed when approximately 280 (62%) PFS events (from Arms A and B combined) have occurred. In addition to the 2 interim analyses, the IDMC will also review evolving safety data at regular time intervals. Details on the interim analyses and IDMC are described in Section 5.8.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



EGFR=epidermal growth factor receptor; IV=intravenous; NSCLC=non-small cell lung cancer; PFS=progression-free survival; QD=once daily
*Weight-based dosing: <80 kg/≥80 kg
†Cycle 1: Days 1/2 (split dose), 8, 15, 22; Cycles 2+: Days 1, 15

Randomization

Participants will be randomly assigned to 1 of 3 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by mutation type (Exon 19del vs Exon 21 L858R), race (Asian vs non-Asian), and history of brain metastasis (present vs absent). For randomization and statistical analyses, a participant will be stratified as Asian if they report their race is either Asian or mixed, with any Asian component.

The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study treatment kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

Blinded treatment will be used in the control arms (Arms B and C) to reduce potential bias during data collection and evaluation of clinical endpoints. Open-label treatment will be used in Arm A due to infusion.

All participants, investigators, site staff and Janssen study team members associated with the study conduct are to remain blinded to treatment group assignment (Arms B and C) until the clinical database is finalized.

Specifically, the image readers responsible for blinded independent central review will remain blinded for all 3 treatment arms.

For the IDMC data review, unblinded data results will be provided by the unblinded external Statistical Supporting Group.

2. STATISTICAL HYPOTHESES

The primary efficacy endpoint of the study is progression-free survival (PFS). The null hypothesis is that there is no difference of treatment effect in PFS between amivantamab and lazertinib combination and single agent osimertinib in participants with EGFR mutation (Exon 19del or Exon 21 L858R) positive, locally advanced or metastatic NSCLC. The alternative hypothesis is that, compared with single agent osimertinib, the amivantamab and lazertinib combination will prolong PFS.

The key secondary efficacy endpoint is overall survival (OS). With OS, the null hypothesis is that there is no difference of treatment effect between amivantamab and lazertinib combination and single agent osimertinib in the aforementioned population. The alternative hypothesis is that, compared with single agent osimertinib, the amivantamab and lazertinib combination will prolong OS.

To strongly control Type I error rate at 0.05 for the study, a hierarchical testing approach for the primary endpoint and key secondary endpoint will be used. The comparison between the combination and osimertinib for OS will be conducted with a total 2-sided alpha of 0.05 only if the testing on PFS shows statistical significance.

3. SAMPLE SIZE DETERMINATION

The primary objective of the study is to assess the efficacy of the combination of amivantamab and lazertinib, compared with single-agent osimertinib, as measured by PFS by BICR, in accordance with RECIST v1.1 guideline. The sample size calculation was based on the assumption that the combination therapy will result in a 27% reduction in the risk of either disease progression or death over the single agent osimertinib therapy (an HR of 0.73, prolongs the median PFS from 19 months[1] to 26 months). A total of 450 PFS events in Arm A and Arm B combined will provide approximately 90% power to detect a statistically significant difference between the 2 treatment arms with the stratified log-rank test (2-sided alpha=0.05).

Approximately 1000 eligible participants will be randomized in a 2:2:1 ratio to the three arms (Arm A: Arm B: Arm C). Assuming a 25-month recruitment period and an annual dropout rate of approximately 5%, 560 PFS events (approximately 450 events in Arm A and Arm B combined) are expected to occur approximately 42 months after the first participant is enrolled.

When approximately 390 deaths (Arms A and B combined) have been observed from long-term survival follow-up, final analysis of OS will occur. This will provide approximately 80% power to detect a 25% reduction in the risk of death (an HR of 0.75, prolongs the median OS from 39[2] months to 52 months) with a log-rank test at a 2-sided alpha of 0.05.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
Full Analysis Set (FAS)	All randomized participants.
Safety	Randomized participants wo received at least 1 dose of any study treatment.
Pharmacokinetics (PK)/ Immunogenicity Analysis Set	Randomized participants who received at least 1 dose of any study treatment and have at least 1 evaluable postbaseline concentration measurement.[a]
Biomarker Analysis Set	Randomized participants who received at least 1 dose of study treatment and have at least 1 biomarker measurement.

a. Participants may be removed from the estimation of certain pharmacokinetic parameters on an individual basis due to, for example, missing pharmacokinetic samples such that the pharmacokinetic parameters cannot be appropriately derived. These participants will be identified at the time of the analyses along with their reason for removal.

5. STATISTICAL ANALYSES

5.1. General Considerations

All statistical hypothesis tests and 95% confidence interval presented will be 2-sided.

5.1.1. Visit Windows

Participants should start study drug within 72 hours after randomization. Visit windowing will be based on cycles. Unless otherwise specified, data to be analyzed or presented over time will be presented by cycle, day and time point (as appropriate) that are recorded in CRF.

5.1.2. Study Day/Relative Day

Study day or relative day is defined as:

- Reference date (Day 1) = randomization date for efficacy assessment, or first dose date of study drug for safety assessment.
- Study Day = assessment date – reference date + 1 for assessment performed on or after the reference date; assessment date – reference date for assessment performed before the reference date.

There is no 'Day 0'.

5.1.3. Study Treatment and Study Drug

In this study, study treatment refers to amivantamab and lazertinib combination (Arm A), single-agent osimertinib (Arm B) and single-agent lazertinib (Arm C). Study drug refers to each study agent within a treatment group.

5.1.4. Baseline Measurement

Baseline measurement is defined as the closest non-missing measurement taken on or prior to the first study drug administration (including time if time is available). If the first administration date

is missing or the administration is not done, then the baseline measurement is the closest non-missing measurement taken on or prior to the corresponding visit date (if visit date is not available, then randomization date should be used).

5.2. Participant Dispositions

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by treatment group and overall:

- Participants randomized
- Participants who received study treatment
- Participants who discontinued study treatment
- Reason for discontinuation of study treatment
- Participants who terminated study prematurely
- Reason for termination of study

A listing of participants will be provided for the following categories:

- Participants who discontinued study treatment
- Participants who terminated study prematurely
- Participants who were unblinded during the study period

5.3. Primary Endpoint Analysis

5.3.1. Definition of Endpoint

Progression-free Survival (PFS) is defined as the time from randomization until the date of objective disease progression or death, whichever comes first, based on blinded independent central review (BICR) using RECIST v1.1. Participants who have not progressed or have not died at the time of analysis will be censored at their last evaluable RECIST v1.1 assessment date. If the participant progresses or dies after 2 or more missed disease assessments, the participant will be censored at the time of the last evaluable RECIST v1.1 assessment. If the participant has no evaluable visits or does not have baseline data, the participant will be censored at Day 1 (randomization) unless the participant dies within 2 visits of baseline.

Key censoring rules for PFS are summarized below.

Key censoring rules for PFS

Situation	Date of Censoring
No evaluable baseline or postbaseline disease assessment	Censored at the date of randomization

Lost to follow-up or withdraw from study	Censored at the date of last evaluable disease assessment
No documented disease progression or death	Censored at the date of last evaluable disease assessment
Documented disease progression or death after 2 or more consecutive missed/unevaluable disease assessments*	Censored at the date of last evaluable disease assessment before the missed/unevaluable visits

*If no evaluable disease assessment before the consecutive missed/unevaluable visits, participants will be censored at the date of randomization.

PFS is calculated in months as follows:

- PFS = (date of PD/death or censoring – date of randomization + 1) / (365.25/12).

5.3.2. Estimand

Estimand Scientific Question of Interest: What is the relative effect of amivantamab and lazertinib combination compared to osimertinib as first-line treatment in prolonging PFS in patients with EGFR mutation (Exon 19del or Exon 21 L858R substitution) positive, locally advanced or metastatic NSCLC not amenable to curative therapy?

Study Intervention:

- Experimental: amivantamab and lazertinib combination
- Control: osimertinib

Population: Patients with EGFR mutation (Exon 19del or Exon 21 L858R substitution) positive, locally advanced or metastatic NSCLC

Variable: PFS

Summary Measure (Population-level summary): hazard ratio (HR) of amivantamab and lazertinib combination vs single-agent osimertinib

Intercurrent events and their corresponding strategies

Intercurrent Events	**Name of Strategy for Addressing Intercurrent Events and Its Description**
Study treatment discontinuation due to any reason	**Treatment Policy strategy:** use time to disease progression or death, regardless of whether or not study treatment discontinuation had occurred
Study treatment switching to other anticancer therapy	**Treatment Policy strategy:** use time to disease progression or death, regardless of whether or not started subsequent anticancer therapies
Death	**Composite Variable strategy:** death being a component of the variable

5.3.3. Primary Analysis Methods

The primary hypothesis will be tested at an overall 2-sided significant level of 0.05. The exact significance level at the interim and final PFS analyses will be determined by group sequential design with the O'Brian Fleming alpha spending approach as implemented by the Lan-DeMets method.

Analysis of PFS will be based on the Full Analysis Set.

The treatment effect of the combination, compared with osimertinib, on PFS will be analyzed using a log-rank test stratified by mutation type (Exon 19del vs Exon 21 L858R), race (Asian vs non-Asian), and history of brain metastasis (present vs absent). The p-value generated from the stratified log-rank test will be used for the primary hypothesis testing. Hazard ratio and its 95% confidence interval will be estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable. In addition, the comparison for Arm A vs Arm C will also be carried out using the same analysis model.

The median PFS with 95% CI will be estimated using Kaplan-Meier method. The Kaplan-Meier PFS curve will also be plotted by treatment group. In addition, PFS rates with 95% CI will be estimated by Kaplan-Meier method at landmarks (e.g. at 6-month, 12-month, and 18-month, etc.) and reported for each treatment group. The number and percentage of participants who had a PFS event or were censored will be reported and reasons for PFS event and censoring will be summarized.

For assessment of internal consistency and investigation of homogeneity of the treatment effect across subgroups, a subgroup analysis on pre-specified subgroups defined in Section 5.7.6 will be conducted. Forest plots of subgroup analysis will be generated.

5.3.4. Sensitivity Analysis

The following sensitivity analyses will be conducted to evaluate the robustness of the primary analysis of PFS.

5.3.4.1. Unstratified Analysis of PFS

Sensitivity analysis using unstratified log-rank test will also be performed.

5.3.4.2. Assess Hazards Proportional Assumption

The proportional hazards assumption will be examined by plotting log(-log[estimated survival distribution function]) against log(survival time). In addition, a treatment by logarithm-transformed time interaction term will be added into the primary Cox model and tested. A p-value greater than 0.05 for the interaction term will be interpreted as no statistical evidence against the proportional hazard assumption.

5.3.5. Supplementary Analysis

5.3.5.1. Censored for Death/PD after Start of Subsequent Anticancer Therapy

Supplementary analysis will be performed using progression or death prior to the start of the subsequent anticancer therapy as events. Participants who have not progressed or have not died before the initiation of subsequent therapy will be censored at the date of the last evaluable disease assessment prior to the start of subsequent therapy.

5.3.5.2. Not Censored for Missing More Than One Disease Evaluation

Additional supplementary analysis will be performed using all progression or death, whichever occur first, as event regardless missed/unevaluable disease assessment for 2 or more consecutive visits.

5.4. Secondary Endpoints Analysis

5.4.1. Overall Survival

5.4.1.1. Definition

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

5.4.1.2. Estimand

Estimand Scientific Question of Interest: What is the relative effect of amivantamab and lazertinib combination compared to osimertinib as first-line treatment in prolonging OS in patients with EGFR mutation (Exon 19del or Exon 21 L858R substitution) positive, locally advanced or metastatic NSCLC not amenable to curative therapy?

Study Intervention:

- Experimental: amivantamab and lazertinib combination
- Control: osimertinib

Population: Participants with EGFR mutation (Exon 19del or Exon 21 L858R substitution) positive, locally advanced or metastatic NSCLC

Variable: OS

Summary Measure (Population-level summary): hazard ratio (HR) of amivantamab and lazertinib combination vs single-agent osimertinib

Intercurrent events and their corresponding strategies

Intercurrent Events	**Name of Strategy for Addressing Intercurrent Events and Its Description**
Study treatment switching to other anticancer therapy	**Treatment Policy strategy:** use time to death, regardless of whether or not started subsequent anticancer therapies

5.4.1.3. Analysis Methods

As the key secondary endpoint, OS will be tested with a total 2-sided alpha of 0.05 only if statistical significance for PFS is achieved. One interim analysis of OS is conducted at the clinical data cut-off for final PFS analysis. Participants will then be followed up for final analysis of OS when 390 death from Arms A and B combined have occurred. The exact significance level at the interim and final OS analyses will be determined by group sequential design with the O'Brian Fleming alpha spending approach as implemented by the Lan-DeMets method.

The comparison between the combination and osimertinib in OS will be carried out using the similar methodology and model as for the primary analysis of PFS in the Full Analysis Set. In addition, the comparison for Arm A vs Arm C will also be performed using the same analysis model.

A subgroup analysis on pre-specified subgroups defined in Section 5.7.6 will be conducted. Forest plots of subgroup analysis will be generated.

Sensitivity Analysis

Sensitivity analysis using unstratified log-rank test will be performed.

Supplementary Analysis

If a significant number of participants randomized to treatment B subsequentially switched to treatment A, analysis will be carried out using Inverse Probability of Censoring Weighting (IPCW) (Robins and Finkelstein 2000)[3] to adjust for confounding from treatment crossover. The weights to reduce the bias will be estimated from baseline covariates and time-dependent covariates predictive of treatment crossover such as baseline disease burden, occurrence of serious adverse event before crossover, based on a logistic regression model. Hazard ratio and its 95% confidence interval will be estimated based on a Cox regression analysis with IPCW.

5.4.2. Objective Response Rate (ORR)

5.4.2.1. Definition

ORR is defined as the proportion of participants who achieve either a complete response (CR) or partial response (PR), as defined by BICR using RECIST v1.1. Data obtained up until progression or last evaluable disease assessment in the absence of progression will be included in the assessment of ORR. However, any CR or PR, which occurred after a further anticancer therapy was received, will not be included in the numerator for the ORR calculation. Participants who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the response rate.

5.4.2.2. Analysis Methods

The analysis of ORR will be based the Full Analysis Set. ORR will be analyzed using a logistic regression stratified by mutation type (Exon 19del vs Exon 21 L858R), race (Asian vs non-Asian), and history of brain metastasis (present vs absent). The results of the analysis will be presented in terms of an odds ratio together with its associated 95% confidence interval and corresponding p-value. Treatment comparisons for Arm A vs Arm B and Arm A vs Arm C will be made within the same model.

The same analysis will be carried out for ORR based on confirmed PR or CR from subsequent assessments. The confirmation by subsequent assessments should be performed not less than 4 weeks after the criteria for PR or CR are first met.

5.4.3. Duration of Response (DoR)

5.4.3.1. Definition

DoR is defined as the time from the date of first documented response (PR or CR) until the date of documented progression or death, whichever comes first, for participant who have PR or CR. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a participant does not progress following a response, then his/her duration of response will be until the PFS censoring time. Participants who started a subsequent anticancer therapy in the absence of progression will be censored at the last disease assessment before the start of subsequent therapy.

5.4.3.2. Analysis Methods

A Kaplan-Meier plot for duration of response and median duration of response with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented by treatment group.

5.4.4. Progression-free Survival After the First Subsequent Therapy (PFS2)

5.4.4.1. Definition

The PFS2 is defined as the time from randomization until the date of second objective disease progression, after initiation of subsequent anticancer therapy, based on investigator assessment (after that used for PFS) or death, whichever comes first. Any deaths are considered as PFS2 events. Participants alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression (i.e., last disease assessment).

Key censoring rules for PFS2

Situation	Date of Censoring
No postbaseline disease assessment	Randomization
Disease progression on study treatment and no subsequent therapy	The date of last disease assessment
Two or more subsequent therapies without a progression	The last date of disease assessment prior to the start of 2nd line of subsequent therapy
Treated beyond progression	The last date of disease assessment

5.4.4.2. Analysis Methods

PFS2 will be analyzed using the similar method as the primary analysis of PFS in the Full Analysis Set.

5.4.5. Time to Symptomatic Progression (TTSP)

5.4.5.1. Definition

TTSP is defined as the time from randomization to documentation in the eCRF of any of the following (whichever occurs earlier): onset of new symptoms or symptom worsening that is considered by the investigator to be related to lung cancer and requires either a change in anticancer treatment and/or clinical intervention to manage symptoms. The TTSP for a participant who does

not experience any of these events will be censored on the date on which the participant was last known to be event-free.

5.4.5.2. Analysis Methods

TTSP will be analyzed using the similar method as the primary analysis of PFS in Full Analysis Set.

In addition, similar analyses will be carried out for the following two components of time to symptomatic progression:

- the time from randomization to documentation in the eCRF of any of the following (whichever occurs earlier): onset of new symptoms or symptom worsening that is considered by the investigator to be related to lung cancer and requires a change in anticancer treatment.

- the time from randomization to documentation in the eCRF of any of the following (whichever occurs earlier): onset of new symptoms or symptom worsening that is considered by the investigator to be related to lung cancer and requires clinical intervention to manage symptoms.

5.4.6. Intracranial Progression-free Survival

5.4.6.1. Definition

Intracranial PFS is defined as the time from randomization until the date of objective intracranial disease progression or death, whichever comes first, based on BICR using RECIST v1.1. Specifically, intracranial disease progression is defined as having progression of brain metastasis or occurrence of new brain lesion. Participants who have not progressed intracranially or died will be censored at their last evaluable intracranial disease assessment date.

5.4.6.2. Analysis Methods

Intracranial PFS will be analyzed using the similar method as the primary analysis of PFS in Full Analysis Set.

Similar analysis will be repeated in the subgroup of randomized participants who had history of brain metastasis at screening. The corresponding Cox model will be stratified by mutation type and race.

5.4.7. Patient Reported Outcome - EORTC-QLQ-C30

5.4.7.1. Definition

EORTC-QLQ-C30 measure cancer patients' functioning for all cancer types. It includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status/quality of life (GHS/QoL) scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The instrument contains 28 items using a verbal rating scale with 4 response options: "Not at All," "A Little," "Quite a Bit," and "Very Much" (scored 1 to 4). Two additional items use response options (1 to 7): 1 = Very

Poor, to 7 = Excellent. All scale and item scores will be linearly transformed to be in the range from 0 to 100 according to the algorithm in EORTC QLQ-C30 scoring manual, version 3.0 (Fayers et al, 2001)[4]. A higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

5.4.7.2. Analysis Methods

Unless otherwise specified, EORTC-QLQ-C30 data will be analyzed based on Full Analysis Set.

Compliance Rates

Compliance rates for completion of EORTC QLQ-C30 at each time point will be generated based on the actual number of assessments received over the number of expected.

Change from Baseline

For EORTC QLQ-C30 domain scores (GHS/QoL, functional scales, symptom scales), and single symptom items, descriptive statistics will be reported at baseline and at each visit for absolute value and for change from baseline.

Line plots of the change from baseline with standard error over time by treatment group will be displayed.

Time to Deterioration

Time to deterioration in EORTC QLQ-C30 measures is defined as the time from randomization until the date of the first clinically meaningful deterioration, or death. A clinically meaningful change is defined as a decrease for GHS/QoL and functional scales or an increase for symptom scales/items in the score from baseline of ≥10 (Osoba et al 1998)[5]. Participants who have not shown a deterioration or have not died at the time of analysis will be censored at their last PRO assessment date.

Time to deterioration in EORTC QLQ-C30 measures will be analyzed using the similar method as the primary analysis of PFS.

Improvement Rate

Improvement rate in EORTC QLQ-C30 measures is defined as the number (%) of patients who showed a clinically meaningful improvement (a ≥10 increase in score from baseline for GHS/QoL and functional scales, or a ≥10 decrease in score from baseline for symptom scales/items).

Improvement rate will be analyzed using a stratified logistic regression with treatment as a factor. Odds ratio together with its 95% confidence interval and corresponding p-value will be provided.

5.4.8. Patient Reported Outcome - NSCLC-SAQ

5.4.8.1. Definition

NSCLC-SAQ is a 7-item PRO measure designed for use in adults to assess symptoms of advanced NSCLC. The NSCLC-SAQ has a seven-day recall period. It contains five domains and

accompanying items that were identified as symptoms of NSCLC: cough (1 item), pain (2 items), dyspnea (1 item), fatigue (2 items), and appetite (1 item). Each item uses a response scale between 0 to 4, with higher scores indicating more severe symptomatology. A single score of pain is created by selecting the higher severity of either item ('chest pain' or 'general pain'). A single score of fatigue is calculated using the mean of 2 items ('low energy' and 'tire easily'). All five of these domains must be non-missing to compute a total score, with a response range from 0 to 20.

Unless otherwise specified, NSCLC-SAQ data will be analyzed based on Full Analysis Set.

5.4.8.2. Analysis Methods

Compliance Rates

Compliance rates for completion of NSCLC-SAQ at each time point will be generated based on the actual number of assessments received over the number of expected.

Change from Baseline

Descriptive statistics will be reported for the five individual scores and total score at baseline and at each visit for absolute value and for change from baseline.

Line plots of the change from baseline with standard error over time by treatment group will be displayed.

Time to Deterioration

Time to deterioration in NSCLC-SAQ measures is defined as the time from randomization until the date of the first clinically meaningful deterioration, or death. A clinically meaningful change in individual score is defined as an increase from baseline of ≥1, and a clinically meaningful change in total score is defined as an increase from baseline of ≥2. Participants who have not shown a deterioration or have not died at the time of analysis will be censored at their last PRO assessment date.

Time to deterioration in NSCLC-SAQ measures will be analyzed using the similar method as the primary analysis of PFS.

Each individual item will also be summarized using count and percentage by treatment and study visit.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

5.5.1. PFS Based on Investigator Assessment

PFS based on investigator review using RECIST v1.1 will be analyzed in a similar manner as described in Section 5.3.3 for PFS based on BICR.

5.5.2. Disease Control Rate (DCR)

5.5.2.1. Definition

DCR is defined as the percentage of participants achieving complete or partial response, or stable disease as defined by BICR using RECIST v1.1.

5.5.2.2. Analysis Methods

DCR will be analyzed using the similar method as the analysis of ORR in Full Analysis Set.

5.5.3. Time to Treatment Discontinuation (TTD)

5.5.3.1. Definition

TTD is defined as the time from randomization to discontinuation of treatment for any reason, including disease progression, treatment toxicity, death, and will be utilized to capture clinical benefit for participants continuing treatment beyond RECIST v1.1 defined disease progression.

5.5.3.2. Analysis Methods

TTD will be analyzed using the similar method as the primary analysis of PFS in Full Analysis Set.

5.5.4. Time to Subsequent Therapy (TTST)

5.5.4.1. Definition

TTST is defined as the time from the date of randomization to the start date of the subsequent anticancer therapy following study treatment discontinuation or death, whichever comes first. Participants alive and not starting subsequent therapy will be censored on the date on which the participant was last known to be alive.

5.5.4.2. Analysis Methods

TTST will be analyzed using the similar method as the primary analysis of PFS in Full Analysis Set.

5.5.5. Intracranial Objective Response Rate

5.5.5.1. Definition

Intracranial ORR is defined as the proportion of participants who achieve either an intracranial CR or intracranial PR, as defined by BICR using RECIST v1.1. , among the participants with a history of brain metastasis at screening. Data obtained up until intracranial disease progression or last evaluable intracranial disease assessment in the absence of progression will be included in the assessment of intracranial ORR. However, any intracranial CR or PR, which occurred after a further anticancer therapy was received, will not be included in the numerator for the intracranial ORR calculation.

5.5.5.2. Analysis Methods

Intracranial ORR will be analyzed using the similar method as the analysis of ORR without the stratification factor of brain metastasis history.

5.5.6. Intracranial Duration of Response

5.5.6.1. Definition

Intracranial DoR is defined as the time from the date of first documented intracranial response (CR or PR) until the date of documented intracranial progression or death, whichever comes first, for participant with a history of brain metastasis at screening who have intracranial CR or PR. The end of response should coincide with the date of intracranial disease progression or death from any cause used for the intracranial PFS endpoint. If a participant does not progress intracranially following a response, then his/her duration of response will be until the intracranial PFS censoring time. Participants who started a subsequent anticancer therapy in the absence of intracranial progression will be censored at the last intracranial disease assessment before the start of subsequent therapy.

5.5.6.2. Analysis Methods

A Kaplan-Meier plot for intracranial DoR and median intracranial DoR with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented by treatment group.

5.5.7. Time to Intracranial Disease Progression

5.5.7.1. Definition

Time to intracranial disease progression is defined as the time from randomization until the date of objective intracranial disease progression, based on BICR using RECIST v1.1. Specifically, intracranial disease progression is defined as having progression of brain metastasis or occurrence of new brain lesion. Participants who have not progressed intracranially will be censored at their last evaluable intracranial disease assessment date.

5.5.7.2. Analysis Methods

Time to intracranial disease progression will be analyzed using the similar method as the primary analysis of PFS in Full Analysis Set.

5.5.8. Time to Response

5.5.8.1. Definition

Time to response (i.e. time to first response) is defined as the time from the date of randomization to the date of first documentation of a response (PR or CR) prior to any disease progression and subsequent anticancer therapy, as defined by BICR using RECIST v1.1., for participants who have PR or CR as their best response.

5.5.8.2. Analysis Methods

Descriptive statistics (mean, standard deviation, median, and range) will be provided to summarize time to response.

5.5.9. Patient Reported Outcome - EQ-5D-5L

5.5.9.1. Definition

The EQ-5D-5L is a validated tool to measure health status and health utility. It is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale (VAS) rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual (but allows for values less than 0 by UK scoring algorithm).

Unless otherwise specified, EQ-5D-5L data will be analyzed based on Full Analysis Set.

5.5.9.2. Analysis Methods

Compliance Rates

Compliance rates for completion of EQ-5D-5L at each time point will be generated based on the actual number of assessments received over the number of expected.

Change from Baseline

Descriptive statistics will be reported for the VAS and utility score at baseline and at each visit for absolute value and for change from baseline.

The change in the VAS and utility score from baseline over time will be analyzed using MMRM in a similar manner to EORTC QLQ-C30 measures. Randomized participants who receive at least 1 dose of study treatment and have at least 1 evaluable postbaseline measurement will be included in the analysis.

Line plots of the change from baseline with standard error over time by treatment group will be displayed.

5.6. Safety Analyses

All safety analyses will be based on the safety analysis set based on actual treatment received, unless otherwise specified.

For all continuous safety variables, descriptive statistics by treatment group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by treatment group using frequency counts and percentages.

5.6.1. Extent of Exposure

All the exposure information will be summarized based on safety analysis set by treatment group, and for each study drug within a treatment group.

Study treatment duration is defined as (date of last dose of study treatment – date of first dose of study treatment) +1. Descriptive statistics for duration of study treatment will be presented in months by treatment group.

The total number of administration cycles of amivantamab received for each participant will be summarized by descriptive statistics. Cumulative duration of amivantamab will be provided by cycle (≥1 cycle, ≥2 cycles, …). Total number of amivantamab infusion and the total dose of amivantamab for each participant will be summarized by descriptive statistics.

Total dose days of study drug, defined as the total number of days that study drug was administered to the participant (excluding days off study drug), will be summarized for lazertinib (Arms A and C) and osimertinib descriptively. Cumulative duration of lazertinib (Arms A and C) and osimertinib will also be provided by month (≥1 month, ≥2 months, …). Total dose administrated for lazertinib (Arms A and C) and osimertinib will be summarized by descriptive statistics.

The relative dose intensity (%) defined as the ratio of total actually received dose versus total prescribed dose will be summarized by descriptive statistics.

The number of interruptions during the amivantamab infusion due to AE will be summarized.

The number (%) of participants with a dose reduction/dose not administrated will be summarized. Reasons for dose reduction/dose not administrated will also be summarized.

The number (%) of participants with cycle delay will be summarized by treatment group. The reason for cycle delay will also be summarized.

5.6.2. Compliance of Disease Evaluation

Tumor assessment will occur at regular intervals, as defined per SoA in study protocol, based on repeated whole body and intracranial imaging, respectively. Descriptive statistics will be provided for whole body and intracranial imaging assessments separately, by treatment and overall for the Full Analysis Set for :

- Number of participants missed at least 1 scheduled disease evaluation
- Number of participants missed 2 or more consecutive scheduled disease evaluation
- Number of missed scheduled disease evaluation per participant

5.6.3. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the

initial administration of study treatment through the day of last dose plus 30 days, or until the start of subsequent anticancer therapy (if earlier), is considered to be treatment emergent. If the event occurs on the day of the initial administration of study treatment, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study treatment based on partial onset date or resolution date. All reported treatment-emergent adverse events (TEAEs) will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group.

The incidence (%) of TEAEs will be summarized overall, by MedDRA system organ class (SOC) and preferred term (PT), by toxicity grade, and by relationship to study drug administration.

5.6.3.1. Treatment Emergent Adverse Events

An overview of TEAEs reported through the study will be provided. The overview will include summaries of participants with TEAEs, with TEAEs related to study drug, with TEAEs of maximum toxicity grade of 1 to 5, Serious TEAEs, TEAEs leading to discontinuation of any study drug, and deaths due to TEAE.

5.6.3.1.1. All TEAEs

- Incidence (%) of TEAEs by SOC and PT

5.6.3.1.2. Toxicity Grade 3 or higher TEAEs

- Incidence (%) of toxicity grade 3 or higher TEAEs by SOC and PT

5.6.3.1.3. Study Drug-Related TEAEs

- Incidence (%) of TEAEs by relationship to treatment/study drug, and by SOC and PT
- Incidence (%) of TEAEs with toxicity grade 3 or higher by relationship to treatment/study drug, and by SOC and PT
- Incidence (%) of TEAEs leading to study drug interruption/dose reduction by relationship to treatment/study drug, and by SOC and PT
- Incidence (%) of TEAEs leading to study drug discontinuation by relationship to treatment/study drug , and by SOC and PT

5.6.3.1.4. Serious TEAEs

- Incidence (%) of serious TEAEs by SOC and PT
- Incidence (%) of serious TEAEs by toxicity grade, and by SOC and PT
- Incidence (%) of serious TEAEs by relationship to treatment/study drug, and by SOC and PT
- Listing of participants with any serious TEAEs

5.6.3.1.5. TEAEs Leading to Study Drug Interruption/Dose Reduction

Incidence (%) of TEAEs leading to study drug/dose reduction will be summarized respectively by SOC and PT. The summaries will be presented for all toxicity grades and for toxicity grade 3 or higher.

5.6.3.1.6. TEAEs Leading to Discontinuation of Study drug

Incidence (%) of TEAEs leading to study drug discontinuation will be summarized by SOC and PT. The summaries will be presented by all toxicity grades and toxicity grade 3 or higher. The AEs leading to discontinuation of any study drug are based on AEs recorded in the AE CRF page with an action taken of drug withdrawal for any study drug.

5.6.3.2. Adverse Events of Special Interest

Adverse events of special interest are pneumonitis/interstitial lung disease (ILD), rash, and infusion-related-reaction (IRR). The MedDRA preferred terms associated with each of these categories are identified in Appendix 6. Additional information will be collected for these events.

Treatment-emergent adverse events of special interest will be included for analysis. Incidence (%) for the following AEs will be provided for each AE of special interest as appropriate:

- TEAEs by PT
- TEAEs by toxicity grade
- TEAEs of toxicity grade 3 or higher by PT
- Serious TEAEs by PT
- TEAEs by relationship to study drug
- Serious TEAEs by PT
- Serious TEAEs by relationship to study drug
- TEAEs leading to study drug discontinuation by PT
- TEAEs leading to study drug discontinuation by relationship to study drug
- TEAEs leading to death by PT

Additional analyses will be provided based on information collected in CRF.

Pneumonitis/ILD

For participants with pneumonitis/ILD, frequency tabulation will be provided for:

- Symptom (fever, dry cough, productive cough, dyspnea, chest pain, other)
- Pleural effusion present at the time of the pneumonitis/ILD (yes/no）

Relative onset day (since day 1) of pneumonitis/ILD will be summarized by descriptive statistics (N, mean, standard deviation, median, and range).

All information related to pneumonitis/ILD collected in CRF page will be presented in listing.

Rash

Relative onset day (since day 1), duration, and time between onset and the preceding infusion administration will be summarized for rash by descriptive statistics (N, mean, standard deviation, median, and range) in days.

IRR

Incidence (%) of IRR leading to infusion modification (infusion interrupted, infusion rate decreased, and infusion aborted) will be presented.

Relative onset day (since day 1), and duration will be summarized for IRR by descriptive statistics (N, mean, standard deviation, median, and range) in days.

5.6.3.3. Deaths

5.6.3.3.1. Death Due to TEAEs

The number of participants who died due to TEAEs will be summarized by preferred term and relationship to study drug. The TEAEs included in this table are AEs with outcome of death or toxicity grade of 5 recorded in the AE CRF page within 30 days of the last dose or until the start of subsequent anticancer therapy (if earlier).

A listing of participants who died due to TEAE will be provided.

5.6.3.3.2. All Deaths

A summary of all death and cause of death will be tabulated. Specifically, the number of participants who died during the study will be summarized. The primary cause of death collected on the death information CRF page will be reported.

The similar summaries will be presented for participants who died within 30 days of last study drug dose.

5.6.4. Additional Safety Assessments

5.6.4.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics will be presented for all chemistry and hematology laboratory tests at scheduled time points. Change from baseline over time will be summarized and displayed. Plots for selected laboratory tests change over time may be provided.

NCI-CTCAE version 5.0 will be used to derive toxicity grades for clinical laboratory tests when applicable. Shift tables from baseline to worst value on treatment (from treatment start to 30 days after last dose or until the start of subsequent anticancer therapy, whichever is later) will be provided. The worst toxicity grade during the treatment will be tabulated.

An eDISH plot of peak ALT/ AST versus peak BILI will be provided along with a listing of participants who had ALT/ AST values > 3xULN or BILI values > 2xULN.

Laboratory criteria for potential Hy's Law cases are defined as:

- Peak aminotransaminases (AT, either ALT or AST) of >3xULN (Upper Limit of Normal);
- Total bilirubin ≥2xULN;
- Alkaline phosphatase (ALK-P) <2xULN prior to or on the same date of the first occurrence of total bilirubin ≥2x ULN.

Note: data from all the on-treatment (postbaseline) visits are combined to check the above laboratory criteria.

All potential Hy's Law cases based on the laboratory criteria will be presented.

5.6.4.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature, respiratory rate, oxygen saturation, pulse/heart rate, blood pressure (systolic and diastolic), as well as weight from physical examination will be summarized at each scheduled timepoint. Change from baseline will be summarized over time. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

Post baseline physical examination findings were collected as AEs, and therefore will not be summarized.

5.6.4.3. Electrocardiogram

Electrocardiograms (ECG) will be performed at Screening, Day 1 of Cycle 1 (within 72 hours before study treatment) and Cycle 2 Day 1 (Arm A: within 30 minutes post-infusion; Arms B/C: 2-4 hours after oral administration), and then to confirm any clinically significant finding during the study. The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QT corrected according to Fridericia's formula (QTcF).

The number and percentage of participants by the following QTcF categories will be summarized at each scheduled time point:

Criteria for Abnormal QTc Values and Changes from Baseline	
QTc value	<=450
	>450 – 480
	>480 – 500
	>500
QTc change from baseline	<=30
	>30 – <=60
	> 60

Descriptive statistics of ECG parameters and change from baseline will be summarized at each scheduled time point.

If ECG measurements are repeated at a visit, they will be averaged. The averaged value will be considered the 'Visit' ECG result.

The interpretation of the ECGs as determined by a qualified physician (investigator or qualified designee) will be displayed by the number and percentage of participants meeting the normality criteria. The interpretation will be summarized over time.

A listing of clinically relevant ECG abnormalities will also be provided.

The above analyses will be carried out for ECG data from both investigator and independent review.

5.6.4.4. Left Ventricular Ejection Fraction (LVEF) Assessments

LVEF will be determined using either echocardiogram (ECHO) or multigated acquisition (MUGA) scan at screening, every 3 cycles starting with C4D1, and End-of-Treatment visit. Descriptive statistics for LVEF and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond the following clinically important limits will be summarized:

- Absolute decrease in LVEF >10% from baseline;
- Absolute LVEF% below LLN.

The above analyses will be carried out for LVEF data from both investigator and independent review.

5.7. Other Analyses

5.7.1. Pharmacokinetics

Serum samples will be collected from participants in Arm A for PK and immunogenicity assessments of amivantamab. Plasma samples will be collected from participants in Arm A for the evaluation of PK of lazertinib. Sampling timepoints are outlined in Table 2 of study protocol.

PK analyses will be performed on the PK analysis set, defined as randomized participants who received at least 1 dose of a corresponding study drug and have at least 1 evaluable postbaseline concentration measurement.

Concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics.

Descriptive statistics (N, mean, SD, median, range, CV (%) and IQ range) will be used to summarize amivantamab and lazertinib concentrations at each sampling time point and for each

PK parameter of amivantamab and lazertinib. PK data may be displayed graphically, such as mean +/- SD PK concentrations over time by study intervention.

Amivantamab concentrations will be presented for all participants and by body weight based on the following baseline body weight categories at each time point:

- <80 kg
- ≥ 80 kg

All participants and samples excluded from the analysis will be clearly documented.

The pharmacokinetic serum/plasma concentration-time data collected from this study will be combined with similar data from other studies to perform population PK and assess the relationship between PK or immunogenicity and selected safety and efficacy endpoints. Details will be provided in a population PK and exposure-response analysis plan and results of the analysis will be presented in a separate report.

5.7.2. Immunogenicity

The incidence (%) of antibodies to Amivantamab will be summarized based on Immunogenicity Analysis Set, defined as all participants who receive at least 1 dose of Amivantamab and have appropriate samples for detection of antibodies to Amivantamab (i.e., participants with at least 1 sample obtained after their first dose of Amivantamab).

A listing of participants who are positive for antibodies to Amivantamab will be provided. The maximum titers of antibodies to Amivantamab will be summarized for participants who are positive for antibodies to Amivantamab.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

5.7.3. Pharmacodynamics (PD)/Biomarkers

Analyses are planned to explore PD and other biomarkers that may be indicative of the mechanisms of action of the study intervention or predictive of efficacy. Correlation of baseline expression levels or changes in expression levels with response or time-to-event endpoints could identify responsive (or resistant) subgroups. Any PD or other biomarker measures will be listed, tabulated, and plotted, as appropriate.

Assessment of additional genes or biomarkers (DNA, RNA, or protein) relevant to lung or other cancers or the mechanism of action of study interventions, may also be performed in blood samples collected during study to better understand mechanisms of response or resistance to study interventions.

Alterations in blood may be evaluated for correlation with response to study interventions, tumor burden, and disease progression as data warrant.

Plasma mutation data derived from ctDNA NGS and PCR analyses collected from this study will be used to perform mutational analysis and assess the relationship of individual mutations, and classes of mutations, to efficacy endpoints. IHC analyses on tissue specimens collected from this study will be used to assess the relationship of exploratory endpoints to efficacy endpoints. Additional exploratory endpoints may be explored from serum samples collected from this study, and may be used to understand the relationship of these endpoints to efficacy endpoints. Results of these analyses will be presented in a separate report.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

The relationship between PK and PD measures may be evaluated by PK/PD modeling. Participants may be grouped by dose schedule or clinical response. Results of PD and exploratory biomarker analyses will be presented in separate reports.

5.7.5. Health Economics

Not Applicable

5.7.6. Definition of Subgroups

The following pre-specified subgroup analyses are to be performed for the efficacy and/or safety endpoints. Additional subgroup analyses may be planned if deemed necessary.

Definition of Subgroups

Subgroup	Definition
Age Group	<65 years, ≥65 years; <75 years, ≥75 years
Sex	Male, Female
Race	Asian, Non-Asian
Weight	<80 kg, ≥80 kg
Mutation Type	Exon 19del, Exon 21 L858R
History of Brain Metastasis	Yes, No
ECOG performance status score	0, 1
History of Smoking	Yes, No

5.8. Interim Analyses

Two interim analyses for PFS are planned for this study.

The first interim analysis with the main purpose of futility assessment will be conducted when approximately 120 PFS events from Arms A and B combined have occurred (27% of the planned events). A nominal 2-sided alpha of 0.00001 will be allocated. If the hazard ratio from a stratified

Cox proportional-hazard model for the combination therapy versus osimertinib is ≥1.0, the study may be stopped for futility.

The second interim analysis of PFS will be performed to assess the superiority of the combination therapy versus osimertinib, when approximately 280 PFS events from Arms A and B combined have occurred (62% of the planned events). The significance level for superiority will be determined based on the observed number of PFS events at the interim analysis, using the O'Brian Fleming alpha spending approach as implemented by the Lan-DeMets method. Assuming 280 PFS events observed at the interim, the 2-sided alpha to be spent at the interim and final PFS analyses are 0.0090, and 0.0472, respectively.

One interim analysis for OS is planned at the time of the final analysis for PFS, when approximately 270 deaths from Arms A and B combined are anticipated (69% of the 390 events planned). The superiority for OS will be tested with a total 2-sided alpha of 0.05 only if statistical significance for PFS is achieved. Assuming 270 deaths observed at the interim from Arms A and B combined, based on the O'Brian Fleming alpha spending approach as implemented by the Lan-DeMets method, the 2-sided alpha to be spent at the interim and final OS analyses are 0.0140 and 0.0457, respectively.

A separate SAP will describe the planned interim analyses in greater detail.

5.8.1. Independent Data Monitoring Committee

An IDMC consisting of 2 clinicians and 1 statistician who are independent experts not otherwise participating in the study, will be established to review safety results after first 60 treated participants have completed 1-month follow-up (or discontinued earlier). In addition, the IDMC will review cumulative safety data on a regular basis before the primary PFS analysis and will also review efficacy and safety results at the 2 planned PFS interim analyses. After each of these reviews, the IDMC will make recommendations regarding the continuation of the study. The details will be provided in a separate IDMC charter.

SUPPORTING DOCUMENTATION

Appendix 1 List of Abbreviations

AE	adverse event
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
BICR	blinded independent central review
BILI	bilirubin
BMI	body mass index
CI	confidence interval
CR	complete response
CRF	case report form
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
DCR	disease control rate
DoR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EQ-5D-5L	EuroQol five-dimensional descriptive system (5-level version)
FAS	full analysis set
ILD	interstitial lung disease
IDMC	independent data monitoring committee
IPCW	inverse probability of censoring weighting
IQ	interquartile
IRR	infusion-related reaction
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
IWRS	interactive web response system
MedDRA	medical dictionary for regulatory activities
MET	mesenchymal-epithelial transition
MUGA	multigated acquisition
NCI CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer - Symptom Assessment Questionnaire
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PFS	progression free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
QT	uncorrected QT interval
QTc	corrected QT
QTcF	corrected QT interval by Fridericia
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTSP	time to symptomatic progression
ULN	upper limit of normal

US	United States
WHO-DD	world health organization drug dictionary

Appendix 2 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by treatment group and overall. In addition, the distribution of participants by country and site ID will be presented unless otherwise noted.

Table below presents a list of the demographic variables that will be summarized by treatment group and overall for the Full Analysis Set.

Continuous Variables	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum].
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age (<65 years, ≥65 years; <75 years, ≥75 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Weight (<80 kg, ≥80 kg)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Race (Asian, non-Asian)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Baseline ECOG performance status (0, 1)	
History of Smoking (Yes, No)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

The following table presents a list of the baseline characteristics variables that will be summarized by treatment group and overall for the Full Analysis Set.

Continuous Variables	**Summary Type**
Time since initial lung cancer diagnosis (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum].
Time since metastatic disease diagnosis (months)	
Number of prior lines of systemic therapy taken from early stage	
Categorical Variables	
Mutation type (Exon 19del, Exon 21 L858R)	Frequency distribution with the number and percentage of participants in each category.
History of brain metastasis (yes, no)	
NSCLC subtype at initial diagnosis (adenocarcinoma, large cell carcinoma, squamous cell carcinoma, other)	
Histology grade at initial diagnosis (moderately differentiated, poorly differentiated, well differentiated, other)	
Cancer stage at initial diagnosis (IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IVA, IVB)	
NSCLC subtype at screening (adenocarcinoma, large cell carcinoma, squamous cell carcinoma, other)	
Histology grade at screening (moderately differentiated, poorly differentiated, well differentiated, other)	
Cancer stage at screening (IIIA, IIIB, IIIC, IVA, IVB)	
Location of metastasis at screening (bone, liver, brain, lymph node, adrenal gland, lung, other)	
Prior systemic therapy (adjuvant, neo-adjuvant, concurrent chemoradiation) taken from early stage	

A summary of stratification factors (mutation type, race, and history of brain metastasis) used in the randomization based on IWRS will be provided to evaluate whether or not randomization process was appropriately executed in the study.

Appendix 3 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category in the Full Analysis Set.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

A listing of all major protocol deviations including participant ID, type of deviation, and reason will be provided.

Appendix 4 Prior and Concomitant Medications

Prior and Concomitant medications collected in the CRF page will be coded using the World Health Organization Drug Dictionary (WHO-DD) and summarized for each treatment group and overall for the Full Analysis Set.

Prior medications will be summarized by ATC level/preferred terms and treatment. The number and percentage of participants who received prior systemic therapy will be summarized.

Summaries of concomitant medications will be presented by ATC level/preferred terms. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

The incidence (%) of pre-infusion and post-infusion medication will be presented by ATC level/preferred terms.

Appendix 5 Medical History

Medical history collected at screening visit will be summarized by system-organ class and preferred term for each treatment group and overall for the Full Analysis Set.

Appendix 6 Adverse Events of Special Interest

Adverse events of special interest are defined as follows:

AE of Special Interest Category	Preferred Term
Infusion Related Reaction	INFUSION RELATED REACTION
Rash	ACNE ACNE CONGLOBATA ACNE CYSTIC ACNE FULMINANS ACNE PUSTULAR ACNE VARIOLIFORMIS ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS DERMATITIS DERMATITIS ACNEIFORM DERMATITIS EXFOLIATIVE DERMATITIS INFECTED DRUG ERUPTION EPIDERMOLYSIS ERYTHEMA ERYTHEMA MULTIFORME EXFOLIATIVE RASH FOLLICULITIS HERPES GESTATIONIS IMPETIGO HERPETIFORMIS MACULE MUCOCUTANEOUS RASH NODULAR RASH PALMAR ERYTHEMA PAPULE PERINEAL RASH PRIDE SYNDROME PUSTULE RASH RASH ERYTHEMATOUS RASH FOLLICULAR RASH MACULAR RASH MACULO-PAPULAR RASH MACULOVESICULAR RASH MORBILLIFORM RASH PAPULAR RASH PRURITIC RASH PUSTULAR RASH VESICULAR SJS-TEN OVERLAP SKIN EXFOLIATION SKIN LESION STEVENS-JOHNSON SYNDROME TOXIC EPIDERMAL NECROLYSIS TOXIC SKIN ERUPTION
Interstitial Lung Disease	ACUTE INTERSTITIAL PNEUMONITIS INTERSTITIAL LUNG DISEASE PNEUMONITIS

Appendix 7 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on 'Common Terminology Criteria for Adverse Events (CTCAE) v5.0'.

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

Text in gray italic in the table is present in the grading scale, but is not applied by Janssen when grading lab data.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood and lymphatic system disorders					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L; *transfusion indicated*	*Life-threatening consequences; urgent treatment indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Leukocytosis	-	-	>100,000/mm3; >100 x 10e9 /L	*Clinical manifestations of leucostasis; urgent treatment indicated*	Clinical signs and symptoms are not taken into consideration for grading; Added ranges in SI unit (x 10e9 /L)
Investigations					
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; *bleeding*	-	Clinical signs and symptoms are not taken into consideration for grading.
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal;	>1.5 - 3.0 x ULN if baseline was normal;	>3.0 - 10.0 x ULN if baseline was normal;	>10.0 x ULN if baseline was normal;	Ranges defined for "abnormal baseline" are

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
	> 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x baseline if baseline was abnormal	applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	
Creatinine increased	Creatine Kinase >ULN - 1.5 x ULN	Creatine Kinase >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	Creatine Kinase >3.0 x baseline; >3.0 - 6.0 x ULN	Creatine Kinase >6.0 x ULN	
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	Ranges defined for "abnormal" are applied only on values < LLN. Grade 0 will be assigned to values > ULN.
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Haptoglobin decreased	<LLN	-	-	-	
Hemoglobin increased	Increase in >0 - 2 g/dL; Increase in >0 - 20 g/L	Increase in >2 - 4 g/dL; Increase in >20 - 40 g/L	Increase in >4 g/dL; Increase in >40 g/L	-	The increase indicates the level of increase above normal (above ULN). Applied as, e.g. grade 1 (g/dL): >ULN – ULN+2 g/dL; Added ranges in SI unit (g/L).
INR increased	>1.2 - 1.5; *>1 - 1.5 x baseline if on anticoagulation; monitoring only indicated*	>1.5 - 2.5; *>1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated*	>2.5; *>2.5 x baseline if on anticoagulation; bleeding*	-	Concomitant therapy or clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN with signs or symptoms; *>5.0 x ULN and asymptomatic*	>5.0 x ULN and with signs or symptoms	"Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied.
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3; >4 - 20 x 10e9 /L	>20,000/mm3; >20 x 10e9 /L	-	Added ranges in SI unit (x 10e9 /L).
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	Both Neutrophils and segmented neutrophils are graded using these criteria.
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN *with signs or symptoms; >5.0 x ULN and asymptomatic*	>5.0 x ULN *and with signs or symptoms*	"Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied.
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	
Metabolism and nutrition disorders					
Acidosis	pH <normal, but ≥7.3	-	pH <7.3	*Life-threatening consequences*	pH <normal is implemented as pH <LLN. Clinical signs and symptoms are not taken into consideration for grading.
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	*Life-threatening consequences*	pH >normal is implemented as pH >ULN. Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; *symptomatic*	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L; *treatment initiated*	Potassium >6.0 - 7.0 mmol/L; *hospitalization indicated*	Potassium >7.0 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypermagnesemia	Magnesium >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	Magnesium >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	Magnesium >8.0 mg/dL; >3.30 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypernatremia	Sodium >ULN - 150 mmol/L	Sodium >150 - 155 mmol/L; *treatment initiated*	Sodium >155 - 160 mmol/L; *hospitalization indicated*	Sodium >160 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypertriglyceridemia	Triglycerides 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	Triglycerides >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	Triglycerides >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	Triglycerides >1000 mg/dL; >11.4 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoalbuminemia	Albumin <LLN - 3 g/dL; <LLN - 30 g/L	Albumin <3 - 2 g/dL; <30 - 20 g/L	Albumin <2 g/dL; <20 g/L	*Life-threatening consequences; urgent treatment indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L;	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L;	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L;	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
		symptomatic	*hospitalization indicated*	*life-threatening consequences*	
Hypoglycemia	Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L	Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L	Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L	Glucose <30 mg/dL; <1.7 mmol/L; *life-threatening consequences; seizures*	Clinical signs and symptoms are not taken into consideration for grading. Urine glucose is not graded.
Hypokalemia	*Potassium <LLN - 3.0 mmol/L*	*Symptomatic with* Potassium <LLN - 3.0 mmol/L; treatment indicated	Potassium <3.0 - 2.5 mmol/L; *hospitalization indicated*	Potassium <2.5 mmol/L; *life-threatening consequences*	"Symptomatic" ranges are applied for grade 2, grade 1 not assigned, i.e. worst case applied. Clinical signs and symptoms are not taken into consideration for grading of grade 3 and 4.
Hypomagnesemia	Magnesium <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	Magnesium <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	Magnesium <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	Magnesium <0.7 mg/dL; <0.3 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyponatremia	Sodium <LLN - 130 mmol/L	*Sodium 125-129 mmol/L and asymptomatic*	*Sodium 125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms* Sodium <130-120 mmol/L	Sodium <120 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading. Worst case ("<130-120 mmol/L" for grade 3 added by Janssen) is applied across grade 2/3 ranges: 120-129 mol/L assigned to grade 3, grade 2 not used.
Renal and urinary disorders					
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs; urinary protein ≥ULN - <1000 mg/day	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs;	**Adult:** 4+ proteinuria; urinary protein ≥3.5 g/24 hrs;	-	In case both 24-h urine collection and dipstick are collected, then worst case is taken, as opposed to having 24-h urine

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
		urinary protein 1000 - <3500 mg/day **Pediatric:** Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9; Urine P/C (Protein/Creatinine) 56.5 – 214.7 g/mol	urinary protein ≥3500 mg/day; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9; Urine P/C (Protein/Creatinine) >214.7 g/mol		collection take precedence over dipstick. Added ranges in SI unit for urinary protein (mg/day) and for urine P/C (g/mol). Pediatric grading is applied to age range 0-<18. Adult grading is applied for ages ≥18.

* Grade 0 is assigned to a lab assessment when the lab test is described in the table, but the lab value is not assigned a grade 1 or higher.

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