Janssen Research & Development *

Statistical Analysis Plan

A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared with Carboplatin-Pemetrexed, in Patients with EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer PAPILLON

Protocol 61186372NSC3001; Phase 3

JNJ-61186372 (amivantamab)

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

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VERSION HISTORY

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
Stable	Not approval	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 study of combination amivantamab and carboplatin-pemetrexed therapy, compared with carboplatin-pemetrexed, in patients with treatment-naïve locally advanced or metastatic NSCLC characterized by epidermal growth factor receptor (EGFR) Exon 20ins activating mutations. 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

Following objectives and end points are defined as per the protocol v1.0 (17 July 2020):

Objectives	Endpoints
Primary	
To compare the efficacy, as demonstrated by PFS, in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone	• PFS (using RECIST v1.1 guidelines), as assessed by blinded independent central review (BICR)
Secondary	
To further assess the clinical benefit achieved with amivantamab in combination with chemotherapy, versus chemotherapy alone	• Objective response rate • Duration of response • Overall survival • Time to subsequent therapy • PFS after first subsequent therapy • Time to symptomatic progression
To assess the safety in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone	• Incidence and severity of adverse events and laboratory abnormalities, assessment of vital signs, and physical examination abnormalities
To assess the relationship between pharmacokinetics or immunogenicity and selected endpoints (including but not limited to efficacy, safety and/or PRO)	• Serum amivantamab concentrations and anti-amivantamab antibodies
To assess health-related quality of life and disease-related symptoms in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone	• EORTC-QLQ-C30 • PROMIS-PF
Exploratory	
To further assess the clinical benefit achieved with amivantamab in combination with chemotherapy, versus chemotherapy alone	• Time to treatment discontinuation
To explore genetic biomarkers predictive of improved outcome in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone	• Tumor genetics by NGS of ctDNA and genetic analysis of tumor biopsy material at baseline, on therapy, and at progression • Circulating mutant allele frequencies by NGS of ctDNA at baseline, on therapy, and at progression
To explore mechanisms of resistance to amivantamab in combination with chemotherapy	• Tumor protein markers by immunohistochemistry (eg, EGFR, MET) at baseline and at progression • Changes in tumor genetics, relative to baseline, by NGS of ctDNA and genetic analysis of tumor biopsy material at progression
To assess health-related quality of life in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone	• EQ-5D-5L

BICR = blinded independent central review; ctDNA = circulating tumor deoxyribonucleic acid; EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = EuroQol five-dimensional descriptive system (5-level version); NGS = next-generation sequencing; PFS = progression free survival;

PK = pharmacokinetics; PRO=patient-reported outcomes; PROMIS-PF = Patient-Reported Outcomes Measurement Information System – Physical Function; RECIST = Response Evaluation Criteria in Solid Tumors.

1.2. Study Design

This is a randomized, open-label, multicenter, Phase 3 study of combination amivantamab and carboplatin-pemetrexed therapy (Arm A), compared with carboplatin-pemetrexed (Arm B), in patients with treatment-naïve, locally advanced or metastatic NSCLC characterized by EGFR Exon 20ins activating mutations.

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. Imaging of disease sites will occur at regular intervals, as defined in the Schedule of Activities, until objective radiographic disease progression. To be randomized, all participants must have been previously diagnosed with NSCLC, characterized by Exon 20ins EGFR mutation.

The Treatment phase for each participant will begin at Cycle 1 Day 1 and continue in 21-day cycles until the End of Treatment visit, approximately 30 days after discontinuation of study treatment or until the start of subsequent anticancer therapy (if earlier). Study treatment will continue until documented clinical or radiographic (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) disease progression or until the participant meets another criterion for discontinuation of study treatment.

Approximately 300 eligible participants will be stratified based on Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1), history of brain metastases (yes or no), and prior EGFR TKI use (yes or no), and assigned randomly in a 1:1 ratio into 1 of 2 treatment arms as follows:

Arm A (amivantamab plus chemotherapy):

- Pemetrexed 500 mg/m^2 intravenous (with vitamin supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression
- Carboplatin area under the concentration-time curve 5 mg/mL per minute (AUC 5) intravenous on Day 1 of each 21-day cycle, for up to 4 cycles
- Amivantamab 1,400 mg (1,750 mg if body weight is ≥80 kg) by intravenous (IV) infusion once weekly up to Cycle 2 Day 1, then 1,750 mg (2,100 mg if body weight is ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3

Arm B (chemotherapy alone):

- Pemetrexed 500 mg/m^2 (with vitamin supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression

- Carboplatin AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles

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 clinical or radiographic disease progression using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Continuation of study treatment after disease progression by RECIST v1.1, as confirmed by blinded independent central review (BICR) may be allowed after approval from the Medical Monitor, if the investigator believes the participant is deriving clinical benefit (participants continuing treatment after documented progression will continue within the Treatment phase of the study and comply with all associated visits and procedures, including scheduled disease assessments, until the termination of study treatment); withdrawal of consent; the investigator believes that for safety reasons or tolerability reasons (e.g., 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 Patient-Reported Outcomes Measurement Information System – Physical Function (PROMIS-PF).

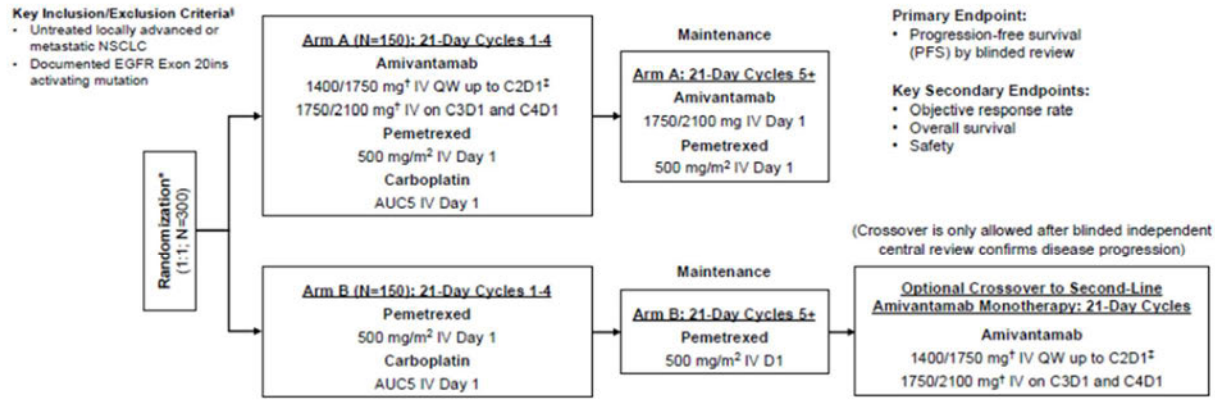
All study evaluations will be conducted according to the SoA in study protocol.

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

An IDMC will be commissioned for this study for periodic review of safety and tolerability data, as well as planned efficacy analyses, if needed. Details on IDMC are described in Section 5.8.1.

A diagram of the study design is provided in Figure 1, as follows:

Figure 1: Schematic Overview of the Study Design



AUC=area under the concentration-time curve; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; IV=intravenously; QW=once weekly; TKI=tyrosine kinase inhibitor.

* Stratification factors: Brain metastases (yes vs no); ECOG performance status (0 vs 1); prior EGFR TKI use (yes or no)

† Doses shown by body weight (<80 kg/≥80 kg)

‡ Cycle 1: Days 1/2 (split dose), 8, 15; Cycle 2: Day 1

Randomization

Participants will be randomly assigned to 1 of 2 study intervention groups (Arm A or Arm B) 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 ECOG performance status (0 or 1), history of brain metastases (yes or no), and prior EGFR TKI use (yes or no).

The interactive web response system (IWRS) will assign a unique study treatment code, which will dictate the study intervention assignment and matching study intervention kit for the participant. The requestor must use his or his 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

This is an open-label study.

2. STATISTICAL HYPOTHESES

The statistical hypothesis is that amivantamab and chemotherapy combination therapy will reduce the risk of either progression or death compared with standard of care combination chemotherapy in patients with locally advanced or metastatic NSCLC characterized by Exon 20ins mutations.

To control the overall type I error rate for the hypotheses testing of primary and secondary endpoints strongly at 5%, a sequential testing strategy will be used. If the testing for the primary endpoint of PFS is statistically significant, key secondary endpoints: objective response rate (ORR) and overall survival (OS) will be sequentially tested, each with an overall 2-sided alpha of 0.05. Test for ORR will be conducted before test for OS.

3. SAMPLE SIZE DETERMINATION

A total of CCI PFS events will provide approximately CCI % power to detect a hazard ratio (HR) of CCI that corresponds to at least CCI month improvement in the median PFS (CCI months for chemotherapy and 8 months for the combination of amivantamab with chemotherapy) with a log-rank test (two-sided alpha=0.05). The total sample size needed for the study is approximately 300 participants (150 per group). The sample size calculation has taken into consideration an annual dropout rate of CCI %. Assuming a 15-month recruitment period, CCI PFS events are expected to occur approximately 18 months after the first participant is randomized in the study.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Population	Description
Full Analysis Set	All randomized participants, classified according to their assigned treatment arm regardless of the actual treatment received.
Safety	Randomized participants who receive at least 1 dose of study treatment.
Pharmacokinetics	Randomized participants who receive at least 1 dose of study treatment and have at least 1 evaluable postbaseline concentration measurement.[a]
Biomarkers	Randomized participants who receive 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.

The Full Analysis Set will be used to summarize the study population and characteristics, as well as efficacy data; the Safety Population will be used to summarize the safety data, unless otherwise specified.

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

The study will consist of 3 phases: a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will start up to 28 days before randomization. The Treatment Phase will extend from Cycle 1 Day 1 to discontinuation of all study treatment. Participants should start study drug within 72 hours after randomization. Scheduled visits within each cycle will have a window up to ±3 day as per SoA in study protocol (except C1D8, C1D15 and C2D1 with ±1 day window).

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.

Subjects will enter the Follow-up Phase once they experience documented disease progression (by BICR) or unacceptable toxicity leading to all study treatment discontinuation until death, withdrawal of consent, lost to follow-up or end of study, whichever happens earliest.

Refer to Appendix 8 for visit windows in crossover arm.

5.1.2. Pooling Algorithm for Analysis Centers

There will be no pooling of centers for analyses.

5.1.3. 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'. First dose date will be the date of starting any of the study drug (amivantamab or carboplatin or pemetrexed).

Refer to Appendix 8 for study day definition in crossover arm.

5.1.4. Study Intervention Groups

Study treatment (in Arm A and Arm B) will be administered open-label, without blinding, in 21-day cycles, until disease progression or until the participant meets another criterion for discontinuation of study treatment.

An optional crossover arm will consist of BICR confirmed progressed subjects from Arm B. Refer to Appendix 8 for details.

5.1.5. 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).

Refer to Appendix 8 for baseline definition in crossover arm.

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 (for each study treatment)
- Participants who discontinued study treatment (for each study treatment)
- Reason for discontinuation of study treatment (for each study treatment)
- Participants who terminated study prematurely
- Reason for termination of study
- Participants who completed the study

The number of participants who discontinued treatment by cycle with reported reasons will also be provide.

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

- Participants who discontinued study treatment (for each study treatment)
- Participants who terminated study prematurely

Refer to Appendix 8 for participant dispositions in crossover arm.

5.3. Primary Endpoint(s) 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.

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(s)

Estimand Scientific Question of Interest: What is the relative effect of amivantamab in combination with chemotherapy, versus chemotherapy alone in prolonging PFS in patients with EGFR mutation Exon 20ins positive, locally advanced or metastatic NSCLC?

Study intervention:

- Experimental: amivantamab in combination with carboplatin and pemetrexed
- Control: combination of carboplatin and pemetrexed

Population: Patients with locally advanced or metastatic NSCLC characterized by Exon 20ins mutations

Variable: PFS

Summary Measure (Population-level summary): hazard ratio (HR) and 95% CI of Arm A (amivantamab plus chemotherapy) vs Arm B (chemotherapy alone).

Intercurrent events and their corresponding strategies:

Intercurrent Events	**Name of Strategy for Addressing Intercurrent Events and Its Description**
Study intervention discontinuation due to any reason	**Treatment Policy strategy:** use time to disease progression or death, regardless of whether or not study intervention discontinuation had occurred
Study intervention 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 efficacy endpoint will be analyzed in the Full Analysis Set. The treatment effect of Arm A will be compared to Arm B based on a log rank test stratified by ECOG performance status (0 or 1), history of brain metastases (yes or no), and prior EGFR TKI use (yes or no) using the Breslow approach for handling ties. 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.

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.

Similar analysis will be carried out for crossover arm as well but it will limited to descriptive summaries only (median PFS with 95% CI and PFS rates with 95% CI will be estimated by Kaplan-Meier method at landmarks).

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. Similar analysis will be carried out for crossover arm as well.

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. Similar analysis will be carried out for crossover arm as well.

5.4. Secondary Endpoint(s) Analysis

5.4.1. Overall Survival (OS)

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 in combination with chemotherapy, versus chemotherapy in prolonging OS in patients with EGFR mutation Exon 20ins positive, locally advanced or metastatic NSCLC?

Study intervention:

- Experimental: amivantamab in combination with carboplatin and pemetrexed
- Control: combination of carboplatin and pemetrexed

Population: Patients with locally advanced or metastatic NSCLC characterized by Exon 20ins mutations

Variable: OS

Summary Measure (Population-level summary): hazard ratio (HR) of Arm A (amivantamab plus chemotherapy) vs Arm B (chemotherapy alone)

Intercurrent events and their corresponding strategies:

Intercurrent Events	**Name of Strategy for Addressing Intercurrent Events and Its Description**
Study intervention 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

OS will be analyzed using the similar methodology and model as for the primary analysis of PFS in the Full Analysis Set provided there are sufficient events available for meaningful analysis.

Sensitivity analysis using non-stratified log-rank test may be performed as supportive analyses.

In addition, forest plots will be provided for subgroups as defined in Section 5.7.6. The comparison between the two intervention groups will be evaluated using the hazard ratio with its 95% CI from a Cox regression model in each subgroup.

Similar analysis will be carried out for crossover arm as well but it will limited to descriptive summaries only (median OS with 95% CI and OS rates with 95% CI will be estimated by Kaplan-Meier method at landmarks).

Sensitivity Analysis

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

Supplementary Analysis

Analysis will be carried out using Inverse Probability of Censoring Weighting (IPCW) (Cole and Hernán, 2004)[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. Analysis using rank preserving failure time model (Robins and Tsiatis, 1991)[1] will also be conducted to estimate true treatment effect on OS in crossover arm. Hazard ratio and its 95% confidence interval will be estimated based on a Cox regression analysis using both the methods.

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. Estimand

Estimand Scientific Question of Interest: What is the relative effect of amivantamab in combination with chemotherapy, versus chemotherapy in ORR in patients with EGFR mutation Exon 20ins positive, locally advanced or metastatic NSCLC?

Study intervention:

- Experimental: amivantamab in combination with carboplatin and pemetrexed
- Control: combination of carboplatin and pemetrexed

Population: Patients with locally advanced or metastatic NSCLC characterized by Exon 20ins mutations

Variable: ORR

Summary Measure (Population-level summary): odds ratio of Arm A (amivantamab plus chemotherapy) vs Arm B (chemotherapy alone)

Intercurrent events and their corresponding strategies:

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description

Study intervention switching to other anticancer therapy	**Hypothetical strategy:** use best overall response till subsequent anti-cancer therapy

5.4.2.3. Analysis Methods

Objective response will be analyzed using a logistic regression model stratified by ECOG performance status (0 or 1) and history of brain metastases (yes or no), and prior EGFR TKI use (yes or no). The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood confidence intervals. 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.

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.

Descriptive analysis of ORR (n, frequency, percentage and 95% CI) will be displayed for crossover arm.

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 CR or PR. 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. Similar analysis will be carried out for crossover arm as well.

5.4.4. Time to Subsequent Therapy (TTST)

5.4.4.1. 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. Participants alive and not starting subsequent therapy will be censored on the date on which the participant was last known alive date.

5.4.4.2. Analysis Methods

TTST will be analyzed using the similar method as the primary analysis of PFS in Full Analysis Set. Similar analysis will be carried out for crossover arm as well.

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

5.4.5.1. 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, Crossover arm should be treated as first subsequent therapy in this analysis.

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 therapy without a progression	The last disease assessment date prior to the start of 2nd line subsequent therapy
Treated beyond progression	The last date of disease assessment

5.4.5.2. Analysis Methods

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

5.4.6. Time to Symptomatic Progression (TTSP)

5.4.6.1. 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.

While measuring TTSP in crossover arm, it will be defined as the time from start of amivantamab monotherapy dose to documentation in the eCRF of any of the above conditions (whichever occurs earlier).

5.4.6.2. Analysis Methods

TTSP will be analyzed using the similar method as the primary analysis of PFS in Full Analysis Set. Similar analysis will be carried out for crossover arm as well.

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.

5.4.7. 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). 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.

The change of scores from baseline over time will be assessed using mixed-effects model for repeated measures (MMRM) analysis based on restricted maximum likelihood (REML). The model will include participants as a random effect the fixed, and baseline value, treatment group,

time in week, treatment-by-time interaction, and stratification factors as fixed effects. The treatment comparison will be based on the least squares means and the 2-sided 95% CI will be estimated. 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.

Time to Symptom Deterioration (TTSD)

Time to symptom 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)[4]. 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 symptom 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.

All data representations will include results from crossover arm along with Arm A and Arm B.

5.4.8. Patient Reported Outcome – PROMIS-PF

5.4.8.1. Definition

Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function (PF) (short-form) is used to characterize and better understand overall health, level of physical disability, and general well-being. Physical function is a foundation for commonly used general and cancer-specific PRO measures.

5.4.8.2. Analysis Methods

Unless otherwise specified, PROMIS-PF data will be analyzed based on Full Analysis Set.

The PROMIS-PF data will be summarized descriptively by treatment group and study visit. Each multi-item scale and individual item will be summarized using count and percent. PROMIS-PF

data will be analyzed based on randomized participants who receive at least 1 dose of study treatment and have at least 1 evaluable postbaseline measurement.

All data representations will include results from crossover arm along with Arm A and Arm B.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

5.5.1. Time to Treatment Discontinuation (TTD)

5.5.1.1. Definition

TTD is defined as the time from randomization to discontinuation of all study treatments 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.

5.5.1.2. Analysis Methods

TTD will be analyzed using the similar method as the primary analysis of PFS in Full Analysis Set. Similar analysis will be carried out for crossover arm as well.

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

5.5.2.1. 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.

All data representations will include results from crossover arm along with Arm A and Arm B.

5.5.2.2. 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. All displays showing safety results will include results from crossover arm under a separate arm.

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.

The relative dose intensity (%) defined as the ratio of total 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. Descriptive statistics will be provided for 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 each 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 each treatment/study drug, and by SOC and PT

- Incidence (%) of TEAEs with toxicity grade 3 or higher by relationship to each treatment/study drug, and by SOC and PT
- Incidence (%) of TEAEs leading to study drug interruption/dose reduction by relationship to each treatment/study drug, and by SOC and PT
- Incidence (%) of TEAEs leading to study drug discontinuation by relationship to each 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 each 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 each 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 each 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 Adverse Events of Special Interest. 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 date or until the start of subsequent anti-cancer 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.

For criteria that do not include an increase or decrease from baseline:

TE will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).

If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

5.6.4.3. Electrocardiogram

Electrocardiograms (ECG) will be performed at CCI [redacted].

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.

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

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

5.6.5. ECOG Performance Status

Frequencies of ECOG performance over time will be summarized. In addition, shift from baseline to best score during treatment will be provided.

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. Sampling timepoints are outlined in **Error! Reference source not found.** 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 concentrations at each sampling time point and for each PK parameter of amivantamab. PK data may be displayed graphically, such as mean +/- SD PK concentrations over time by study intervention.

Amivantamab concentrations will be presented 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.

All data representations will include results from crossover arm along with Arm A and Arm B.

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.

All data representations will include results from crossover arm along with Arm A and Arm B.

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 and tumor tissue NGS 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.

All data representations will include results from crossover arm along with Arm A and Arm B.

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
History of Brain Metastasis	Yes, No
ECOG performance status score	0, 1
Prior EGFR TKI use	Yes, No
History of Smoking	Yes, No

5.8. Interim Analyses

Not applicable

5.8.1. Independent Data Monitoring Committee

An IDMC consisting of at least one medical expert in the relevant therapeutic area and at least one statistician not otherwise participating in the study, will be established to review safety results. The IDMC will review safety results for amivantamab in combination with carboplatin and pemetrexed in the ongoing Phase 1 study prior to enrollment of participants in this Phase 3 study. A IDMC meeting may occur after approximately 20 participants have been randomized and treated for 2 cycles with the protocol treatment for additional review of the safety with this combination. Regular safety review meetings will occur approximately every 4 months thereafter.

The frequency of safety meetings may change at any moment as per IDMC request. During safety analysis for IDMC review, enrollment will continue.

Other meetings or data reviews may be scheduled at the discretion of the IDMC or upon request by the Sponsor Committee.

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)	
Prior EGFR TKI use (Yes, No)	
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	
NSCLC subtype at initial diagnosis (adenocarcinoma, large cell carcinoma, squamous cell carcinoma, other)	Frequency distribution with the number and percentage of participants in each category.
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 (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, Curative/Palliative/Any other intent, Concurrent Chemoradiation) taken from early stage	

A summary of stratification factors (prior EGFR TKI use, ECOG performance status 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
- Any major PD due to COVID
- 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 baseline or 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 Safety Run-in

The safety of amivantamab in combination with carboplatin and pemetrexed is being investigated in the ongoing Phase 1 Study (61186372EDI1001), in parallel to Phase 3 study development, and will be confirmed prior to enrollment of participants in this Phase 3 study. If regulatory or health authorities request region-specific safety experience for amivantamab in combination with carboplatin-pemetrexed, an optional Safety Run-in may be performed prior to enrollment of participants in the randomized Phase 3 portion of the study in that region/country. Refer to Appendix 10 in the protocol.

Collection times for PK and immunogenicity samples in the Safety Run-in are shown in Table 2 in the protocol. Tumor biopsies are not required for participants in the Safety Run-in; other activities in the Safety Run-in will be conducted as listed in the Schedule of Activities (Table 1 in the protocol).

PK and safety analyses will be performed per Section 5.7.1 and Section 5.6.

Appendix 8 Optional Crossover After Disease Progression to Second-Line Amivantamab Monotherapy (Arm B Only)

A participant who was randomized into the Arm B (platinum-based doublet chemotherapy) may cross over to amivantamab monotherapy after disease progression, as confirmed by blinded independent central review (BICR) (see Figure 1 in protocol). A participant crossing over to second-line amivantamab monotherapy will be rescreened to ensure eligibility is met to receive amivantamab. Refer to Appendix 11 for details.

Study Design
This phase of the study will not be randomized or controlled. All participants in the Crossover Phase will receive amivantamab in 21-day cycles as follows:

- Amivantamab 1,400 mg (1,750 mg if body weight is ≥80 kg) by intravenous (IV) infusion once weekly up to Cycle 2 Day 1, then 1,750 mg (2,100 mg if body weight is ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3

Crossover participants must not initiate treatment with amivantamab earlier than 21 days or later than 90 days after their last dose of chemotherapy, regardless of the time of progression.

Other treatment related procedures are described in Table 20 in protocol.

Visit Windows
As per Appendix 11 and Table 20 of protocol. Definitions of three study phases will remain same as Section 5.1.1.

Baseline Measurement
Baseline measurement is defined as the closest non-missing measurement taken on or prior to the first amivantamab 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.

Study Day/Relative Day
Study day or relative day is defined as:

- Reference date (Day 1) = first amivantamab dose date of study drug for efficacy and 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'.

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 enrolled
- 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
- Participants who completed the study

The number of participants who discontinued treatment by cycle with reported reasons will also be provide.

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

- Participants who discontinued study treatment
- Participants who terminated study prematurely

ORR

ORR is defined as the proportion of participants who achieve either a complete response (CR) or partial response (PR), 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. Descriptive analysis of ORR (n, frequency, percentage) will be displayed for crossover arm.

Duration of Response (DoR)

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 CR or PR within the crossover arm. 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.

PFS

Progression-free Survival (PFS) is defined as the time from amivantamab monotherapy treatment start date until the date of objective disease progression (investigator-assessed) or death, whichever comes first, 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. A Kaplan-Meier plot for PFS and median PFS with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented.

OS

OS is defined as the time from the date of amivantamab monotherapy treatment start date 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. A Kaplan-Meier plot for OS and median OS with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented.

Time to Subsequent Therapy (TTST)

TTST is defined as the time from amivantamab monotherapy treatment start date to the start date of the subsequent anticancer therapy following study treatment discontinuation. Participants alive and not starting subsequent therapy will be censored on the date on which the participant was last known alive date. A Kaplan-Meier plot for TTST and median TTST with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented.

Appendix 9 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

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
					into consideration for grading.
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;	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L;	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L;	Corrected serum calcium of <6.0 mg/dL; <1.5 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
	Ionized calcium <LLN - 1.0 mmol/L	Ionized calcium <1.0 - 0.9 mmol/L; *symptomatic*	Ionized calcium <0.9 - 0.8 mmol/L; *hospitalization indicated*	Ionized calcium <0.8 mmol/L; *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					

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
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; 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	**Adult:** 4+ proteinuria; urinary protein ≥3.5 g/24 hrs; urinary protein ≥3500 mg/day; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9; Urine P/C (Protein/Creatinine) >214.7 g/mol	-	In case both 24-h urine collection and dipstick are collected, then worst case is taken, as opposed to having 24-h urine 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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