Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 3, Open-Label, Randomized Study of Amivantamab and Lazertinib in Combination with Platinum-Based Chemotherapy Compared with Platinum-Based Chemotherapy in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer After Osimertinib Failure

MARIPOSA-2

Protocol 61186372NSC3002 Amendment 7; Phase 3

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

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Studies conducted at sites in the United States (US) will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312). Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation European Union [EU] No 536/2014.

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IND: 146319
EU Trial NUMBER: 2023-506518-33

Status:	Approved
Date:	05 April 2024
Prepared by:	Janssen Research & Development, LLC
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 7	05 April 2024
Amendment 6	22 December 2022
Amendment 5	25 November 2022
Amendment 4	23 August 2022
Amendment 3	27 June 2022
Amendment 2	24 March 2022
Amendment 1	06 August 2021
Original Protocol	09 July 2021

Amendment 7 (05 April 2024)

Overall Rationale for the Amendment:

The MARIPOSA-2 study has completed its primary analysis for progression-free survival (PFS). To continue collecting data of clinical relevance/importance while reducing the burden on participants after completion of the second interim analysis for overall survival (OS) an option is being added for the study to transition to an Open-label extension (OLE) phase or Long-term extension (LTE) phase with reduced protocol-required visits and assessments. All efficacy and key safety assessments continue during the OLE Phase of the study. Protocol-required assessments will be further reduced in the LTE phase, while continuing to provide access to study treatment.

Clarifications related to the management of pneumonitis/interstitial lung disease (ILD) have also been added to the protocol.

Additionally, changes related to the transition to the European Union (EU)/European Economic Area (EEA) Clinical Trial Regulations (CTR) have also been added to the protocol.

The changes made to the clinical protocol 61186372NSC3002 as part of Protocol Amendment 7 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.16 Appendix 16: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
Changes related to adding an OLE Phase and an LTE Phase to the study		
1.1. Synopsis (Overall Design); 4.1.4. Open-label Extension Phase and Long-Term Extension Phase (new subheading)	A description of the new OLE and LTE phases was added, with cross-references to the newly added appendices.	To add the new OLE and LTE phases to the overall study design.
1.2. Schema, Figure 1, Figure 2 (Schematic Overview of the Study)	The schematic was revised to add the new OLE and LTE phases.	To add the 2 new phases (OLE and LTE) to the study design.
1.3. Schedule of Activities: Table 1	Added text to the title to indicate that the Schedule of Activities for the OLE and LTE Phases are provided in Table 20 and Table 21, respectively. Added the following note: Guidance on study conduct during natural disaster, major disruption, or pandemic (eg,	To highlight the distinct Schedules of Activities in the OLE and LTE phases. To clarify the guidance to study conduct during natural disaster, major disruption, or pandemic.

Section Number and Name	Description of Change	Brief Rationale
	COVID 19), is provided in a standalone appendix that will be provided to the site with the protocol.	
1.3. Schedule of Activities: Table 2	Added text to the title to indicate that this Schedule of Activities is not applicable to the OLE and LTE phases.	Pharmacokinetic and immunogenicity samples are not collected in OLE and LTE phases.
6.8. Continued Access to Study Treatment	Text referring to the OLE and LTE phases was added.	For guidance on details related to continued access to study treatment for participants who are still benefiting from study treatment.
10.4 Appendix 4: Anticipated Events	The text shown below was added under the subheading for Safety Assessment Committee (SAC). The review of anticipated events was stopped after the database lock associated with the primary endpoint of the study.	To transition anticipated events review from SAC to ongoing medical review.
10.14 Appendix 14: Open-Label Extension Phase	This appendix was added.	To specify content related to the addition of this study phase.
10.15 Appendix 15: Long-Term Extension Phase	This appendix was added.	To specify content related to the addition of this study phase.
Changes related to the management of pneumonitis/ILD		
6.5.3.6. Pulmonary Toxicity	The section for Pulmonary Toxicity was updated to add the text shown below. Study treatment should not be restarted until pneumonitis/ILD is ruled out.	To clarify actions for managing pneumonitis/ILD.
Changes related to the EU CTR requirements, and other template-specific changes		
Cover page	The EU Trial number was added.	To comply with the EU CTR requirements.
Cover page	Added text on EU regulation, per EU CTR requirement. Revised text for US regulation.	To align with the current protocol template.
1.1. Synopsis	The IND number and EU Trial number were added.	To comply with the EU CTR requirements.
1.1. Synopsis (Benefit Risk Assessment) (new section)	A summary of the benefit-risk assessment for the study was added.	To comply with the EU CTR requirements.
5.1 Inclusion Criteria Criterion 10	Text has been updated as shown below. A ~~woman~~ **participant** of childbearing potential must have a negative serum pregnancy test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.	To make language more inclusive and gender-neutral (in alignment with the current protocol template).
5.1 Inclusion Criteria Criterion 11.1	Text has been updated as shown below. A ~~woman~~ **participant** must be either of the following (as defined in Appendix 5: Contraceptive Guidance):	To make language more inclusive and gender-neutral (in alignment with the current protocol template).

Section Number and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria Criterion 12.1	Text has been updated as shown below. A ~~woman~~ **participant** must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 7 months after receiving the last dose of study treatment.	To make language more inclusive and gender-neutral (in alignment with the current protocol template).
5.1 Inclusion Criteria Criterion 13.1	Text has been updated as shown below. A ~~man~~ **participant** must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for 6 months after receiving the last dose of study treatment. A ~~man~~ **participant** who is sexually active with a ~~woman~~ **person** of childbearing potential must agree to use a condom and ~~his~~ **the** partner must also be practicing a highly effective method of contraception (see Appendix 5: Contraceptive Guidance). A ~~male~~ **participant** who is vasectomized must still use a condom for prevention of passage of exposure through ejaculation, but the participant's ~~female~~ **partner** is not required to use contraception.	To make language more inclusive and gender-neutral (in alignment with the current protocol template).
5.1 Inclusion Criteria Criterion 14.1	Text in strikethrough was deleted. A ~~male~~ participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 6 months after receiving the last dose of study treatment.	To make language more inclusive and gender-neutral (in alignment with the current protocol template).
5.4. Screen Failures	Added the text shown below under Participant Identification, Enrollment, and Screening Logs This study will use an interactive web response system (IWRS). The investigator will generate screening and enrollment logs directly from IWRS.	To align with the current protocol template.
6.1. Study Treatments Administered	Added text related to study treatment and a new table categorizing the study treatments as investigational medicinal products (IMPs) or non-investigational medicinal products (NIMPs)/auxiliary medicinal products (AxMPs).	To align with the current protocol template and comply with EU CTR guidance.
8.3.4. Regulatory Reporting Requirements for Serious Adverse Events	Text was revised as shown below. For the purposes of this study, anticipated events ~~are discussed~~ **will be periodically analyzed as specified** in Appendix 4: Anticipated Events.	To align with the current protocol template.
8.3.5. Pregnancy	Text was revised as shown below. All initial reports of pregnancy in ~~female~~ participants or their partners of ~~male~~ participants (**through sperm of participant/from sexual intercourse and** if appropriate consent is given) must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of	To align with the current protocol template and to include additional requirements in the pregnancy reports.

Section Number and Name	Description of Change	Brief Rationale
	the event using the appropriate pregnancy notification form.	
10.2.4. Recruitment Strategy (new subheading)	Section added.	To comply with EU CTR guidance.
10.2.5. Data Protection	Text related to measures by the sponsor to mitigate possible adverse effect in the event of a data security breach was added.	To comply with the EU CTR requirements.
10.2.8. Use of Information and Publication	Revised text regarding publication by Investigator. Added optional text on disclosure of the study results per EU CTR requirement.	To align with the current protocol template and to comply with the EU CTR requirement.
10.2.14. Record Retention	Additional text added on record retention under EU regulation.	To comply with EU CTR requirement.
10.3.4. Special Reporting Situations	Text was revised as shown below. **Participant-specific** special reporting situations should be recorded in the eCRF.	To align with the current protocol template.
10.5. Appendix 5 Contraceptive Guidance	Text was revised as follows: • permanent~~ly sterile~~ **absence of reproductive potential (for the purpose of this study)** - **Has undergone a procedure that precludes reproductive potential.** - **Has a congenital abnormality that precludes reproductive potential.** ~~Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.~~	To align with the current protocol template.
10.5. Appendix 5 Contraceptive Guidance	Text was revised as follows: (eg, a ~~woman~~ **participant** ~~who is not heterosexually active~~ becomes **sexually** active **where pregnancy can occur**)	To make language more inclusive and gender-neutral (in alignment with the current protocol template).
10.5. Appendix 5 Contraceptive Guidance	Text was revised in the section on "Examples of Contraceptives" as follows: • Sexual abstinence **from intercourse where pregnancy could occur** (Sexual abstinence is considered a highly effective method only if defined as refraining from ~~hetero~~sexual intercourse **where the possibility of pregnancy exists** during the entire period of risk associated with **exposure to** the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)	To make language more inclusive and gender-neutral (in alignment with the current protocol template).
Other miscellaneous changes		
4.3.1 Study-Specific Ethical Design Consideration	Additional text added related to LAR and information on sources to obtain written consent	To align with the current protocol template.

Section Number and Name	Description of Change	Brief Rationale
7.2.1 Withdrawal From the Use of Study Samples	Header and text were revised	To align with the current protocol template.
7.3 Lost to Follow-up	Additional bullet has been added • Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.	To align with the current protocol template.
8.3.6 Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events.	Updated the criteria for disease related events and outcomes not qualifying as adverse events or serious adverse events	To align with the current protocol template.
9.4.3 Secondary Endpoints	Death was included in the definition of Time to Symptomatic Progression (TTSP) endpoint.	Death was inadvertently omitted from the definition of TTSP in the protocol. Additional clarification regarding the definition of TTSP to include both symptomatic progression and death as events was provided in Statistical Analysis Plan (SAP) Amendment 3 (dated 19 May 2023, prior to the primary analysis for PFS).
9.4.3 Secondary Endpoints 3. Objective and Endpoints;	Intracranial endpoints (ORR, DoR, time to intracranial disease progression) have been included.	To align with the intracranial endpoints included in SAP Amendment 3 (dated 19 May 2023, prior to the primary analysis for PFS).
Throughout the protocol	The words “female” and “male” were removed and replaced by participant.	To make the protocol more inclusive and gender-neutral (in alignment with the current protocol template).
	Changes were made to text. ‘legally acceptable representative’ replaced by ‘legally designated representative’.	To align with the current protocol template.
10.3.2 Attribution Definitions	Listed factors to be considered in causality assessment and specified that a causal relationship to study intervention should be documented in the participant’s medical records. Removed “reasonable causal relationship”.	To align with the current protocol template.
10.2.6 Storage, Use, Transfer, and Retention of Data and Samples	Heading and text has been revised.	To align with the current protocol template.
Throughout the protocol	Minor editorial and formatting changes were made.	Minor errors, discrepancies, or omissions were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 3, Open-Label, Randomized Study of Amivantamab and Lazertinib in Combination with Platinum-Based Chemotherapy Compared with Platinum-Based Chemotherapy in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer After Osimertinib Failure

IND: 146319
EU Trial NUMBER: 2023-506518-33

Third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are becoming standard of care as first-line therapy for non-small cell lung cancer (NSCLC) harboring EGFR Exon 19del or L858R mutations. While the third-generation EGFR TKI osimertinib represents a significant advance over earlier EGFR TKIs, almost all patients eventually relapse. Platinum-based chemotherapy is the current standard of care for NSCLC that progresses during or after osimertinib treatment, despite the fact that osimertinib-resistant disease may remain dependent upon EGFR and/or MET signaling. This remains an unmet need for the treatment of EGFR-mutated NSCLC after osimertinib.

Amivantamab (JNJ-61186372) is a low fucose, fully human IgG1-based bispecific antibody directed against EGFR and MET tyrosine kinase receptors. It shows clinical activity against tumors with primary activating EGFR mutations Exon 19del and Exon 21 L858R substitution, EGFR Exon 20ins mutations, EGFR resistance mutations T790M and C797S, or activation of the MET pathway.

Lazertinib (JNJ-73841937; YH-25448) is an oral, highly potent, third-generation EGFR TKI. It selectively inhibits both primary activating EGFR mutations (Exon 19del, Exon 21 L858R substitution) and the EGFR T790M resistance mutation, with less inhibition of wild-type EGFR.

The combination of lazertinib and amivantamab results in more robust and durable antitumor activity, with a higher confirmed objective response rate (ORR), greater median duration of response, and improved clinical benefit rate compared with amivantamab monotherapy. Lazertinib also provides antitumor activity within the central nervous system. These findings support adding amivantamab and lazertinib to standard of care platinum-based chemotherapy after osimertinib failure. This study will compare the efficacy and safety of lazertinib, amivantamab, carboplatin, and pemetrexed ("LACP"; Arm A) versus carboplatin and pemetrexed ("CP"; Arm B) in participants with EGFR-mutated locally advanced or metastatic NSCLC following progression on or after osimertinib treatment. On 07 November 2022, an Urgent Safety Measure was implemented to modify the dosing schedule of lazertinib on Arm A whereby it is only started after carboplatin therapy is completed. This dosing schedule is termed ACP-L. The primary efficacy analysis of LACP/ACP-L (Arm A) versus CP remains unchanged, and will include all participants randomized to Arm A. The contribution of lazertinib to the activity of LACP/ACP-L will be assessed descriptively by comparing the efficacy of LACP/ACP-L with that of amivantamab, carboplatin, and pemetrexed ("ACP"; Arm C).

An open-label randomized extension cohort will be used to further describe the safety and efficacy of the ACP-L dosing schedule versus ACP with additional data.

BENEFIT-RISK ASSESSMENT

The safety profiles of amivantamab and lazertinib are largely distinct from those associated with chemotherapeutic agents, and amivantamab has demonstrated safety and tolerability in addition to either lazertinib or chemotherapy in Phase 1 studies.

Platinum-based chemotherapy is the current standard of care treatment for patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletion or Exon 21 L858R mutations whose disease has

progressed on or after treatment with osimertinib. All participants in the study will accordingly be treated with platinum-based chemotherapy (carboplatin and pemetrexed). Combining amivantamab with chemotherapy or with chemotherapy plus lazertinib is hypothesized to provide improved clinical benefit for this patient population through targeted anti-EGFR and anti-MET action, antitumor activity within the central nervous system (CNS), and recruitment of immune cells with antitumor activity. The distinct mechanisms of action of amivantamab and lazertinib have the potential to inhibit the EGFR pathway more potently than either agent alone.

This study protocol includes elements to mitigate unforeseen safety risks for study participants. In addition to monitoring participants closely for safety throughout the study, an Independent Data Monitoring Committee (IDMC) reviewed safety and tolerability data periodically. Dose modification guidance is also provided to manage toxicities that occur during the study. Taking into account these measures to minimize risk to participants in the study, the potential risks associated with amivantamab and lazertinib are justified by the anticipated benefits that may be afforded to participants in the study.

OBJECTIVES AND ENDPOINTS

The dual primary objectives of the study are to assess the efficacy of LACP/ACP-L versus CP, and ACP versus CP in participants with locally advanced or metastatic EGFR Exon 19del or Exon 21 L858R substitution NSCLC. Key secondary objectives are further measures of clinical benefit and safety. All secondary and exploratory objectives and endpoints are described in the protocol.

For the extension cohort, the primary objectives are to further describe the safety and efficacy of the ACP-L dosing schedule versus ACP using additional data.

Hypothesis

The study has dual primary hypotheses:

- LACP/ACP-L will demonstrate superior progression-free survival (PFS) compared with CP.
- ACP will demonstrate superior progression-free survival (PFS) compared with CP.

There is no separate hypothesis for extension cohort.

OVERALL DESIGN

This study is a randomized, open-label, active-controlled, parallel, multicenter, Phase 3 study to compare the efficacy and safety of LACP/ACP-L (Arm A) versus CP (Arm B) and ACP (Arm C) versus CP (Arm B) in participants with EGFR-mutated locally advanced or metastatic nonsquamous NSCLC who have progressed on or after treatment with osimertinib. The study consists of a Screening Phase (up to 28 days), a Treatment Phase (from randomization until the End of Treatment visit) and a Follow-up Phase (from End of Treatment Visit until the end of study, death, lost to follow-up, or withdrawal of consent, whichever comes first).

To further describe the safety and efficacy of the ACP-L dosing schedule versus ACP, a separate open-label randomized extension cohort has been added to the study. Enrollment of participants into the extension cohort may begin after enrollment into the main study is complete and when the Sponsor opens the extension cohort for enrollment. The extension cohort will have the same eligibility criteria, study procedures and operate within the same investigational sites as the main study.

This study may transition to an open-label extension (OLE) phase or long-term extension (LTE) phase following the second interim analysis for OS.

If an OLE Phase is implemented, participants will be provided the option to reduce certain protocol-specified procedures and assessments while continuing their current study treatment until protocol specified discontinuation criteria are met. (see details provided in Section 10.14 [Appendix 14]).

If an LTE Phase is implemented, participants will be provided continued access to study treatment with further reduction in protocol-specified procedures and assessments. During the LTE phase, only serious adverse event data and study treatment compliance will be collected (see details provided in Section 10.15 [Appendix 15]).

NUMBER OF PARTICIPANTS

Approximately 600 eligible participants will be randomly assigned to study treatment in a 2:2:1 ratio (Arms A:B:C). Randomization will be stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes vs no), and Asian race (yes vs no).

In the extension cohort, approximately 90 eligible participants will be randomly assigned to receive ACP-L or ACP in a 2:1 ratio (Arms A2:C2) – the same ratio as in the main study. Randomization will be stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes vs no), and Asian race (yes vs no), also as in the main study.

STUDY TREATMENT GROUPS AND DURATION

Main Study Arms

Arm A Dosing Schedule 1 (LACP, from study start until 6 November 2022) :

- Lazertinib 240 mg orally, once daily
- Amivantamab by intravenous (IV) infusion in 21-day cycles:
  - 1,400 mg (1,750 mg if body weight ≥80 kg) on Cycle 1 Days 1/2, 8, and 15, and Cycle 2 Day 1
  - 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3
- Carboplatin and pemetrexed as in Arm B.

Arm A Dosing Schedule 2 (started on 07 November, 2022, ACP-L):

- Lazertinib 240 mg orally, once daily starting Cycle 5 Day 1 or sooner if carboplatin is discontinued earlier
- Amivantamab by IV infusion in 21-day cycles:
  - 1,400 mg (1,750 mg if body weight ≥80 kg) on Cycle 1 Days 1/2, 8, and 15, and Cycle 2 Day 1
  - 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3
- Carboplatin and pemetrexed as in Arm B.

Arm B (CP):

- Carboplatin AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles
- Pemetrexed 500 mg/m^2 on Day 1 of each 21--day cycle, with carboplatin for up to 4 cycles, and then as maintenance until disease progression

Arms C (ACP):

- Amivantamab as in Arm A
- Carboplatin and pemetrexed as in Arm B

Extension Cohort Arms

Arm A2 (ACP-L):

- Lazertinib 240 mg orally, once daily starting Cycle 5 Day 1 or sooner if carboplatin is discontinued earlier
- Amivantamab by IV infusion in 21-day cycles:
  - 1,400 mg (1,750 mg if body weight ≥80 kg) on Cycle 1 Days 1/2, 8, and 15, and Cycle 2 Day 1
  - 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3
- Carboplatin AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles
- Pemetrexed 500 mg/m^2 on Day 1 of each 21-day cycle, with carboplatin for up to 4 cycles, and then as maintenance until disease progression

Arm C2 (ACP):

- Amivantamab by IV infusion in 21-day cycles:
  - 1,400 mg (1,750 mg if body weight ≥80 kg) on Cycle 1 Days 1/2, 8, and 15, and Cycle 2 Day 1
  - 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3
- Carboplatin AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles
- Pemetrexed 500 mg/m^2 on Day 1 of each 21-day cycle, with carboplatin for up to 4 cycles, and then as maintenance until disease progression

Study treatment may be withheld, and dosages may be modified, as needed to manage adverse events (AEs). If toxicity results in withholding or discontinuing 1 study treatment, then it may be possible to continue the other study treatment(s). Refer to Section 6.5 of the protocol for specific guidance.

Study treatment should continue until the following occurs: BICR confirmed disease progression using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, withdrawal of consent, the investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study treatment, or noncompliance with study treatment or procedure requirements.

EFFICACY EVALUATIONS

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]) should be performed no more than 28 days prior to randomization. Repeat imaging will occur at regular intervals, as defined in the Schedule of Activities, until disease progression is confirmed by BICR.

PHARMACOKINETIC EVALUATIONS

Blood samples will be collected from participants in Arms A/A2 for the measurement of serum amivantamab and plasma lazertinib concentrations and in Arms C/C2 for measurement of serum amivantamab concentrations. Sample collection and testing will comply with local regulations.

IMMUNOGENICITY EVALUATIONS

Blood samples will be collected from participants receiving amivantamab and will be analyzed for antibodies to amivantamab using a validated immunoassay in Arms A/A2 and Arms C/C2. Serum samples will be screened for antibodies binding to amivantamab, and other immunogenicity analyses may be performed to further characterize any immune responses generated. Sample collection and testing will comply with local regulations.

BIOMARKER EVALUATIONS

Blood samples and tumor tissue collected at screening and during the study may be evaluated for biomarkers relevant to cancer to understand the molecular biology of the tumor, efficacy observed with study treatments, and mechanisms of acquired resistance to study treatments. Sample collection and testing will comply with local regulations.

SAFETY EVALUATIONS

Safety will be assessed by physical examinations, laboratory tests, vital signs, electrocardiograms, Eastern Cooperative Oncology Group (ECOG) performance status, monitoring of AEs, and concomitant medication usage.

STATISTICAL METHODS

Two dual hypotheses will be independently investigated: LACP/ACP-L and ACP will reduce the risk of either disease progression or death by 35%, as individually compared with CP (median PFS of 8.5 and 5.5 months, respectively). The primary efficacy analysis of LACP/ACP-L versus CP will include all participants randomized to Arm A. The median PFS for CP is estimated to be 5.5 months (Mok 2017; Soria 2015). Assuming a median PFS of 8.5 months for both LACP/ACP-L and ACP, with an approximate 16-month accrual period and an additional 3-month follow-up, a total of 350 PFS events across all 3 arms combined will provide approximately 93% power for LACP/ACP-L over CP, and 83% power for ACP over CP to detect a 35% reduction in the risk of either progression or death, (HR of 0.65 for LACP/ACP-L vs CP and ACP vs CP, respectively) with a log-rank test, assuming an overall family-wise Type I error rate at two-sided significance level of 5%. Taking account of the accrual period, follow-up, and an annual dropout rate of 5%, the total sample size is approximately 600 eligible participants will be randomized in a 2:2:1 ratio (Arm A: Arm B: Arm C) in the study. Comparison of LACP/ACP-L (Arm A) with ACP (Arm C) will be performed to describe the contribution of lazertinib based on intracranial PFS, ORR, DoR, and PFS, using summary statistics and nominal p-values; there will be no formal hypothesis testing for this comparison.

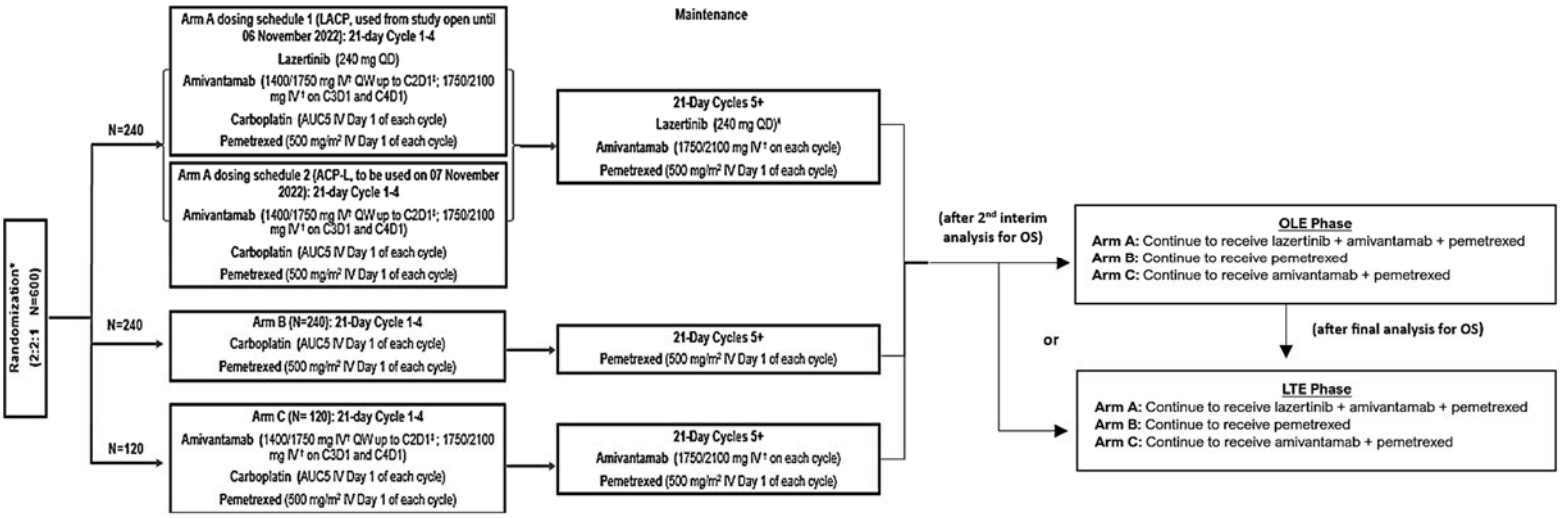
To control the overall Type I error rate at 5% for the hypotheses testing of primary endpoint (PFS) and key secondary endpoints (ORR and overall survival [OS]), a graphical approach in a group sequential design setting as described by Maurer (2013) will be applied.

The primary efficacy endpoint of PFS by BICR will be analyzed using a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), Asian race (yes vs no), and history of brain metastasis (yes vs no) for each of the dual primary analyses. The hazard ratio (HR) for PFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test.

The primary objectives of the extension cohort are to further describe the safety and efficacy of the ACP-L dosing schedule (Arm A2) versus ACP (Arm C2) with additional data. Arms A2 and C2 are only a part of the extension cohort – not the main study. No hypothesis testing will be performed. The statistical analysis plan will provide details on descriptive statistics of combining data from the main study and the extension cohort to provide additional data on safety and tolerability of ACP-L dosing schedule.

1.2. Schema

Figure 1: Schematic Overview of the Study



ACP-L=amivantamab, carboplatin, pemetrexed, and lazertinib (lazertinib started after carboplatin treatment is completed); AUC=area under the concentration-time curve; C#D#=Cycle # Day #; IV=intravenously; LACP=lazertinib, amivantamab, carboplatin, and pemetrexed (all drugs started C1D1); LTE=long-term extension; OLE=open-label extension; OS=overall survival; QD=once daily; QW=once weekly.

Arm A Dosing schedule 2 (ACP-L) started on 7 November 2022.

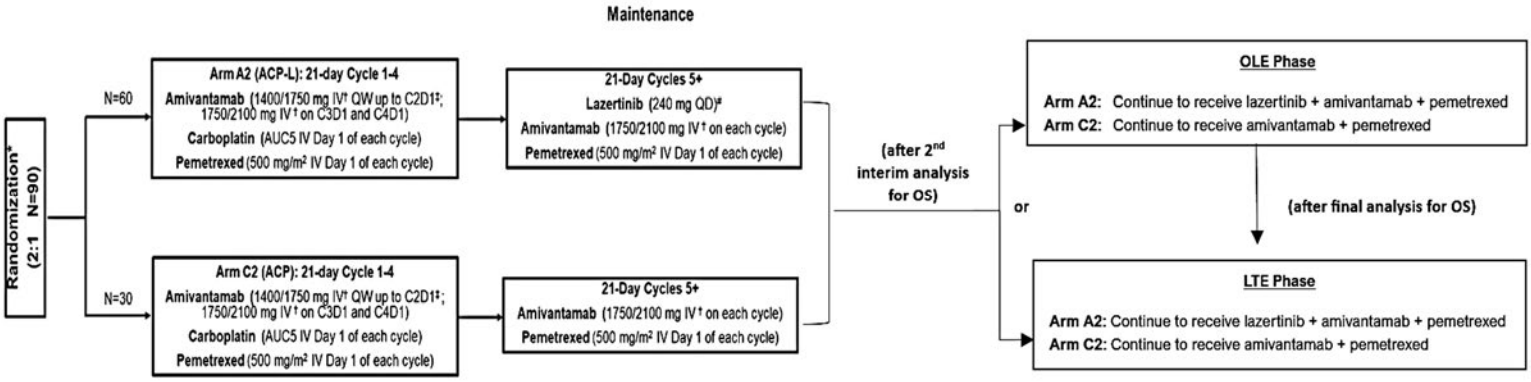
* Stratification factors: osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes vs no), Asian race (yes vs no)

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

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

\# Lazertinib for participants receiving dosing schedule 2 in Arm A may start sooner if carboplatin discontinued earlier than Cycle 4.

Figure 2: Schematic Overview of the Extension cohort



ACP-L=amivantamab, carboplatin, pemetrexed, and lazertinib (lazertinib started after carboplatin treatment is completed); AUC=area under the concentration-time curve; C#D#=Cycle # Day #; IV=intravenously; LTE=long-term extension; OLE=open-label extension; OS=overall survival; QD=once daily; QW=once weekly.

* Stratification factors: osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes vs no), Asian race (yes vs no)

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

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

\# Lazertinib for participants in Arm A2 may start sooner if carboplatin is discontinued earlier than Cycle 4

1.3. Schedule of Activities

Table 1: Schedule of Activities (All Treatment Arms, Unless Otherwise Indicated)

For OLE and LTE phases, refer to Table 20 and Table 21, respectively.

Study Phase	Screening	Treatment (21 Days/Cycle)								End of Treatment Visit[a]	Follow-up (Visit/Call)	Notes
Cycle		C1				C2	C3	C4	C5+			
Cycle Day		1	2 (Arms A/A2/C/C2)	8	15	1	1	1	1	30 Days After Last Dose	Every 12 Weeks	
Visit Window (Days)	-28 to -1	-	-	±1	±1	±1	±3	±3	±3	+7	±14	
STUDY PROCEDURES Treatment cycles are 21 days in duration. In Arms A/A2, lazertinib is administered once daily, beginning Cycle 5 Day 1 or earlier if carboplatin is discontinued before Cycle 4 for dosing schedule 2. In Arms A/A2 and Arms C/C2, amivantamab is administered in Cycle 1 on Days 1, 2, 8 and 15, in Cycle 2 on Day 1, then once every 3 weeks on Day 1 of each 21-day cycle. Assessments during in-clinic dosing days should be performed prior to administration of study treatment unless otherwise stated. For Arms A/A2, starting with Cycle 2 Day 1: if a dose interruption or missed dose leads to a cycle delay or a dose delay, the sampling schedule (except disease assessments) should be delayed accordingly to ensure sampling relative to amivantamab dose administration. Investigator must confirm that the participant meets treatment criteria before administration of study treatment/s. In the Follow-up Phase, collect data until the end of study for each participant. Clinic visits may be replaced with remote/virtual visits during a national disaster or pandemic, with clinic visits resuming as soon as possible thereafter.												
Screening Assessments												
Informed consent	X											Must be signed before any study related procedures are performed and can be performed >28 days prior to randomization All other screening procedures must be completed within 28 days before randomization.
Inclusion/exclusion criteria	X											Confirm all criteria are met before randomization[b]
Demography	X											Age (year of birth), gender, ethnicity, race
Disease characteristics	X											Tumor type, tumor stage at diagnosis, diagnosis date, prior anticancer therapies and date(s) of disease progression on each therapy
Medical history	X											Diagnoses, relevant surgeries/procedures, tobacco use, conditions, symptoms (with grade)
ECOG performance status	X[c]	X[b,c]				X	X	X	X	X		Within 72 hours of Day 1 of each cycle
Serology	X		As clinically indicated									HIV antibody, HBsAg, HBsAb, HBcAb, anti-HCV antibody, HBV viral load (if needed) and HCV viral load (if needed)
Coagulation	X		As clinically indicated									
Urinalysis	X		As clinically indicated									
Pregnancy test	X	X[b,c]				X	X	X	X	X	X (See Notes)	For participants of childbearing potential, a serum pregnancy test is required at Screening and within 72 hours before the first dose of Cycle 1. A serum or urine pregnancy test is required within 72 hours before the first dose of each subsequent treatment cycle, and monthly for 6 months after the last dose for participants in Arms A/A2 and Arms C/C2.
Ophthalmologic examination	X		As clinically indicated									Including slit lamp and fundoscopic examinations and visual acuity test

Table 1: Schedule of Activities (All Treatment Arms, Unless Otherwise Indicated)

For OLE and LTE phases, refer to Table 20 and Table 21, respectively.

Study Phase	Screening	Treatment (21 Days/Cycle)								End of Treatment Visit[a]	Follow-up (Visit/Call)	Notes
Cycle		C1				C2	C3	C4	C5+			
Cycle Day		1	2 (Arms A/A2/C/C2)	8	15	1	1	1	1	30 Days After Last Dose	Every 12 Weeks	
Visit Window (Days)	-28 to -1	-	-	±1	±1	±1	±3	±3	±3	+7	±14	
Safety Assessments (predose, except as noted)												
Hematology and chemistry (up to 72h predose)	X[c]	X[b,c]		X	X	X	X	X	X	X		Results of screening assessments must be reviewed by the Investigator prior to randomization; laboratory assessments must be reviewed by the Investigator prior to each dose of chemo or amivantamab. Additional testing as needed, per local guidelines/practice, with clinically significant abnormalities reported as AEs. If chemo and amivantamab are administered on different days, obtain laboratory assessments before each study treatment, if the period between the pre-chemo laboratory assessments and pre-amivantamab laboratory assessments is expected to be >72 h. Hematology and chemistry schedule applies to all arms, including C1D8 and C1D15.
12-lead ECG	X[c]	X[b,c]	As clinically indicated									Triplicate ECG at screening (approximately 2 min between each ECG), and single ECG at other times
ECHO or MUGA	X	As clinically indicated										
Vital signs	X	X	X	X	X	X	X	X	X	X		Heart rate, BP, respiratory rate, temperature, and O_2 saturation for all arms prior to administration of study drug on Day 1 of each cycle. **Arms A/A2 & C/C2**: Also ≤30 min before, 30-min intervals (±5 minutes), and at end of amivantamab infusion (+5 minutes). If chemo and amivantamab are administered on different days, obtain vital signs before each study treatment. **Arm B**: Also at C1D8 and C1D15 visits.
Weight	X[c]	X[c]				X	X	X	X	X		
Physical examination (PE) [d]	X	See Notes										Screening includes, at a minimum, height, general appearance, and PE of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Thereafter, within 72 hours of Day 1 of each cycle and at the end of treatment visit, perform symptom-directed PE of involved organs and other body systems as indicated, with clinically significant abnormalities reported as AEs. If chemo and amivantamab are administered on different days, obtain symptom-directed PE before each study treatment, if the period between the pre-chemo PE and pre-amivantamab PE is expected to be >72 h.
Adverse events	X											Continuous from the time ICF is signed through 30 days after the last dose of study treatment or before starting subsequent anticancer treatment, whichever occurs first (or >30 days for an SAE, if considered related to study treatment)
Prior and concomitant medications	X											Record all prescription and over-the-counter treatments administered up to 28 days before randomization through 30 days after the last dose of study treatment (or the start of a subsequent systemic anticancer therapy, if earlier); >30 days after the last dose of study treatment in conjunction with SAEs considered related to study treatment, until resolution of event or start of subsequent therapy. For participants with Grade 3 or 4 AEs considered related to study drug, record concomitant medications through the end of follow-up of that AE.

Table 1: Schedule of Activities (All Treatment Arms, Unless Otherwise Indicated)

For OLE and LTE phases, refer to Table 20 and Table 21, respectively.

Study Phase	Screening	Treatment (21 Days/Cycle)								End of Treatment Visit[a]	Follow-up (Visit/Call)	Notes
Cycle		C1				C2	C3	C4	C5+			
Cycle Day		1	2 (Arms A/A2/C/C2)	8	15	1	1	1	1	30 Days After Last Dose	Every 12 Weeks	
Visit Window (Days)	-28 to -1	-	-	±1	±1	±1	±3	±3	±3	+7	±14	
Efficacy Assessments												
CT/MRI tumor imaging	X	Disease assessment of the chest, abdomen, pelvis, and any other disease location at 6 weeks (+1 week) (ie, no earlier than 42 days from randomization), then every 6 weeks (±1 week) for the first 12 months, and every 12 weeks (±1 week) thereafter. Timing is relative to randomization.										Use same method throughout study. Continue imaging until disease progression is confirmed by BICR. Submit images to central vendor per Imaging Manual until BICR confirmed disease progression. Study treatment should continue until documented disease progression is confirmed by BICR For participants who discontinue treatment prior to disease progression, tumor imaging should continue until disease progression is confirmed by BICR, if clinically feasible. If participant begins a new cancer therapy before disease progression, obtain tumor imaging before the new therapy, and then continue imaging per schedule until BICR confirms disease progression. If a participant receives study treatment beyond confirmed documented disease progression, continue disease assessments as scheduled. Imaging obtained as part of standard care before signing the ICF, but within 28 days of randomization, may be used for the screening assessment if parameters meet the imaging manual requirements.
Brain MRI	X	Post baseline MRI to be conducted at 6 weeks (+1 week) (ie, no earlier than 42 days after randomization), at 12 weeks (±1 week), and then every 12 weeks (±1 week). Timing is relative to randomization.										Brain MRI should be performed with (or without if contradicted) contrast. More frequent brain MRI may be performed if clinically indicated. For those who have BICR confirmed extracranial progression per RECIST v1.1, brain MRI should be continued, if feasible, until BICR confirmed intracranial progression. For participants who discontinue treatment prior to disease progression, tumor imaging should continue until disease progression is confirmed by BICR, if clinically feasible. If a participant begins a new cancer therapy before disease progression, obtain tumor imaging before the new therapy and continue imaging per schedule until BICR confirms progression. If a participant receives study treatment beyond confirmed documented disease progression, continue disease assessments as scheduled. If MRI is medically prohibited, CT with or without contrast may be acceptable (see Imaging Manual) until BICR confirmed intracranial disease progression. Submit images to central vendor per Imaging Manual. Imaging obtained as part of standard care before signing the ICF, but within 28 days of randomization, may be used for the screening assessment if parameters meet imaging manual requirements.
Symptomatic progression events		X										Collect continuously from randomization (including Follow-up Phase)
Survival/disease status											X	
Subsequent anticancer therapy(ies)											X	Collect information on name of therapy and treatment start and end dates
Preinfusion Medications												
Folic acid	Daily from 7 days before first dose of pemetrexed to 21 days after last dose of pemetrexed											Folic acid should be started during the screening period, 7 days prior to the anticipated first dose of pemetrexed
Vitamin B12	One dose on or within 7 days of Cycle 1 Day 1, then every 3 cycles. May be administered on the same day as pemetrexed.											Vitamin B12 may be started during the screening period

Table 1: Schedule of Activities (All Treatment Arms, Unless Otherwise Indicated)

For OLE and LTE phases, refer to Table 20 and Table 21, respectively.

Study Phase	Screening	Treatment (21 Days/Cycle)								End of Treatment Visit[a]	Follow-up (Visit/Call)	Notes
Cycle		C1				C2	C3	C4	C5+			
Cycle Day		1	2 (Arms A/A2/C/C2)	8	15	1	1	1	1	30 Days After Last Dose	Every 12 Weeks	
Visit Window (Days)	-28 to -1	-	-	±1	±1	±1	±3	±3	±3	+7	±14	
Corticosteroid	Day -1	X	X			X	X	X	X			Day before, day of, and day after each pemetrexed dose, or per local regulations and practice
Prior and Concomitant Medication												
(Arms A/A2 & C/C2 only) Preinfusion medications for amivantamab		X	X	X	X	X	X	X	X			Record all preinfusion medications (Section 6.7.2.2)
Prophylactic-dose anticoagulation[g]	X	X										Recommended during the first 4 months of treatment for participants receiving the combination of amivantamab and lazertinib: for Arm A dosing Schedule 1 (LACP) start Cycle 1 Day 1, for Arm A dosing Schedule 2 and Arm A2 (ACP-L) start when lazertinib is initiated (Cycle 5 Day 1 or sooner if carboplatin discontinued earlier than Cycle 4).
Randomization & Study Treatment												
Randomization		X										Randomization can only occur after results from C1D1 laboratory assessments, ECG, and ECOG have been reviewed by the investigator and confirmed to meet enrollment criteria. May be done within 72 hours prior to start of study treatment, if C1D1 predose labs, ECG, and ECOG are completed early (as allowed by Footnote "b")
Lazertinib administration **(Arms A/A2 only)**		For Arm A dosing schedule 1 (LACP), lazertinib starts Cycle 1 Day 1 (~30 min before preinfusion medications for chemo), then approximately the same time each day, with or without food. For Arm A dosing schedule 2 and Arm A2 (ACP-L), lazertinib starts on Cycle 5 Day 1 (or sooner if carboplatin discontinued earlier than Cycle 4).										On the day of each clinic visit, lazertinib should be given on site and before other study drugs are administered.
Record lazertinib treatment compliance **(Arms A/A2 only)**		X				X	X	X	X			For Arm A dosing schedule 2 and Arm A2 (ACP-L), participants receive lazertinib starting Cycle 5 Day 1 or sooner if carboplatin discontinued earlier than Cycle 4.
Pemetrexed administration		X				X	X	X	X			On Day 1 of each cycle, pemetrexed should be the first IV-administered study treatment. Creatinine clearance (Appendix 10) must be determined prior to administration of pemetrexed.
Carboplatin administration		X				X	X	X				On Day 1 of Cycles 1-4, carboplatin should be administered after pemetrexed (and before amivantamab in Arms A and C). Carboplatin administration cannot exceed a total of 4 cycles.
Amivantamab administration **(Arms A/A2 & C/C2 only)**		X	X	X	X	X	X	X	X			Administered after all chemo. Split first dose on C1D1 and C1D2. Typically administered every 3 weeks beginning in Cycle 2 but can be at any interval between 2 and 4 weeks to align with a delayed chemo dose (Appendix 12). If a dose is delayed in Cycle 2 or beyond, then subsequent doses will be scheduled based on the timing of the previous dose of amivantamab If amivantamab is delayed for >6 weeks, discuss with the Medical Monitor prior to redosing.

Table 1: Schedule of Activities (All Treatment Arms, Unless Otherwise Indicated)

For OLE and LTE phases, refer to Table 20 and Table 21, respectively.

Study Phase	Screening	Treatment (21 Days/Cycle)								End of Treatment Visit[a]	Follow-up (Visit/Call)	Notes
Cycle		C1				C2	C3	C4	C5+			
Cycle Day		1	2 (Arms A/A2/C/C2)	8	15	1	1	1	1	30 Days After Last Dose	Every 12 Weeks	
Visit Window (Days)	-28 to -1	-	-	±1	±1	±1	±3	±3	±3	+7	±14	
Patient-Reported Outcomes (predose on clinic visit days; when possible, complete before other study procedures at that visit)												
PGIS		X				X	X	X	X	X	X	Continue in Follow-up phase (collection by phone allowed) for 1 year after progression, regardless of whether subsequent therapy has been started
PGIC						X	X	X	X	X	X	
NSCLC-SAQ EORTC-QLQ-C30 PROMIS-PF EQ-5D-5L		X				X	X	X	X	X	X	
PRO CTCAE		X				X	X	X	X	X		
Biomarkers												
ctDNA blood sample	X									X (see notes)		As permitted by local regulations. Obtain ctDNA blood sample within 30 days of disease progression but before next anticancer therapy. If participant receives study treatment/s beyond disease progression, collect additional samples at each post-progression disease assessment.
Blood samples for exploratory biomarkers (Arms A/A2 and C/C2 only)	X					X	X	X	X (C5D1, C6D1, C7D1, C8D1)	X		As permitted by local regulations.
Tumor biopsy	X									X		As permitted by local regulations. If tumor tissue was collected at or after the diagnosis of locally advanced or metastatic NSCLC, and after progression on or after treatment with osimertinib, it should be submitted to the central laboratory. If it is not available, then participants may undergo an optional biopsy during screening. Tumor biopsy after progression on study treatment is also optional but strongly recommended for participants for whom a baseline biopsy was provided.

ACP-L=amivantamab, carboplatin, pemetrexed, and lazertinib (lazertinib started after carboplatin treatment is completed); BICR=blinded independent central review; BP=blood pressure; C#D#=Cycle # Day #; chemo=chemotherapy; CT=computerized tomography; ctDNA=circulating tumor deoxyribonucleic acid; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=EuroQol 5-dimensional descriptive system (5-level version); h=hour; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; min=minutes; LACP=lazertinib, amivantamab, carboplatin, and pemetrexed (all drugs started C1D1); MUGA=multigated acquisition; MRI=magnetic resonance imaging; O_2=oxygen; PE=physical examination; PK=pharmacokinetics; PRO CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PROMIS-PF=Patient-Reported Outcomes Measurement Information System – Physical Function; VTE = venous thromboembolic.

Guidance on study conduct during natural disaster, major disruption, or pandemic (eg. COVID 19), is provided in a standalone appendix that will be provided to the site with the protocol.

a. With the exception of the end-of-treatment pregnancy test for participants of childbearing potential, which must occur at least 30 days after the last dose of study treatment, end of treatment procedures may be conducted before 30 days after last dose of study treatment if new anticancer therapy is to be initiated.
b. Must be reviewed by the investigator and confirmed to meet eligibility requirements per Section 5.1 (Inclusion Criteria) and Section 5.2 (Exclusion Criteria) prior to randomization. See also Footnote c.
c. If performed within 72h before the first dose of study treatment, then the assessment does not need to be repeated at predose on C1D1.
d. Evaluate for signs and symptoms of VTE events. A focused physical examination of extremities and evaluation of respiratory status (including pulse oximetry) should be performed.
e. See Section 6.5.3.12 for additional information. Refer to NCCN Guidelines Version 1.2022 Cancer-Associated Venous Thromboembolic Disease, Section VTEB for examples of prophylactic-dose anticoagulants in ambulatory cancer participants.

Table 2: Collection Times for Pharmacokinetics and Immunogenicity Samples[a] (Arms A/A2 and C/C2)

Not applicable to OLE and LTE phases.

Study Day		Sampling Time	Time Allowance	Plasma Sample for Pharmacokinetics[b] (Lazertinib) Arm A LACP only	Serum Sample[c] for Pharmacokinetics (Amivantamab) Arms A/A2 and C/C2	Serum Sample[c] for Immunogenicity (Amivantamab) Arms A/A2 and C/C2
Cycle 1[d]	Day 1	Predose/preinfusion	0-2 hours	X	X	X
		End of infusion (amivantamab)[e]	0-15 minutes		X	
		2 hours post-lazertinib administration	± 1 hour	X		
		4 hours post-lazertinib administration[b]	± 1 hour	X		
	Day 2	Predose/preinfusion	0-20 minutes		X	
		End of infusion (amivantamab)[e]	0-15 minutes		X	
Cycle 2	Day 1[f]	Predose/preinfusion	0-2 hours	X	X	X
		End of infusion (amivantamab)[e]	0-15 minutes		X	
		2 hours post-lazertinib administration	± 1 hour	X		
		4 hours post-lazertinib administration[b]	± 1 hour	X		
Cycles 3, 5, 7, 10, 13, 17	Day 1[f]	Predose/preinfusion	0-2 hours	X	X	X
		End of infusion (amivantamab)[e]	0-15 minutes		X	
End -of -treatment		30 days after last dose	± 7 days	X	X	X

a. Sample collection and testing should comply with local regulations. In Arms A/A2 and C/C2, draw blood samples for unscheduled pharmacokinetics analysis when liver chemistry is assessed (Appendix 6).

b. Lazertinib 4-hour postdose plasma pharmacokinetics sample will be obtained after amivantamab end of infusion. If infusion of amivantamab goes beyond 5 hours, then lazertinib sampling should be done within the provided time allowance (3-5 hours after lazertinib administration) from the opposite arm.

c. Separate blood draws are not required for amivantamab pharmacokinetics and immunogenicity when collected at the same time point.

d. If Cycle 1 Day 1 dosing of amivantamab is delayed to Cycle 1 Day 2, samples scheduled for Cycle 1 Day 1 should be collected on Cycle 1 Day 2, and samples scheduled for Cycle 1 Day 2 should be collected on Cycle 1 Day 3.

e. End of infusion sample will be obtained relative to amivantamab (ie, within 15 minutes of the end of amivantamab infusion) from the opposite arm.

f. If a dose interruption or missed dose leads to a cycle delay or a dose delay, the sampling schedule for postdose/postinfusion should be delayed accordingly to ensure sampling relative to amivantamab dose administration.

Table 3: Collection Times for Pharmacokinetics Samples[a] for Lazertinib (Arms receiving ACP-L – Arm A Dosing Schedule 2 and Arm A2)
Not applicable to OLE and LTE phases.

Study Day		Sampling Time	Time Allowance	Plasma Sample for Pharmacokinetics[c] (Lazertinib) Arms receiving ACP-L (Arm A dosing schedule 2 and Arm A2)
Cycle 5[c]	Day 1	Predose	0-2 hours	X
		2 hours post lazertinib administration	± 1 hour	X
		4 hours post lazertinib administration[b]	± 1 hour	X
Cycles 7, 10, 13, 17	Day 1	Predose	0-2 hours	X
End-of-treatment		30 days after last dose	± 7 days	X

a. Sample collection and testing should comply with local regulations. Draw blood samples for unscheduled pharmacokinetic analysis when liver chemistry is assessed (Appendix 6).
b. For Cycle 5 Day 1 lazertinib 4-hour postdose plasma pharmacokinetics sample will be obtained after amivantamab end of infusion. If infusion of amivantamab goes beyond 5 hours, then lazertinib sampling should be done within the provided time allowance (3-5 hours after lazertinib administration) from the opposite arm.
c. Lazertinib can be initiated earlier, if carboplatin has been discontinued prior to Cycle 4.

2. INTRODUCTION

This study will compare the efficacy and safety of adding lazertinib and amivantamab to carboplatin and pemetrexed (LACP and ACP-L dosing schedules) versus standard-of-care chemotherapy (carboplatin and pemetrexed; CP) alone in participants with epidermal growth factor receptor (EGFR)-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or after treatment with osimertinib.

Amivantamab (JNJ-61186372) is a low fucose, fully human IgG1-based bispecific antibody directed against EGFR and mesenchymal-epithelial transition (MET) tyrosine kinase receptors that is being developed for the treatment of solid tumors, including EGFR-mutated NSCLC. Lazertinib (JNJ-73841937; YH-25448) is an oral, highly potent, third-generation, EGFR tyrosine kinase inhibitor (TKI). Lazertinib selectively inhibits both primary activating EGFR mutations (Exon 19del, Exon 21 L858R substitution) and the EGFR T790M resistance mutation, while having less activity versus wild-type EGFR. After progression on or after osimertinib treatment, adding lazertinib to amivantamab results in more robust and durable antitumor activity, with a higher confirmed objective response rate (ORR), greater median duration of response, and improved clinical benefit rate compared with amivantamab monotherapy (see Section 2.2.3). Lazertinib also provides antitumor activity within the central nervous system (CNS; see Section 2.2.2).

Treatment guidelines for locally advanced or metastatic NSCLC recommend platinum-based combination chemotherapy regimens, including carboplatin-pemetrexed, in patients with EGFR -mutated NSCLC who experience disease progression on or after EGFR TKI treatment (ESMO 2020, NCCN 2021, Planchard 2018). Carboplatin is a platinum coordination compound that exerts its cytotoxic effects via formation of deoxyribonucleic acid (DNA) cross-links (Carboplatin USPI 2018). Pemetrexed inhibits enzymes involved in folate -dependent metabolism, thereby disrupting cellular replication (Alimta USPI 2019).

For the most comprehensive nonclinical and clinical information regarding amivantamab and lazertinib refer to the latest version of the Investigator's Brochure (IB) and Addenda for amivantamab and lazertinib. For further information regarding carboplatin and pemetrexed, refer to the local prescribing information for each product.

The term "study treatment" throughout the protocol refers to study drug (lazertinib, amivantamab, carboplatin, or pemetrexed) as defined in Section 6.1, Study Treatments Administered.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "patient".

2.1. Background

Lung cancer is one of the most common types of cancer and is the most common cause of death from cancer. Lung cancer is a major global health concern, with more than 235,000 new diagnoses annually in the United States, 490,000 in the European Union, and over 1 million in Asia, with the highest reported incidence rates in Korea and China (Bray 2018; Pakzad 2015; SEER 2021). NSCLC accounts for approximately 85% of lung cancers (Globocan 2012). Advanced NSCLC is a serious terminal illness that accounts for approximately 20% of all cancer mortality, and until recently had a median overall survival (OS) of approximately 1 year. Patients with locally advanced or metastatic NSCLC and EGFR mutations also have poor health-related quality of life (Leighl 2020).

Over the past decade, there has been significant advancement in the understanding of the underlying biology of NSCLC, including the identification of multiple "driver" mutations that can result in a constitutive activation of pro-growth signaling pathways, typically occurring in NSCLC of adenocarcinoma histology. In patients with metastatic disease, driver mutations are observed in approximately 60% of adenocarcinomas (Herbst 2018). Among patients with NSCLC adenocarcinoma, the most prevalent of these driver mutations are those that result in the activation of EGFR, which are identified in approximately 15% of Western patients (Pao 2011) and in up to 40% to 50% of Asian patients (Jänne 2006). The most frequently identified EGFR mutations, Exon 19del and L858R, are identified in approximately 85% of subjects with activating EGFR mutations (Harrison 2020).

The third-generation EGFR TKI osimertinib is indicated for the first- and second-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations. Compared with first- and second-generation EGFR TKIs, third-generation EGFR TKIs provide better efficacy benefits in general and may penetrate the blood-brain barrier better and more effectively treat brain metastasis, which occurs in approximately 10% to 20% of patients with treatment-naïve EGFR-mutated NSCLC (Reungwetwattana 2018). With its demonstrated activity against the EGFR T790M+ resistance mutation, as well as brain metastases, it was hypothesized that osimertinib as a first-line treatment would delay emergence of T790M-mediated resistance, as well as relapse within the central nervous system, resulting in improved disease control. The FLAURA study compared the third-generation EGFR TKI osimertinib versus a standard EGFR TKI (gefitinib or erlotinib) as first-line therapy for patients with metastatic NSCLC and Exon 19del or L858R mutations (Soria 2018) and demonstrated a statistically significant improvement in progression-free survival (PFS) and OS for participants randomized to osimertinib treatment. In patients receiving osimertinib versus a first-generation EGFR TKI, median PFS was 18.9 versus 10.2 months, respectively, with a HR of 0.46; and median OS was 38.6 versus 31.8 months, respectively, with a HR of 0.80 (Ramalingam 2020; Soria 2018). This significant improvement in median PFS with osimertinib treatment was not associated with an improved ORR, suggesting the majority of benefit may have been derived from activity of osimertinib against the T790M+ resistance mutation and improved activity within the central nervous system.

Despite improved initial disease control with osimertinib front-line therapy, all patients treated with osimertinib will relapse. Once emergence of resistance renders treatment with osimertinib ineffective, there are no targeted therapies approved in osimertinib-relapsed disease, despite evidence that many patients have disease that continues to be dependent on signaling through either EGFR and/or MET pathways (Leonetti 2019). Standard of care, therefore, remains platinum- based doublet chemotherapy, such as carboplatin and pemetrexed (ESMO 2020; NCCN 2021; Planchard 2018). The ORR associated with this therapy, as determined in Phase 3 studies of similar populations, have been approximately 30%, with a median PFS of 4-5 months (Mok 2017; Soria 2015). Therefore, treatment options for patients with EGFR-mutated NSCLC are limited after front-line or second-line osimertinib, and there is a high unmet need for additional therapeutics that further control tumor growth before non-targeted therapies are used.

2.2. Study Rationale

2.2.1. Amivantamab

Unlike EGFR TKIs, which bind to the intracellular portion of the EGFR, amivantamab is a novel bispecific antibody that targets the extracellular domain of both EGFR and MET. Nonclinical data have demonstrated at least 3 potential mechanisms of action, including 1) inhibition of ligand-dependent signaling, 2) receptor degradation, and 3) initiation of antibody-dependent cellular cytotoxicity (ADCC). It is hypothesized that by targeting the extracellular domain of EGFR and MET, amivantamab can inhibit tumor growth driven by EGFR and MET receptors, including tumors that display primary resistance to EGFR TKIs (Exon 20ins) or have acquired resistance through either EGFR resistance mutations (T790M or C797S) or secondary activation of the MET pathway (MET amplification).

On 21 May 2021, the US Food and Drug Administration (FDA) granted accelerated approval to amivantamab for adult patients with locally advanced or metastatic NSCLC with EGFR Exon 20ins mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. Evidence of clinical activity has also been observed across patients with diverse EGFR-mutated disease, including those characterized by primary EGFR L858R, Exon 19del, G719A, and Exon 20ins disease, as well as EGFR T790M or C797S resistance mutations, and MET-based EGFR TKI resistance (both MET amplification and MET Exon 14skip mutation) (Haura 2019; Park 2020). As of 28 December 2020, 108 evaluable participants had received amivantamab in the post-osimertinib setting, including 85 participants with documented EGFR-based or MET-based resistance. Among the 108 evaluable participants, amivantamab demonstrated antitumor activity as a monotherapy, with a majority of participants demonstrating evidence of tumor shrinkage and approximately 30% achieving a best response of partial response (PR), per investigator assessment. Not all responses were durable, however, as the confirmed ORR was 20% (95% confidence interval [CI]: 13%, 29%) and clinical benefit rate (complete response [CR], PR, or stable disease) was 46% (95% CI: 37%, 56%). Median duration of response was 5.9 months (95% CI: 4.1, 13.4) and median PFS was 4.3 months (95% CI: 2.8, 5.4).

As of 08 October 2020, among 302 participants treated with amivantamab monotherapy at the recommended Phase 2 dose (RP2D), the most common treatment-emergent adverse events (TEAEs) (ie, frequency ≥20%) were infusion-related reactions (IRRs; 66%), paronychia (40%), dermatitis acneiform (36%) and rash (34%), hypoalbuminemia (26%), nausea (23%), constipation (22%), dyspnea (21%), and peripheral edema (20%). Nearly all IRRs occurred during the first infusion (Cycle 1 Day 1) and generally did not recur with subsequent infusions. Grade 3 or higher treatment-related TEAEs were reported in 49 (16%) participants, the most common (≥2%) of which were IRRs (2%) and paronychia (2%). Treatment-related serious TEAEs were reported in 18 (6%) participants. There were no treatment-related deaths. TEAEs leading to dose reduction or drug discontinuation, considered related to amivantamab, were observed in 11% and 3% of participants, respectively. For additional information, refer to the IB.

2.2.2. Lazertinib

The activity and tolerability of lazertinib, a novel third-generation EGFR TKI, as a single agent has been demonstrated in EGFR-mutated NSCLC after prior treatment with an EGFR TKI in the ongoing Phase 1/2 Study 73841937NSC2001. This study has enrolled 181 participants with EGFR-mutated advanced NSCLC that progressed following prior therapy with an EGFR TKI. In participants with T790M+ disease, the ORR was 57% and the median PFS was 9.7 months (95% CI: 8.1, 15.0) across all dose levels of lazertinib. Among participants in the Phase 1/2 study with measurable brain metastasis at baseline (n=22), the intracranial ORR of lazertinib at any dose was 55%, indicating effective blood-brain barrier penetration, with intracranial responses observed in participants beginning at lazertinib 40 mg (Cho 2020). The available safety and efficacy profile of lazertinib in this study appeared consistent with that of osimertinib as a second-line therapy (Mok 2017). The most common TEAEs (any grade) were rash, pruritus, diarrhea, paresthesia, constipation, upper respiratory tract infection, and decreased appetite. Treatment related events of ≥Grade 3 were observed in 10% of patients and treatment related serious TEAEs in 3%. Overall, the incidence and severity of AEs seen in this study were similar to those of osimertinib in the Phase 1 AURA study (Jänne 2015). However, cardiac safety assessment in these participants has shown that lazertinib has no clinically relevant effect on QT interval and left ventricular ejection fraction (LVEF) at doses of 20 mg to 320 mg (Ahn 2019; Jang 2021). For additional information, refer to the IB.

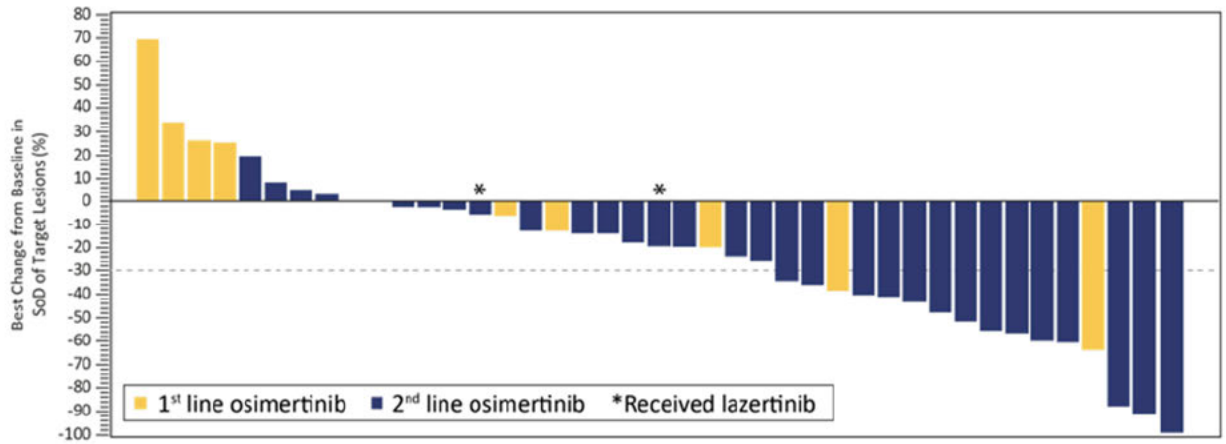
2.2.3. Amivantamab and Lazertinib Combination

The combination of amivantamab and lazertinib is being investigated in ongoing clinical studies including the Phase 1 Study 61186372EDI1001, the Phase 1 Study 73841937NSC1001, and the Phase 3 Study 73841937NSC3003. As a third-generation EGFR-TKI targeting activating EGFR mutations, lazertinib has a distinct mechanism of action from amivantamab, which targets the extracellular domains of both the EGFR and cMET proteins. The distinct mechanisms of action of amivantamab and lazertinib targeting the extracellular ligand binding domain and the intracellular active site, respectively, have the potential to inhibit the EGFR pathway more potently than either agent alone. CCI [redacted] In addition, the potential of the combined antibody and TKI/small molecule approach has been

previously recognized and investigated in human proof-of-concept studies in NSCLC (using cetuximab and afatinib) (Janjigian 2014) and breast cancer (using trastuzumab and lapatinib) (Blackwell 2010), which demonstrated not only the feasibility of this approach, but also superior clinical activity than could be expected from either agent alone.

In a cohort of 45 osimertinib-relapsed but chemotherapy-naïve participants with EGFR Exon 19del or L858R NSCLC enrolled without biomarker selection in Study 61186372EDI1001, the combination of amivantamab and lazertinib demonstrated evidence of antitumor activity in the majority of participants, with 36% of participants achieving PR as their best response. Within this cohort, all initial responses were confirmed upon subsequent disease assessment, for a confirmed ORR of 36% (95% CI: 22%, 51%), including 1 CR and 15 PR (Figure 3) (Cho 2020). As of 22 December 2020, with 11 of 16 responders continuing in response, the median duration of response was not estimable after a median follow-up of 8.2 months, again demonstrating improved disease control with the amivantamab-lazertinib combination. The clinical benefit rate of 60% was similarly increased with the combination, as compared to amivantamab monotherapy (see Section 2.2.1) and with 20 of 45 participants continuing on combination therapy, the median PFS was 4.9 months (95% CI: 3.7, 8.3) (Bauml 2020).

Figure 3: Waterfall Plot of Investigator-Assessed Best Percentage Change from Baseline in Sum of Diameters (SoD) of Target Lesions by Combination Therapy (Amivantamab + Lazertinib) Expansion Cohorts; Response Evaluable at RP2CD Analysis Set in Combination Therapy (JNJ-61186372 + Lazertinib) (Study 61186372EDI1001)



RP2D: Amivantamab 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
RP2CD: Amivantamab RP2D + lazertinib 240 mg.
RP2D=recommended Phase 2 dose; RP2CD=recommended Phase 2 combination dose.
Source: (Cho 2020)

As of the 22 December 2020 data cutoff, the safety profile of the combination, assessed in the 148 participants (91 in Study 61186372EDI1001 and 57 in Study 73841937NSC1001), was similar to that observed among participants treated with amivantamab monotherapy, with increased incidence of EGFR-associated AEs, but no new safety signals. The median duration of exposure was 8.3 months (range: 0.23 to 19.78 months) for 61186372EDI1001 and 0.74 months (range: 0.03 to 9.23 months) for 73841937NSC1001. The most common TEAEs (occurring in

≥20% of participants) were IRR (60%), paronychia (47%), dermatitis acneiform (45%), hypoalbuminemia (37%), stomatitis (35%), rash (30%), alanine aminotransferase (ALT) increased (25%), nausea (23%), pruritis (22%), and peripheral edema and aspartate aminotransferase (AST) increased (22% each). TEAEs of Grade 3 or Grade 4 severity were reported in 48 participants (32%) and 3 participants (2%), respectively, with 32 participants (22%) experiencing treatment (amivantamab or lazertinib)-related TEAEs of ≥Grade 3 severity. There was no consistent pattern of TEAEs with Grade ≥3 severity; those events seen in >2% of participants were dermatitis acneiform (5%); dyspnea, pneumonia, and hypoalbuminemia (4% each); paronychia and ALT increased (3% each); and hyponatremia and AST increased (3%). A single Grade 5 TEAE, pneumonitis, was reported as being related to study treatment. This was originally reported as a Grade 3 event but was upgraded to Grade 5 when the participants died as a result of rapidly progressing disease.

2.2.4. Rationale for Adding EGFR-Targeted Therapy to Chemotherapy

With the approval of EGFR TKIs for the treatment of NSCLC, several studies have investigated the optimal application of these agents, including potentially adding EGFR TKIs to chemotherapy. While early studies evaluating the potential of EGFR TKI plus chemotherapy failed to demonstrate clinical benefit, the failure to use molecular markers to select for populations with EGFR-driven disease may have confounded the interpretation of these results. With the significant improvement in efficacy observed with second- and third-generation EGFR TKIs relative to chemotherapy, platinum-based chemotherapies were reserved for salvage therapy after TKI failure, after tumors had developed mutations that made them resistant to targeted approaches.

More recent studies have suggested a possible benefit with EGFR TKI plus chemotherapy in the subset of patients with EGFR-mutated NSCLC. A meta-analysis of nine trials of adding TKI therapy to chemotherapy reported that erlotinib and chemotherapy resulted in significant improvement of PFS and OS, compared to chemotherapy alone (Xu 2015), in the subset of patients with EGFR-mutated NSCLC. Subsequently, two recent prospective studies that added gefitinib (a first-generation EGFR TKI) to carboplatin and pemetrexed demonstrated improved outcomes, as compared to gefitinib alone, in terms of ORR, PFS, and OS (Hosomi 2020; Noronha 2020). In addition to the suggested benefit of adding targeted inhibition of the EGFR pathway to chemotherapy, amivantamab antitumor activity is hypothesized to include ADCC -dependent mechanisms that are not associated with EGFR TKIs. Thus, there may be additional benefit with amivantamab plus chemotherapy arising from disruption of an inhibitory tumor microenvironment (Galluzzi 2015) and targeting of Fc receptor-bearing immune cells to tumor cells.

2.2.5. Rationale for Amivantamab and Platinum Doublet Chemotherapy

Participants in Arms C/C2 will receive amivantamab, carboplatin, and pemetrexed (ACP), which was first explored in the Phase 1 Study 61186372EDI1001. In this regimen, amivantamab is dosed weekly for first 4 doses on Cycle 1 Day 1/Day 2, Day 8, Day 15 and Cycle 2 Day 1 (at 1,400 mg for <80kg, 1,750 mg for ≥80 kg), followed by Q3 week dosing starting with Cycle 3 Day 1 (at 1,750 mg for <80kg, 2,100 mg for ≥ 80 kg), and added to standard-of-care carboplatin (AUC 5) and pemetrexed (500 mg/m^2) on Day 1 of each cycle in a 21-day cycle for up to 4 cycles, followed by maintenance with pemetrexed and amivantamab in 21-day cycles. The first dose of

amivantamab is split over 2 days, with 350 mg administered on Cycle 1 Day 1, and the remainder administered on Day 2. On 26 August 2020, the Safety Evaluation Team (SET) reviewed data (with a cutoff of 20 August 2020) from 5 participants enrolled in the initial dose-finding cohort and recommended expansion to the full cohort (N=20).

Data collected through 20 October 2020 from 16 participants in Study 61186372EDI1001 who had received at least 1 dose of amivantamab with carboplatin and pemetrexed (500 mg/m^2 [or per local guidance]) in 21-day cycles and found neither evidence of additive toxicity nor evidence that the anticipated hematologic toxicity with chemotherapy was worsened or prolonged by adding amivantamab. The most frequently reported (>20% of participants) TEAEs were IRR (69%), constipation (44%), thrombocytopenia (38%), rash (31%) and dermatitis acneiform (44%), fatigue (31%), and neutropenia (25%). The EGFR and MET-associated toxicities of rash, stomatitis, peripheral edema, and diarrhea were reported at an incidence and severity consistent with the monotherapy experience of amivantamab. TEAEs of ≥Grade 3 severity occurred in 7 of 16 (44%) participants, with the most frequently reported ≥Grade 3 TEAEs collectively reflecting anticipated chemotherapy-related cytopenia (neutropenia [19%], anemia [6%], and thrombocytopenia [6%]). Importantly, Cycle 1 declines in absolute neutrophil count (ANC) and platelet count that were observed in all participants recovered in time to allow each participant to receive the Cycle 2 Day 1 dose of chemotherapy and amivantamab, as scheduled. Consistent with the protocol, no participants received prophylactic granulocyte colony stimulating factor (G-CSF) during Cycle 1; however, 1 participant with Grade 3 neutropenia and 2 participants with Grade 4 neutropenia required treatment with G-CSF for chemotherapy-related neutropenia. All events of ≥Grade 3 severity were unrelated to amivantamab, with the exception of Grade 3 nausea in a participant with baseline Grade 1 nausea who was reported to have experienced worsening Grade 3 nausea, which was attributed to all 3 study agents. There were no Grade 5 events. The addition of amivantamab to chemotherapy is currently being investigated as a frontline regimen for the treatment of EGFR Exon 20ins NSCLC in Study 61186372NSC3001 (NCT04538664).

2.2.6. Rationale for Adding Lazertinib and Amivantamab to Platinum-Doublet Chemotherapy

Participants in Arms A/A2 will receive LACP or ACP-L. Recent studies have demonstrated the improved outcomes that can be achieved by adding targeted therapy to chemotherapy in patients with EGFR- mutated NSCLC (Hosomi 2020; Noronha 2020). The combination of amivantamab and lazertinib has demonstrated significant antitumor activity in patients with EGFR-mutated NSCLC who have progressed on or after osimertinib (Section 2.2.3). The level of activity with this combination exceeds that observed with amivantamab monotherapy and is consistent with the activity of the current standard of care for osimertinib-relapsed disease, platinum-based chemotherapy, while additionally providing CNS protection with lazertinib. The addition of amivantamab and lazertinib to platinum-based chemotherapy, therefore, has the potential to provide superior clinical efficacy as compared to standard-of-care chemotherapy alone.

Amivantamab, which has been demonstrated to exhibit ADCC-dependent mechanisms in preclinical models, may provide additional benefit arising from disruption of an inhibitory tumor microenvironment (Galluzzi 2015) and targeting of Fc receptor-bearing immune cells to tumor

cells. The safety profiles for amivantamab and lazertinib are largely distinct from those associated with chemotherapeutic agents, and amivantamab has been demonstrated to be safe and tolerable in addition to either lazertinib or chemotherapy.

The Phase 1 Study 73841937NSC1001 will include a cohort of 20 participants with locally advanced or metastatic EGFR-mutated NSCLC who have received a maximum of 3 lines of prior therapy in the metastatic setting and progressed on or after an EGFR TKI as the most recent line of therapy. These participants will be treated with LACP. A SET for the Phase 1 study will review safety and tolerability results for this cohort before enrollment begins in 61186372NSC3002.

In summary, the addition of amivantamab and lazertinib to standard-of-care platinum-based chemotherapy is hypothesized to provide improved clinical benefit for patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R mutations whose disease has progressed on or after treatment with osimertinib, through targeted anti-EGFR and anti-MET action, antitumor activity within the CNS, and recruitment of immune cells with antitumor activity.

2.2.7. Rationale for Chemotherapy Comparator

Participants in the comparator arm of this study (Arm B) will receive CP, without EGFR--targeted therapy. There are no approved targeted therapies for patients with EGFR-mutated NSCLC who have progressed on or after osimertinib therapy. Treatment guidelines for locally advanced or metastatic NSCLC recommend platinum-based combination chemotherapy regimens, including carboplatin pemetrexed or cisplatin-pemetrexed, in patients with EGFR-mutated NSCLC who experience disease progression on or after EGFR TKI treatment (ESMO 2020; NCCN 2021; Planchard 2018). The median PFS associated with platinum-based chemotherapy after failure of an EGFR TKI, as determined in Phase 3 studies of similar populations, is 4.4 to 5.4 months (Mok 2017; Soria 2015). The activity of carboplatin and cisplatin in NSCLC are largely similar, with no associated difference in OS (Griesinger 2019).

Pemetrexed, which is approved for use in patients with non-squamous NSCLC, has become the recommended agent for use in combination with platinum-based chemotherapy in the treatment of NSCLC, both as a result of improved safety profile and the ability to continue pemetrexed monotherapy as a maintenance therapy. The addition of pemetrexed to carboplatin or cisplatin treatment regimens with additional pemetrexed maintenance following 4 cycles of carboplatin or cisplatin treatment has been demonstrated to improve outcomes (PFS and OS) for patients compared to docetaxel or gemcitabine combinations (Ciuleanu 2009; Li 2012; Treat 2012).

Platinum-based chemotherapy with cisplatin is typically reserved for therapies with curative intent, where a potential slight benefit in ORR may outweigh greater toxicity and patient burden in patients who can tolerate it. Carboplatin-based regimens, with their improved safety profile, are used more often in the metastatic NSCLC setting, within clinical regimens with palliative intent, especially in frailer patients. This study will enroll patients with locally advanced or metastatic disease after progressing on or after osimertinib, which is the best available standard of care for

EGFR-mutated NSCLC. Thus, carboplatin and pemetrexed is a more appropriate combination than cisplatin and pemetrexed for this patient population.

The importance of an improved toxicity profile and reduced infusion times associated with carboplatin administration, as well as the decreased need for preinfusion and postinfusion hydration for these patients, is reflected in reviews of real-world usage patterns, which demonstrate that carboplatin-pemetrexed is the most frequently used platinum-based doublet regimen in the US for the first-line treatment of metastatic, nonsquamous NSCLC, and cisplatin-based regimens are used infrequently in this setting (<5%) (Abernethy 2017). Thus, carboplatin-pemetrexed has become the standard of care in the US for the intended study population.

Given the above, the use of carboplatin-pemetrexed combination chemotherapy in this study ensures every enrolled participant will receive treatment with standard-of-care treatment for EGFR mutated NSCLC that progresses on or after osimertinib, which will enable the most robust assessment of amivantamab and lazertinib efficacy and safety when administered in combination with carboplatin and pemetrexed.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of amivantamab and lazertinib may be found in the IB for each product. Information about the benefits and risks of carboplatin and pemetrexed may be found in the local prescribing information.

2.3.1. Risks for Study Participation

As clinical data for the addition of amivantamab to chemotherapy are limited, unforeseen safety risks associated with the study treatments are possible. Previous studies adding EGFR TKIs or anti-EGFR mAbs to chemotherapy have shown they were generally well tolerated (Hosomi 2020; Noronha 2020; Park 2020; Peeters 2010). Amivantamab with chemotherapy is expected to have a similar safety profile to adding an EGFR TKI or mAb to chemotherapy.

The safety profiles of amivantamab and lazertinib are largely distinct from those associated with chemotherapeutic agents. However, pemetrexed has been reported to be associated with bullous and exfoliative skin toxicity as well as interstitial pneumonitis, which should be considered when evaluating and managing potential skin and pulmonary toxicities.

The safety and tolerability of amivantamab monotherapy was shown in the Phase 1 Study 61186372EDI1001 (Section 2.2.1). The safety and tolerability of single-agent lazertinib was shown in the Phase 1/2 Study 73841937NSC2001 (Section 2.2.3). The safety and tolerability of amivantamab and lazertinib in combination was also shown in the Phase 1 Study 61186372EDI1001 (Section 2.2.3) and is being further explored in 73841937NSC1001. The safety and tolerability of carboplatin and pemetrexed were shown in clinical trials (refer to local prescribing information).

Unforeseen safety risks associated with the study treatments are possible. This study protocol includes the following elements to mitigate risks for study participants:

- An Independent Data Monitoring Committee (IDMC) will review safety results for LACP in the ongoing Phase 1 Study 73841937NSC1001 prior to randomization of participants in this Phase 3 study. Participants will be monitored closely for safety throughout the study (Section 8.2) and the IDMC will review safety and tolerability data periodically.
- Dose modification guidance is provided to manage toxicities that occur during the study (Section 6.5.3), including specific guidance for IRRs, rash, pruritus, interstitial lung disease (ILD), cardiac adverse events (AEs), liver chemistry abnormalities, oral mucositis, paronychia, ocular toxicity, paresthesia, and venous thromboembolic (VTE) events.

2.3.2. Benefits for Study Participation

Given the heterogeneity of mechanisms that lead to osimertinib resistance, there is an unmet need for therapies that can be widely used in this setting without the need for biomarker selection. Platinum-based chemotherapy is the standard of care in this patient population. All participants in the study will accordingly be treated with platinum-based chemotherapy.

Amivantamab, lazertinib, and the combination have each demonstrated activity in patients with locally advanced or metastatic NSCLC with EGFR mutations. Amivantamab, as a monotherapy or in combination with lazertinib, has demonstrated activity in the osimertinib-relapsed setting. Antitumor activity for addition of amivantamab to platinum-based chemotherapy has been observed in the Phase 1 Study 61186372EDI1001. It is anticipated that efficacy offered by the unique mechanisms of action of amivantamab and lazertinib, the CNS protection demonstrated by lazertinib, and the addition of platinum-based chemotherapy to target TKI resistant tumor cells will be more effective than platinum-based chemotherapy alone for the treatment of patients with TKI-sensitive, EGFR-mutated NSCLC who have relapsed on osimertinib.

2.3.3. Benefit-Risk Assessment for Study Participation

Considering the measures taken to minimize risk to participants in this study, the potential risks identified for addition of lazertinib and amivantamab to standard-of-care carboplatin and pemetrexed are justified by the anticipated benefits that may be afforded to participants with locally advanced or metastatic NSCLC and EGFR Exon 19del or L858R mutations who have progressed on or after osimertinib.

CCI [redacted]

VTE event related changes implemented during protocol amendment 4 for this study are intended to 1) provide guidance to increase awareness of the potential increased incidence of VTE events during the first 4 months of treatment with the amivantamab and lazertinib combination, 2) describe measures to increase monitoring for these VTE events, 3) increase data collection

related to all treatment-emergent VTE events to better understand these events and their potential relatedness to study drugs, and 4) recommend prophylactic anticoagulation during the first 4 months of combination therapy (For participants receiving the LACP dosing schedule this would start Cycle 1 Day 1, for those receiving the ACP-L dosing schedule this would start when lazertinib is initiated on Cycle 5 Day 1 or sooner if carboplatin discontinued earlier than Cycle 4). These measures are being implemented in each study of amivantamab and lazertinib combination therapy to further optimize the benefit-risk balance for participants.

CCI

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The lazertinib dosing schedule for participants randomized to Arm A is thus modified in this protocol amendment 5. The changes to be implemented in Arm A are: 1) new participants randomized to Arm A should begin treatment with amivantamab, carboplatin and pemetrexed and only start lazertinib once treatment with carboplatin treatment is complete. This dosing schedule is referred to as ACP-L throughout the protocol.; 2) participants currently in Arm A receiving LACP must withhold lazertinib immediately; lazertinib treatment may begin, along with continued amivantamab and pemetrexed when treatment with carboplatin is complete (on Cycle 5 Day 1 or sooner if carboplatin is discontinued earlier than Cycle 4), after all hematologic toxicities, nausea, and stomatitis have resolved per protocol. The addition of lazertinib on Cycle 5 Day 1 (or sooner if carboplatin is discontinued earlier) is hypothesized to provide CNS protection while minimizing potential adverse events, therefore providing favorable benefit-risk. Participants currently in Arm A who have already completed carboplatin treatment may continue lazertinib, pemetrexed, and amivantamab maintenance therapy as tolerated. All participants randomized to Arm A2 will receive the ACP-L schedule.

3. OBJECTIVES AND ENDPOINTS

Objectives of the Study	Endpoints
Dual Primary	
To assess the efficacy of LACP/ACP-L, compared with CP, in participants with locally advanced or metastatic EGFR Exon 19del or Exon 21 L858R substitution NSCLC	• PFS using RECIST v1.1 guidelines, as assessed by BICR

Objectives of the Study	Endpoints
To assess the efficacy of ACP, as compared with CP, in participants with locally advanced or metastatic EGFR Exon 19del or Exon 21 L858R substitution NSCLC	• PFS using RECIST v1.1 guidelines, as assessed by BICR
Secondary[a]	
To further assess the clinical benefit of • LACP/ACP-L vs CP • ACP vs CP	• Objective response (by BICR) • Overall survival • Duration of response (by BICR) • Time to subsequent therapy • PFS after first subsequent therapy (PFS2) • Time to symptomatic progression • Intracranial PFS (by BICR) • Intracranial ORR (by BICR) • Intracranial Duration of response (by BICR) • Time to intracranial disease progression (by BICR)
To assess the safety of • LACP/ACP-L vs CP • ACP vs CP	• Incidence and severity of adverse events and clinical laboratory abnormalities
To assess the relationship between pharmacokinetics or immunogenicity and selected endpoints (including but not limited to efficacy, safety, and/or patient-reported outcomes)	• Serum amivantamab and plasma lazertinib concentrations, and serum anti-amivantamab antibodies
To assess health-related quality of life and disease-related symptoms in participants treated with • LACP/ACP-L vs CP • ACP vs CP	• NSCLC-SAQ • EORTC-QLQ-C30 • PROMIS-PF
To describe the contribution of lazertinib to the efficacy of LACP/ACP-L (vs ACP)	• Intracranial PFS (by BICR) • Objective response (by BICR) • Duration of response (by BICR) • PFS (by BICR) • Intracranial ORR (by BICR) • Intracranial Duration of response (by BICR) • Time to intracranial disease progression (by BICR)
Exploratory	
To further assess the clinical benefit of • LACP/ACP-L vs CP • ACP vs CP	• Disease control rate • Time to treatment discontinuation
To further assess health-related quality of life in participants treated with • LACP/ACP-L vs CP • ACP vs CP	• EQ-5D-5L • PRO CTCAE
To explore biomarkers predictive of improved outcome, and mechanisms of resistance, in participants treated with • LACP/ACP-L vs CP • ACP vs CP	• Characterization of tumor genetics by NGS of ctDNA at baseline, and changes at progression

ACP-L=amivantamab, carboplatin, pemetrexed and lazertinib (lazertinib started after carboplatin treatment is completed); BICR=blinded independent central review; ctDNA=circulating tumor deoxyribonucleic acid; EGFR=epidermal growth factor receptor; EORTC-QLQ-C30=European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L=EuroQol 5-dimension 5-level descriptive system; LACP=lazertinib, amivantamab, carboplatin, and pemetrexed

(all drugs started C1D1); NGS=Next-Generation Sequencing; NSCLC=non-small cell lung cancer; NSCLC-SAQ=Non-Small Cell Lung Cancer - Symptom Assessment Questionnaire; ORR= Objective response rate ; PFS=progression-free survival; PRO CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PROMIS-PF=Patient-Reported Outcomes Measurement Information System Physical Function; RECIST=Response Evaluation Criteria in Solid Tumors.

[a] Secondary endpoints of intracranial ORR, duration of response (DoR), and time to intracranial disease progression were included in statistical analysis plan (SAP) Amendment 3 (dated 19 May 2023), which was prior to the primary analysis for PFS.

The primary objectives of the extension cohort are to further describe the safety and efficacy of the ACP-L dosing schedule versus ACP; see Appendix 13: Open-label Randomized Extension Cohort for details.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

This study has dual primary hypotheses that:

- LACP/ACP-L will demonstrate superior progression-free survival (PFS) compared with CP
- ACP will demonstrate superior progression-free survival (PFS) compared with CP

The secondary hypotheses are that LACP/ACP-L and ACP, compared with CP independently in the aforementioned population, will demonstrate superior ORR and overall survival.

There is no separate hypothesis for extension cohort.

4. STUDY DESIGN

4.1. Overall Design

This study is a randomized, open-label, active-controlled, parallel, multicenter, Phase 3 study to compare the efficacy and safety of LACP/ACP-L (Arm A) versus CP (Arm B) and ACP (Arm C) versus CP (Arm B) in participants with EGFR-mutated locally advanced or metastatic NSCLC who have progressed on or after treatment with osimertinib. Participants in a third treatment arm will receive ACP, in order to be independently compared to CP, and to describe the contribution of lazertinib to the activity of LACP/ACP-L in this setting. Approximately 600 eligible participants will be randomly assigned in this study. The study will include a Screening Phase (Section 4.1.1), a Treatment Phase (Section 4.1.2), and a Follow-up Phase (Section 4.1.3).

An Independent Data Monitoring Committee will be commissioned for this study. Refer to Committee Structure in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations for details. A diagram of the study design is provided in Section 1.2.

Under Protocol Amendment 6, after enrollment for the main study is completed, a separate open-label randomized extension cohort will enroll approximately an additional 90 participants to further describe the safety and efficacy of the ACP-L dosing schedule versus ACP with additional data, but no formal hypothesis testing is planned within the extension cohort. The primary and secondary analyses for the hypothesis testing described above will be based on the data from the main study only, and the data from the extension cohort will not be included.

4.1.1. Screening

The informed consent form (ICF) must be signed before the first study-related activity is conducted but can be signed >28 days prior to randomization. All other screening procedures must be completed within 28 days before randomization.

To be eligible for participation, all participants must have locally advanced or metastatic non-squamous NSCLC with Exon 19del or Exon 21 L858R substitution EGFR mutations, as determined by local testing with an FDA-approved or other validated test in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (sites in the US) or accredited local laboratory (sites outside of the US). A copy of the test report documenting the EGFR mutation must be included in the participant records and a de-identified copy must also be submitted to the sponsor for review during the Screening Phase. If provision of this report is not permitted by the site or local policies, then sponsor-approved equivalent documentation must be provided. If tumor tissue collected at or after the diagnosis of locally advanced or metastatic NSCLC is available, it should be submitted to the central laboratory (as permitted by local regulations). Participants may also undergo an optional biopsy during screening.

All participants must have progressed on or after osimertinib monotherapy as the most recent line of treatment. To ensure the study population is balanced for participants who failed first-line versus second-line treatment with osimertinib, this study will limit enrollment of those who failed treatment with osimertinib in the second line to approximately 40% (~240 participants).

All information required for randomization purposes must be available at the time of randomization, including all screening assessments per the Schedule of Activities (Table 1), documentation to support mutation status. In addition, results of the Cycle 1 Day 1 assessments such as ECOG performance status, ECG, laboratory values, pregnancy test (as applicable), and symptom-directed physical exam should be available and reviewed by the Investigator prior to randomization. See the Schedule of Activities for details on completion of assessments within 72 hours prior to the first dose of study treatment.

4.1.2. Treatment Phase

The Treatment Phase will begin at randomization, with first treatment on Cycle 1 Day 1 to occur within 72 hours, and continue in 21-day cycles until the End of Treatment visit, approximately 30 days after the last dose of study treatment. Study treatment will continue until documented disease progression (using Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) confirmed by BICR, or until the participant meets another criterion for discontinuation of study treatment (Section 7.1). Participants will be stratified based on osimertinib line of therapy (first- line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no), and assigned randomly in a 2:2:1 ratio into 1 of 3 treatment arms as follows:

Main Study Arms

Arm A Dosing Schedule 1 (LACP, from study start until 06 November 2022):

- Lazertinib 240 mg orally once daily

- Amivantamab by intravenous (IV) infusion in 21-day cycles:
  - 1,400 mg (1,750 mg if body weight ≥80 kg) on Cycle 1 Days 1/2, 8, and 15, and Cycle 2 Day 1
  - 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3
- Carboplatin and pemetrexed as in Arm B.

Arm A Dosing Schedule 2 (started on 07 November, 2022) (ACP-L):

- Lazertinib 240 mg orally, once daily starting Cycle 5 Day 1 or sooner if carboplatin discontinued earlier than Cycle 4
- Amivantamab by IV infusion in 21-day cycles:
  - 1,400 mg (1,750 mg if body weight ≥80 kg) on Cycle 1 Days 1/2, 8, and 15, and Cycle 2 Day 1
  - 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3
- Carboplatin and pemetrexed as in Arm B.

Arm B (CP):

- Carboplatin AUC 5, up to 750 mg, on Day 1 of each 21-day cycle, for up to 4 cycles
- Pemetrexed 500 mg/m^2 (with folic acid and vitamin B12 supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance until disease progression

Arms C (ACP):

- Amivantamab as in Arm A
- Carboplatin and pemetrexed as in Arm B

- **<u>Extension cohort Arms</u>**

Arm A2 (ACP-L):

- Lazertinib 240 mg orally, once daily starting Cycle 5 Day 1 or sooner if carboplatin is discontinued earlier
- Amivantamab by IV infusion in 21-day cycles:
  - 1,400 mg (1,750 mg if body weight ≥80 kg) on Cycle 1 Days 1/2, 8, and 15, and Cycle 2 Day 1
  - 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3
- Carboplatin AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles
- Pemetrexed 500 mg/m^2 on Day 1 of each 21-day cycle, with carboplatin for up to 4 cycles, and then as maintenance until disease progression

Arm C2 (ACP):

- Amivantamab by IV infusion in 21-day cycles:
  - 1,400 mg (1,750 mg if body weight ≥80 kg) on Cycle 1 Days 1/2, 8, and 15, and Cycle 2 Day 1
  - 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3
- Carboplatin AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles
- Pemetrexed 500 mg/m^2 on Day 1 of each 21-day cycle, with carboplatin for up to 4 cycles, and then as maintenance until disease progression

Disease assessments will occur as close as possible to the start of treatment (baseline screening scans), 6 weeks (+1 week) after randomization (the first on study assessment should be no earlier than 42 days after randomization), then every 6 weeks (±1 week) for the first 12 months and every 12 weeks (±1 week) thereafter, until objective radiographic disease progression is confirmed by BICR. Timing of disease assessments is relative to randomization, regardless of when study treatment is administered.

At each study visit during the Treatment Phase, participants will undergo safety evaluations, including physical examinations and assessment of TEAEs, vital signs, concomitant medication usage, and clinical laboratory parameters. Participants will complete questionnaires for patient- reported outcomes (PROs) at selected visits. Participants will also have blood samples drawn for assessment of pharmacokinetics (PK) and immunogenicity parameters, and for biomarker evaluations, at selected visits. If a participant provides a baseline biopsy, an optional post-progression biopsy may be obtained if the participant consents and the procedure is clinically feasible within 30 days of disease progression but before subsequent anticancer therapy.

Continuation of study treatment after BICR-confirmed disease progression by RECIST v1.1 may be allowed after approval from the Medical Monitor, if the investigator believes the participant is deriving clinical benefit, as described in Section 7.1, Discontinuation of Study Treatment. 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.

4.1.3. Follow-up Phase

For participants who discontinue treatment prior to disease progression, tumor imaging should continue as scheduled (see Table 1) until disease progression is documented, if clinically feasible. Participants who discontinue study treatment for any reason will be followed for survival and symptomatic progression in the Follow-up Phase. Survival, subsequent anticancer treatment, and disease status will be assessed every 12 weeks (±14 days) after the last dose of study treatment or disease progression (whichever occurs first), until the end of study, death, lost to follow-up, or withdrawal of consent, whichever comes first. If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the participant has died, the date and cause of death will be collected and documented on the electronic case report form (eCRF). Investigators may recontact the participant to obtain long-term follow-up information regarding the participant's safety or survival status as

noted in the ICF (refer to Informed Consent in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations).

4.1.4. Open-label Extension Phase and Long-Term Extension Phase

Following the second interim analysis for OS, the study may transition to an OLE Phase or LTE phase. If the study transitions to an OLE phase, then upon completion of the final analysis for OS the study can subsequently transition to an LTE phase. There is also a possibility for the study to directly transition to an LTE phase if statistical significance for OS as outlined in the SAP is met at the time of the second interim analysis for OS.

A determination as to whether and how the study transitions to an OLE or LTE phase will be made by the Sponsor after completion of the second interim analysis and after approval of Amendment 7 by health authorities of countries/territories in which this study is being conducted at the time of transition, and by study site Independent Ethics Committees/Institutional Review Boards (IECs/IRBs). The timing of the initiation of OLE or LTE phase will be made by the Sponsor based on regulatory interactions and the Sponsor will communicate at the time the decision is made to initiate either the OLE or LTE phase.

In the OLE phase, the purpose is to continue to collect clinically relevant data, while reducing protocol-required visit procedures and assessments and the burden on participants (see details provided in Section 10.14 [Appendix 14]). Participants will be provided the option to continue their current study treatment in the OLE phase until the study transitions to an LTE phase. In the LTE phase, (see details provided in Section 10.15.1 [Appendix 15]), participants will be provided continued access to study treatments with further reduction in protocol-required visit procedures and assessments. In the LTE phase, only serious adverse event data and study treatment compliance will be collected. The LTE phase will continue until the last participant meets the discontinuation criteria described in Section 7.1, or until 4 years after local marketing authorization is obtained for the studied indication, whichever occurs first. Consent will be obtained from participants prior to inclusion into any of these phases.

4.2. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study assessment shown in the Schedule of Activities for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if the participant has died before the end of the study or has not prematurely discontinued the study for another reason.

4.3. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Treatment Groups

Randomization will be used to minimize bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Due to differences in safety profile, safety monitoring, premedication requirements, and administration, blinded study treatment and a placebo control will not be used.

Clinical Pharmacology Assessments

Blood samples will be analyzed for serum amivantamab and plasma lazertinib concentrations. Immunogenicity (antibodies to amivantamab) will be evaluated for impact on PK, safety and efficacy. A population PK model will be developed as a means to derive the individual participant's exposure, for determination of participant covariates that influence the PK of amivantamab and lazertinib, and for exposure-response analysis to support regulatory submission. Sample collection and testing will comply with local regulations.

ctDNA and Biomarker Collection

Circulating tumor deoxyribonucleic acid (ctDNA) will be collected to identify co-occurring EGFR mutations, MET alterations, and mutations in other key oncogenes to characterize the tumor to explain interindividual variability in clinical outcomes, or to identify population subgroups that respond differently to a treatment. The ctDNA and biomarker samples may be used to explore the potential to predict clinical benefit, relapse, and/or identify mechanisms of resistance to assigned therapy, and to enable the development of safer, more effective, and ultimately individualized therapies. Sample collection and testing will comply with local regulations.

4.3.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. If the participant requires a legally designated representative the legally designated representative must confirm with their signature on the ICF that the participant understands the purpose of and procedures required for the study and the participant is willing to participate. Written consent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and patient preferences.

Thorough scientific evaluation of any treatment before marketing authorization is an ethical and regulatory requirement. As the benefits and risks of adding amivantamab, lazertinib, carboplatin, and pemetrexed in this study population are not fully known, this study will evaluate safety and clinical activity. Participants will be closely monitored throughout the study, as discussed

throughout this protocol, for both safety and clinical benefit. The IDMC will review evolving safety data from this study, as well as efficacy data as appropriate. Based on the observed activity of both amivantamab and lazertinib in this setting, there is adequate justification for evaluating the addition of these drugs to chemotherapy for the treatment of NSCLC in participants who are eligible for this study.

All participants will undergo regular disease assessments to monitor the underlying disease. Prior EGFR testing in accordance with site standard of care, obtained at or after the diagnosis of locally advanced or metastatic NSCLC and before signing informed consent will be used to document EGFR mutation status. Pre- or post-treatment tumor biopsies are optional in this study. Archival tumor material collected at or after the time of locally advanced or metastatic diagnosis will be submitted if available, or a participant may undergo an optional pre-treatment biopsy. A participant for whom a pre-treatment biopsy was collected may elect to also undergo a post-treatment biopsy. Although biopsy collection is associated with risk, the complication rate for these procedures is low. The data obtained from this procedure will generate valuable scientific data on the effect of these study treatments in this study population.

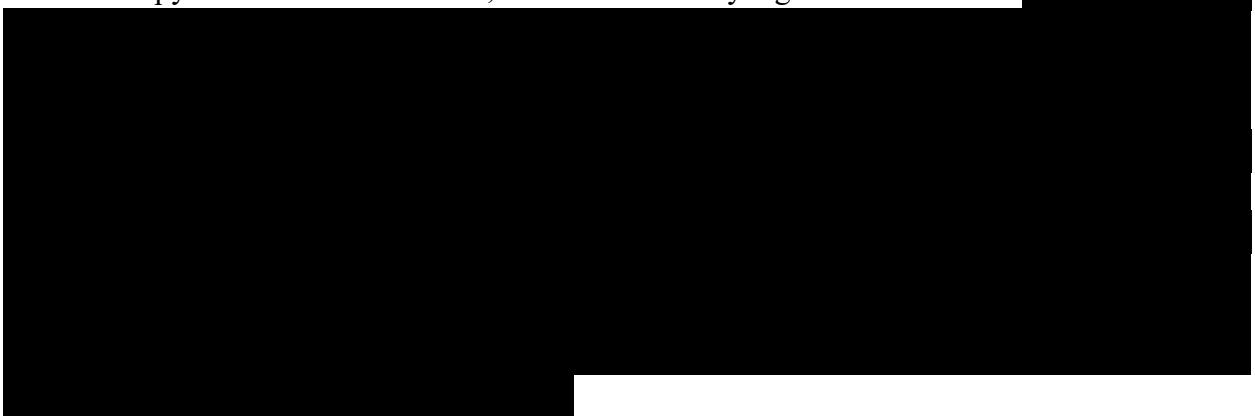
As with all clinical studies, there are risks associated with venipuncture and multiple blood sample collection. The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the pharmacology of the study treatment. This minimizes the number of venipunctures and the total volume of blood collected from each participant during the study. The total blood volume be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the blood donation standards of the American Red Cross (2020) and the World Health Organisation (WHO 2012).

4.4. Justification for Dose

The combinations of amivantamab and lazertinib, as well as amivantamab and platinum-based chemotherapy, have been explored in the ongoing Phase 1 Study 61186372EDI1001. The safety and tolerability of the lazertinib and amivantamab combination was demonstrated when administered at the respective RP2Ds of lazertinib 240 mg once daily and amivantamab 1,050 mg (1,400 mg for body weight ≥80 kg). No dose-limiting toxicities (DLTs) were identified and no new safety signals were observed. The safety profile of the combination, as assessed in 91 total participants with a 6-month median follow-up, suggested a tolerable profile. The majority of toxicities were Grade 1 or 2 in severity (a treatment-related TEAE of ≥Grade 3 severity was reported for 11% of participants), and TEAEs leading to discontinuation of either or both drugs occurred in 6% of participants. The lack of any PK interaction was confirmed when lazertinib and amivantamab were administered in combination, resulting in predictable exposures of both agents consistent with their respective monotherapy PK profiles.

In the Part 1 “Chemotherapy Combination” cohort of Study 61186372EDI1001, amivantamab was dosed in 21-day cycles at 1,400 mg (1,750 mg if body weight was ≥80 kg) on Cycle 1 Day 1/Day 2, Day 8, and Day 15, and then on Cycle 2 Day 1. Beginning on Cycle 3 Day 1, the dose of amivantamab was increased to 1,750 mg (2,100 mg if body weight was ≥80 kg) administered on

Day 1 of each 21-day cycle. Carboplatin (AUC 5 through Cycle 4 Day 1) and pemetrexed (500 mg/m^2) were administered on Day 1 of each 21-day cycle. Adding amivantamab to chemotherapy was safe and tolerable, and no new safety signal was detected. CCI



The dosages for LACP in this study will also be supported by data from the ongoing Phase 1 study 73841937NSC1001. That study will include a cohort ("the Phase 1b LACP Combination Cohort") of 20 participants. Results for LACP will be assessed by an IDMC prior to the initiation of enrollment into the current Study 61186372NSC3002 and will support the chosen dosage.

The ACP-L dosing schedule for Arms A and A2, which starts lazertinib on Cycle 5 Day 1 (or sooner if carboplatin is discontinued earlier than Cycle 4) is recommended by the IDMC based on the review of the unblinded safety data and is also supported by the emerging data that concurrent chemotherapy with third generation EGFR TKIs is associated with a higher than expected rate of toxicities traditionally in association with chemotherapy (Tanaka 2021). In an open-label, randomized phase 2 study where osimertinib combined with carboplatin and pemetrexed, Tanaka, et al presented that the incidence of AEs of ≥ Grade 3 was significantly higher in the osimertinib combination group (83.8%) compared to the osimertinib monotherapy group (45.2%), and the majority were hematologic AEs (leukopenia 38.7% vs 3.2%, neutropenia 51.6 vs 9.7%, anemia 25.8% vs 0%, and thrombocytopenia 29.0% vs 0%, respectively). The grade 3 or 4 non-hematologic adverse events occurred only in the combination group (stomatitis, nausea, diarrhea, and paronychia, each at 3.2%), The reported AEs were also significantly higher than those in AURA3 study with similar population treated with platinum and pemetrexed, where the reported ≥ Grade 3 AEs were leukopenia 4%, neutropenia 12%, anemia 12%, and thrombocytopenia 7% (Mok 2017). These data, CCI , indicate that there may be a class effect for the combination of 3rd generation EGFR TKIs with chemotherapy. The ACP-L dosing schedule is designed to minimize such toxicities while still evaluating the efficacy benefit of continuing a 3rd generation EGFR TKI among patients with EGFR mutated NSCLC.

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before randomization. Refer to Section 5.4 for conditions under which the repeat of any screening procedures is allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor

representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. At least 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).

2. Participant must have histologically or cytologically confirmed, locally advanced or metastatic, non-squamous NSCLC, characterized at or after the time of locally advanced or metastatic disease diagnosis by either EGFR Exon 19del or Exon 21 L858R mutation, by an FDA-approved or other validated test of either ctDNA or tumor tissue in a CLIA certified laboratory (sites in the US) or an accredited local laboratory (sites outside of the US). A de-identified copy of the initial test report documenting the EGFR mutation must be included in the participant records and must be submitted to the sponsor during the Screening Phase. If provision of this report is not permitted by the site or local policies, then sponsor-approved equivalent documentation must be provided.

3. Criterion modified per Amendment 2

   3.1 Participant must have progressed on or after osimertinib monotherapy as the most recent line of treatment. Osimertinib must have been administered as either the first-line treatment for locally advanced or metastatic disease or in the second-line setting after prior treatment with first- or second-generation EGFR TKI as a monotherapy.

   Participants who received either neoadjuvant and/or adjuvant treatment of any type are eligible if progression to locally advanced or metastatic disease occurred at least 12 months after the last dose of such therapy and then the participant progressed on or after osimertinib in the locally advanced or metastatic setting.

   Treatment with osimertinib must be discontinued at least 8 days (4 half-lives) prior to randomization (ie, last dose no later than Day -8).

4. Participant must have at least 1 measurable lesion, according to RECIST v1.1, that has not been previously irradiated. Measurable lesions should not have been biopsied during screening, but if only 1 non-irradiated measurable lesion exists, it may undergo the optional diagnostic biopsy and be acceptable as a target lesion, provided the baseline tumor assessment scans are performed at least 14 days after the biopsy.

5. Criterion modified per Amendment 2

   5.1 Participants with a history of brain metastases must have had all lesions treated as clinically indicated (ie, no current indication for further definitive local therapy). Any

definitive local therapy to brain metastases must have been completed at least 14 days prior to randomization and the participant can be receiving no greater than 10 mg prednisone or equivalent daily for the treatment of intracranial disease.

6. Participant must have Eastern Cooperative Oncology Group (ECOG) status of 0 or 1. Refer to Appendix 7: Eastern Cooperative Oncology Group (ECOG) Performance Status.

7. Criterion modified per Amendment 2

   7.1 Participant must have adequate organ and bone marrow function as follows, without history of red blood cell transfusion, platelet transfusion, erythropoietin stimulating agents, or platelet-boosting treatments within 7 days prior to the date of the laboratory test:

   - Hemoglobin ≥10 g/dL
   - Absolute neutrophil count ≥1.5×10^9/L, without use of G-CSF within 10 days prior to the date of the test
   - Platelets ≥100×10^9/L
   - ALT and AST ≤3×upper limit of normal (ULN)
   - Total bilirubin ≤1.5×ULN if no liver metastasis, or ≤3×ULN in the presence of liver metastasis (participants with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits)

   Creatinine clearance >50 mL/min as measured or calculated by Cockcroft-Gault formula (see Appendix 10: Cockcroft-Gault Formula for Estimated Creatinine Clearance)

8. Any toxicities from prior systemic anticancer therapy must have resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 Grade 1 or baseline level (except for alopecia [any grade], Grade ≤2 peripheral neuropathy, or Grade ≤2 hypothyroidism stable on hormone replacement).

9. Participant must sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.

10. A participant of childbearing potential must have a negative serum pregnancy test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.

11. Criterion modified per Amendment 2

    11.1 A participant must be either of the following (as defined in Appendix 5: Contraceptive Guidance):

    a. Not of childbearing potential; or

b. Of childbearing potential and

- practicing true abstinence during the entire period of the study, including up to 7 months after the last dose of study treatment is given; or
- have a sole partner who is vasectomized; or
- practicing at least 1 highly effective user independent method of contraception (examples are located in Appendix 5: Contraceptive Guidance).

Participant must agree to continue contraception throughout the study and through 7 months after the last dose of study treatment.

Note: If a participant becomes of childbearing potential after start of the study, the participant must comply with point (b.).

12. Criterion modified per Amendment 2

12.1 A participant must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 7 months after receiving the last dose of study treatment.

13. Criterion modified per Amendment 2

13.1 A participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for 6 months after receiving the last dose of study treatment. A participant who is sexually active with a participant of childbearing potential must agree to use a condom and the partner must also be practicing a highly effective method of contraception (see Appendix 5: Contraceptive Guidance).

A participant who is vasectomized must still use a condom for prevention of passage of exposure through ejaculation, but the participant's partner is not required to use contraception.

14. Criterion modified per Amendment 2

14.1 A participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 6 months after receiving the last dose of study treatment. Participants should be advised to consider preservation of sperm prior to treatment with pemetrexed or carboplatin, as these agents may impair fertility.

15. Participant must be willing and able to adhere to the lifestyle restrictions specified in this protocol.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Participant has an uncontrolled illness, including but not limited to:

   - Uncontrolled diabetes
   - Ongoing or active infection (includes infection requiring treatment with antimicrobial therapy [participants will be required to complete antibiotics at least 1 week prior to starting study treatment] or diagnosed or suspected viral infection), except as allowed by Exclusion Criterion 17 for HIV
   - Active bleeding diathesis
   - Impaired oxygenation requiring continuous oxygen supplementation
   - Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of study treatment
   - Psychiatric illness or any other circumstances (including social circumstances) that would limit compliance with study requirements
   - Any ophthalmologic condition that is clinically unstable

2. Participant received prior systemic anticancer therapy in the locally advanced or metastatic setting, or in the adjuvant setting, for the same nonsquamous NSCLC intended for treatment now, except as allowed by Inclusion Criterion 3.

3. Participant received radiotherapy for palliative treatment of NSCLC less than 14 days prior to randomization.

4. Criterion modified per Amendment 2

   4.1 Participants with symptomatic or progressive brain metastases.

5. Participant previously enrolled in the Sponsor's study 73841937NSC3003 (NCT04487080).

6. Criterion modified per Amendment 2

   6.1 Participant has history of or current evidence of leptomeningeal disease, or participant has spinal cord compression not definitively treated with surgery or radiation.

7. Participant has known small cell transformation.

8. Participant has uncontrolled tumor-related pain. Symptomatic lesions amenable to palliative radiotherapy (eg, bone metastases, or metastases causing nerve impingement) should be treated at least 14 days prior to randomization.

9. Participant has a medical history of ILD, including drug-induced ILD or radiation pneumonitis.

10. Participant has a history of hypersensitivity to carboplatin or pemetrexed, or to any excipient of carboplatin, pemetrexed, amivantamab, or lazertinib.

11. Participant has an active malignancy (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. Exceptions include participants who have undergone curative therapy and have no evidence of disease recurrence since completion of that therapy, and those with local cancers that have been apparently cured such as:

    a. Non-muscle invasive bladder cancer (NMIBC) treated within the last 24 months that is considered completely cured.
    b. Skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
    c. Non-invasive cervical cancer treated within the last 24 months that is considered completely cured.
    d. Localized prostate cancer (N0M0):
        - with a Gleason score of 6, treated within the last 24 months or untreated and under surveillance,
        - with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence,
        - or history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.
    e. Breast cancer:
        - lobular carcinoma in situ or ductal carcinoma in situ that is considered completely cured, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
    f. Other malignancy that is considered cured with minimal risk of recurrence.

12. Participant has any contraindication to treatment with pemetrexed or carboplatin or participant has a history of hypersensitivity to, or cannot take, vitamin B12 or folic acid.

13. Criterion modified per Amendment 2

    Criterion 13.1 modified per Amendment 5

    13.2 Participant has a history of clinically significant cardiovascular disease including, but not limited to the following:

    - Diagnosis of deep vein thrombosis or pulmonary embolism within 4 weeks prior to randomization, or any of the following within 24 weeks prior to randomization: myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, or acute coronary syndrome. (Note:

clinically non-significant thrombosis, such as non-obstructive catheter-associated thrombus, or incidental or asymptomatic pulmonary embolism, is not exclusionary.)

- Participant has a significant genetic predisposition to venous thromboembolic events (VTE; such as Factor V Leiden).
- Participant has a prior history of VTE and is not on appropriate therapeutic anticoagulation as per NCCN or local guidelines.
- Prolonged corrected QT (QTcF) interval >480 msec, uncontrolled hypokalemia or clinically significant cardiac arrhythmia or electrophysiologic disease (eg, placement of implantable cardioverter defibrillator or atrial fibrillation with uncontrolled rate).
- Uncontrolled (persistent) hypertension despite optimal treatment: systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg.
- Congestive heart failure (CHF) defined as New York Heart Association (NYHA) class III-IV (see Appendix 8: New York Heart Association Criteria) or hospitalization for CHF (any NYHA class) within 6 months of randomization.
- Pericarditis, pericardial effusion, or myocarditis that is clinically unstable. Pericardial effusion considered due to the disease under study is permitted if clinically stable at screening.
- Baseline LVEF below the institution's lower limit of normal (LLN) at screening, as assessed by echocardiogram or multigated acquisition (MUGA) scan.

14. Participant had major surgery or had significant traumatic injury within 4 weeks before randomization, or will not have fully recovered from surgery, or has surgery planned during study participation that will require general anesthesia.

- Note: Placement of vascular access or tumor biopsy within 4 weeks before randomization is permitted.
- Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

15 Participant has at screening:

- Positive hepatitis B (hepatitis B virus [HBV]) surface antigen (HBsAg)

  Note: Participants with a prior history of HBV demonstrated by positive hepatitis B core antibody are eligible if they have at screening 1) a negative HBsAg and 2) an HBV DNA (viral load) below the lower limit of quantification, per local testing. Participants with a positive HBsAg due to recent vaccination are eligible if HBV DNA (viral load) is below the lower limit of quantification, per local testing.

- Positive hepatitis C (hepatitis C virus [HCV]) antibody (anti-HCV)

  Note: Participants positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA).

- Other clinically active infectious liver disease.

16. Participant has received a live or live attenuated vaccine within 4 weeks before randomization.

17. Participant is known to be positive for human immunodeficiency virus (HIV) with 1 or more of the following:

    - Not receiving highly active antiretroviral therapy (ART)
    - Had a change in ART within 6 months of the start of screening
    - Receiving ART that may interfere with study treatment (consult Sponsor for review of medication prior to enrollment)
    - CD4 count <350 at screening
    - AIDS-defining opportunistic infection within 6 months of start of screening
    - Does not agree to start ART and be on ART>4 weeks plus having HIV viral load <400 copies/mL at end of 4-week period (to ensure ART is tolerated and HIV controlled).

18. Criterion modified per Amendment 3

    18.1 Participant is currently receiving a medication or herbal supplement known to be a strong cytochrome P450 (CYP) 3A4/5 inducer and is not able to stop use for an appropriate washout period prior to randomization (For a list of such medications refer US FDA 2022).

19. Participant has received an investigational agent within 12 months before randomization or is currently enrolled in an investigational study. (An investigational COVID-19 vaccine within 12 months before randomization is permitted.)

20. Criterion modified per Amendment 2

    20.1 Participant is pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 7 months after the last dose of study treatment.

21. Participant plans to father a child while enrolled in this study or within 6 months after the last dose of study treatment.

22. Participant has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

NOTE: Investigators must ensure that all study enrollment procedures have been completed during the screening period and eligibility confirmed on the date of, and prior to, randomization. If a participant's clinical status changes/declines during the screening period, eligibility must be reconfirmed prior to randomization. The required source documentation to support meeting the enrollment criteria is noted in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Refer to Section 6.7, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. Criterion modified per Amendment 2

   3.1 Criterion modified per Amendment 6

   3.2 Participants in Arms A/A2 and C/C2 must agree to use sun protective measures, such as a hat, sunglasses, protective clothing, and broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥30, avoid unnecessary exposure to natural sunlight, and avoid artificial sunlight (tanning beds or phototherapy) from baseline until 2 months after the last dose of study treatment.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness. This study will use interactive web response system (IWRS). The investigator will generate screening and enrollment logs directly from IWRS.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Participants who are determined to be eligible for the study after their condition changes must sign a new ICF prior to re-screening.

5.5. Criteria for Temporarily Delaying Randomization

Not applicable.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

Study treatment administration must be captured in the source documents and the eCRF. Study site personnel will instruct participants on how to store study treatment for at-home use as indicated for this protocol.

Refer to the Investigational Product Preparation Instructions (IPPI) or the study Site Investigational Product and Procedures Manual (SIPPM) for detailed guidance on dosage and administration for amivantamab and lazertinib (SIPPM only). Refer to the local prescribing information for detailed guidance on administration of carboplatin and pemetrexed.

6.1. Study Treatments Administered

For this study, "study treatment" refers to JNJ-61186372 (amivantamab), lazertinib, pemetrexed and carboplatin. Amivantamab and lazertinib are considered investigational medicinal products (IMPs), and carboplatin and pemetrexed are considered non-investigational medicinal products (NIMPs)/auxiliary medicinal product (AxMPs).

All other study-specified medications (see Section 6.7) are considered concomitant medications.

<table>
<tr><th>Designation</th><th>Product</th></tr>
<tr><td>Investigational Medicinal Product(s)</td><td>Authorization status in the EU:
<table><tr><td>Authorized</td><td>JNJ-61186372 (amivantamab)</td></tr><tr><td>Unauthorized</td><td>lazertinib</td></tr></table>The IMP will not be used in accordance with the terms of its marketing authorization.</td></tr>
<tr><td>Non-investigational Medicinal Product(s) (NIMP)/Auxiliary Medicinal Product(s) (AxMP)</td><td><table><tr><td>Authorized</td><td>carboplatin</td></tr><tr><td></td><td>pemetrexed</td></tr><tr><td>Unauthorized</td><td>Not applicable</td></tr></table></td></tr>
</table>

Amivantamab and lazertinib will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for amivantamab and the IB for lazertinib for lists of excipients. Refer to the local prescribing information for carboplatin and pemetrexed for the list of excipients for each agent.

For information related to study treatment overdose, refer to Section 6.6, Treatment of Overdose.

6.1.1. Scheduled Dosage and Timing

Administration of study treatment should begin within 3 days of randomization. On Day 1 of each cycle in which treatment is administered in Arms A/A2, it should occur in the following order: 1) lazertinib (for patients receiving lazertinib with the ACP-L dosing schedule in Arms A/A2, lazertinib will start on Cycle 5 Day 1 or sooner if carboplatin discontinued earlier than Cycle 4), 2) pemetrexed, 3) carboplatin (dosing should not exceed 4 cycles), and 4) amivantamab. In Arms C/C2, ACP therapy should be administered in the following order: 1) pemetrexed, 2) carboplatin, and 3) amivantamab.

The infusion times for carboplatin and pemetrexed should be according to the local guidelines and regulatory labeling (eg, pemetrexed can be given over approximately 10 to 15 minutes and carboplatin can be given over approximately 30 to 60 minutes). Refer to IPPI for detailed information on amivantamab administration. Due to the multiple infusions in Arms A/A2 and C/C2, dosing should be scheduled to begin with sufficient time to accommodate all infusions on Cycle 1 Day 1. If, however, delays in initiation of therapy leave insufficient time on Cycle 1 Day 1 for full amivantamab dosing, the initial split dose of amivantamab (Cycle 1 Day 1 and Day 2) may be delayed (until Cycle 1 Day 2 and Day 3), with corresponding changes to scheduled activities (PK and vital signs) and pre-medications and should be reported in the eCRF as a dose delay. If amivantamab treatment is delayed from Cycle 1 Day 1 to Day 2 and Cycle 1 Day 2 to Day 3, appropriate premedications should be administered before amivantamab infusion.

Please refer to Table 17 in Section 6.7.2.2 for premedications required with amivantamab. The sequence of administration and dosage of study treatments in each arm are outlined in Table 4. For carboplatin and pemetrexed dosages, local prescribing information/guidelines may be followed.

Table 4: Study Treatment Dosing

Cycle	Days Study Treatment	Treatment Arm A/A2	 B	 C/C2	Study Treatment Dosage
Cycle 1	Days 1-21 Lazertinib (Dosing Schedule 1 (LACP) only*)	X			240 mg
	Day 1 Pemetrexed Carboplatin Amivantamab	 X X X	 X X 	 X X X	 500 mg/m^2 AUC 5 (up to 750 mg) 350 mg
	Day 2 Amivantamab	X		X	1,050 mg (<80 kg) / 1,400 mg (≥80 kg)
	Day 8 and Day 15 Amivantamab	X		X	1,400 mg (<80 kg) / 1,750 mg (≥80 kg)
Cycle 2	Days 1-21 Lazertinib (Dosing Schedule 1 (LACP) only*)	X			240 mg
	Day 1 Pemetrexed Carboplatin Amivantamab	 X X X	 X X 	 X X X	 500 mg/m^2 AUC 5 (up to 750 mg) 1,400 mg (<80 kg) / 1,750 mg (≥80 kg)
Cycles 3-4	Days 1-21 Lazertinib (Dosing Schedule 1 (LACP) only*)	X			240 mg
	Day 1 Pemetrexed Carboplatin Amivantamab	 X X X	 X X 	 X X X	 500 mg/m^2 AUC 5 (up to 750 mg) 1,750 mg (<80 kg) / 2,100 mg (≥80 kg)
Cycles 5+	Days 1-21 Lazertinib	X			240 mg
	Day 1 Pemetrexed Amivantamab	 X X	 X 	 X X	 500 mg/m^2 1,750 mg (<80 kg) / 2,100 mg (≥80 kg)

* For Arms A dose schedule 2/A2 (ACP-L), Lazertinib may be administered from Cycle 5 Day 1 or sooner if carboplatin is discontinued earlier than Cycle 4.

6.1.2. Lazertinib

Lazertinib 80 mg for oral administration is an oval, yellow, and film-coated tablet. Refer to the IB for a list of excipients. Participants in Arms A/A2 will self-administer lazertinib as an oral therapy, with an initial dosage of 240 mg (3 tablets) once daily. Lazertinib tablets can be administered with or without food. Lazertinib should be dosed at the study site on Cycle 5 Day 1 or sooner if carboplatin discontinued earlier than Cycle 4. Lazertinib should only start once all hematologic toxicities, nausea, and stomatitis from the combination of amivantamab, carboplatin, and pemetrexed have resolved. Resolution is defined as ≤ Grade 1 or back to baseline status for the participant (except for oral mucositis which should recover to ≤ Grade 2 or baseline). Lazertinib should be taken at approximately the same time each day, approximately 24 hours apart, if possible. If a participant misses taking a scheduled dose, it is acceptable to take the dose within a window of 12 hours. If it is more than 12 hours after the scheduled dose time, the missed dose should not be taken, and the participant should be instructed to take the next dose at the next scheduled time. If a participant vomits after taking lazertinib, the participant should not make up for this dose but should take the next scheduled dose. The time of vomiting should be captured in the source document.

6.1.3. Chemotherapy

Depending on regional requirements, chemotherapy may be sourced centrally or locally. When provided by the sponsor, chemotherapy will be supplied as carboplatin (600 mg/vial, with concentration 10 mg/mL in a 60 mL vial) and pemetrexed (500 mg/vial powder concentrate for solution for infusion). For locally sourced carboplatin and pemetrexed, refer to local prescribing information for each agent for a list of excipients.

6.1.4. Amivantamab

Amivantamab is supplied for this study in a glass vial containing 350 mg/vial with concentration 50 mg/mL, 7 mL per vial. Amivantamab will be manufactured and provided under the responsibility of the sponsor. Refer to the amivantamab IB for a list of excipients.

The dosage of amivantamab will be based on the participant's body weight at screening. The dose remains based on body weight at screening regardless of subsequent changes in body weight during the course of treatment. Qualified site personnel will administer amivantamab as an IV infusion in 21-day cycles as follows:

- 1,400 mg (1,750 mg if body weight ≥80 kg) on Cycle 1 Days 1/2, 8, and 15, and Cycle 2 Day 1
- 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3.

Amivantamab will be administered by IV using the escalating infusion rate regimen as specified in the IPPI. The product must be infused via a peripheral vein for all Cycle 1 doses; Infusion via central line is allowed only at Cycle 1 Day 15 and onwards if the participant’s most recent dose (eg, Cycle 1 Day 8) was successfully administered without an infusion related reaction.

Infusion durations that exceed the planned length of time due to IV bag overfill, minor equipment calibration factors, and/or participant factors not under the control of administering personnel will not be considered protocol deviations. The actual start and end times of each infusion and infusion rate(s) should be accurately recorded. Refer to IPPI for information describing the stability and administration of amivantamab.

Amivantamab must be administered according to the procedures described in the IPPI and clinical protocol, under the supervision of qualified staff. Additional guidance is provided below:

- Do not mix or dilute amivantamab with other drugs.
- IV tubing should be primed with diluent, rather than amivantamab solution.
- Amivantamab must not be administered as an IV push or bolus.
- Due to the risk of infusion-related reactions, equipment and agents for treating anaphylaxis (eg, epinephrine, corticosteroids, IV antihistamines, bronchodilators, oxygen, resuscitation equipment) must be available during amivantamab administration. Trained personnel (eg, resuscitation team) must also be available.

6.2. Preparation/Handling/Storage/Accountability

The instructions below on study treatment preparation, handling, and storage apply only to lazertinib, amivantamab and/or centrally sourced chemotherapy. For locally sourced chemotherapy, please follow the instructions on the local package insert.

Preparation/Handling/Storage

All study treatment must be stored at controlled temperatures according to the requirements on the label. Amivantamab must be protected from light prior to use. For additional guidance on study treatment preparation, handling, and storage, refer to the IPPI/SIPPM for amivantamab, the SIPPM for lazertinib, and local prescribing information for carboplatin and pemetrexed.

Accountability

The investigator is responsible for ensuring that all study treatment received at the site is inventoried and accounted for throughout the study. For amivantamab, the study treatment administered to the participant must be documented on the treatment accountability form. All study treatment will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study treatment containers.

For lazertinib, the dispensing of study treatment to the participant, and the return of study treatment from the participant (if applicable), must be documented on the treatment accountability form. Participants, or their legally designated representatives where applicable, must be instructed to return all original containers, whether empty or containing study treatment.

Study treatment must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study treatment, and study treatment returned by the participant,

must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study treatment, or used returned study treatment for destruction, will be documented on the treatment return form. When the study site is an authorized destruction unit and study treatment supplies are destroyed on-site, this must also be documented on the treatment return form.

Potentially hazardous materials containing hazardous liquids, such as used ampules, needles, syringes and vials, should be disposed of immediately in a safe manner and therefore will not be retained for treatment accountability purposes.

Study treatment should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study treatment will be supplied only to participants participating in the study. Returned study treatment must not be dispensed again, even to the same participant. Whenever a participant brings his or her study treatment to the study site for pill count, this is not seen as a return of supplies. Study treatment may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study treatment from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study treatments are provided in the SIPPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

Study Treatment Allocation

Procedures for Randomization

Central randomization will be implemented in this study. In the main study, participants will be randomly assigned to 1 of 3 study treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. In the extension cohort, participants will be randomly assigned to 1 of 2 study treatment groups based on a computer-generated randomization schedule prepared before the extension cohort by or under the supervision of the sponsor. In both the main study and the extension cohort, the randomization will be balanced by using randomly permuted blocks and will be stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes vs no), and Asian race (yes vs no). Participants who have adequate treatment for metastatic brain lesions, including a complete response or resection, must be identified as having a history of brain metastases. 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

As this is an open-label study, blinding procedures are not applicable.

6.4. Study Treatment Compliance

Study treatments should be prescribed only by the principal investigator or a qualified physician listed as a sub-investigator on required forms. The study personnel at the study site will account for all study treatments dispensed and for appropriate return. The certificates of delivery and return should be signed. Study drugs provided by the sponsor may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

Preinfusion Medications

Administration of preinfusion medications and chemotherapy prophylaxis will be documented in the source documents and eCRF.

Lazertinib

The dispensing of lazertinib to the participant and the return of lazertinib from the participant must be documented on the treatment accountability form. Participants, or their legally designated representatives where applicable, must be instructed to return all original containers, whether empty or containing lazertinib. Study-site personnel must not combine contents of the lazertinib containers.

Chemotherapy (Carboplatin and Pemetrexed)

Carboplatin and pemetrexed will be administered as IV infusions by qualified study-site personnel according to local guidelines and/or product labeling, and the details of each administration will be recorded in the eCRF (including date, start, and stop times of the IV infusion, and volume infused). Dispensing of all study drug must also be recorded in the participant's source documents.

Amivantamab

Amivantamab will be administered as an IV infusion by qualified study-site personnel and the details of each administration will be recorded in the eCRF (including date, start, and stop times of the IV infusion, and volume infused). Dispensing of all study treatment must also be recorded in the participant's source documents.

6.5. Dose Modification

Any dose/dosage adjustment should be overseen by medically qualified study site personnel (principal or sub-investigator unless an immediate safety risk appears to be present). Based on clinical experience with the study treatments, the anticipated toxicities of amivantamab (Arms A/A2 and C/C2) and lazertinib (Arms A/A2) are expected to be distinct from those associated with chemotherapy. Hematologic toxicities are expected to be most likely associated with chemotherapy, whereas anti-EGFR toxicities are likely to be associated with both amivantamab (Arms A/A2 and C/C2) and lazertinib (Arms A/A2), and anti-MET toxicities associated with amivantamab alone.

If a participant experiences a clinically significant CTCAE Grade 3 (except for VTE; see Section 6.5.3.12) or higher and/or unacceptable toxicity (any grade) then dosing of the causative

treatment(s) should be interrupted and supportive therapy administered in accordance with local practice/guidelines. The sections below provide further guidance on managing dose delays (Section 6.5.1) and dose modifications for amivantamab and lazertinib (Sections 6.5.2 and 6.5.3) and chemotherapy (Section 6.5.4).

6.5.1. Dose Delay Guidance

In instances where treatment delay is indicated, treatment with chemotherapy and/or amivantamab (Arms A/A2 and C/C2) may be delayed until recovery of toxicity to a level allowing continuation of therapy. A participant for whom treatment was delayed should be assessed at least weekly to ensure adequate supportive care is being administered and to assess for improvement of toxicity.

Participants must meet retreatment criteria for chemotherapy (as per Section 6.5.4.1 based on product labeling and as per local regulations and guidelines) and/or amivantamab (as per Section 6.5.2), in accordance with protocol, prior to redosing with the respective agents.

- All Arms:

Chemotherapy: If retreatment criteria are not met for carboplatin and/or pemetrexed, then treatment should be delayed by 1 week at a time. If chemotherapy administration is delayed beyond 42 days (±3 days) from the last treatment, chemotherapy will be discontinued unless continued treatment is approved by the sponsor. Carboplatin administration cannot exceed a total of 4 cycles.

For Arms A/A2

For VTE events associated with clinical instability (eg, respiratory failure or cardiac dysfunction) in participants receiving the combination of amivantamab and lazertinib, study treatment should be held until the patient recovers from the event. Thereafter, the treatment can be resumed at the discretion of the investigator.

- Arms A/A2 and Arms C/C2:

Chemotherapy: If chemotherapy cannot be administered on the scheduled day, dosing with amivantamab should proceed as planned, if amivantamab retreatment criteria are met. If chemotherapy is delayed by a week (eg, administered on Day 8 of the cycle) subsequent cycle dosing of amivantamab may be delayed by 1 week to align with the chemotherapy dosing schedule. Alternatively, if chemotherapy is delayed by 2 weeks (eg, administered on Day 15 of the cycle), then the subsequent cycle dosing of amivantamab can be accelerated by 1 week to align with chemotherapy (see Appendix 12: Dosing Synchronization for Arms A/A2 and C/C2). While some flexibility in the amivantamab dosing schedule is allowed as described above, combination chemotherapy must be dosed at a minimum interval of 21 days (-1 day for Cycle 2 or -3 days beginning with Cycle 3).

Amivantamab: In the event amivantamab dosing on Day 1 of the cycle is delayed, but retreatment criteria for chemotherapy are met, dosing with chemotherapy should continue as planned and participants should be evaluated weekly for retreatment with amivantamab.

If both chemotherapy and amivantamab must be delayed, participants should be re-evaluated weekly for retreatment. Dosing with amivantamab may proceed once retreatment criteria are met, whether on Day 8 or Day 15 of the cycle. The dosing of both chemotherapy and amivantamab may resume on the subsequent cycle once retreatment criteria for pemetrexed ± carboplatin are met, as

described above. The Medical Monitor may be consulted if there are questions regarding restarting of protocol treatment after dose delays.

6.5.2. Dose Modification of Amivantamab and Lazertinib

Decisions regarding dose modification of the individual study treatments should be guided by the observed toxicity, the safety profile of each drug, the likelihood of causality to each agent, as well as each agent's potential contribution to any observed clinical benefit.

Arms A/A2: For toxicities associated with EGFR inhibition that require treatment modification, and which can be attributed to either drug, modification should be instituted for lazertinib prior to modification of amivantamab dosing. Refer to Table 5 for guidance on dose modification based on the toxicity grade of AEs other than those specified in Section 6.5.3, with dose reductions of lazertinib and amivantamab conducted according to Table 6 and Table 7, respectively. In the case of a second occurrence of the same Grade 4 toxicity, permanently discontinue lazertinib or amivantamab or both lazertinib and amivantamab, if investigator considers the event related to either or both study drugs, respectively.

Arms C/C2: In the case of a second occurrence of the same Grade 4 toxicity, permanently discontinue amivantamab, if investigator considers the event related to this study drug.

Table 5: Arms A/A2: General Guidance for Withholding Doses for Toxicities Considered Related to Lazertinib or Amivantamab, Based on Grade[a]

Grade[b]	Action[c]	Dose Modification After Resolution of Toxicity[d,e]
1	None	Continue both agents at current dose level; consider supportive care according to local standards as appropriate
2	None, or consider withholding lazertinib (unless the experienced toxicity is strongly suspected to be related to amivantamab alone, in which case amivantamab should be withheld).	If lazertinib is withheld, restart on Day 1 of next cycle at either the same or a reduced dose (see Table 6 for lazertinib dose reduction guidance). If amivantamab is withheld, restart study treatment at current dose level at either Day 8 or Day 15 of the current cycle or Day 1 of the following cycle.
3	Withhold lazertinib and amivantamab	If Grade 3 adverse reaction improves to Grade 0-2 after withholding study drugs for up to 3 weeks, then upon resolution: • Restart amivantamab at the same dose or a reduced dose on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle. • Restart lazertinib at a reduced dose on Day 1 of next cycle. If Grade 3 adverse reaction does not improve to Grade 0-2 after withholding study drugs for up to 3 weeks, permanently discontinue lazertinib, amivantamab, or both.

Table 5: Arms A/A2: General Guidance for Withholding Doses for Toxicities Considered Related to Lazertinib or Amivantamab, Based on Grade[a]

Grade[b]	Action[c]	Dose Modification After Resolution of Toxicity[d,e]
4	Withhold lazertinib and amivantamab	If Grade 4 adverse reaction improves to Grade 0-2 after withholding study drugs for up to 3 weeks, then upon resolution: • Restart amivantamab at a reduced dose on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle. • Restart lazertinib at a reduced dose on Day 1 of next cycle. If Grade 4 adverse reaction does not improve to Grade 0-2 after withholding study drugs for up to 3 weeks, permanently discontinue lazertinib, amivantamab, or both. If a Grade 4 adverse reaction reoccurs, permanently discontinue lazertinib or amivantamab, or both, if investigator considers the event related to either or both study drugs, respectively.

a. For rash related events in Arms A/A2, see Table 10
b. Per National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0.
c. For all toxicities, consider supportive care according to protocol as appropriate.
d. Resolution defined as: ≤Grade 1 or back to baseline status for the participant (except for rash, oral mucositis, or paronychia, which should recover to ≤Grade 2 or baseline).
e. For VTE events associated with clinical instability (eg respiratory failure or cardiac dysfunction) in participants being treated with the combination of amivantamab and lazertinib, study treatment should be held until the patient recovers from the event. Thereafter, the treatment can be resumed at the discretion of the investigator.

Table 6: Guidance for Lazertinib Stepwise Dose Reduction (Arms A/A2)

Dose Level	Lazertinib (any cycle)
0 (starting dose)	240 mg
-1	160 mg
-2	80 mg
-3	Discontinue

Table 7: Guidance for Amivantamab Stepwise Dose Reduction (Arms A/A2 and Arms C/C2)

Dose Level	Amivantamab (up to Cycle 2 Day 1)	Amivantamab (Cycle 3+)
0 (starting dose)	1,400 mg (1,750 mg if body weight ≥80 kg)	1,750 mg (2,100 mg if body weight ≥80 kg)
-1	1,050 mg (1,400 mg if body weight ≥80 kg)	1,400 mg (1,750 mg if body weight ≥80 kg)
-2	700 mg (1,050 mg if body weight ≥80 kg)	1,050 mg (1,400 mg if body weight ≥80 kg)
-3	Discontinue	Discontinue

Arms C/C2: Refer to Table 8 for guidance on dose modification based on the toxicity grade of AEs other than those specified in Section 6.5.3. Dose reductions for amivantamab should occur as specified in Table 7.

Table 8: Arms C/C2: General Guidance for Withholding Doses for Toxicities Considered Related to Amivantamab, Based on Grade[a]

Grade[b]	Action[c]	Dose Modification After Resolution of Toxicity[d]
1	None	Continue amivantamab at current dose level.
2	None, or consider withholding amivantamab	Restart study treatment at current dose level.
3	Withhold amivantamab	If Grade 3 adverse reaction improves to Grade 0-2 after withholding study drug for up to 3 weeks, study drug may be restarted at the same dose or a reduced dose on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle. If Grade 3 adverse reaction does not improve to Grade 0-2 after withholding study drugs for up to 3 weeks, permanently discontinue amivantamab.
4	Withhold amivantamab	If Grade 4 adverse reaction improves to Grade 0-2 after withholding study drug for up to 3 weeks, study drug may be restarted at a reduced dose on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle. If Grade 4 adverse reaction does not improve to Grade 0-2 after withholding study drugs for up to 3 weeks, permanently discontinue amivantamab. If Grade 4 adverse reaction reoccurs, permanently discontinue amivantamab, if investigator considers the event related to the study drug.

a. For rash related events in Arms C/C2, see Table 11.
b. Per National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0.
c. For all toxicities, consider supportive care according to protocol as appropriate.
d. Resolution defined as: ≤Grade 1 or back to baseline status for the participant (except for rash, oral mucositis, or paronychia, which should recover to ≤Grade 2 or baseline).

Note: This table discusses Arms C/C2. For details pertaining to Arms A/A2, see Table 5.

Re-escalation of amivantamab and/or lazertinib after a prior dose reduction is allowed if determined to be in the best interest of the participant.

6.5.3. Dose Modification and Management of Specific Adverse Events (Arms A/A2 and Arms C/C2)

6.5.3.1. Infusion-Related Reactions

General Guidelines for Infusion-Related Reactions

Infusion-related reactions have been commonly observed during treatment with amivantamab, predominantly with the first exposure on Cycle 1 Day 1, and typically within the first 90 minutes of the infusion. The majority of IRRs are Grade 1 or 2 (Section 2.2.1). Refer to Summary of Data and Guidance for Investigators in the current version of the IB for amivantamab. The guidelines described here relate to the safe administration of amivantamab during initial dosing.

During the amivantamab infusions, participants should be clinically monitored at regular intervals as specified in the Schedule of Activities (including an assessment prior to the start of infusion).

The monitoring should include heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation measurements.

Particularly with the initial dose (Cycle 1, Day 1 and Day 2), participants should be educated on 1) the likelihood of experiencing an IRR with the initial dose, 2) the symptoms to anticipate (which include chills, dyspnea, chest discomfort, fever, flushing, among others), 3) that they should alert nursing staff if they experience these symptoms, and 4) that the experience of an IRR will not preclude further therapy with amivantamab. Participants must be monitored closely for early signs and symptoms indicative of an acute IRR. Even with mild symptoms, the study treatment infusion should be interrupted immediately, as described in the tables below, to prevent more serious grade IRRs from occurring. Trained clinical personnel should be prepared to intervene in the event of IRRs. Resources necessary for resuscitation (ie, agents such as epinephrine, aerosolized bronchodilator, IV antihistamines, IV corticosteroids; medical equipment such as oxygen, airway management equipment including suction, and a defibrillator) must be readily available.

Prevention of Infusion-Related Reactions

Required prophylaxis for IRRs is described in Section 6.7.2.2.

Treatment of Infusion-Related Reactions

Participants who experience early symptoms of IRRs, manifesting, but not limited to, as fever, chills, rigors, bronchospasm, headache, rash, pruritus, arthralgia, hypo- or hypertension or other symptoms, must have their amivantamab infusion interrupted, if indicated, and the symptoms managed according to the recommendations provided in Table 9. With the initial dose of amivantamab (Cycle 1, Days 1 and 2), interrupting the infusion should be considered even with mild symptoms to prevent more severe manifestations of IRR. All Grade 3 or 4 IRRs should be reported within 24 hours to the Medical Monitor. The start and end time and grade of each IRR symptom as well as the overall IRR should be reported in the eCRF.

Table 9: Management of Infusion-Related Reactions

Toxicity Grade*	Treatment	Premedication at Subsequent Dosing or Other Action to be Taken
Grade 1 Mild reaction	Monitor participant as medically indicated until recovery from symptoms. If occurring with initial dose (ie, Cycle 1 Day 1 or Day 2), consider early infusion interruption to prevent more severe symptoms. If infusion is interrupted, follow the guidance for Grade 2 interruptions.	Antihistamine, antipyretic, and glucocorticoid, as per Table 17 (Section 6.7.2.2)
Grade 2 Mild to moderate reaction; therapy or infusion interrupted but responds promptly to symptomatic treatment	**Interrupt infusion** If clinically indicated, start IV fluids; give diphenhydramine 50 mg (or equivalent) IV and/or paracetamol (acetaminophen) 650 to 1,000 mg; consider corticosteroids and bronchodilator therapy; antiemetic and supplemental oxygen; monitor participant closely until recovery from symptoms **First interruption for IRR: Restart infusion at 50% of the rate at the time of interruption**: if no further evidence of IRR after 30 minutes, the rate may be increased to 100% of the infusion rate at the time of interruption; monitor participant closely. Infusion rate escalation may resume per the IPPI schedule, after the infusion has been administered for at least 30 minutes at 100% of the infusion rate used at the time of dose interruption. **Second interruption for IRR:** Stop and consider discontinuation of further study treatment at that visit; administer diphenhydramine 50 mg IV or equivalent and monitor participant until resolution of symptoms. The amount of study treatment infused must be recorded in the eCRF. If continuing administration after the second interruption, restart infusion at 50% of the rate at the time of the second interruption. If no further evidence of IRR after 30 minutes, the rate may be increased to 100% of the infusion rate at the time of interruption; monitor participant closely. Infusion rate escalation may resume per the IPPI schedule, after the infusion has been administered for at least 30 minutes at 100% of the infusion rate used at the time of dose interruption.	Antihistamine, antipyretic, and glucocorticoid, as per Table 17 (Section 6.7.2.2) Consider meperidine if participant experiences chills and rigors.
Grade 3 Severe reaction that is prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)	**Stop infusion** Start IV saline infusion; recommend bronchodilators, supplemental oxygen; epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed (other drugs as appropriate). Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids), as appropriate.	Based on severity of symptoms, consider permanent discontinuation of amivantamab. Consultation with Medical Monitor required before continuing with subsequent dosing.
Grade 4 Life-threatening; pressor or ventilator support indicated	Same as for Grade 3	Amivantamab treatment must be permanently discontinued.

eCRF=electronic case report form; IPPI=Investigational Product Preparation Instructions; IRR=infusion-related reaction; IV=intravenous.
*Per National Cancer Institute - Common Terminology Criteria for Adverse Events Version 5.0

6.5.3.2. Rash-Related Adverse Events

The prevention and management of EGFR inhibitor-induced rash-related TEAEs can be conducted in accordance with local institutional guidelines, or according to the recommendations below. For participants receiving amivantamab and lazertinib (Arms A/A2), more proactive management of rash is warranted, given the anticipated synergistic anti-EGFR activity.

Prophylaxis Recommendations

The prophylactic regimen can be managed according to local practice and guidelines; however, it should include the following:

- Avoid exposure to sunlight.
- Wear protective clothing (including hat, sunglasses, etc.).
- Use broad-spectrum sunscreen with an SPF of ≥30 and reapply as necessary. UVA light can penetrate glass; therefore, sunscreen should also be worn indoors and in vehicles if exposed to direct sunlight. Recommended active sunscreen ingredients are zinc oxide and/or titanium dioxide.
- Apply alcohol-free emollient cream or ointments (eg, glycerin, cetomacrogol, or ceramide-based cream) or skin moisturizer on dry areas of the body. These topical agents can be applied on a daily basis starting on Day 1, and more often as needed. Ideal time for application is after bathing. Creams and ointments are preferred over gels, lotions and oils.
- Alcohol-based (eg, gel formulations) topical agents such as steroids, antibiotics, or hand sanitizers can dry the skin and should be avoided.
- A proactive approach is recommended, given the anticipated increase in anti-EGFR activity:

These participants should have prescriptions (preferably already filled) for topical antibiotics, oral antibiotics, and topical steroids at the time of initial dosing, to minimize any delay in reactive management once rash is observed.

Strongly consider initiating antibiotic therapy on Cycle 1 Day 1 and continuing antibiotic therapy for the first 8 weeks: a topical antibiotic (clindamycin, mupirocin, or fusidic acid) on sun-exposed skin, or an oral antibiotic (such as doxycycline 100 mg once daily, minocycline 100 mg once daily, or cephalexin 500 mg once daily), or both.

A topical corticosteroid of medium to low potency twice daily on the face and chest (such as alclometasone 0.05% or desonide 0.05% cream) may also be considered.

Reactive Management Recommendations

It is strongly recommended that participants who develop rash/skin toxicities receive evaluations for management on the specific AE.

- Consider consultation with a dermatologist, especially if the rash is Grade 3, atypical in appearance or distribution, or does not improve within 2 weeks (for Grade 2 rash).
- Consultation with a dermatologist is required if the rash is Grade 4.
- Initiate a topical corticosteroid (cream or ointment) twice daily.

Examples to use for face: betamethasone valerate 0.05%, hydrocortisone valerate 0.2% or desonide 0.05%

Examples to use for body: betamethasone valerate 0.1%, triamcinolone acetonide 0.1%

- If not already initiated for prophylaxis, initiate systemic antibiotic (such as doxycycline 100 mg twice daily, minocycline 100 mg twice daily, or cephalexin 500 mg twice daily), or increase the dosing if already administered.
- If an associated skin infection is suspected, obtain bacterial and fungal cultures followed by adjustment of antibiotic or antifungal therapy, based upon culture and susceptibility determination.
- For reactive management of pruritic lesions, see Section 6.5.3.3.
- For skin fissures, use of Monsel's solution (ferric subsulfate solution), silver nitrate, or zinc oxide cream is recommended.
- For xerosis, fragrance-free moisturizing creams or sprays are recommended.
- For desquamation, emollients and mild soap are recommended.
- After the rash is controlled, consider gradually tapering the antibiotic.

A suggested algorithm for stepwise management of rash is provided in Table 10 for Arms A/A2 and Table 11 for Arms C/C2.

Table 10: Suggested Algorithm for Management of Rash (Arms A/A2)

Grade[a]	Management	Dose Adjustment
1	• Initiate reactive management as above • Reassess weekly	Continue current dose(s) of study treatment
2	• Initiate reactive management as above • Reassess weekly	Continue current dose(s) of study treatment; *or* If intolerable, consider withholding lazertinib. Upon satisfactory resolution, restart on Day 1 of next cycle at either the same or a reduced dose. See Table 6 for lazertinib dose reduction and Table 7 for amivantamab dose reduction guidance.
3	• Initiate reactive management as above • Start moderate strength topical corticosteroids[b] and systemic antibiotics as above, plus systemic prednisone (0.5 mg/kg) for 7 days • Consider low doses of acitretin or isotretinoin (20-30 mg/day) • Reassess weekly • Consider dermatology consultation and manage rash per recommendation	Withhold lazertinib and amivantamab until rash improves to ≤Grade 2. If Grade 3 adverse reaction improves to Grade 0-2 after withholding study drugs for up to 3 weeks, then upon resolution[c]: • Restart amivantamab at the same dose or a reduced dose on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle. • Restart lazertinib at a reduced dose on Day 1 of next cycle. If Grade 3 adverse reaction does not improve to Grade 0- 2 after withholding study drugs for up to 3 weeks, permanently discontinue either lazertinib or amivantamab or both.

4	• Initiate reactive management as above • Start moderate strength topical corticosteroids[b] and systemic antibiotics as above, plus systemic prednisone (0.5 mg/kg) for 7 days • Consider low doses of acitretin or isotretinoin (20-30 mg/day) • Reassess weekly • Consult dermatologist and manage rash per recommendation	Permanently discontinue all study drugs (amivantamab, lazertinib, pemetrexed, and carboplatin).
Severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN)	• Consult dermatologist and manage rash per recommendation	Permanently discontinue all study drugs (amivantamab, lazertinib, pemetrexed, and carboplatin).

a. Grading per National Cancer Institute - Common Terminology Criteria for Adverse Events (Version 5.0).
b. For example, hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream.
c. Resolution defined as: ≤Grade 2 or back to baseline status for the participant.

Table 11: Suggested Algorithm for Management of Rash (Arms C/C2)

Grade[a]	Management	Dose Adjustment
1	• Initiate reactive management as above • Reassess weekly	Continue current dose(s) of study treatment
2	• Initiate reactive management as above • Reassess weekly	Continue current dose(s) of study treatment; *or* If intolerable, consider withholding amivantamab. Upon satisfactory resolution, restart on Day 8 or Day 15 of the current cycle or Day 1 of next cycle at either the same or a reduced dose (see Table 7 for amivantamab dose reduction guidance).
3	• Initiate reactive management as above • Start moderate strength topical corticosteroids[b] and systemic antibiotics as above, plus systemic prednisone (0.5 mg/kg) for 7 days • Consider low doses of acitretin or isotretinoin (20-30 mg/day) • Reassess weekly • Consider dermatology consultation and manage rash per recommendation	Withhold amivantamab until rash improves to ≤Grade 2. If Grade 3 adverse reaction improves to Grade 0-2 after withholding amivantamab for up to 3 weeks, restart amivantamab at the same dose or a reduced dose on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle. If Grade 3 adverse reaction does not improve to Grade 0-2 after withholding amivantamab for up to 3 weeks, permanently discontinued amivantamab.
4	• Initiate reactive management as above • Start moderate strength topical corticosteroids[b] and systemic antibiotics as above, plus systemic	Permanently discontinue all study drugs (amivantamab, pemetrexed, and carboplatin).

Table 11: Suggested Algorithm for Management of Rash (Arms C/C2)

	prednisone (0.5 mg/kg) for 7 days • Consider low doses of acitretin or isotretinoin (20-30 mg/day) • Reassess weekly • Consult dermatologist and manage rash per recommendation	
Severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN)	• Consult dermatologist and manage rash per recommendation	Permanently discontinue all study drugs (amivantamab, pemetrexed, and carboplatin).

a. Grading per National Cancer Institute - Common Terminology Criteria for Adverse Events (Version 5.0).
b. For example, hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream.

Scalp Rash

Atypical scalp rash and associated infection may develop over time with the use of EGFR inhibitors. Treatment options include:

- A topical steroid shampoo (eg, clobetasol 0.05%), or an anti-dandruff shampoo with anti- inflammatory, antibacterial, and antifungal properties (eg, ketoconazole, selenium sulfide [Selsun®], zinc pyrithione [Head and Shoulders®], or Ciclopirox). These shampoos should be used twice/week, massaging into scalp, leaving on for 2-5 minutes, and then rinsing.
- Application of a steroid lotion may also be effective (eg, betamethasone valerate 0.1% lotion, mometasone furoate 0.1% lotion, or betamethasone dipropionate 0.05% lotion).
- Initiation of a systemic antibiotic (eg, doxycycline 100 mg twice daily, minocycline 100 mg twice daily) may also be used to treat acute scalp infection.

Of note, while wearing hats to avoid sun damage to the scalp is suggested in a prophylactic setting, avoiding any headwear for a participant with established scalp rash is strongly recommended to prevent further spread of the rash.

6.5.3.3. Pruritus

Reactive Management Recommendations (Fischer 2013)

Grade 1 pruritus:

- Apply topical low to moderate strength steroid cream (eg, hydrocortisone 2.5%, desonide 0.05%, or betamethasone valerate 0.05%), topical calcineurin inhibitor (eg, tacrolimus or pimecrolimus), or topical antipruritic containing numbing agent (eg, pramoxine) and menthol.

Grade 2 pruritus:

- Apply topical moderate to high strength steroid cream (eg, betamethasone valerate 0.1%, triamcinolone acetate 0.1%) or topical antipruritic containing numbing agent (eg, pramoxine) and menthol.
- Initiate an oral antipruritic (eg, cetirizine, fexofenadine, rupatadine, bilastine) one dose twice daily. If still pruritic after 2-5 days, may increase to double dose twice daily.

Grade 3 pruritus:

- Initiate an oral antipruritic (as above for Grade 2 pruritus).
- Initiate oral pregabalin or gabapentin.
- Initiate an oral corticosteroid (eg, prednisone 0.5-1.0 mg/kg/day or equivalent for 5 days).

6.5.3.4. Paronychia

Paronychia is a well-recognized toxicity associated with anti-EGFR therapeutics. As a result, there are recommendations that should be followed to prevent or minimize patient discomfort associated with this toxicity.

Prophylaxis Recommendations

- Avoid skin irritants.
- Cushion affected areas.
- Wear gloves and comfortable shoes.
- Apply moisturizer to nails.

Reactive Management Recommendations

Grade 1 paronychia:

- Use antimicrobial soaks once or twice daily: warm bowl of water + 5 mL of bleach (sodium hypochlorite) or vinegar (DO NOT USE BOTH TOGETHER); soak for 5 minutes, rinse, pat dry, and then apply either emollient or topical treatments below.
- Apply topical antiseptic (povidone-iodine 10% solution) twice daily.
- Apply a topical steroid ointment (eg, betamethasone valerate 0.1% or clobetasol) or topical calcineurin inhibitor (eg, tacrolimus 0.1%) twice daily. If using topical steroid, once resolved, switch to topical calcineurin inhibitor daily or decrease to twice per week to maintain.

Grade 2 or 3 paronychia:

- In addition to the guidance for Grade 1 paronychia above:

Apply topical antibiotic/antifungal agent (eg, mupirocin, fusidic acid, clotrimazole, or miconazole) twice daily.

Initiate oral antibiotic for at least 14 days (eg, doxycycline 100 mg twice daily, minocycline 100 mg twice daily, or cephalexin 500 mg twice daily).

Consult a dermatologist or podiatrist.

6.5.3.5. Oral Mucositis

Mucositis is a well-recognized toxicity associated with anti-EGFR therapeutics and may be mild/moderate and localized (Grades 1-2) or severe and widespread (≥Grade 3). As a result, there are recommendations that should be followed to prevent or minimize patient discomfort associated with this toxicity. Prophylaxis should occur according to local institutional practice and guidelines, and should include the following:

Prophylaxis Recommendations

- Use good oral hygiene, dentition review and referral to an oral hygienist if necessary.
- Use a soft toothbrush.
- Use mild-flavored toothpastes.
- Use saline-peroxide or salt and soda mouthwashes 3 or 4 times per day.
- Use water soluble lubrication agents like artificial saliva (for xerostomia or dry mouth).
- Avoid spicy, acidic, hard, and hot food and beverages.

Reactive Management Guidelines

- Asymptomatic or mild symptoms: topical steroid (dexamethasone 0.5/mL elixir) and lidocaine 2%-5% jelly or solution (swish and spit) 4 times per day.
- Co-trimoxazole lozenges can be used to prevent secondary candida infection.
- In cases of moderate to severe pain:

Compounded mouthwash (eg, "magic mouthwash") including an antifungal, steroid, antihistamine, anesthetic, and/or antacid/mucosal coating agent as per local practice and guidelines.

Dexamethasone solution 3.3 mg/5 mL swish and spit 4 times per day, and lidocaine jelly 2% to 5% or solution 4 times per day.

6.5.3.6. Pulmonary Toxicity

Patients with NSCLC are at risk of multiple AEs affecting pulmonary function, including disease progression, pulmonary embolus, infectious pneumonias, and more rarely, drug-related ILD/pneumonitis. Participant respiratory status should be assessed at every visit; any clinically significant change in respiratory status should prompt immediate investigation into the etiology in accordance with local practice/guidelines to institute appropriate treatments and to rule out early ILD/pneumonitis. If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pulmonary AE is observed, including ILD/pneumonitis, all study treatments, including carboplatin and pemetrexed, should be withheld, and appropriate treatment/management should be promptly initiated.

The following evaluations are recommended in order to exclude alternative etiologies such as lymphangitic carcinomatosis, pulmonary embolism, infection, allergy, and cardiogenic edema:

- Detailed focused history reviewing respiratory status and exercise tolerance.
- Focused physical exam including full assessment of vital signs (with pulse oximetry).
- Unscheduled radiological assessment, including chest x-ray or computerized tomography (CT) scan (high-resolution CT is preferred).
- Infectious evaluation, including blood and sputum cultures, atypical pneumonia panels, and SARS-CoV-2 testing, if indicated.

- Hematology and other laboratory tests, including serum albumin levels.
- Referral to pulmonologist for evaluation, including bronchoscopy with biopsy, cell counts, and cultures as feasible.
- Evaluation of cardiac function, if indicated.

Where other causes of respiratory symptoms have been excluded, a diagnosis of ILD/pneumonitis should be considered, and study treatment permanently discontinued. Study treatment should not be restarted until pneumonitis/ILD is ruled out. For participants with symptomatic pneumonitis (Grade 2 or above), treatment with steroids should be initiated per local guidelines, in addition to withholding of study treatment.

Confirmation of ILD/pneumonitis of any grade should prompt discontinuation of all study treatments and should be reported as a serious adverse event (SAE). In the absence of a diagnosis of ILD/pneumonitis, study treatment may be restarted after discussion with Medical Monitor.

6.5.3.7. Cardiac Adverse Events

Newly diagnosed or suspected changes in cardiac status, including QTcF prolongation or change in LVEF, should prompt additional investigations, including referral to cardiologists as per local practice or guidelines.

QTcF Prolongation

- Check the quality of electrocardiogram (ECG) recording and check for electrolyte abnormalities (eg, potassium, calcium, magnesium); correct as needed.
- QTc prolongation of >60 msec from baseline, or absolute value of >500 msec:

For QTcF prolongation >60 msec from baseline, or absolute value >500 msec (from a manual ECG read), medications should be reviewed to rule out new or existing concomitant medications with potential for QT prolongation (Appendix 11: Medications With Potential for QT Interval Prolongation), and these should be discontinued, if possible, with action reported in eCRF.

Check for electrolyte abnormalities and correct as needed (eg, potassium, calcium, magnesium).

If QTcF prolongation is confirmed and potentially attributable to study treatments, then all study treatments, including carboplatin and pemetrexed, should be withheld.

  - Retreatment, at a reduced dose, should only occur once QTc interval is ≤480 msec, as measured by repeat triplicate ECG, or recovery to baseline is documented. If retreatment is indicated, lazertinib and amivantamab should be reduced by 1 dose level each (see Table 6 and Table 7).

Treat as per local standard of care in consultation with a cardiologist.

- QTc interval prolongation with signs/symptoms of life-threatening arrhythmia, including but not limited to the following: documented episode of ventricular tachycardia, ventricular fibrillation, complete heart block (Grade III atrioventricular block) or second-degree atrioventricular block Mobitz type II, QTc >500 msec at repeated ECG measurements, after dose adjustment was performed:

Permanently discontinue study treatment.

Change in LVEF

- Absolute LVEF decline of >10% and absolute LVEF value below the LLN:

For participants experiencing absolute decline of LVEF of >10% from baseline and absolute LVEF percentage below LLN, the decline should first be confirmed by having the 2 assessments read, and measurements confirmed, by the same cardiologist.

Confirmed drops in LVEF assessments should prompt withholding study treatment, referral to a cardiologist for further evaluation, and consultation with the Medical Monitor; repeat LVEF assessment within at least 2 weeks to monitor status.

- Symptomatic CHF:

Permanently discontinue all study treatments, including carboplatin and pemetrexed.

6.5.3.8. Liver Chemistry Abnormalities

Liver chemistry threshold stopping criteria have been established to provide safety to the participants and to better assess the etiology of a liver event. Liver chemistry should be monitored according to the Schedule of Activities and study treatment should be withheld for any liver chemistry abnormality of ≥Grade 3 severity (refer to Section 6.5.2). In addition, if the following criteria are observed, then study treatment should be withheld, and the event should be reported as an SAE to the sponsor within 24 hours:

a) ALT or AST ≥3×ULN (if baseline was normal; ≥3×baseline if baseline was abnormal) and bilirubin ≥2×ULN (if baseline was normal; ≥2×baseline if baseline was abnormal) (>35% direct bilirubin).

    - Exception to the bilirubin elevation is made if the participant has Gilbert's disease and the elevated bilirubin is predominantly unconjugated.

b) ALT or AST ≥3×ULN (if baseline was normal; ≥3×baseline if baseline was abnormal) and international normalized ratio (INR) >1.5 if INR is measured.

c) ALT or AST ≥3×ULN (if baseline was normal; ≥3×baseline if baseline was abnormal) with the concomitant appearance of worsening symptoms attributable to drug induced liver injury, such as the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or new onset eosinophilia (>5%).

In the event abnormalities of liver function tests require withholding study treatment, liver chemistry should be repeated within 1-3 days and until abnormal values resolve/return to baseline. Etiology of the liver chemistry abnormality should be investigated, as described in Appendix 6: Liver Event Follow-Up Requirements. If no alternative etiology of liver toxicity is identified, all study treatments, including carboplatin and pemetrexed, should be permanently discontinued.

6.5.3.9. Ocular Toxicity

Ophthalmologic complications are infrequently observed with anti-EGFR therapeutics. In the case of signs or symptoms associated with ophthalmologic toxicity, including change in vision (including change in acuity or visual distortion), eye inflammation, lacrimation, light sensitivity, or eye pain, among others, the participant should be referred for ophthalmologic assessment

(Section 8.2.6). Participants should be advised of the increased risk for eye toxicity associated with anti-EGFR therapeutics with the use of contact lenses.

6.5.3.10. Diarrhea

If participants experience diarrhea, they should be encouraged to drink 8 to 10 large glasses (total volume of 2 L) of clear liquids per day while on study to maintain adequate hydration. Maintenance of electrolyte balance using electrolyte containing drinks, broth, and clear juices should be considered. If an infectious cause of the diarrhea is suspected, perform stool testing and administer antibiotic therapy (avoiding strong CYP3A4 inhibitors, when possible) as appropriate.

General dietary measures to limit impact of diarrhea include the following:

- Stop all lactose-containing products in participants with evidence of lactose intolerance
- Eat frequent small meals if experiencing increased frequency of stools
- Consider low-fat regimen enriched with bananas, rice, applesauce, and toast

Diarrhea management guidelines are shown in Table 12 for Arms A/A2 and Table 13 for Arms C/C2.

Table 12: Suggested Algorithm for Management of Diarrhea for Arms A/A2

Grade	Management	Study Treatment
1	• Loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours). • Fluid intake of at least 2 L as described above.	• Continue study treatment(s).
2	• Loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours), or consider diphenoxylate and atropine formulations. • Fluid intake of at least 2 L as described above. Monitor participant closely and consider intravenous hydration.	• If not improved to ≤Grade 1 within 24 hours despite use of loperamide, hold lazertinib treatment until ≤Grade 1. • Upon satisfactory resolution, restart on Day 1 of next cycle at either the same or a reduced dose. See Table 6 for lazertinib dose reduction and Table 7 for amivantamab dose reduction guidance.
3	• Oral therapy with diphenoxylate and atropine formulations, or tincture of opium. • Fluid intake of at least 2 L should be maintained as described above, intravenously if necessary. • Consider use of octreotide 100-150 µg subcutaneously twice daily with escalation to 500 µg 3 times daily. • Consider hospitalization if does not improve to ≤Grade 2 within 24 hours, or in presence of fever, abdominal pain, etc.	• Hold lazertinib. Upon resolution to ≤Grade 1, resume lazertinib with consideration of reduction by 1 dose level. Restart lazertinib at a reduced dose on Day 1 of next cycle.
4	• Maximal inpatient fluid and nutritional support, antibiotics as indicated in judgment of investigator for fever, leukocytosis, marked dehydration, etc.	Hold lazertinib and amivantamab. Upon resolution to ≤Grade 1:

		• Restart amivantamab at a reduced dose on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle. • Restart lazertinib at a reduced dose on Day 1 of next cycle.

Table 13: Suggested Algorithm for Management of Diarrhea for Arms C/C2

Grade	Management	Study Treatment
1	• Loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours). • Fluid intake of at least 2 L as described above.	• Continue study treatment(s).
2	• Loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours), or consider diphenoxylate and atropine formulations. • Fluid intake of at least 2 L as described above. Monitor participant closely and consider intravenous hydration.	• If not improved to ≤Grade 1 within 24 hours despite use of loperamide, hold amivantamab treatment until ≤Grade 1. • If diarrhea of >Grade 1 recurs after initial improvement, consider reduction of amivantamab dose by one dose level
3	• Oral therapy with diphenoxylate and atropine formulations, or tincture of opium. • Fluid intake of at least 2 L should be maintained as described above, intravenously if necessary. • Consider use of octreotide 100-150 µg subcutaneously twice daily with escalation to 500 µg 3 times daily. • Consider hospitalization if does not improve to ≤Grade 2 within 24 hours, or in presence of fever, abdominal pain, etc.	• Hold amivantamab. Upon resolution to ≤Grade 1, resume amivantamab on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle. • Consider reducing dose by 1 level.
4	• Maximal inpatient fluid and nutritional support, antibiotics as indicated in judgment of investigator for fever, leukocytosis, marked dehydration, etc.	• Hold amivantamab until ≤Grade 1. Upon resolution to ≤Grade 1, resume amivantamab at a reduced dose on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle.

6.5.3.11. Paresthesia

If a participant experiences paresthesia, contributing medical conditions should first be considered and optimally managed. For example:

- Vitamin or mineral deficiency (eg, Vitamin B1 [thiamine], B6 [pyridoxine], B12 [cobalamin], B9 [folate], Vit E, Copper) should be corrected
- Diabetes should be optimally managed
- General safety measures are recommended to protect against injury, infection etc.

The following symptomatic management guidance is provided in the event the paresthesia is considered related to study drug:

- Grade 1: Nutraceutical/non-pharmacologic interventions may be considered (ie, vitamin supplementation including vitamins B1, B6, B9, B12, E, glutamine, alpha-lipoic acid, glutathione, calcium/magnesium, copper). Topical therapy (eg, capsaicin) may be considered.
- Grade 2: Duloxetine, pregabalin, or gabapentin are recommended. Titrate dose for efficacy and tolerability. Adding tricyclic or selective serotonin reuptake inhibitor antidepressant may be considered. Opioids (tramadol or strong opioids) may be considered. Neurologic consultation if symptoms persist on medication.
- Grade 3: Neurologic consultation. Duloxetine, pregabalin, or gabapentin are recommended. Titrate dose for efficacy and tolerability. Adding tricyclic or selective serotonin reuptake inhibitor antidepressant may be considered. Opioids (tramadol or strong opioids) may be considered.

If treatment modification is indicated, consider preferential interruption or dose reduction of lazertinib for participants in Arms A/A2.

Refer to Table 5 and Table 8 for recommended dose adjustment.

6.5.3.12. Venous Thromboembolic Events

Participants with NSCLC are at risk of developing complications, including VTE events. Investigators should closely monitor all participants for signs and symptoms of VTE events, specifically pulmonary embolism and deep vein thrombosis, throughout the duration of the study. Physical examinations (see Section 8.2.1) should include focus on signs and symptoms of VTE events, including upper- or lower-extremity swelling and discoloration. There should be a low threshold to perform additional diagnostic testing (eg, CT angiogram or lower-extremity ultrasound) for VTE events beyond the scheduled disease evaluations. For participants that have experienced VTE, if symptoms persist or in case of worsening VTE, further imaging studies (which may include doppler studies) should be performed to assess the resolution of the event with corrective measures, as per the treating physician's discretion.

All study participants receiving the combination of amivantamab and lazertinib (Arms A/A2) are recommended to receive prophylactic-dose anticoagulation as per local guidelines during the first 4 months of combination therapy (For patients receiving the LACP dosing schedule this would start Cycle 1 Day 1, for those receiving the ACP-L dosing schedule this would start when lazertinib is initiated - on Cycle 5 Day 1 or sooner if carboplatin discontinued earlier than Cycle 4). Vitamin K antagonists are not recommended due to numerous drug interactions. The benefit-risk assessment for participants to tolerate prophylactic-dose anticoagulation is at the discretion of the treating investigator. Notably, prophylactic-dose anticoagulation has been found to be safe and effective in multiple prior studies (Carrier 2019; Rutjes 2020).

If a VTE event is diagnosed, the participant should be treated with treatment-dose anticoagulation as per local guidelines. Vitamin K antagonists are not recommended because of numerous drug interactions. For VTE events associated with clinical instability (eg respiratory failure or cardiac dysfunction) in participants receiving the combination of amivantamab and lazertinib, study treatment should be held until the patient recovers from the event. Thereafter, the treatment can be resumed at the discretion of the investigator.

In the case of a recurrent VTE whilst on therapeutic anticoagulation therapy, the combination of amivantamab and lazertinib should be permanently discontinued. Participants may continue to receive treatment with either amivantamab or lazertinib (but not both) at the discretion of the treating physician.

Refer to Table 5, Table 6, Table 7, and Table 8 for recommended dose adjustment for any adverse events.

6.5.4. Chemotherapy Dose Modification

Dose modifications of chemotherapy should be based on the maximum toxicity experienced during a cycle. Treatment should be delayed until the toxicity resolves to ≤Grade 1 or the baseline status of the participant. Final treatment decisions should depend on clinical judgment, based on local regulations and labeling. Decisions on study treatment dose modification should be guided by the safety profile of each drug and the likelihood of causality.

Dose modifications will be based on the maximum toxicity experienced during a cycle. Participants may have a maximum of 2 dose modifications to each treatment throughout the study for toxicities before the agent should be discontinued. Dose reduction should be based upon the most severe toxicity if multiple toxicities are experienced concurrently. Do not re-escalate chemotherapy dosing after a prior dose reduction.

6.5.4.1. Management of Chemotherapy Toxicities

Given the prevalent use of platinum-based doublet chemotherapy in the treatment of NSCLC, the safety profiles of both carboplatin and pemetrexed are well described. Safety monitoring and dose modifications should therefore follow local regulations and labeling.

In general, participants should be monitored for chemotherapy-related toxicities and should undergo laboratory assessments including a complete blood count with platelet counts, as well as an evaluation of liver and kidney function, per the respective approved prescribing information (for example, Alimta USPI 2019, Carboplatin USPI 2018). Chemotherapy should be delayed if absolute neutrophil count is <1,500/µL, platelet count is <100,000/µL, or the participant is experiencing non-hematologic toxicity of > Grade 2 severity. All participants who experience hematologic toxicities while on treatment are recommended to receive colony stimulating factors as per international guidelines (eg, MGF-3 and TGF-1 from the NCCN Guidelines for Hematopoietic Growth Factors as an example). Table 14 and Table 15 provide additional guidance for dose modification to manage hematologic and non-hematologic toxicities related to chemotherapy based on product labeling. Refer to local labeling for complete information regarding dose adjustment for carboplatin and pemetrexed.

Table 14: **Guidance for Dose Modifications for Hematologic Chemotherapy Toxicity**

Platelets (Nadir)	Absolute Neutrophil Count (Nadir)	Pemetrexed Dosage	Carboplatin Dosage
≥50,000/μL	≥500/μL	100% of previous dose	100% of previous dose
≥50,000/μL	<500/μL	75% of previous dose	75% of previous dose
<50,000/μL without bleeding	Any	75% of previous dose	75% of previous dose
<50,000/μL with ≥Grade 2 bleeding	Any	50% of previous dose	50% of previous dose
≥50,000/μL	<1,000/μL + fever ≥38.5°C (101°F)	75% of previous dose	75% of previous dose

Table 15: Guidance for Dose Modifications for Non-Hematologic Chemotherapy Toxicity

	Pemetrexed Dosage	Carboplatin Dosage
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

Pemetrexed therapy should be discontinued if the participant experiences any hematologic or nonhematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed. Refer to local labeling for complete information.

6.6. Treatment of Overdose

There are no data on overdose from studies of amivantamab or lazertinib (refer to IB for each agent). In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

6.7. Concomitant Therapy

6.7.1. Recording Prestudy and Concomitant Therapies

Prestudy therapies administered up to 28 days before randomization must be recorded. Concomitant therapies must be recorded throughout the study beginning with randomization to 30 days after the last dose of study treatment or start of subsequent anticancer therapy, whichever is first. Concomitant therapies should also be recorded beyond 30 days only in conjunction with SAEs and Grade 3 or Grade 4 AEs considered related to study treatment, until resolution of event or start of subsequent therapy.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study treatment must be recorded in the eCRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.7.2. Permitted and Required Medications and Therapies

6.7.2.1. Pre- and Post-Infusion Medications for Chemotherapy

Corticosteroids, folic acid, and vitamin B12 will be administered concomitantly with pemetrexed (Table 16), according to local prescribing information or per standard local practice.

Table 16: Concomitant Medications for Pemetrexed

Medication	Dose	Timing
Corticosteroid	Dexamethasone 4 mg orally twice daily or equivalent	1 day before, the day of, and 1 day after each dose of pemetrexed[a]
Folic Acid[b]	350-1,000 µg orally	Daily beginning 7 days prior to first infusion and continuing until 21 days after the last dose of pemetrexed
Vitamin B12	1,000 µg intramuscularly	1 dose within 7 days prior to and including Cycle 1 Day 1, then every 3 cycles afterwards. Vitamin B12 may be administered on the same day as pemetrexed

a. For participants in Arms A/A2 and C/C2, dexamethasone 4 mg orally twice daily dose can be skipped on Cycle 1 Day 1 and Day 2, at the discretion of the investigator since IV dexamethasone is administered as a pre-infusion medication for amivantamab on those days per Table 17.
b. Folic acid may be given either as a separate preparation or as a component of a multivitamin.

Participants may receive other pre-treatment or concomitant treatment for pemetrexed or carboplatin as recommended by local prescribing information, local practice guidelines, or as clinically indicated. Permitted prophylactic medications include the following:

- Appropriate prophylactic antiemetic regimens for high risk of emesis associated with carboplatin (eg, ondansetron, aprepitant, dexamethasone), in accordance with institutional practice or current NCCN and/or ESMO guidelines.
- Leukocyte-depleted blood transfusions are allowed at any time after Cycle 1 Day 1.
- G-CSFs should not be used prophylactically during screening. Use of prophylactic colony stimulating factors may be considered after first dose as per local guidelines or prescribing information.

Concomitant medications for the symptomatic treatment of related toxicities (Grade 1-4) may be administered according to the standard of care at the site and at the treating physician's discretion, as clinically indicated. Supportive care and other medications that are considered necessary for the participant's well-being may be given at the discretion of the investigator.

6.7.2.2. Pre- and Post-Infusion Medications for Amivantamab (Arms A/A2 and Arms C/C2)

Preinfusion Medications

Required preinfusion medications and optional preinfusion medications for amivantamab are summarized in Table 17.

Table 17: Preinfusion Medications for Amivantamab

Cycle/Day	Medication	Dose	Route of Administration	Recommended Dosing Window Before Amivantamab Infusion
Required Preinfusion Medications[a,b,c]				
Cycle 1 Day 1	Glucocorticoid	Dexamethasone 20 mg[d]	IV	60 to 120 minutes
Cycle 1 Day 2	Glucocorticoid	Dexamethasone 10 mg or Methylprednisolone 40 mg	IV	45 to 60 minutes
All	Antipyretic	Paracetamol (acetaminophen) 650 to 1,000 mg (or equivalent)	IV	15 to 120 minutes
			Oral	30 to 150 minutes
All	Antihistamine	Diphenhydramine 25 to 50 mg (or equivalent)	IV	15 to 120 minutes
			Oral	30 to 150 minutes
Optional Preinfusion Medications[a]				
Cycle 1 Day 8 and beyond	Glucocorticoid[e]	Dexamethasone 10 mg or methylprednisolone 40 mg	IV	45 to 60 minutes
			Oral	60 to 90 minutes
Any	Histamine H_2-antagonist	Ranitidine 50 mg (or equivalent)	IV	15 to 30 minutes
Any	Antiemetic	Ondansetron 8-16 mg (or equivalent)	Oral or IV	15 to 120 minutes

IV=intravenous.

a. If a medication noted in this table is not locally available, a similar medication and dose may be substituted and administered per local guidelines.
b. Participants for whom required medications are contraindicated should explore alternative medications with their study doctor. If alternative medications are not suitable for the intent above, participants are not required to take the corresponding medication.
c. If the dose of amivantamab is delayed until Cycle 1 Day 2 and Cycle 1 Day 3, then the dosing days of preinfusion medications should be adjusted accordingly.
d. This dose and recommended dosing window allow a single dose of dexamethasone to serve as the pre-infusion glucocorticoid for both chemotherapy and amivantamab. If chemotherapy is dosed on Cycle 1 Day 1 and amivantamab is dosed on Cycle 1 Day 2 and Cycle 1 Day 3, then the amivantamab preinfusion glucocorticoid dose should be dexamethasone 10 mg (or methylprednisolone 40 mg) on Cycle 1 Day 2 and Cycle 1 Day 3.
e. Beginning with Cycle 1 Day 8, optional predose steroids may be administered prior to amivantamab if clinically indicated for participants who experienced an infusion-related reaction during either day of the first dose of amivantamab.

On days when multiple study drugs are dosed together, the order of medications should be as follows:

a. Lazertinib (Arms A/A2 only)
b. Preinfusion medications for chemotherapy (eg, antiemetic, antihistamine, glucocorticoid) per local guidelines or site practice
c. Pemetrexed per label/site practice

d. Carboplatin (up to a maximum of 4 cycles) per label/site practice

e. Premedications for amivantamab (per Table 17), to commence after completion carboplatin infusion (Arms A/A2 and C/C2). Note: Participants in Arms A/A2 and C/C2 should receive the required pre-medications, but if the medications are already administered prior to chemotherapy, administration does not need to be repeated prior to initiation of the amivantamab infusion if dose was administered within the recommended window.

f. Amivantamab (Arms A/A2 and C/C2)

Postinfusion Medications

Optional postinfusion medications may be prescribed and continued for up to 48 hours after any infusion if clinically indicated, at the discretion of the investigator (Table 18).

Table 18: Postinfusion Medications for Amivantamab

Medication	Dose	Route of Administration	Administration Instructions	Cycle/ Day
Optional Postinfusion Medications[a]				
Glucocorticoid	Dexamethasone 10 mg or comparable corticosteroid	IV or Oral	As clinically indicated	Any
Antihistamine	Diphenhydramine 25 to 50 mg or equivalent	IV or Oral	As clinically indicated	Any
Antipyretic	Paracetamol (acetaminophen) 650 to 1,000 mg	IV or Oral	As clinically indicated	Any
Opiates	Meperidine 25 to 100 mg	IV or Oral	As clinically indicated	Any
Antiemetic	Ondansetron 8 to 16 mg or equivalent	IV	As clinically indicated	Any
	Ondansetron 8 mg or equivalent	Oral		

a. Optional medications can be used prophylactically as clinically indicated. If a medication noted in this table is not locally available, a similar medication and dose may be substituted and administered per local guidelines.

6.7.2.3. Supportive Care

Supportive care (eg, antibiotics, analgesics, transfusions, diet) and concomitant medications may be administered according to the standard of care at the site, and at the treating physician's discretion, as clinically indicated.

6.7.2.4. Radiotherapy

Localized, limited radiotherapy of short duration (eg, 5 days or less) for palliative purposes of nontarget lesions may be permitted, but only after consultation with the Medical Monitor. Study treatment interruption is not required but is allowed as per investigator discretion. Radiotherapy should be scheduled for the weeks between scheduled doses of amivantamab.

6.7.2.5. Hormonal Contraception

Participants using hormonal contraceptives as a means of birth control must continue to use the same hormonal contraceptives throughout the study and through 7 months after the last dose of study treatment.

6.7.3. Prohibited or Restricted Medications and Therapies

Prohibited Medications and Therapies

The following concomitant medications and therapies are prohibited until the End of Treatment visit. The sponsor must be notified as soon as possible of any instances in which prohibited therapies were administered.

- Any chemotherapy, anticancer therapy, or experimental therapy (other than study treatments) for the treatment of NSCLC is prohibited.
- Radiotherapy to a target lesion is prohibited.
- Use of live or live attenuated vaccines is prohibited until at least 90 days after the last dose of study treatment.
- Use of phenytoin or fosphenytoin with carboplatin is prohibited.
- Prescription and over the counter medications, herbal supplements or ingestion of foods with known potent inducer effects on CYP3A4/5 activity (For a list of such medications, refer US FDA 2022). Strong inducers of CYP3A4/5 are prohibited and should be discontinued for an appropriate period (at least 4 elimination half-lives) before starting study treatment regimens that include lazertinib. Appropriate medical judgment is required, if any of the strong CYP3A4/5 inducer medications should be utilized, if clinically indicated, for the treatment of AEs. Please contact the local pharmacist or Medical Monitor with any questions.

Restricted Medications and Therapies

The following concomitant medications and therapies are restricted until the End of Treatment visit and should be avoided, when possible, or used with caution.

- Use caution with co-administration of medicines that prolong QT interval (Appendix 11: Medications With Potential for QT Interval Prolongation). If there are no other alternative medications that can be used, limit treatment duration when possible. Please contact the local pharmacist or Medical Monitor with any questions.
- Avoid concomitant use of CYP3A4/5 substrate drugs and medications known to be strong inhibitors of CYP3A4/5 (For a list of such medications, refer US FDA 2022). If no other alternatives exist monitor participants more closely for adverse reactions. Please contact the local pharmacist or Medical Monitor with any questions.
- Medications that are substrates of P-glycoprotein (P-gp), multi-drug resistance protein 4 (MRP4), Breast Cancer Resistance Protein (BCRP), and Organic Cation Transporter 1 (OCT1) should be used with caution. (For a list of such medications, refer US FDA 2022). Please contact the local pharmacist or Medical Monitor with any questions.
- Due to the potential for hypomagnesemia associated with EGFR inhibitors, concomitant medications that may decrease serum magnesium should be avoided if possible.
- Nephrotoxic or ototoxic agents should be used cautiously with carboplatin. Nephrotoxic drugs should also be used cautiously with pemetrexed. Concomitant administration of aminoglycosides should be avoided with carboplatin.

- Caution should be exercised when administering pemetrexed concurrently with a nonsteroidal anti-inflammatory drug to a participant whose creatinine clearance is <80 mL/min (exception: low-dose aspirin once daily is permitted during the study). Ibuprofen should be avoided from 2 days before until 2 days after administration of pemetrexed.

6.8. Continued Access to Study Treatment

At the end of the study, participants who are benefiting from the study treatment, as determined by their investigator, will be able to receive continued access via post-study independent requests from their investigators, as permitted by local regulations and guidelines. See details for the OLE Phase (Section 10.14 [Appendix 14]) and the LTE Phase (Section 10.15 [Appendix 15]).

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

A participant's study treatment must be discontinued if any of the following apply:

- The participant experiences a Grade 4 rash, severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN).
- The participant withdraws consent to receive study treatment
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study treatment
- The participant becomes pregnant
- Noncompliance with study drug administration or procedure requirements as judged by the investigator
- Radiographic disease progression by BICR using RECIST (Version 1.1) (**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. In general, this implies the absence of significant worsening of clinical symptoms or signs of disease progression, including clinically significant worsening of laboratory abnormalities, deterioration in ECOG performance status, or rapid progression at critical anatomical sites which may require urgent alternative medical intervention.)

If a participant discontinues study treatment for any reason before the end of the treatment period, then the End of Treatment assessments should be obtained and scheduled assessments off study treatment should be continued. Study treatment assigned to the participant who discontinued study treatment may not be assigned to another participant. Additional participants will not be entered.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion), as local regulations permit.

7.2.1. Withdrawal From the Use of Study Samples

Withdrawal From the Use of Study Samples

The participant may withdraw consent for use of study samples, including optional study samples, for research not required by the protocol. In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of sample retention are presented in the ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant (eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members).

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, emails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's medical records.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of measurements applicable to this study.

When possible, all PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses.

The total blood volume to be collected from each participant depends upon the duration of participation and the required blood volume for local laboratory assessments, but through 17 cycles of treatment and the End of Treatment visit, the total amount of blood drawn from each participant in this study is anticipated to be approximately 390 mL in Arms A/A2, 210 mL in Arm B, and 370 mL in Arms C/C2. Depending on country-specific regulations, volume requirements at local laboratories, and availability of blood collection tubes the total blood volume may vary.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the Schedule of Activities for the timing and frequency of all sample collections. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Sample collection and testing should comply with local regulations.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB for amivantamab
- IB for lazertinib
- Local prescribing information for carboplatin (if carboplatin is centrally sourced)
- Local prescribing information for pemetrexed (if pemetrexed is centrally sourced)
- IPPI and SIPPM
- Laboratory manual and kits
- eCRF completion guidelines
- IWRS Manual
- Imaging Manual
- NCI CTCAE Version 5.0
- RECIST guidelines, Version 1.1
- Sample ICF
- Wallet cards
- Study treatment (lazertinib and amivantamab will be supplied centrally; depending on regional requirements, chemotherapy may be sourced centrally or locally)
- Ancillary supplies (as needed)

- Tablet (for PRO collection)

8.1. Efficacy Assessments

Blinded independent central review (BICR) will use RECIST v1.1 criteria to assess participant response to treatment: CR, PR, stable disease, progressive disease, or unevaluable. Disease assessments will include the chest, abdomen, and pelvis, and any other disease location(s). Baseline disease assessments should be performed no more than 28 days prior to randomization. Post-randomization disease assessments will occur at 6 weeks (+1 week) after randomization (ie, no earlier than 42 days after randomization), then every 6 weeks (±1 week) for the first 12 months and every 12 weeks (±1 week) afterward until disease progression is confirmed by BICR. Timing is relative to randomization; if an assessment is delayed, subsequent assessments should occur according to the original schedule. For participants who discontinue treatment prior to disease progression, tumor imaging should continue until disease progression is confirmed by BICR, if clinically feasible.

CT scan of the chest, abdomen, pelvis, and any other disease location(s) should be performed with an IV contrast agent and oral contrast. Participants not able to undergo CT scans with IV contrast (eg, due to allergy or renal insufficiency) may have non-contrast CT of the thorax and contrast enhanced magnetic resonance imaging (MRI) of the abdomen and pelvis. MRI can also be used to evaluate sites of disease that cannot be adequately imaged using CT. Identical methodology (CT scan with contrast agent or MRI) should be used for disease assessment at baseline and throughout the study. Techniques other than CT or MRI may be used based upon investigator's judgment, local standard of care, and RECIST v1.1 guidelines for the use of these alternative techniques. For example, bone scintigraphy may be used to identify bone lesions at screening or new bone lesions during treatment. Further details are provided in the Imaging Manual.

Brain MRI (or brain CT scan if MRI is medically prohibited) will be performed at screening, at 6 weeks (+1 week) and 12 weeks (±1 week), and then every 12 weeks (±1 week). Postbaseline brain MRI will be scheduled relative to randomization and will continue until intracranial disease progression is confirmed by BICR. Unscheduled brain MRI may also be conducted if clinically indicated. For those who have confirmed extracranial progression per RECIST v1.1, brain MRI should be continued, if feasible, until intracranial progression is confirmed by BICR. Further details are provided in the Imaging Manual.

Timing for each disease assessment is relative to randomization, regardless of dose modifications, and will continue until disease progression. If an assessment is performed outside of the scheduled visit and the participant has not progressed, every attempt should be made to perform the subsequent assessment at their scheduled visit timepoint. Any other area at which new disease is suspected should also be imaged.

Sites will be required to obtain digital copies of radiologic images (eg, CT, MRI) used for all scheduled and unscheduled disease assessments and submit to a Janssen-appointed Clinical Research Organization for central review by BICR.

For participants who discontinue study treatment due to toxicity or a reason other than objective progressive disease, tumor assessments should be continued per schedule until radiographic progressive disease is confirmed by BICR. Following disease progression, these participants should continue to be followed up for survival every 12 weeks (±14 days). Additional follow-up calls may be made in the 2 weeks before a data cutoff date to assess participant survival before the next scheduled assessment.

If a participant begins a new cancer therapy before disease progression, obtain tumor imaging before the new therapy and continue imaging per schedule until BICR confirms progression.

If a participant is treated beyond BICR-confirmed disease progression, disease assessments will continue according to the Schedule of Activities.

If the investigator is in doubt as to whether progression has occurred, particularly with respect to nontarget lesions or the appearance of a new lesion, treatment should be continued until the next scheduled assessment (or sooner if clinically indicated) and the participant's status should then be reassessed. If the repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression. To achieve "unequivocal progression" on the basis of nontarget lesions, there must be an overall substantial worsening in nontarget lesions such that, even in the presence of stable disease or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

If symptomatic deterioration (on the basis of global deterioration of health status) is recorded as the basis for discontinuation of study treatment, then the clinical findings used to make the determination must be specified in the eCRF and documented in the source documents. Every effort should be made to document radiographic progression even after discontinuation of treatment for symptomatic deterioration, but prior to subsequent therapy, if possible.

8.1.1. Symptomatic Progression

Symptoms, attribution, and related treatments will be recorded on the eCRF at the times specified in the Schedule of Activities.

8.1.2. Patient-Reported Outcomes

Patient-reported outcomes measures will be collected at the times specified in the Schedule of Activities. When feasible, PROs should be administered prior to other assessments. The PRO instrument will be provided in the local language in accordance with local guidelines. The PRO instrument must be available for regulators and for IRB/IRC submissions, therefore the PRO instrument or screen shots need to be attached to the protocol or provided in a companion manual with the instruments that will be submitted with the protocol. The PRO and AE data will not be reconciled with one another.

The Non-Small Cell Lung Cancer - Symptom Assessment Questionnaire (NSCLC-SAQ) was developed in accordance with US FDA PRO Guidance and scientific best practices for use in

clinical trials of NSCLC (McCarrier 2016). It contains 7 items that assess cough, pain, dyspnea, fatigue, and poor appetite over a 7-day recall period.

Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) are single-item questionnaires that provide an anchor-based comparison for the NSCLC-SAQ. The PGIS and PGIC should be administered prior to other PRO assessments. The PGIC will not be administered at the first visit because it captures change.

The EuroQol 5-dimensional descriptive system (5-level version) (EQ-5D-5L) is a validated tool to measure health status and health utility, including mobility, self-care, usual activities, pain, discomfort, and anxiety/depression (Herdman 2011).

The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) assesses functioning domains and common cancer symptoms with recall in the past week (Montazeri 1998).

The PROMIS-PF short-form v2.0 (8c 7-day version) will be used to characterize and better understand the level of physical ability and conduct of activities of daily living (Kluetz 2016). This version of PROMIS-PF contains 6 items to capture physical ability, including walking and climbing stairs, with a 7-day recall period.

The National Cancer Institute (NCI) Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a validated tool to assess the symptomatic toxicities self-reported by participants in clinical trials (NIH 2021).

8.2. Safety Assessments

Details regarding the IDMC are provided in Committees Structure in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations. The frequency of IDMC meetings will be described in the IDMC charter. AEs will be reported and followed by the investigator as specified in Section 8.3 and Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.2.1. Physical Examinations

The screening physical examination will include, at a minimum, the participant's height, weight, and general appearance and an examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system.

Participants should be questioned for skin and eye symptoms at all visits with directed physical examinations conducted as appropriate and specialty referral as indicated. In addition, participants should similarly be questioned for signs and symptoms of VTE events, and a focused physical examination of extremities and evaluation of respiratory status (including pulse oximetry) should be performed, particularly during the first 4 months of assigned therapy. Any changes from baseline should prompt consideration for further diagnostic evaluation, including unscheduled CT exam or lower-extremity Doppler evaluation.

On Day 1 of each cycle, and at the end of treatment visit, directed physical examinations of involved organs and other body systems, as indicated, will be performed and participant body weight will be obtained using a calibrated scale.

8.2.2. Vital Signs

Vital sign measurements will include the following assessments and be obtained as indicated in the Schedule of Activities (Table 1).

- Temperature
- Heart rate
- Respiratory rate
- Oxygen saturation
- Blood pressure

Blood pressure and pulse/heart rate measurements should be assessed in a seated or supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Electrocardiograms

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, and procedures are less than 1 hour apart, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Collection of ECGs will be obtained as indicated in the Schedule of Activities (Table 1). For triplicate ECGs at Screening and other times if clinically indicated, 3 individual ECG tracings should be obtained as closely as possible in succession, approximately 2 minutes apart. The clinical investigator will review the ECG, including ECG morphology, for immediate management. The results will be entered into the eCRF. Abnormalities noted at screening should be included in the medical history.

8.2.4. Left Ventricular Ejection Fraction

During the Screening Phase each participant will undergo a baseline LVEF assessment performed locally by cardiac echocardiogram or MUGA scan to demonstrate eligibility (ie, an LVEF within the normal range).

8.2.5. Pregnancy Testing

For participants of childbearing potential, a negative serum pregnancy test is required at screening and within 72 hours before the first dose of study treatment. A serum or urine pregnancy test is required within 72 hours before the first dose of each subsequent treatment cycle, at the End of Treatment Visit, and monthly for 6 months after the last dose for participants in Arms A/A2 and Arms C/C2. Additional serum or urine pregnancy tests may be performed as determined necessary by the investigator, or as required by local regulation, to establish the absence of pregnancy at any time during participation in the study.

8.2.6. Ophthalmologic Assessment

An ophthalmologic assessment, including slit lamp examination, fundoscopic examination, and visual acuity test will be performed at screening and should be repeated if a participant experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs, especially of anterior eye, should be performed to record any clinically significant findings. These photographs should be available for review by the Medical Monitor if necessary. Ophthalmology examination results should be recorded in the eCRF.

8.2.7. ECOG Performance Status

ECOG performance status (refer to Appendix 7: Eastern Cooperative Oncology Group (ECOG) Performance Status) will be assessed at timepoints described in the Schedule of Activities (Table 1).

8.2.8. Clinical Safety Laboratory Assessments

Clinical laboratory assessments will be performed locally. Blood samples for serum chemistry, hematology, coagulation, and a urine sample for urinalysis as noted in Appendix 9: Clinical Laboratory Tests will be collected at the times listed in the Schedule of Activities. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event section of the eCRF. The laboratory reports must be filed with the source documents. At the start of each new cycle, the investigator must confirm that participants meet treatment criteria.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies including AEs, SAEs, and product quality complaints (PQC) are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory

requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally designated representative). Further details on AEs, SAEs, and PQC can be found in Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until through 30 days after the last dose of study treatment or before starting subsequent anticancer treatment, whichever occurs first (or >30 days for an SAE, if considered related to study treatment).

Serious Adverse Events

All SAEs as well as PQC occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities.

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study, anticipated events will be periodically analyzed as specified in Appendix 4: Anticipated Events.

8.3.5. Pregnancy

All initial reports of pregnancy in participants or their partners (through sperm of participant/from sexual intercourse) must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study treatment.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

Expected progression of disease, which is part of the natural course of the disease under study, should not be considered or reported as an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than being expected from the underlying disease, the treatment-invoked progression (ie, the -treatment invoked signs/symptoms

of such progression) should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Death or hospitalization that is attributed by the Investigator to progression of disease should not be considered nor reported as an AE (or SAE). Of note, worsening of disease (and associated hospitalization or death) determined by the investigator to be caused by the study treatment should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Appendix 3).

However, if determined by the investigator to be more likely related to the study treatment than being expected from the underlying disease, the treatment-invoked death due to progression should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Progression of disease and death due to disease progression should be documented on the appropriate eCRF forms (eg, the Disease Progression form and the Death form). Signs or symptoms of disease progression that are of clinical significance, such as spinal cord compression, vena cava superior syndrome, major vessel rupture, efflux obstruction or organ failure should be documented on the appropriate eCRF forms (eg, the Symptomatic Progression form).

8.3.7. Adverse Events of Special Interest

AEs of special interest are pneumonitis/ILD, rash, IRR and VTE events. Additional information will be collected for these events. Refer to the monitoring and management guidelines for these events in Section 6.5.3. Confirmed cases of pneumonitis/ILD (regardless of grade) should be reported as SAEs (see Section 8.3.1). All Grade 3 or 4 IRRs should be reported within 24 hours to the Medical Monitor. Events of rash and VTE should follow standard reporting guidelines.

8.4. Pharmacokinetics

Serum samples will be used to evaluate the PK of amivantamab, and plasma samples will be used to evaluate the PK of lazertinib. Serum or plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.4.1. Evaluations

Serum samples will be collected from participants in Arms A/A2 and Arms C/C2 for PK and immunogenicity assessments of amivantamab at the time points outlined in Table 2. Plasma samples will be collected from participants in Arm A LACP for the evaluation of PK of lazertinib at the time points outlined in Table 2 (For participants receiving the LACP dosing schedule this would start on Cycle 1 Day 1) and for participants receiving the ACP-L dosing schedule (those in

Arms A/A2) evaluation of PK of lazertinib will be collected at the time points outlined in Table 3 (For those receiving the ACP-L dosing schedule this would start when lazertinib is initiated on Cycle 5 Day 1 or sooner if carboplatin discontinued earlier than Cycle 4). The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Refer to the Laboratory Manual for sample collection requirements. Blood collected for PK may additionally be used to identify circulating metabolites and/or evaluate safety or efficacy aspects that address concerns arising during or after the study period.

8.4.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of amivantamab using a validated, specific, and sensitive electrochemiluminescence-based immunoassay (ECLIA) method by or under the supervision of the sponsor.

Plasma samples will be analyzed to determine concentrations of lazertinib using a validated liquid chromatography-tandem mass spectrometry method.

If required, some plasma and serum samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma and serum PK samples may be stored for future analysis of other co-administered treatments, protein binding, and the metabolite profile.

8.4.3. Pharmacokinetic Parameters and Evaluations

Pharmacokinetic analysis of serum/plasma concentration data for amivantamab and lazertinib will be performed. Serum (amivantamab) and plasma (lazertinib) concentrations and PK parameters will be listed and summarized by sampling interval. The concentration-time data from this study may be analyzed using a population PK approach. PK parameters derived using population PK analysis may be used to assess the relationship between PK or immunogenicity and selected safety and efficacy endpoints.

8.5. Biomarkers

Blood Samples

Mandatory screening blood samples collected from all participants will undergo ctDNA analysis by the sponsor to evaluate pre-treatment mutational status of EGFR, MET, and other key oncogenes to characterize the tumor. Additional blood samples will be collected during the study and may be evaluated for ctDNA to assess changes in the levels or types of genetic alterations observed over time, and to monitor for the emergence of potential markers of resistance to the study therapy.

Blood samples will also be collected at time points specified in the Schedule of Activities for potential analysis of circulating biomarkers (eg, cytokines, growth factors) in samples taken prior to and after exposure to study treatment(s). Changes in circulating markers may be assessed in pre- and post-treatment samples and levels correlated with response to study treatments.

Additional biomarkers (eg, DNA, RNA, and protein) relevant to cancer and/or metabolism of study treatments may also be assessed in blood and tissue samples collected during the study to better understand the disease and mechanisms of response or resistance to study therapy.

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.

Additional Collections

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded tumor sample for the successful completion of the protocol- specified analyses, the sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study treatment(s) or diseases being investigated.

8.6. Immunogenicity Assessments

Serum samples will be collected for immunogenicity assessments of amivantamab (anti-drug antibodies to amivantamab) from participants in Arms A/A2 and Arms C/C2 at the time points outlined in Table 2. Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. The detection and characterization of antibodies to amivantamab will be performed using a validated immunoassay by or under the supervision of the sponsor. All serum samples collected for detection of antibodies to amivantamab will also be evaluated for amivantamab serum concentration to enable interpretation of the immunogenicity data. Immunogenicity assessment may also be performed on any PK sample. Serum samples will be screened for antibodies binding to amivantamab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to amivantamab and/or further characterize the immunogenicity of amivantamab.

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Analytical Procedures

The detection and characterization of antibodies to amivantamab will be performed using a validated immunoassay assay method by or under the supervision of the sponsor. Antibodies may

be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment(s).

8.7. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below the main study, unless otherwise specified. A general description of analysis of data from the extension cohort will be in Appendix 13: Open-label Randomized Extension Cohort. Specific details will be provided in the Statistical Analysis Plan for both the main study and the extension cohort.

9.1. Statistical Hypotheses

This study has dual primary hypotheses to be tested in participants with osimertinib-relapsed EGFR-mutated locally advanced or metastatic NSCLC:

- LACP/ACP-L will demonstrate superior progression-free survival (PFS) compared with CP
- ACP will demonstrate superior progression-free survival (PFS) compared with CP

The secondary hypotheses are that LACP/ACP-L and ACP, compared with CP independently in the aforementioned population, will demonstrate superior ORR and overall survival.

There is no separate hypothesis for the extension cohort.

9.1.1. Multiplicity

Multiplicity due to multiple hypotheses of interest and multiple analyses will be addressed using a graphical approach applied in a group sequential design setting as described by Maurer (2013). A primary analysis for PFS and key secondary endpoints (ie, ORR and OS) is planned in the study. In addition, OS will be analyzed at 2 additional timepoints, at 75% information fraction of OS and final OS analysis. Additional sensitivity analyses of PFS by dosing schedule will be performed.

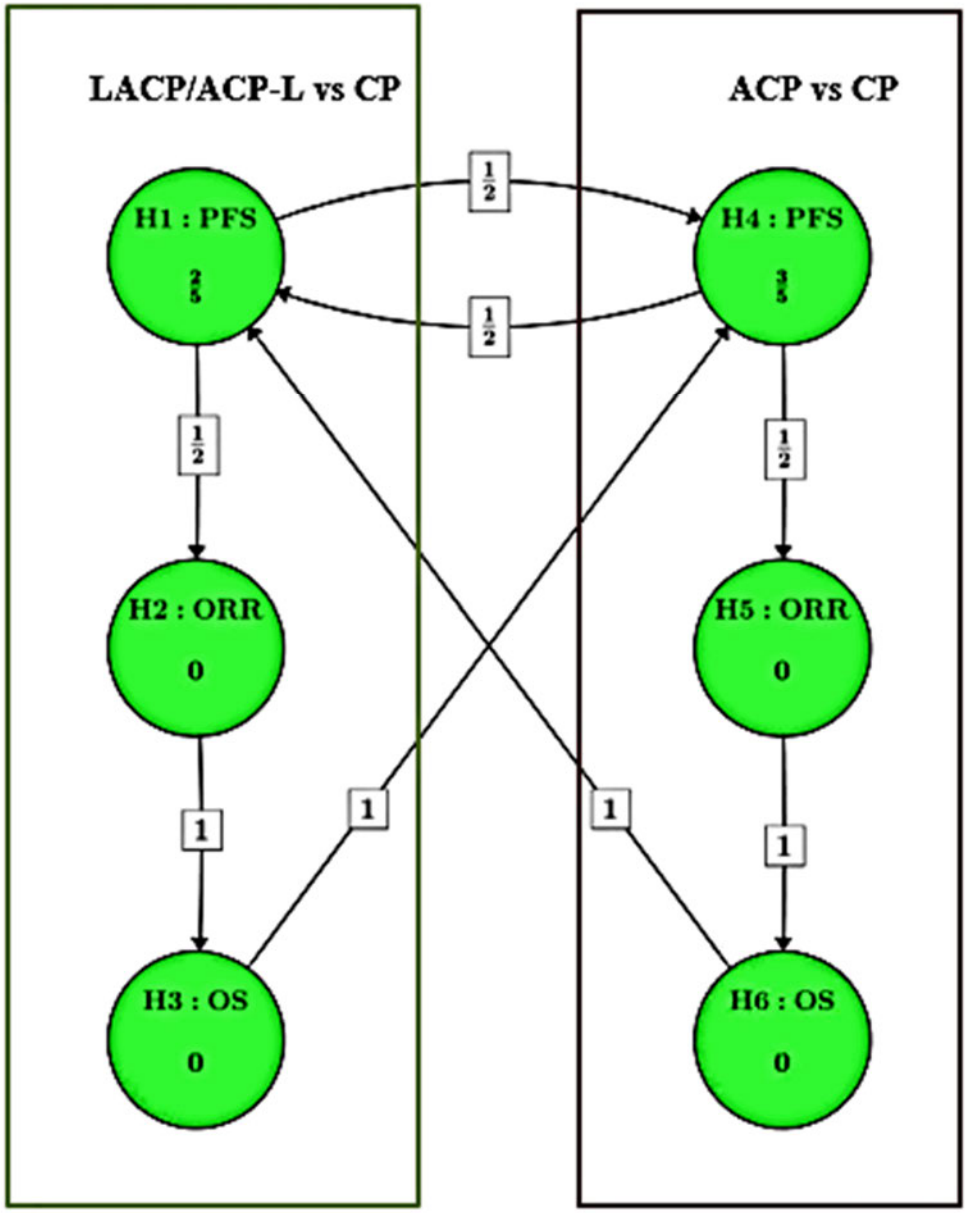
The proposed graphical testing strategy controlling an overall family-wise Type I error rate at the two-sided significance level of 0.05 is presented by Figure 4. The 6 elementary hypotheses are grouped into the 2 families of F1 = {H1: PFS, H2: ORR, H3: OS} and F2 = {H4: PFS, H5: ORR, H6: OS} for the comparison of LACP/ACP-L vs CP and ACP vs CP, respectively. A sequential (hierarchical) testing approach is utilized within each family starting with PFS, followed by ORR, and OS.

Figure 4 schematically shows the distribution of initial amount of alpha (local significance level) allocated to the 6 hypotheses; the local significance levels are represented as numerical values within the circular nodes corresponding to each hypothesis of interest. Particularly H1 and H4 have

the initial assigned local alpha of $\frac{2}{5}\alpha$ and $\frac{3}{5}\alpha$, respectively. The local significance levels are re-allocated after each hypothesis is rejected per the algorithm described (Maurer 2013) according to the directed edges with the associated weights, and the weights are represented as numerical values within the squares. For example, after the primary endpoint (H1:PFS) rejection, the local significance level associated with H1:PFS is split between the corresponding 2 hypotheses, the half of $\frac{2}{5}\alpha$ is passed to test the next hypothesis of interest in the same family (H2:ORR) and the half of $\frac{2}{5}\alpha$ is allocated to test the primary endpoint in the other family (H4:PFS).

The O'Brien Fleming alpha spending function as implemented by the Lan-DeMets method will be used to determine the statistical boundary for each of the interim analyses of OS.

Figure 4: Graphical Testing Strategy Controlling an Overall Family-wise Type I Error Rate



ACP-L=amivantamab, carboplatin, pemetrexed, and lazertinib (lazertinib started after carboplatin is completed); ACP= amivantamab, carboplatin, and pemetrexed combination therapy; CP=carboplatin and pemetrexed; LACP=lazertinib, amivantamab, carboplatin, and pemetrexed (all drugs started C1D1); PFS=progression-free survival; OS=overall survival; ORR=objective response rate.

9.2. Sample Size Determination

A total of approximately 600 eligible participants will be randomized in a 2:2:1 ratio (Arm A: Arm B: Arm C) in the study. The median PFS for CP is estimated to be 5.5 months (Mok 2017; Soria 2015). Assuming a median PFS of 8.5 months for LACP/ACP-L and ACP, respectively, with an approximate 16-month accrual period and an additional 3-month follow-up, a total of 350

PFS events in all 3 arms combined will provide approximately 93% power for LACP/ACP-L over CP, and 83% power for ACP over CP to detect a 35% reduction in the risk of either progression or death, (HR of 0.65 for LACP/ACP-L vs CP and ACP vs CP, respectively) with a log-rank test, assuming an overall family-wise Type I error rate at two-sided significance level of 5%.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined for the main study:

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.

Participants enrolled in the extension cohort (Arms A2 and C2) are not considered part of the Full Analysis Set or Safety population in the main study.

9.4. Statistical Analyses

The Statistical Analysis Plan will be finalized prior to database lock for the primary analysis and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Continuous variables will be summarized using number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Discrete variables will be summarized with frequency counts and percentages. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

Hypothesis testing of the primary efficacy endpoints and key secondary efficacy endpoints will be performed for LACP/ACP-L (Arm A) versus CP (Arm B) and ACP (Arm C) versus CP (Arm B), respectively. Comparison of LACP/ACP-L (Arm A) with ACP (Arm C) will be performed to describe the contribution of lazertinib based on intracranial PFS, ORR, DoR, and PFS, using summary statistics and nominal p-values; there will be no formal hypothesis testing for this comparison.

9.4.2. Primary Endpoint

The primary efficacy endpoint of PFS is defined as the time from randomization until the date of objective disease progression or death, whichever comes first, based on BICR using RECIST v1.1.

Participants who have not progressed or have not died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment.

The primary estimand for PFS, the main clinical quantity of interest to be estimated, is defined by the following components:

- **Study treatment**:

Experimental: LACP/ACP-L and ACP

Control: CP

- **Population**: participants with osimertinib-relapsed EGFR-mutated locally advanced or metastatic NSCLC
- **Variable**: time to event, PFS
- **Population-level summary**: hazard ratio for LACP/ACP-L vs CP and ACP vs CP
- **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

Primary analysis of PFS will be conducted when 350 PFS events in all 3 arms combined have been observed. PFS will be analyzed in the Full Analysis Set using the log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes vs no), and Asian race (yes vs no). The HR for PFS will be calculated, along with its 95% CI, from a stratified Cox model using the same stratification factors as for the log-rank test. The Kaplan--Meier method will be used to estimate the distribution of PFS by treatment group. Additional sensitivity analyses of PFS by dosing schedule will be performed, details will be described in the Statistical Analysis Plan.

9.4.3. Secondary Endpoints

Secondary endpoints will be analyzed using the Full Analysis Set. Additional analyses by dosing schedule on the secondary endpoints listed below will be performed, details will be described in the Statistical Analysis Plan.

Objective Response Rate (ORR)

The key secondary endpoint of overall response is defined as those participants who achieve either a PR or CR as their best response, 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. 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.

The primary estimand for ORR, the main clinical quantity of interest to be estimated, is defined by the following components:

- **Study treatment**:

Experimental: LACP/ACP-L and ACP

Control: CP

- **Population**: participants with osimertinib-relapsed EGFR-mutated locally advanced or metastatic NSCLC
- **Variable**: overall response
- **Population-level summary**: odds ratio for LACP/ACP-L vs CP and ACP vs CP
- **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	**Hypothetical strategy**: use best overall response until subsequent anti-cancer therapy

ORR will be analyzed using a logistic regression stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes vs no), and Asian race (yes vs no). The results of the analysis will be presented in terms of an odds ratio together with its associated 95% CI and corresponding p-value.

Overall Survival (OS)

The key secondary endpoint of 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.

The primary estimand for OS, the main clinical quantity of interest to be estimated, is defined by the following components:

- **Study treatment**:

Experimental: LACP/ACP-L and ACP

Control: CP

- **Population**: participants with osimertinib-relapsed EGFR-mutated locally advanced or metastatic NSCLC
- **Variable**: OS
- **Population-level summary**: hazard ratio for LACP/ACP-L vs CP and ACP vs CP
- **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

OS will be analyzed using the same methodology and model as for the analysis of PFS.

Two interim analyses of OS will be performed (see Section 9.5). The final analysis of OS will be conducted at the end of study. The O'Brien Fleming alpha spending function as implemented by the Lan-DeMets method will be used to determine the statistical boundary for each of the interim analyses of OS.

Duration of Response (DoR)

The 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 participants 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 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. A Kaplan–Meier plot for duration of response and median duration of response with 95% CI (calculated from the Kaplan–Meier estimate) will be presented by treatment group.

Time to Subsequent Therapy (TTST)

The 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. The TTST will be analyzed using the similar method as the primary analysis of PFS.

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

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. 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 (ie, last disease assessment). PFS2 will be analyzed using the similar method as the primary analysis of PFS.

Time to Symptomatic Progression (TTSP)

The 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 or death. 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. The TTSP will be analyzed using the similar method as the primary analysis of PFS.

Intracranial Progression-Free Survival

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

Intracranial Objective Response Rate (ORR)

Intracranial ORR is defined as the proportion of participants who achieve either an intracranial complete response (CR) or partial response (PR), as defined by BICR using RECIST v1.1. Data obtained up until intracranial progression or last intracranial evaluable 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 subsequent 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. Intracranial ORR will be analyzed using the similar method as the primary analysis of ORR for subjects with baseline intracranial disease by BICR.

Intracranial Duration of Response (DoR)

Intracranial DoR is defined as the time from the date of first documented intracranial response (PR or CR) until the date of documented intracranial progression or death, whichever comes first, for participants who have intracranial CR or PR. The end of response should coincide with the date of intracranial progression or death from any cause used for the intracranial PFS endpoint. If a participant does not progress following an intracranial 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. Intracranial DoR will be analyzed using the similar method as the primary analysis of DoR.

Time to Intracranial Disease Progression

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

9.4.4. Exploratory Endpoints

Analyses of exploratory endpoints will be described in the Statistical Analysis Plan.

9.4.5. Safety Analyses

All safety analyses will use the Safety Population. Additional safety analyses by dosing schedule will be performed, details will be described in the Statistical Analysis Plan.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs 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. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue treatment due to an AE, or who experience a ≥Grade 3 AE or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Parameters with predefined NCI CTCAE toxicity grades will be summarized. Change from baseline to the worst AE grade experienced by the participant during the study will be provided as shift tables.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values (the predose ECG will be used as baseline).

Electrocardiogram data will be summarized by ECG parameter. 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).

Vital Signs

Vital signs including weight, temperature, pulse/heart rate, respiratory rate, oxygen saturation, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics

and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

9.4.6. Other Analyses

Pharmacokinetic Analyses

The PK analyses will use the PK Population (Section 9.3). For participants randomized to Arms A/A2 and Arms C/C2, all plasma/serum concentrations (when applicable) below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or Statistical Analysis Software (SAS) dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All participants and samples excluded from the analysis will be clearly documented in the CSR.

Individual PK parameters will be estimated by inspection of the concentration-time profiles. Based on the individual plasma or serum concentration-time data, using the actual sampling times, the following PK parameters of amivantamab will be determined.

- C_{max}: maximum plasma/end of infusion (EOI) serum concentration
- $C_{max,ss}$: maximum plasma/EOI serum concentration at steady state
- t_{max}: time to reach the maximum plasma concentration
- $t_{max,ss}$: time to reach the maximum plasma concentration at steady state
- C_{trough}: plasma/serum concentration immediately prior the next study treatment administration
- $C_{trough,ss}$: plasma/serum concentration immediately prior the next study treatment administration at steady state

The PK data collected from this study may also be combined with similar data from other studies to perform population PK. 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.

Biomarkers Analyses

Biomarkers analyses will use the Biomarkers Population (Section 9.3). Each baseline tumor status will be evaluated by ctDNA NGS analysis, for exploratory purposes, to characterize potential mechanisms of resistance to LACP/ACP-L, as permitted by local regulations.

Assessment of additional genes or biomarkers (DNA, RNA, or protein) relevant to lung or other cancers and assessment of the mechanism of action or metabolism of study treatments may also be performed in blood and tissue samples collected on study to better understand mechanisms of response or resistance to study treatments. Alterations in blood characteristics may be evaluated for correlation with response to study treatments, tumor burden, and disease progression as data warrant.

Immunogenicity Analyses

The incidence of anti-amivantamab antibodies will be summarized for all participants in the PK Population (Section 9.3). 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.

Pharmacokinetic/Pharmacodynamic Analyses

The exposure-response relationship between amivantamab and lazertinib measures of exposure (eg, derived AUC or trough concentrations) and key efficacy (eg, PFS and OS) and safety parameters (eg, skin rash), will be explored graphically, as data allow. In addition, the relationship may be characterized using an exposure-response or logistic regression model. Exposure-response analysis with relevant PROs may also be explored as data permit. Details will be provided in an analysis plan and detailed results may be reported separately from the CSR.

Patient-Reported Outcomes Analyses

NSCLC-SAQ and PROMIS-PF will be summarized descriptively by treatment group and study visit. It is hypothesized that mean change from baseline will demonstrate proximal symptom and physical functioning stability compared to the effect of the active comparator. PGIS is an numeric rating anchor in the NSCLC-SAQ for clinical meaningful change. Time to worsening in EORTC-QLQ-C30 total score and individual scales will be analyzed using a Kaplan–Meier method and stratified Cox proportional-hazards model. Additional analysis may be done, if appropriate. Analysis details will be provided in the Statistical Analysis Plan.

9.5. Interim Analysis

There is no interim analysis planned for PFS.

For both LACP/ACP-L vs CP and ACP vs CP, two interim analyses are planned for OS. The first interim analysis for OS will be performed at the time of the analysis for PFS, when approximately 170 deaths (all 3 Arms combined, approximately 43% of the total planned OS events) are anticipated. The second interim analysis for OS will be performed approximately 32 months after the first participant is randomized, when approximately 300 deaths (all 3 arms combined, approximately 75% of the total planned OS events) are anticipated. Final analysis for OS will be conducted at approximately 48 months after the first participant is randomized, when approximately 400 deaths (all 3 arms combined) are anticipated.

Following the testing algorithm for multiple hypotheses using the graphical procedure as described in Section 9.1.1, OS will be tested in the FAS population at the two-sided alpha re-allocated from previous rejected hypotheses to the respective comparisons of LACP/ACP-L vs CP and ACP vs CP. The significance level at the interim analyses for OS will be determined based on the O'Brien Fleming alpha spending approach as implemented by the Lan-DeMets method.

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ACP-L	Amivantamab, carboplatin, pemetrexed, and lazertinib (lazertinib started after carboplatin is completed)
ADCC	antibody-dependent cellular cytotoxicity
ALT	alanine aminotransferase
anti-HCV	hepatitis C virus antibody
ART	antiretroviral therapy
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BCRP	breast cancer resistance protein
BICR	blinded independent central review
CHF	congestive heart failure
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum plasma/serum concentration
$C_{max,ss}$	maximum plasma/serum concentration at steady state
CNS	central nervous system
CR	complete response
CT	computerized tomography
ctDNA	circulating tumor deoxyribonucleic acid
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
ECLIA	electrochemiluminescence-based immunoassay
EGFR	epidermal growth factor receptor
EQ-5D-5L	EuroQol five-dimensional descriptive system (5-level version)
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HGF	hepatocyte growth factor
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormonal replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILD	interstitial lung disease
IMP	investigational medicinal product
INR	international normalized ratio
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
IWRS	interactive web response system

LACP	lazertinib, amivantamab, carboplatin, and pemetrexed (all drugs started C1D1)
LLN	lower limit of normal
LTE	long-term extension
LVEF	left ventricular ejection fraction
MET	mesenchymal-epithelial transition
MRI	magnetic resonance imaging
MRP4	multi-drug resistance protein 4
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NIMP	non-investigational medicinal product
NSCLC	non-small cell lung cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer – Symptom Assessment Questionnaire
NYHA	New York Heart Association
OLE	open-label extension
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PQC	product quality complaint
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
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAC	Safety Assessment Committee
SAP	statistical analysis plan
SAE	serious adverse event
SET	Safety Evaluation Team
SIPPM	Site Investigational Product and Procedures Manual
SPF	skin protection factor
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTSP	time to symptomatic progression
ULN	upper limit of normal
US	United States
VTE	venous thromboembolic

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

10.2.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-or territories specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a PCC may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, LTMs, CTMs, and/or CROs who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with IECs/IRBs per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

In situations where a departure from the protocol is unavoidable during the study, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territories, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study treatment to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study treatment
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants

- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country/Territory Selection

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.3.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.3.1.

10.2.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study. Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.2.3. Informed Consent Process

Each participant, or a legally designated representative, (unless prohibited by local regulations) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Informed consent may be obtained remotely by telephone or video conferencing where local policies and regulations permit.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants or their legally designated representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally designated representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant or legally designated representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the participant's or his or her legally designated representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

If the participant or legally designated representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant or legally designated representative is obtained.

When prior consent of the participant is not possible and the participant's legally designated representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well- being of the participant and to ensure compliance with applicable regulatory requirements. The participant or legally designated representative must be informed about the study as soon as possible and give consent to continue.

10.2.4. Recruitment Strategy

Enrollment is now complete; the last participant was randomized in the Extension cohort on 05 September 2023.

Refer to Recruitment and Informed Consent Procedure Template for details.

10.2.5. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant (or his or her legally designated representative, as permitted by local regulations) includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.2.6. Storage, Use, Transfer, and Retention of Data and Samples

Study samples will be coded or anonymized at all times in accordance with the informed consent and will not be labeled with personal identifiers.

Investigator and study site will only store, use, transfer and retain data and study samples, including optional study samples, in accordance with the informed consent and applicable law, and in accordance with any separate written agreement with sponsor. Other than what is specified in a separate written agreement with sponsor, study site and investigator shall not conduct or facilitate any research by a third party not required by the protocol (i) on participants if such research interferes with the conduct of the study or (ii) on samples collected from study participants during the study, including optional samples, if the research relates to amivantamab or lazertinib (iii) on data collected from study participants during the study if the research relates to amivantamab or lazertinib.

Sponsor may store, use, transfer or retain the data and study samples, including optional study samples, for uses not specified by the protocol, including compatible research, in compliance with the informed consent and applicable law.

10.2.7. Committees Structure

Independent Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis. This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter.

The first IDMC meeting will occur after the first 50 participants have been randomized and treated for at least 2 cycles. Thereafter, the committee will meet periodically to review interim data. After the review, the IDMC will make recommendations regarding the continuation of the study.

10.2.8. Use of Information and Publication

All information, including but not limited to information regarding amivantamab or lazertinib, supplied by the sponsor to study site or investigator and not previously published, and any data analysis generated as a result of this study, are considered confidential and remain the sole property of the sponsor. Study site and investigator shall not use this information except in the performance of this study and shall not disclose this information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use.

Study site and investigator shall not publish study results except as required by law or as specified in a separate, written agreement between the sponsor and the study site or the investigator.

The Sponsor will register the study and publish the study results in compliance with applicable law and may register the study or publish study results when not required.

Authorship of any peer-reviewed publications will be determined by mutual agreement in line with International Committee of Medical Journal Editors authorship guidelines.

In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the interim results of clinical studies as required by law.

For studies conducted in the EU under Regulation EU 536/2014 appropriate provisions for interim analyses should always be described in the protocol. Use one of the options below as appropriate. Other options might be considered in specific situations.

The summary of the results from the interim analysis 2 [second interim analysis for OS] as described in Section 9.5, may be submitted to the EU database within one year of the intermediate data analysis date.

The disclosure of the study results will be performed after the end of study.

10.2.9. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study. The sponsor may review the eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.2.10. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

10.2.11. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; treatment receipt/dispensing/return records; study treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that patient-reported outcomes (PROs) are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by trial participants into source records cannot be overridden by site staff or investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or another equivalent document).

The minimum source documentation requirements for Section 5.1 and Section 5.2 that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for

use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the eCRF.

10.2.12. Monitoring

The sponsor will use a combination of monitoring techniques: central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post- initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor may compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.2.13. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a

regulatory submission. The investigator should immediately notify the sponsor if the participant has been contacted by a regulatory agency concerning an upcoming inspection.

10.2.14. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. For trials performed under Regulation [EU] No. 536/2014, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.2.15. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

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

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

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

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

10.3. Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, for time of last AE recording).

Serious Adverse Event

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious. This also includes the situation when treatment-invoked signs and symptoms of disease progression are determined by the investigator to be more likely related to the study treatment than being expected from the underlying disease.

Note: Events that do not qualify as AEs cannot be reported as SAEs, even if seriousness conditions are met. This in particular is the case for events due to disease progression.

Expected signs or symptoms of disease progression should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study treatment and the event (eg, death from anaphylaxis), the event must be reported as a Suspected Unexpected Serious Adverse Reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For amivantamab or lazertinib, the expectedness of an AE will be determined by whether or not it is listed in the IB. For carboplatin or pemetrexed, the expectedness of an AE will be determined by whether or not it is listed in the local prescribing information.

10.3.2. Attribution Definitions

Assessment of Causality

The causal relationship to study treatment is determined by the Investigator and documented in the Medical Records.

The assessment of causality must consider the following factors:

- Temporal relationship
- Clinical characteristics of event
- Pharmacological plausibility
- Confounding risk factors:

  Concomitant medication

  Underlying/concurrent disease

  Family/social history
- Challenge:

  De-challenge: Did the reaction improve when the investigational product was withdrawn, in the absence of any other treatment?

  Re-challenge: What happens if participant is re-challenged with investigational product?
- Other considerations: Participant characteristics and past medical history, and quality of information

The following selection must be used to assess all AEs.

Related

There is a reasonable causal relationship between study treatment administration and the AE. Related events include those that are probably and possibly related events.

Not Related

There is not a reasonable causal relationship between study treatment administration and the AE. Not related events include those that are doubtfully related events.

10.3.3. Severity Criteria

Adverse event severity is a clinical determination of the intensity of an AE. The severity assessment for an AE or serious AE should be completed using the NCI-CTCAE, Version 5.0. Any AE or SAE not listed in the NCI-CTCAE, Version 5.0 will be graded according to the investigator clinical judgment by using the standard grades as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental activities of daily living[a]
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living[b]
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refers to bathing; dressing and undressing; feeding self; using the toilet; taking medications; and not bedridden.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.3.4. Special Reporting Situations

Safety events of interest on a sponsor study treatment in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study treatment
- Suspected abuse/misuse of a sponsor study treatment
- Accidental or occupational exposure to a sponsor study treatment

- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study treatment from breastfeeding

Participant-specific special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

10.3.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number

Serious Adverse Events

All SAEs that have not resolved by the end of SAE reporting period, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study treatment or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the treatment period.

10.3.6. Product Quality Complaint Handling

Definition

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.3.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.4. Appendix 4: Anticipated Events

An anticipated event is an AE (serious or nonserious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen. For the purposes of this study, the events in Table 19 will be considered anticipated events.

Table 19: Anticipated Events

Constitutional	**Cardiovascular**
Dehydration	Superior vena cava syndrome
Sepsis	Pericardial effusion
Weakness/asthenia	Cardiac tamponade (associated with pericardial metastasis)
Fatigue	Myocardial infarction
Fever/pyrexia	Stroke
Weight loss	
Failure to thrive	**Gastrointestinal**
Decreased appetite/anorexia	Dysphagia
General physical health deterioration	Esophageal obstruction
	Intestinal obstruction
Respiratory	Bleeding ulcers
Pneumonia	Diverticulitis
Upper respiratory infection	
Lower lung infection	**Musculoskeletal (associated with metastatic or advanced disease)**
Hypoxia	Pain
Dyspnea	Fracture (pathologic fracture)
Bronchitis	
Emphysema	**Hematologic**
Chronic obstructive pulmonary disease exacerbation	Thromboembolic events – deep vein thromboses, pulmonary emboli
	Anemia
Malignant pleural effusion	
Cough	**Neurologic (associated with metastatic or advanced disease)**
Empyema	Cranial nerve palsies
Pulmonary emboli	Weakness of upper, lower extremities
Respiratory failure	Confusion
Pneumothorax	Mental status changes
Hemoptysis	Seizures
Radiation pneumonitis	Unstable gait
	Spinal cord compression

Reporting of Anticipated Events

All AEs will be recorded in the eCRF, regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 8.3. Any anticipated event that meets serious criteria will be reported to the sponsor as described in Section 8.3. Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related will undergo expedited reporting (if appropriate) per applicable clinical trial legislation to Health Authorities and IRB/IECs (Note: Japan will not identify anticipated events for the Health Authorities). If an anticipated event is considered disease-related or not related to study drug the event will be exempt from expedited reporting.

To meet US regulatory clinical trial legislation, the sponsor will perform aggregate review of anticipated events as outlined below, and if determined to be drug-related will implement expedited reporting of these events to Health Authorities and IRBs/IECs.

Safety Assessment Committee (SAC)

A Safety Assessment Committee (SAC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The SAC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The SAC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study treatment based on a review of the aggregate data by arm.

The review of anticipated events was stopped after the database lock associated with the primary endpoint analysis of the study.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

10.5. Appendix 5: Contraceptive Guidance

Participants must follow contraceptive measures as outlined in Section 5.1. Pregnancy information will be collected and reported as noted in Section 8.3.5 and Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Participants of Childbearing Potential (POCBP)

A participant is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Participants Not of Childbearing Potential

- **Premenarchal:** state in which menarche has not yet occurred.
- **Postmenopausal:** defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in participants on HRT, the participants will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if they wish to continue HRT during the study.
- **Permanent absence of reproductive potential (for the purpose of this study):**
  - Has undergone a procedure that precludes reproductive potential.
  - Has a congenital abnormality that precludes reproductive potential.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal participant experiences menarche) or the risk of pregnancy changes (eg, a participant becomes sexually active where pregnancy can occur), a participant must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by participants should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Pregnancy During the Study

Participants who become pregnant during the study will be withdrawn from the study treatment and followed for safety.

Examples of Contraceptives

1. HIGHLY EFFECTIVE METHODS *(Failure rate of <1% per year when used consistently and correctly.)*

1.1. USER INDEPENDENT – Highly Effective Methods.

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner

(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the participant of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 74 days.)

1.2. USER DEPENDENT – Highly Effective Methods

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

oral

intravaginal

transdermal

injectable

- Progestogen-only hormone contraception associated with inhibition of ovulation

oral

injectable

- Sexual abstinence from intercourse where pregnancy could occur

(Sexual abstinence is considered a highly effective method only if defined as refraining from sexual intercourse where the possibility of pregnancy exists during the entire period of risk associated with exposure to the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

2. NOT HIGHLY EFFECTIVE METHODS *(Failure rate of >1% per year)*[a]

- **USER DEPENDENT and NOT considered to be (highly) effective methods.** Progestogen- only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
- Condom[b]

- Cap, diaphragm, or sponge with spermicide
- A combination of external condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[b]
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus-interruptus)
- Spermicides alone
- Lactational amenorrhea method (LAM)

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Multiple types of condoms should not be used together (due to risk of failure with friction).

10.6. Appendix 6: Liver Event Follow-Up Requirements

The following follow-up assessments should be conducted for any participant meeting liver chemistry stopping criteria:

- Monitor liver chemistries (ALT, AST, alkaline phosphatase, bilirubin [including bilirubin fractions], and INR), creatinine phosphokinase, and lactate dehydrogenase, 1 to 2 times per week until resolution, stabilization, or return to participant's baseline values
- Monitor clinical condition closely
- In Arms A and C, draw blood samples for unscheduled PK analysis at timepoints when liver chemistry is assessed
- Record use of concomitant medications, acetaminophen, herbal remedies, other over- the- counter medications, or known hepatotoxins
- Record alcohol use in the eCRF
- Check the viral hepatitis serology as appropriate and include:

Hepatitis A IgM antibody

Hepatitis B surface antigen and Hepatitis B core antibody (IgM)

Hepatitis C RNA

Hepatitis E IgM antibody

Cytomegalovirus IgM antibody

Epstein-Barr viral capsid antigen IgM antibody (or equivalent test)

- Assess anti-nuclear antibody, anti-smooth muscle antibody, and type 1 anti-liver kidney microsomal antibodies
- Conduct liver imaging (ultrasound, MRI, or CT) to evaluate liver disease
- Refer to a specialist as appropriate

Rechallenge Criteria

Resumption of study treatment(s) may be considered if all the following criteria are met:

- Hy's Law has been excluded
- A reversible underlying cause not associated with study treatment(s) (eg, alcohol use or concomitant medication) is clearly identified and agreed upon in consultation with the Medical Monitor.
- Liver chemistry abnormalities have resolved, or values have returned to baseline.

10.7. Appendix 7: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken 1982.

10.8. Appendix 8: New York Heart Association Criteria

The following table presents the NYHA classification of cardiac disease:

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

10.9. Appendix 9: Clinical Laboratory Tests

The following tests will be performed by the local laboratory according to the Schedule of Activities during the study. Table 20 specifies the tests performed during the OLE Phase:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Hemoglobin Platelet count Mean corpuscular volume (MCV)	Absolute neutrophil count White blood cell (WBC) count with differential
Clinical Chemistry	**At Each Assessment (Including Screening)** Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyl transferase (GGT) Alkaline phosphatase Total bilirubin Lactic acid dehydrogenase (LDH) Magnesium Potassium Calcium Sodium Creatinine[a] Albumin	**Additional Tests at Screening only** Total protein Blood urea nitrogen (BUN) Blood glucose
Urinalysis[b] (Dipstick)	Specific gravity pH Glucose Protein Blood	Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase
Coagulation	Prothrombin time (PT)	Activated partial thromboplastin time (APTT) International normalized ratio (INR)
Serology	• Anti-HIV antibody • Hepatitis B surface antigen (HbsAg), hepatitis B surface antibody (HbsAb), and hepatitis B core antibody (HbcAb) (participants with a history of hepatitis B virus [HBV] are also required to have HBV DNA quantification) • Anti-hepatitis C virus (HCV) antibody (participants with a history of HCV are also required to have HCV RNA quantification.)	

a. Creatinine clearance, calculated using the Cockcroft-Gault formula, will be recorded in the eCRF.
b. If urinalysis reveals bacteria and leukocytes (positive nitrite, leukocyte esterase) or an infection is otherwise suspected, a urine culture must be done to rule out a urinary tract infection prior to randomization.

10.10. Appendix 10: Cockcroft-Gault Formula for Estimated Creatinine Clearance

Cockcroft-Gault Formula for Estimated Creatinine Clearance for Adults

$$eCrCl = \frac{(140\text{-Age}) \times \text{Mass (Kilograms)} \times [0.85 \text{ if female}]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

OR

$$eCrCl = \frac{(140\text{-Age}) \times \text{Mass (Kilograms)} \times \text{Constant}}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where Constant = 1.23 for men and 1.04 for women

Reference: http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation/

10.11. Appendix 11: Medications With Potential for QT Interval Prolongation

Although lazertinib and amivantamab have not shown liability for QT prolongation, the following drugs are known to or may possibly prolong QT interval or induce Torsades de Pointes and should be used with caution for any participant in this study. This list is not meant to be exhaustive, and similar restrictions should be applied to other drugs known to prolong QT interval or induce Torsades de Pointes. Appropriate medical judgment is required.

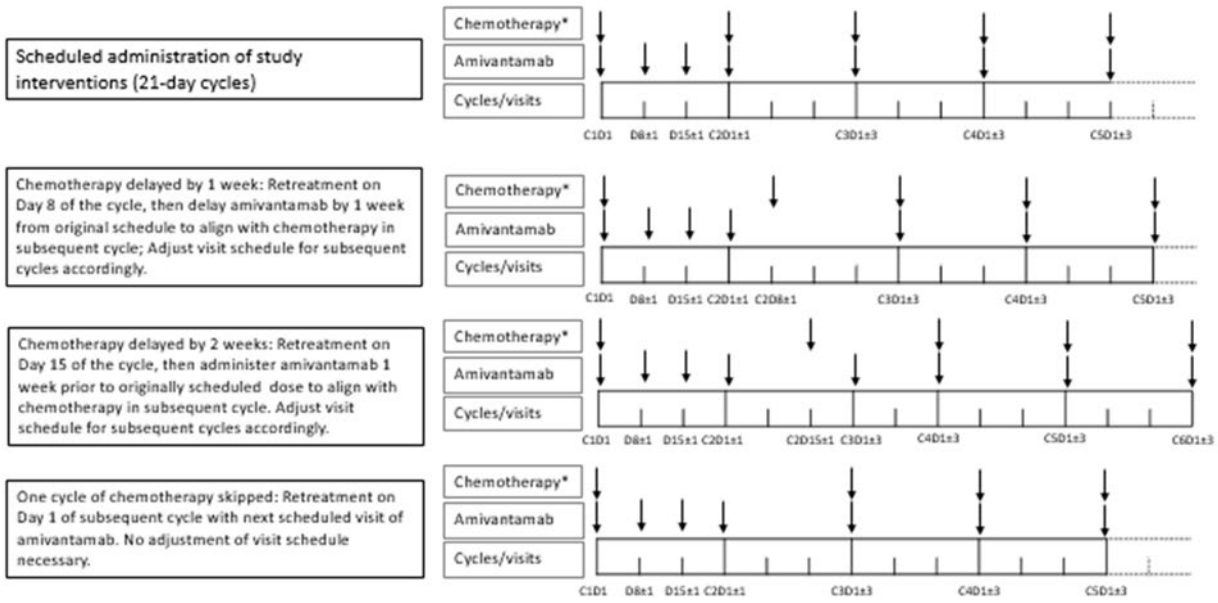
Medications known to prolong QT interval or induce Torsades de Pointes
anagrelide, ciprofloxacin, clarithromycin, cocaine (only medical use), domperidone, droperidol, erythromycin, ibutilide, levofloxacin, ondansetron, papaverine HCl (intra- coronary), procainamide, quinidine, sulpiride, sultopride, terlipressin, thioridazine
chlorpromazine, cilostazol, disopyramide, dofetilide, dronedarone, ibogaine, levosulpiride, moxifloxacin, sotalol
citalopram, escitalopram, flecainide, fluconazole, levomepromazine (ethotrimeprazine), roxithromycin, sevoflurane
methadone, pimozide, terodiline
azithromycin, donepezil, propofol
halofantrine, pentamidine
Haloperidol
amiodarone, chloroquine

Medications that may prolong QT interval or induce Torsades de pointes

apomorphine, benperidol, clotiapine, dexmedetomidine, dolasetron, eliglustat, encorafenib, gemifloxacin, granisetron, hydrocodone-ER, isradipine, melperone, nicardipine, ofloxacin, oxytocin, perflutren lipid microspheres, pilsicainide, primaquine phosphate, prothipendyl, risperidone, saquinavir, telavancin, tetrabenazine, tiapride, tolterodine, tramadol, tropisetron, vardenafil
alfuzosin, clozapine, cyamemazine (cyamepromazine), deutetrabenazine, dextromethorphan/quinidine, ezogabine (retigabine), lacidipine, lopinavir/ritonavir, mifepristone, moexipril/HCTZ, pasireotide, perphenazine, promethazine, telithromycin, venlafaxine
asenapine, atomoxetine, betrixaban, felbamate, imipramine (melipramine), ketanserin, nortriptyline, paliperidone, pipamperone, trimipramine, valbenazine, zotepine, zuclopenthixol (oral)
buprenorphine, delamanid, desipramine, iloperidone, lithium, maprotiline, mirabegron, mirtazapine, palonosetron, rilpivirine, tacrolimus, tizanidine
aripiprazole, clomipramine, efavirenz, memantine
artemether/lumefantrine, sertindole
fingolimod, flupentixol, pimavanserin
zuclopenthixol (IM injection)
artenimol/piperaquine
Clofazimine
Nusinersen
Bedaquiline

10.12. Appendix 12: Dosing Synchronization for Arms A/A2 and C/C2

The examples below use Cycles 1-5 for explanatory purposes, but the principles apply to any cycles.



*Chemotherapy refers to carboplatin + pemetrexed or pemetrexed alone, depending on cycle.

10.13. Appendix 13: Open-label Randomized Extension Cohort

10.13.1. Synopsis

Following the 04 November 2022 safety data review for MARIPOSA-2, the IDMC recommended modification of Arm A to withhold lazertinib during administration of carboplatin due to an apparent imbalance in AEs affecting Arm A. The lazertinib dosing schedule for participants randomized to Arm A was thus modified in Amendment 5 of the protocol, such that new participants randomized to Arm A began treatment with amivantamab, carboplatin, and pemetrexed, and only started lazertinib after treatment with carboplatin treatment was complete. This dosing schedule is referred to as ACP-L throughout the protocol.

To further describe the safety and efficacy of the ACP-L dosing schedule versus ACP with additional data, the Sponsor is adding a separate open-label randomized extension cohort to the study. Enrollment of participants into the extension cohort may begin after enrollment into the main study is complete and when the Sponsor opens the extension cohort for enrollment. The extension cohort will have the same eligibility criteria, study procedures and operate within the same investigational sites as the main study.

The statistical considerations and the primary analyses for the main study are described in Section 9. Participants from the extension cohort (those randomized to Arms A2 and C2) will not be included in the primary analysis of the study. The analysis plan for the extension cohort is described in Section 10.13.9 and further details are provided in a separate Statistical Analysis Plan.

10.13.2. Background and Rationale

At the 04 November 2022 safety data review for MARIPOSA-2, the IDMC observed an imbalance in the incidence of SAEs, related SAEs, and Grade 4 AEs for participants receiving the combination of lazertinib, amivantamab, carboplatin, and pemetrexed (LACP) in Arm A, where the vast majority of these events occurred during the first 4 cycles, when participants are being treated with carboplatin in addition to lazertinib, amivantamab, and pemetrexed. The majority of these adverse events were toxicities typically associated with the use of chemotherapy: hematologic toxicities (eg, neutropenia, thrombocytopenia), opportunistic infections due to immunosuppression from chemotherapy, and GI toxicities (eg, nausea and stomatitis). These AE incidences led to a higher than expected rate of dose reduction and dose interruption of standard of care chemotherapy on Arm A. The reduced exposure to standard of care chemotherapy raised concerns to the IDMC that the efficacy could be compromised, but notably, efficacy data was not the part of this review for the IDMC. The IDMC recommended modification of Arm A to withhold lazertinib during the administration of carboplatin.

The lazertinib dosing schedule for participants randomized to Arm A was thus modified in Amendment 5 of the protocol such that new participants randomized to Arm A began treatment with amivantamab, carboplatin, and pemetrexed, and only started lazertinib after treatment with carboplatin was complete. This dosing schedule is referred to as ACP-L throughout the protocol. The addition of lazertinib on Cycle 5 Day 1 (or sooner if carboplatin is discontinued earlier than

Cycle 4) is hypothesized to provide CNS protection while minimizing potential adverse events, therefore providing favorable benefit-risk.

The extension cohort of Study 61186372NSC3002 is designed to generate data to further describe the safety and efficacy of the ACP-L dosing schedule versus ACP with additional data.

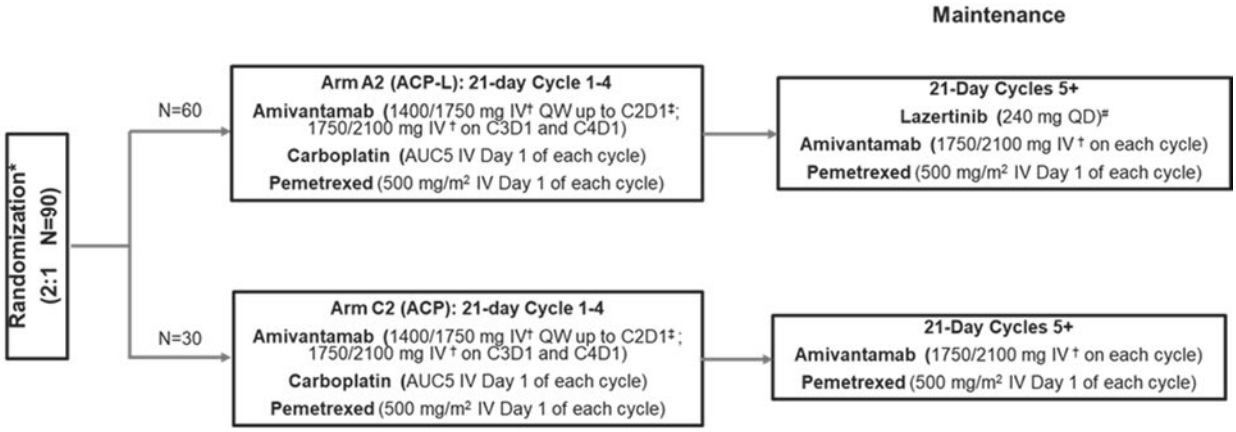
10.13.3. Objectives and Endpoints

The primary objectives of the extension cohort are to further describe the safety and efficacy of the ACP-L dosing schedule versus ACP with additional data. See Section 10.13.9 below for a general description of planned analyses; full details are in the Statistical Analysis Plan.

10.13.4. Study Design

Approximately 90 eligible participants will be randomly assigned to receive ACP-L or ACP in a 2:1 ratio (Arms A2:C2, see Figure 5) in the extension cohort of Study 61186372NSC3002. Stratification methods and study procedures for the extension cohort of Study 61186372NSC3002 are largely the same as those for the main study. Procedures specific to the extension cohort are outlined below; otherwise, procedures should be followed per Table 1 of the protocol.

Figure 5: Schematic Overview of the extension cohort



ACP-L=amivantamab, carboplatin, pemetrexed, and lazertinib (lazertinib started after carboplatin treatment is completed); AUC=area under the concentration-time curve; C#D#=Cycle # Day #; IV=intravenously; QD=once daily; QW=once weekly.

* Stratification factors: osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes vs no), Asian race (yes vs no)

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

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

\# Lazertinib for participants in Arm A2 may start sooner if carboplatin is discontinued earlier than Cycle 4.

10.13.5. Study Population: See Section 5 of the Protocol

The prescreening, inclusion, and exclusion criteria for the extension cohort are the same as for the main study.

10.13.6. Study Treatment and Concomitant Therapy: See Section 6 of the Protocol

Enrollment into the extension cohort will be undertaken only following full approval of Protocol Amendment 6 from the Health Authorities and IEC/IRB (as applicable) at a site, completion of enrollment into the main study, and when the sponsor opens the extension cohort for enrollment. Dosing is as follows:

Arm A2 (ACP-L):

- Lazertinib 240 mg orally, once daily starting Cycle 5 Day 1 or sooner if carboplatin is discontinued earlier
- Amivantamab by IV infusion in 21-day cycles:
  - 1,400 mg (1,750 mg if body weight ≥80 kg) on Cycle 1 Days 1/2, 8, and 15, and Cycle 2 Day 1
  - 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3
- Carboplatin AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles
- Pemetrexed 500 mg/m^2 on Day 1 of each 21-d-ay cycle, with carboplatin for up to 4 cycles, and then as maintenance until disease progression

Arm C2 (ACP):

- Amivantamab by IV infusion in 21-day cycles:
  - 1,400 mg (1,750 mg if body weight ≥80 kg) on Cycle 1 Days 1/2, 8, and 15, and Cycle 2 Day 1
  - 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3
- Carboplatin AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles
- Pemetrexed 500 mg/m^2 on Day 1 of each 21-day cycle, with carboplatin for up to 4 cycles, and then as maintenance until disease progression

Dose modification (including dose reduction, dose interruption, and drug discontinuation) procedures for the extension cohort are the same as those for participants receiving the relevant regimen in the main study (See Section 6.5 of the protocol).

10.13.7. Discontinuation of Study Treatment and Participant Discontinuation/Withdrawal: See Section 7 of the Protocol

Procedures related to discontinuation of study treatment and participant discontinuation/withdrawal for the extension cohort are the same as those for the main study.

10.13.8. Study Assessments and Procedures: See Section 8 of the Protocol

All study assessments and procedures for the extension cohort are the same as those for the main study, except that participants in the extension cohort will be randomized in a 2:1 ratio between Arms A2 and C2.

10.13.9. Statistical Considerations and Analyses

The primary objectives of the extension cohort are to further describe the safety and efficacy for the ACP-L dosing schedule versus ACP with additional data. Primary analysis of the extension cohort will evaluate the safety data using the same methods specified in Section 9 of the main study. Secondary analysis of the extension cohort will assess the contribution of lazertinib to the activity of ACP-L descriptively through additional data collection based on intracranial PFS, ORR, DoR, and PFS. The same analysis methods as specified in Section 9 of the protocol will be used. There is no hypothesis testing for the comparison. Details will be provided in the Statistical Analysis Plan including an analysis plan using descriptive statistics to combine data from the main study and the extension cohort to provide additional data on safety and tolerability of ACP-L dosing schedule.

10.14. Appendix 14: Open-Label Extension Phase

The purpose of the OLE Phase is to collect data of clinical relevance/importance while reducing protocol-required visit procedures and assessments and burden on participants. Data collected during this phase will be limited to those procedures and assessments specified in Table 20.

The OLE Phase may begin at a time determined by the sponsor following completion of the second interim analysis for OS and after approval of Amendment 7 by health authorities of countries/territories in which this study is being conducted at the time of transition, and by study site ECs/IRBs.

During the OLE Phase:

- All participants will continue to receive the open-label study treatment they are currently receiving at the time of transition to the OLE Phase and until the discontinuation criteria described in Section 7.1 are met, or until the end of the OLE Phase or transition to the LTE Phase.

- Participants who have already discontinued study treatment and are in the Follow-up Phase of the study will continue Follow-up as specified in the Schedule of Activities for the OLE Phase (Table 20).

10.14.1. Eligibility Criteria

All participants who remain in the study at the time of transition are eligible to transfer to the OLE Phase. Informed consent must be obtained.

10.14.2. Study Treatment Administration

Study treatment administration should continue as specified in Section 6.1.

10.14.3. Study Procedures

All participants in the OLE Phase should follow the Schedule of Activities for the OLE Phase (Table 20).

Laboratory tests should be conducted by a local laboratory as specified in the Schedule of Activities for the OLE Phase (Table 20). The investigator should review the laboratory report, document this review, record only clinically significant abnormalities or changes in the adverse event eCRF along with documentation of the corresponding laboratory value in the eCRF. Additional follow-up monitoring as specified in the Schedule of Activities in Table 20 should be performed. Pregnancy reporting should continue as described in Section 8.3.5. A positive pregnancy test should be reported via the adverse event/serious adverse event process (see Section 8.3.5 and Appendix 3).

During the OLE Phase, data for the following study assessments will be collected.

- Dosing, including pre-infusion and post-infusion medications
- Investigator-assessed disease assessment by RECIST v1.1
- Tumor response by blinded independent central review (BICR) according to RECIST v1.1.

- Survival data
- Symptomatic progression
- Subsequent anticancer therapy
- PROs:EQ-5D-5L, EORTC-QLQ-C30, NSCLC-SAQ, PROMIS-PF and PRO CTCAE, PGIS, and PGIC
- All adverse events (including serious adverse events and adverse events of special interest)
- Laboratory test results related to adverse events
- Vital sign values related to adverse events and for Arm A/A2 and Arm C/C2 and all vital signs related to amivantamab administration.
- Concomitant medications
- Biomarkers

After notification from the sponsor to the site that the OLE Phase is complete, participants on study treatment in the OLE Phase will be provided the option to transfer to the LTE Phase (see Section 10.15 [Appendix 15]).

Table 20 Schedule of Activities in the Open Label Extension Phase (All Arms, Unless Otherwise Indicated)

Study Phase	Treatment Phase	End of Treatment Visit[a]	Follow-up (Visit/Call)	Notes
Study Procedure	**Subject Continuing on Previously Received Study Treatment on a 21 Day Cycle (±3 Days)**	**30 (+7) Days After Last Dose**	**Q12 W (±14) Days**	
Screening Assessments				
Informed consent	X			Must be signed before any study related procedures in the OLE Phase.
Pregnancy test	X	X	X (See Notes)	A serum or urine pregnancy test is required within 72 hours before the first dose of each treatment cycle, and monthly for 6 months after the last dose for participants of childbearing potential in Arms A/A2 and Arms C/C2.
Safety Assessments (predose, except as noted)				
Hematology and chemistry (up to 72h predose)	X	X		Laboratory assessments must be reviewed by the Investigator prior to study treatment. Report only clinically significant abnormalities as adverse events, along with documentation of the corresponding abnormal laboratory value in the eCRF.
Vital signs	X	X		Arms A/A2 & C/C2: ≤30 min before infusion of amivantamab, ~30-min intervals (±5 min) during each infusion, and at end of infusion (+5 min) All Arm A/A2 & C/C2 infusion administration vitals must be recorded in eCRF All treatment Arms: All non-infusion vitals must be reviewed by the Investigator prior to study treatment. Report only clinically significant abnormalities as AEs, along with documentation of the corresponding abnormal value in the eCRF.
Physical examination (PE)[b]	X	X		Perform symptom-directed PE of involved organs and other body systems as indicated within 72 hours of Day 1 of each cycle and at the end of treatment visit with clinically significant abnormalities reported as AEs. If chemotherapy and amivantamab are administered on different days, obtain symptom-directed PE before each study treatment, if the period between the pre-chemotherapy PE and pre-amivantamab PE is expected to be >72 h.
Adverse events	X			Continuous from the time ICF is signed through 30 days after the last dose of study treatment or before starting subsequent anticancer treatment, whichever occurs first (or >30 days for an SAE, if considered related to study treatment)

Study Phase	Treatment Phase	End of Treatment Visit[a]	Follow-up (Visit/Call)	Notes
Study Procedure	**Subject Continuing on Previously Received Study Treatment on a 21 Day Cycle (±3 Days)**	**30 (+7) Days After Last Dose**	**Q12 W (±14) Days**	
Concomitant medications	X			Record all prescription and over-the-counter treatments administered from the time ICF is signed through 30 days after the last dose of study treatment (or the start of a subsequent systemic anticancer therapy, if earlier); >30 days after the last dose of study treatment in conjunction with SAEs considered related to study treatment, until resolution of event or start of subsequent therapy. For participants with Grade 3 or 4 AEs considered related to study drug, record concomitant medications through the end of follow-up of that AE.
Efficacy Assessments				
CT/MRI tumor imaging	X Disease assessment of the chest, abdomen, pelvis, and any other disease location every 6 weeks (±1 week) for the first 12 months, and every 12 weeks (±1 week) thereafter. Timing is relative to start of treatment.			Use same method throughout study. Continue imaging until disease progression is confirmed by BICR. Submit images to central vendor per Imaging Manual until BICR confirmed disease progression. Study treatment should continue until documented disease progression is confirmed by BICR For participants who discontinue treatment prior to disease progression, tumor imaging should continue until disease progression is confirmed by BICR, if clinically feasible. If participant begins a new cancer therapy before disease progression, obtain tumor imaging before the new therapy, and then continue imaging per schedule until BICR confirms disease progression. If a participant receives study treatment beyond confirmed documented disease progression, continue disease assessments as scheduled.
Brain MRI	X Post baseline MRI to be conducted every 12 weeks (±1 week). Timing is relative to start of treatment.			Brain MRI should be performed with (or without if contradicted) contrast. More frequent brain MRIs may be performed if clinically indicated. For those who have BICR confirmed extracranial progression per RECIST v1.1, brain MRI should be continued, if feasible, until BICR confirmed intracranial progression. For participants who discontinue treatment prior to disease progression, tumor imaging should continue until disease progression is confirmed by BICR, if clinically feasible. If a participant begins a new cancer therapy before disease progression, obtain tumor imaging before the new therapy and continue imaging per schedule until BICR confirms progression. If a participant receives study treatment beyond confirmed documented disease progression, continue disease assessments as scheduled. If MRI is medically prohibited, CT with or without contrast may be acceptable (see Imaging Manual) until BICR confirmed intracranial disease progression. Submit images to central vendor per Imaging Manual.

Study Phase	Treatment Phase	End of Treatment Visit[a]	Follow-up (Visit/Call)	Notes
Study Procedure	**Subject Continuing on Previously Received Study Treatment on a 21 Day Cycle (±3 Days)**	**30 (+7) Days After Last Dose**	**Q12 W (±14) Days**	
Symptomatic progression events	X			Collect continuously (including during the Follow-up Phase)
Survival/disease status			X	Collect continuously (including during the Follow-up Phase)
Subsequent anticancer therapy(ies)			X	Collect information on name of, therapy and treatment start and end dates
Preinfusion Medications				
Folic acid	Daily from 7 days before first dose of pemetrexed to 21 days after last dose of pemetrexed			
Vitamin B12	May be administered on same day as pemetrexed.			
Corticosteroid	X			Day before, day of, and day after each pemetrexed dose, or per local regulations and practice
Prior and Concomitant Medication				
(Arms A/A2 & C/C2 only): Preinfusion medications for amivantamab	X			Record all preinfusion medications (Section 6.7.2.2)
Study Treatment				
Lazertinib administration **(Arms A/A2 only)**	X			On the day of each clinic visit, lazertinib should be given on site and before other study drugs are administered.
Record lazertinib treatment compliance **(Arms A/A2 only)**	X			For Arm A dosing schedule 2 and Arm A2 (ACP-L), participants receive lazertinib starting Cycle 5 Day 1 or sooner if carboplatin discontinued earlier than Cycle 4.
Pemetrexed administration	X			On Day 1 of each cycle, pemetrexed should be the first IV-administered study treatment. Creatinine clearance (Appendix 10) must be determined prior to administration of pemetrexed.
Amivantamab administration **(Arms A/A2 & C/C2 only)**	X			Administered after all chemotherapy. Typically administered every 3 weeks beginning in Cycle 2 but can be at any interval between 2 and 4 weeks to align with a delayed chemotherapy dose (Appendix 12). If a dose is delayed in Cycle 2 or beyond, then subsequent doses will be scheduled based on the timing of the previous dose of amivantamab If amivantamab is delayed for >6 weeks, discuss with the Medical Monitor prior to redosing.

Study Phase	Treatment Phase	End of Treatment Visit[a]	Follow-up (Visit/Call)	Notes
Study Procedure	**Subject Continuing on Previously Received Study Treatment on a 21 Day Cycle (±3 Days)**	**30 (+7) Days After Last Dose**	**Q12 W (±14) Days**	
Patient-Reported Outcomes (predose on clinic visit days; when possible, complete before other study procedures at that visit)				
PGIS (predose every 2 cycles continuing with the next odd-numbered cycle)	X	X		Continue in Follow-up phase (collection by phone allowed) for 1 year after progression, regardless of whether subsequent therapy has been started
PGIC (predose every 2 cycles continuing with the next odd-numbered cycle)	X	X		
NSCLC-SAQ EORTC-QLQ-C30 PROMIS-PF EQ-5D-5L (predose every 2 cycles continuing with next odd-numbered cycle)	X	X	X (up to 1 year after EOT)[d]	
PRO CTCAE (predose every 2 cycles continuing with next odd-numbered cycle)	X	X		
Biomarkers				
ctDNA blood sample		X (see notes)		As permitted by local regulations. Obtain ctDNA blood sample within 30 days of disease progression but before next anticancer therapy. If participant receives study treatment(s) beyond disease progression, collect additional samples at each post-progression disease assessment.
Blood samples for exploratory biomarkers **(Arms A/A2 and C/C2 only)**		X		As permitted by local regulations.
Tumor biopsy		X		As permitted by local regulations. Tumor biopsy after progression on study treatment is optional but strongly recommended for participants for whom a baseline biopsy was provided.

ACP-L=amivantamab, carboplatin, pemetrexed, and lazertinib (lazertinib started after carboplatin treatment is completed); BICR=blinded independent central review; C#D#=Cycle # Day #; CT=computerized tomography; ctDNA=circulating tumor deoxyribonucleic acid; EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EOT= End of Treatment; EQ-5D-5L=EuroQol 5-dimensional descriptive system (5-level version); h=hour; ICF=informed consent form; min=minutes; LACP=lazertinib, amivantamab, carboplatin, and pemetrexed (all drugs started C1D1); MRI=magnetic resonance imaging;

NCCN=National Comprehensive Cancer Network; PE=physical examination; PGIC =Patient Global Impression of Change; PGIS =Patient Global Impression of Severity; PRO CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PROMIS-PF=Patient-Reported Outcomes Measurement Information System – Physical Function; Q12W=every 12 weeks; VTE=venous thromboembolic.

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a. With the exception of the end-of-treatment pregnancy test for participants of childbearing potential, which must occur at least 30 days after the last dose of study treatment, end of treatment procedures may be conducted before 30 days after last dose of study treatment if new anticancer therapy is to be initiated.
b. Evaluate for signs and symptoms of VTE events. A focused physical examination of extremities and evaluation of respiratory status (including pulse oximetry) should be performed.
c. See Section 6.5.3.12 for additional information. Refer to NCCN Guidelines Version 1.2022 Cancer-Associated Venous Thromboembolic Disease, Section VTEB for examples of prophylactic-dose anticoagulants in ambulatory cancer participants.
d. Continue data collection for 1 year after end of treatment, reducing data collection frequency from every 3 months to every 6 months.

10.15. Appendix 15: Long-term Extension Phase

The purpose of the LTE Phase is to continue providing participants access to study treatment while further reducing protocol-required visit procedures and assessments, and burden on participants. Investigators should monitor and assess each participant's disease status (response, progression, survival) and safety according to routine standard practice and local label requirements. The LTE Phase will continue until the discontinuation criteria described in Section 7.1 are met, or until 4 years after local marketing authorization is obtained for the studied indication, whichever occurs first. After notification from the sponsor that the LTE phase will be initiated, participants remaining in the study be provided with the option to transfer to the LTE Phase. Upon entering the LTE Phase, participants will continue to receive the study treatment they were receiving.

Data collection will be limited during this phase. Study treatment compliance will be recorded. Serious adverse events will be reported on the appropriate serious adverse event form and recorded by the sponsor in the Global Medical Safety database. Study treatment dispensation and accountability will be performed via IWRS.

Pregnancy reporting should continue as described in Section 8.3.5. Other safety and efficacy data will not be collected during the LTE Phase. No analyses other than routine periodic safety reviews consisting of reported serious adverse events are planned for the LTE Phase.

Participants who had discontinued study treatment and are in the Follow-up Phase, or participants who elect not to enter the LTE Phase will be discontinued from the study upon the start of the LTE Phase.

10.15.1. Eligibility Criteria

All participants who remain on study at the time of transition are eligible to transfer into the LTE Phase. Informed consent must be obtained.

10.15.2. Study Treatment Administration

Study treatment should continue as specified in Section 6.1.

10.15.3. Study Procedures

All participants in the LTE Phase should follow the Schedule of Activities for the LTE Phase (Table 21).

Participants in the LTE Phase should be followed up for disease assessment and safety per local practice and follow the local label(s). No efficacy data will be collected in the eCRF. Only serious adverse events will be collected via the serious adverse event form per the serious adverse event reporting process. Pregnancy reporting should continue as described in Section 8.3.5. A positive pregnancy test should be documented in the subject file/source notes. Other procedures and safety assessments may be performed per local practice.

No data will be collected in the eCRF during the LTE Phase. However, assessments performed should continue to be documented in the subject file/source notes.

Table 21: Schedule of Activities in the Long-term Extension Phase (All Arms, Unless Otherwise Indicated)

Study Phase	Treatment Phase	End of Treatment Visit[a]	Notes
Study Procedure	**Subject Continuing on Previously Received Study Treatment on a 21 Day Cycle (±3 Days)**	**30 (+7) Days After Last Dose**	
Informed consent	X		Must be signed before any study related procedures in the LTE Phase.
Pregnancy test	X	X	A serum or urine pregnancy test is required within 72 hours before the first dose of each treatment cycle, and monthly for 6 months after the last dose for participants in Arms A/A2 and Arms C/C2.
Efficacy Assessments: All participants continuing in the LTE Phase should be followed up for disease assessment per the local practice and following the local label(s).			
Safety Assessments All participants continuing in the LTE Phase should be followed up for safety per the local practice and following the local label(s).			
Serious adverse events (SAEs only)	Continuous from the time ICF is signed through 30 days after the last dose of study treatment (or >30 days, if considered related to study treatment)		
Preinfusion Medications			
(Arms A/A2 & C/C2 only) Preinfusion medications for amivantamab	X		Record all preinfusion medications (Section 6.7.2.2)
Study Treatment			
Lazertinib administration (**Arms A/A2 only**)	X		On the day of each clinic visit, lazertinib should be given on site and before other study drugs are administered.
Record lazertinib treatment compliance **(Arms A/A2 only)**	X		For Arm A dosing schedule 2 and Arm A2 (ACP-L), participants receive lazertinib starting Cycle 5 Day 1 or sooner if carboplatin discontinued earlier than Cycle 4.
Pemetrexed administration	X		On Day 1 of each cycle, pemetrexed should be the first IV-administered study treatment. Creatinine clearance (Appendix 10) must be determined prior to administration of pemetrexed.
Amivantamab administration **(Arms A/A2 & C/C2 only)**	X		Administered after all chemotherapy. Typically administered every 3 weeks beginning in Cycle 2 but can be at any interval between 2 and 4 weeks to align with a delayed chemotherapy dose (Appendix 12). If a dose is delayed in Cycle 2 or beyond, then subsequent doses will be scheduled based on the timing of the previous dose of amivantamab If amivantamab is delayed for >6 weeks, discuss with the Medical Monitor prior to redosing.

ICF=informed consent form; min=minutes; IV=Intravenous;; LTE=Long-term Extension; SAE=serious adverse events; ACP-L= Amivantamab, carboplatin, pemetrexed, and lazertinib (lazertinib started after carboplatin is completed).

a. With the exception of the end-of-treatment pregnancy test for participants of childbearing potential, which must occur at least 30 days after the last dose of study treatment, end of treatment procedures may be conducted before 30 days after last dose of study treatment if new anticancer therapy is to be initiated.

10.16. Appendix 16: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 6 (22 December 2022)

Overall Rationale for the Amendment: The overall purpose of this amendment is to add an open-label randomized extension cohort to further describe the safety and efficacy of the ACP-L dosing schedule versus ACP with additional data.

The changes made to the clinical protocol 61186372NSC3002 as part of Protocol Amendment 6 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in 10.16 Appendix 16: Protocol Amendment History.

Section number and Name	Description of Change	Brief Rationale
1.1. Synopsis; (Objectives and Endpoints, Overall Design, Number of Participants, Study treatment groups and duration, Statistical Methods); 1.3. Schedule of Activities; 3. Objectives and Endpoints; 4.1. Overall Design; 4.1.2. Treatment Phase; 4.4. Justification for Dose; 6.3. Measures to Minimize Bias: Randomization and Blinding 9. Statistical Considerations; 9.3. Populations for Analysis Sets;	Text was added to add an open-label randomized extension cohort.	To further describe the safety and efficacy of the ACP-L dosing schedule versus ACP with additional data.
1.2. Schema	Figure 2 was added to represent the schematic overview of the extension cohort.	
Section 13: Appendix 13	Appendix 13 was added to describe the design, background, rationale, and statistical considerations for the extension cohort. The subsequent section and appendix were renumbered.	
Throughout the protocol	Mention of Arm A or Arm C was updated to “Arms A/A2” or “Arms C/C2”, respectively, to align with addition of the extension cohort, as appropriate.	
1.3. Schedule of Activities (Table 1)	Blood samples for exploratory biomarkers were updated to include collection of blood samples on	Serum collections will undergo analysis for circulating factors that

Section number and Name	Description of Change	Brief Rationale
	C5D1, C6D1, C7D1, and C8D1 for Arms A/A2 and C/C2.	may be related to clinical or physiological responses to study treatments.
8. Study Assessments and Procedures	Approximate blood volumes to be collected from participants were updated.	
1.3. Schedule of Activities (Table 2)	The term LACP was deleted from the table heading and added to column "Plasma Sample for Pharmacokinetics (Lazertinib) Arm A **LACP** only.	To align with the updates resulting from the urgent safety measure on 07 November 2022.
8.4.1. Evaluations	Text was updated to indicate that samples will be collected from participants in Arm A **LACP** as per Table 2 and **for participants receiving ACP-L in Arms A/A2** as per Table 3 for the evaluation of PK of lazertinib.	
1.3. Schedule of Activities (Table 3)	Added 'Arm A Dosing Schedule 2 and Arm A2' in the table heading and the plasma sample for pharmacokinetics column.	To align with the updated text.
	The end of infusion row was deleted.	This table describes lazertinib pharmacokinetics – lazertinib is not administered as an infusion.
4.3. Scientific rationale for Study Design	Added the missing word 'lazertinib' in Clinical Pharmacology Assessments.	To correct an error.
6.1.1. Scheduled Dosage and Timing	The abbreviation "LACP" was replaced with the word "treatment" for clarity.	Not all participants in Arm A will be receiving LACP.
6.1.2. Lazertinib	Recommendations for resolution of specific toxicities prior to initiating lazertinib were added.	Clarification for safety reasons.
6.1.3. Chemotherapy	The description of pemetrexed was updated from "powder for concentration" to "powder for concentrate."	To correct an error.
6.5.3.2. Rash-Related Adverse Events (Table 11)	Lazertinib was deleted from dose adjustment column.	To correct an error.
7.3. Lost to Follow-up	The following language was removed: "Should the participant continue to be unreachable, they will be considered to have withdrawn from the study."	Language was inconsistent with other instructions allowing collection of information using alternative follow-up mechanisms.
8.2.7. ECOG Performance Status	Language indicating that a decline in ECOG performance status should be reported as an adverse event was removed.	Language was inconsistent with adverse event reporting instructions in other sections of the protocol.
11. Reference	One reference was deleted as it was an incorrect reference.	To correct an error.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 5 (25 November 2022)

Overall Rationale for the Amendment: The overall purpose of this amendment is to formalize the study changes required by the Urgent Safety Measure (tolerability risk treated in Arm A with combination of amivantamab, lazertinib, carboplatin and pemetrexed) released on 07 November 2022. In addition, this amendment will incorporate additional changes that were recommended by health authorities in response to the Urgent Safety Measure (VTE risk with combination of amivantamab and lazertinib) released on July 22 2022.

The changes made to the clinical protocol 61186372NSC3002 as part of Protocol Amendment 5 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis (Study treatment groups and duration); 2 Introduction; 2.2.6 Rationale for Adding Lazertinib and Amivantamab to Platinum Doublet Chemotherapy 2.3.3 Benefit-Risk Assessment for Study Participation 3. Objectives and Endpoints 4.1 Overall Design 4.1.2 Treatment Phase 4.4 Justification of Dose 6.1.1 Scheduled Dosage and Timing 6.5.3.12 Venous Thromboembolic Events 8.4.1 Evaluations 9.1 Statistical Hypotheses 9.1.1 Multiplicity (Figure 3) 9.2 Sample Size Determination 9.4.1. General Considerations 9.4.2 Primary Endpoint 9.4.3 Secondary Endpoints 9.4.6 Other Analyses (Biomarker Analyses) 9.5 Interim Analysis	• Added text pertaining to a USM whereby the dosing schedule of lazertinib on Arm A has been modified to only start after carboplatin therapy is completed. This dosing schedule is termed 'ACP-L'. • The primary efficacy analyses remains unchanged and includes all participants in Arm A. • Benefit-Risk Assessment was updated for results of the IDMC meeting which recommended modification of Arm A to withhold lazertinib during administration of carboplatin. • The treatment phase was updated to reflect Arm A Dosing Schedule 2 (ACP-L, started on 7 November 2022) • Dose justification was updated to align with the findings of the IDMC meeting based on the review of the unblinded safety data and is also supported by the emerging data that concurrent chemotherapy with third generation EGFR TKIs is associated with a higher than expected rate of toxicities traditionally association with chemotherapy. Overall: Addition of 'ACP-L' across the protocol to align with this change in dosing schedule.	Change to lazertinib dosing schedule to minimize the tolerability risks, as per IDMC recommendation.
1.2 Schema	Updated to reflect Arm A Dosing schedule 2 (ACP-L) started on 7 November 2022.	Change to lazertinib dosing schedule to minimize the tolerability risks, as per IDMC recommendation
1.3 Schedule of Activities, Table 1: Schedule of Activities (All Treatment Arms, Unless Otherwise Indicated)	In prophylactic anticoagulation row, 2 columns were merged to indicate that prophylactic dose anticoagulation is recommended during the first 4 months of treatment for participants receiving the combination of amivantamab and lazertinib.	To correct the editorial error and align free text and table regarding the duration for the prophylaxis.
1.3 Schedule of Activities, Table 1: Schedule of Activities (All Treatment Arms, Unless Otherwise Indicated)	Lazertinib administration and record of compliance rows (Arm A only): Updated to reflect dosing schedule modification and implementation of ACP-L.	To align the lazertinib dose schedule.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities, Table 1: Schedule of Activities (All Treatment Arms, Unless Otherwise Indicated)	CT/MRI Tumor imaging and Brain MRI: Notes were updated to reflect *that study treatment should continue until documented disease progression is confirmed by BICR*. If participant begins a new cancer therapy before disease progression, obtain tumor imaging before the new therapy, and *then continue imaging per schedule until BICR confirms disease progression*	To clarify the protocol requirement of imaging schedule.
1.3 Schedule of Activities Table 3: Collection times for Pharmacokinetics (PK) Samples (Arm A ACP-L); 8.4.1 Evaluations	• Added a table to describe collection times for PK sampling for lazertinib. • Updated evaluations to indicate PK sampling timepoints and conditions	Clinic visit for the second dose of lazertinib was not needed and PK samples are not collected on Day 2.
5.2 Exclusion Criteria; 6.5.1 Dose Delay Guidance; 6.5.2 Dose Modification of Amivantamab and Lazertinib; 6.5.3.12 Venous Thromboembolic Events;	• Criterion 13.1 updated to include participants who have a significant genetic predisposition to venous thromboembolic events (such as Factor V Leiden) or have a prior history of VTE and are not on appropriate therapeutic anticoagulation as per NCCN guidelines or local guidelines. • Subheading Arm A was updated for VTE. • Table 5; Footnote ‘e’ updated for VTE in participants being treated with the combination of amivantamab and lazertinib. • Table 8; Footnote ‘e’ deleted. • Section for VTE updated with: o Further imaging studies to assess a resolution in case of worsening VTE and/or symptoms o Recommendations for participants receiving LACP and ACP-L schedule. • Resolutions in case of VTE events associated with clinical instability. • Recommendations in case of recurrent VTEs have been included.	To clarify and align with the VTE risk mitigation and management
6.1.4 Amivantamab	• Updated the central line infusion criteria to infusion via central line being allowed only at Cycle 1 Day 15 and onwards if the participant’s most recent dose (eg, C1D8) was successfully administered without an infusion related reaction.	To clarify the requirement for central line infusion.
6.5.3.2 Rash-Related Adverse Events, Table 10 and Table 11; 7.1 Discontinuation of Study Treatment	Added text to indicate that in case of a Grade 4 rash or severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN), all study drugs (amivantamab [Arms A and C], lazertinib [Arm A], pemetrexed, and carboplatin) should be permanently discontinued.	This change was to optimize safety of participants
6.5.4.1 Management of Chemotherapy Toxicities	Added: participants who experience hematologic toxicities while on treatment are recommended to receive colony stimulating factors as per international guidelines	To mitigate the risk and optimize safety

Section Number and Name	Description of Change	Brief Rationale
9.4.2 Primary Endpoint; 9.4.3 Secondary Endpoints; 9.4.5 Safety Analyses	Added analysis by dose schedule. • Updated to indicate that additional sensitivity analyses of PFS by dosing schedule subgroups will be performed. • Updated to indicate that additional analyses by dosing schedule subgroups on the secondary endpoints will be performed. • Updated to indicate that additional safety analyses by dosing schedule subgroups will be performed. Details will be provided in the SAP.	To add analysis for Lazertinib dosing schedule change per IDMC recommendation.
11. References	Newly added references: Ardizzoni A (2012) and Tanaka K (2021).	
Throughout the protocol	• Minor grammatical, formatting, or spelling changes were made. • The term 'subjects' was replaced with 'participants'.	Minor errors were noted. Changes were made for the purpose of consistency and accuracy of terms used in the protocol draft.

Amendment 4 (23 August 2022)

Overall Rationale for the Amendment: To implement the Adverse Event of Special Interest of venous thromboembolic (VTE) events, as well as associated measures for monitoring and prophylaxis of these events.

The changes made to the clinical protocol 61186372NSC3002 as part of Protocol Amendment 4 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (Table 1)	Row added for prophylactic-dose anticoagulation during the first 4 months of treatment. Venous thromboembolic (VTE) events-related footnotes added for physical examination and anticoagulation.	To implement the Adverse Event of Special Interest of VTE events, as well as associated measures for monitoring and prophylaxis of these events.
1.3 Schedule of Activities (Table 1) 8 Study Assessments and Procedures; overview	Added blood sample collection timepoints for exploratory biomarkers at C2, C3, and C4 treatment cycles for Arm A and Arm C. Also, updated blood withdrawn volume of Arm A and Arm C participants to align with additional blood sample collection timepoints for exploratory biomarkers.	
2.3.1 Risks for Study Participation	VTE events and paresthesia has been added to the list of possible risks for the amivantamab and lazertinib combination.	
2.3.3 Benefit-Risk Assessment for Study Participation	The rationale for and aims of the VTE events-related measures have been added.	
6.5.2 Dose Modification of Amivantamab and Lazertinib	In Table 4 and Table 7, a new footnote e has been added to provide dosing guidance for VTE events.	

Section Number and Name	Description of Change	Brief Rationale
6.5.3.12 Venous Thromboembolic Events	A new section has been added to provide guidance on the management of VTE events.	
8.2.1 Physical Examinations	Additional guidance has been added for detection of VTE events through physical examination.	
8.3.7 Adverse Events of Special Interest	VTE events have been added to the list of AEs of special interest. It is noted that events of VTE events should follow standard reporting guidelines.	
11 References	Three new references (Carrier 2019, NCCN 2022, and Rutjes 2020) have been added to the list of references to support VTE-related information.	
6.5 Dose Modification	Updated guidance on the dose modification for the participants who experiences clinically significant CTCAE Grade 3.	To provide more flexibility in dose modification.
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Updated guidance on the timeframe for reporting adverse events.	To align reporting requirements with the Schedule of Activities.
10.3.3 Severity Criteria	The following text has been removed: ~~Any AE will be graded as per the above. Should an AE become fatal or have a fatal outcome, the original grade is not changed but "fatal" shall be reported as an outcome. A Grade 5 event is to be reported only in the following cases:~~ ~~• Death NOS: only for deaths due to unknown reason (pending follow up information; if further information becomes available this should be adapted as adequate)~~ ~~• Sudden death: a sudden (defined as instantaneous or within 1 hour of the onset of symptoms) cessation of life that cannot be attributed to a CTCAE term~~	To ensure all Grade 5 events are captured.
10.3.5 Procedures: Serious Adverse Events	Revised information related to SAE reporting period.	To align with revised time period and frequency for collecting all adverse events information.
Title page, 10.2 Appendix 2: Regulatory, Ethical, and Study Oversight Considerations	Expanded "countries" terminology to "countries/territories."	To align with Janssen template.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 3 (27 June 2022)

Overall Rationale for the Amendment: To add hypothesis testing for amivantamab, carboplatin, and pemetrexed (ACP) versus carboplatin and pemetrexed (CP) as a dual primary and secondary hypotheses with an increased study population to provide sufficient power; modify the statistical analysis plan for such analyses; remove biomarker defined subgroup analyses.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis: Objectives and Endpoints, Hypothesis, overall design, and Statistical Methods; 3 Objectives and Endpoints and Hypothesis; 4.1 Overall Design; 9.1 Statistical Hypotheses; 9.4.2 Primary Endpoint; 9.4.3 Secondary Endpoints; 9.5 Interim Analysis	Text was updated to add dual primary efficacy hypothesis specifying that efficacy will also be assessed for ACP versus CP in addition to lazertinib, amivantamab, carboplatin, and pemetrexed (LACP) versus CP. Text was updated specifying that objectives of efficacy, safety, health-related quality of life and disease related symptoms, and biomarkers will also be also assessed for ACP versus CP in addition to LACP versus CP.	To add hypothesis testing for the analysis of ACP vs CP.
1.1 Synopsis: Statistical Methods; 9.1 Statistical Hypotheses; 9.4.1 General Considerations	Text describing comparison of LACP versus CP was revised to add comparison of ACP versus CP.	
CCI [redacted]		
1.1 Synopsis: Number of Participants and Statistical Methods; 1.2 Schema; 4.1 Overall	Number of participants was increased from 500 to 600. Sample size calculation text was updated accordingly.	To provide sufficient power for hypothesis testing for both LACP versus CP and ACP versus CP.

Section Number and Name	Description of Change	Brief Rationale
Design; 9.2 Sample Size Determination		
1.1 Synopsis: Statistical Methods; 9.1.1 Multiplicity	Text was added to specify that a graphical approach will be applied in a group sequential design setting for testing of primary endpoints (PFS) and key secondary endpoints (ORR and overall survival [OS]). Earlier text for the hypothesis testing for these endpoints was removed. A new subsection for multiplicity was added.	To adjust the statistical hypothesis testing strategy to control overall family-wise Type I error rate after adding ACP versus CP comparison.
1.1 Synopsis: Statistical Methods	Following text was added to synopsis: Comparison of LACP (Arm A) with ACP (Arm C) will be performed to describe the contribution of lazertinib based on intracranial PFS, ORR, DoR, and PFS, using summary statistics and nominal p-values; there will be no formal hypothesis testing for this comparison.	For consistency with protocol text.
4.1.1 Screening	Enrollment of number of participants who failed treatment with osimertinib in the second line to approximately 40% was changed from 200 to 240.	To increase the size in proportion with new sample size.
6.5.3.2 Rash-Related Adverse Events	In Table 9 it was mentioned to permanently discontinue amivantamab and hold lazertinib and lazertinib to restart once resolved per investigator assessment of causality for Grade 4 event in Arm A. In Table 10 it was mentioned to permanently discontinue amivantamab for Grade 4 event in Arm C. Dose adjustment and management of severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis was added to Table 9 and Table 10.	To clarify for safety of the participants.
6.5.3.10 Diarrhea	Study treatment algorithm is updated for lazertinib and added for amivantamab for Arm A in Table 11. A new table, Table 12 was added for algorithm for management of diarrhea for Arm C. Subsequent tables were renumbered.	To clarify for safety of the participants.
5.2 Exclusion Criteria; 6.7.3 Prohibited or Restricted Medications and Therapies; Appendix 12: Prohibited and Restricted Medications and Therapies That Induce, Inhibit, or Are Substrates of CYP3A4/5; Appendix 13 Substrates of P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), and multi-drug resistance protein 4	Prohibited and restricted medications that induce, inhibit, or are substrate of CYP3A4/5, and substrates of P-glycoprotein, Breast Cancer Resistance Protein, and multi-drug resistance protein 4 are added in-text and the appendices were deleted and text was added to contact local pharmacist or Medical Monitor in case of any questions. The reference for these appendices within the protocol text was removed. A new reference of US FDA 2022 was added for list of medications. Subsequent appendices were renumbered.	To remove the duplicate information as these information are added in-text.

Section Number and Name	Description of Change	Brief Rationale
(MRP4): Exercise Caution		
8 Study Assessments and Procedures: Overview	Bold text was added to the statement: Depending on country specific regulations, **volume requirements at local laboratories, and availability of blood collection tubes** the total blood volume may vary.	For further clarification
8.6 Immunogenicity Assessments	Text in the section revised to remove redundancy.	For further clarification
9.4.2 Primary Endpoint	Text was updated to show that primary analysis of PFS will be conducted when 350 PFS events in all 3 arms combined have been observed.	To update the text based on updated statistical analysis plan.
9.4.3 Secondary Endpoints	Following text was added: Secondary endpoints will be analyzed using the Full Analysis Set.	
9.4.6 Other Analyses: Pharmacokinetic Analyses	Arm C was added with Arm A for pharmacokinetic analyses.	To update PK analysis for Arm C based on updates to statistical analysis plan.
9.5 Interim Analysis	The timepoint for interim analysis is updated as 170 deaths (all 3 Arms combined, approximately 43% of the total planned overall survival (OS) events) for first interim analysis for OS and the second interim analysis for OS will be performed approximately 32 months after the first participant is randomized, when approximately 300 deaths (all 3 arms combined, approximately 75% of the total planned OS events). The timepoint for final analysis was also updated to 400 deaths (all 3 arms combined). Text was updated for the analysis of OS.	To update the timing and number of OS events to be expected for interim and final analysis of OS per increased sample size.
10.12 Appendix 12 Dosing Synchronization of Arms A and C	The example figure for administration of study treatments is updated.	To correct the error in previous protocol amendment.
11 Reference	The references were updated according to changes in the document.	To update the references.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made	Minor errors were noted.

Amendment 2 (24 March 2022)

Overall Rationale for the Amendment: To update the timeframe for conduct of the primary progression-free survival (PFS) analysis per the request of the United States Food and Drug Administration (US FDA), modify inclusion criteria related to brain metastases, provide additional and clarified guidance to investigators for the management of toxicities, modify prohibited and restricted medications based on the availability of new information, and to incorporate feedback received from health authorities.

Section number and Name	Description of Changes	Brief Rationale
9.4.2 Primary Endpoint	The timeframe for conduct of the primary analysis for PFS was updated at the request of the USFDA.	To update the timing of the final analysis to be strictly event-driven without any contingency for follow-up for the last randomized participant.
1.1 Synopsis: Efficacy	Text was added for CT/MRI tumor imaging and	To provide more clarification.

Section number and Name	Description of Changes	Brief Rationale
Evaluations; 1.3 Schedule of Activities; 4.1.2 Treatment Phase; 8.1 Efficacy Assessments	brain MRI to indicate that imaging or study treatment should continue until progression is confirmed by blinded independent central review. The term 'radiographic' was deleted with respect to disease progression.	
5.1 Inclusion Criteria	Criterion 5 was updated to allow participants with brain metastases who had all lesions treated as clinically indicated, local therapy must have been completed at least 14 days prior to randomization, and participant receiving no greater than 10 mg daily prednisone or equivalent.	To align with current clinical practice.
5.2 Exclusion Criteria	Text in **bold** was added to the criterion 4: Participant has **history of or current evidence of** leptomeningeal disease, or participant has spinal cord compression not definitively treated with surgery or radiation.	
6.5.2 Dose Modification of Amivantamab and Lazertinib; Table 5; Table 8	Text was added to discontinue lazertinib or amivantamab or both lazertinib and amivantamab (Arm A) and amivantamab (Arm C) permanently in case of a second occurrence of the same drug-related Grade 4 toxicity.	To incorporate request from health authorities.
6.5 Dose Modification	Text was updated to indicate that only the study treatment(s) for which the investigator assessed causal relatedness will be interrupted in the event of a Grade 3 or higher toxicity. Exceptions for hematologic toxicities were removed.	To correct the error in prior versions of the protocol.
6.5.3.1 Infusion-Related Reactions Table 9	Text was added to follow guidance for Grade 2 interruptions, if infusion is interrupted for Grade 1 infusion-related reactions (IRR). Added 'antiemetic' to the list of medications for Grade 2 infusion-related reactions.	To provide guidance for management of IRR in case of infusion interruption. To provide additional medications for Grade 2 IRR.
6.5.3.2 Rash-Related Adverse Events	Text was updated to indicate that topical or oral antibiotics or both are recommended for rash prophylaxis.	To provide more clarification.
6.5.3.10 Diarrhea	New section including Table 12 was added to provide guidance for diarrhea management. Subsequent tables were renumbered accordingly.	To provide guidance on management of diarrhea.
6.5.3.11 Paresthesia	New section was added to provide guidance for paresthesia management.	To provide guidance on management of paresthesia.
2.2.2 Lazertinib; 11 References	The outcome of cardiac safety study was added, and the corresponding reference was added.	To update the sections based on new data available which show that lazertinib has no clinically relevant effect on QT interval and left ventricular ejection fraction at doses of 20 mg to 320 mg and supports the removal of prohibitions on the use of medications with the potential to prolong the QTc interval.
6.7.3 Prohibited or Restricted Medications and Therapies; 10.11 Appendix 11: Medications With Potential for QT Interval Prolongation	Text was updated to remove prohibitions and wash-out periods for medications affecting QT interval or induce Torsades de pointes.	
6.7.2.1 Pre- and Post-Infusion Medications for Chemotherapy	Text was modified to indicate that prophylactic use of leukocyte-depleted blood transfusions are allowed at any time after Cycle 1 Day 1.	To provide more clarification
Appendix 12 Prohibited and Restricted	Fluconazole, cimetidine, and aprepitant were removed from the list of strong inhibitors of	To update the section with new available information.

Section number and Name	Description of Changes	Brief Rationale
Medications and Therapies That Induce, Inhibit, or Are Substrates of CYP3A4/5	CYP3A4. Following text was removed: "Appropriate medical judgment is required, and any of these medications should be utilized, if clinically indicated, for the treatment of AEs."	
1.3 Schedule of Activities; 4.1.1 Screening	Added a note that informed consent signature can be performed > 28 days prior to randomization, but all other screening procedures must be completed within 28 days of randomization.	To provide flexibility and convenience and define the criterion for repetition of screening assessments.
1.3 Schedule of Activities;	Text was added to clarify when laboratory assessments and physical examination need to be repeated if chemotherapy and amivantamab are administered on different days.	To clarify the criterion for repetition of laboratory assessments and physical examination. The original language was unclear.
	Notes were updated to clarify when predose Cycle 1 Day 1 assessments must be conducted relative to randomization.	To provide more clarification as the original language was unclear.
	Text indicating that amivantamab doses delayed for >7 days could not be made up was deleted.	To correct the error in prior versions of the protocol.
	Arm C was added for carboplatin to be administered after pemetrexed and before amivantamab.	
	Footnote 'b' was updated to specify that the results must be reviewed by the investigator to confirm eligibility for the study.	To provide clarification.
	Footnote 'c' was added to some screening activities.	To provide flexibility and convenience.
4.1.2 Treatment Phase	A reference of Section 7.1 Discontinuation of Study Treatment is provided for continuation of study treatment after disease progression.	To provide clarification.
5.1 Inclusion Criteria; 5.2 Exclusion Criteria; 6.7.2.5 Hormonal Contraception	Inclusion Criteria 11, 12, and Exclusion Criterion 20 and text in other section was updated to increase the duration to follow contraceptive measures for a female participant from 6 to 7 months after the last dose of study treatment.	To incorporate request from a health authority.
5.1 Inclusion Criteria; 10.5 Appendix 5 Contraceptive Guidance	Inclusion criteria 13 and text in other section was updated to remove the use of spermicidal foam/gel/film/cream/suppository along with condom for contraception.	To provide flexibility.
5.1 Inclusion Criteria	Criteria 3, 7, and 14 were updated for clarity; text in **bold** was added to following criteria: Criterion 3: Osimertinib must have been administered as either the first-line treatment for locally advanced or metastatic disease or in the second-line setting after prior treatment with first- or second-generation EGFR TKI **as a monotherapy**. Participants who received either neoadjuvant and/or adjuvant treatment **of any type** are eligible if progression to locally advanced or metastatic disease occurred at least 12 months after the last dose of such therapy. Criterion 7: Participant must have adequate organ and bone marrow function as follows, without history of red blood cell transfusion, platelet	To provide more clarification, as the original language was unclear.

Section number and Name	Description of Changes	Brief Rationale
	transfusion, **erythropoietin stimulating agents**, or **platelet-boosting treatments** within 7 days prior to the date of the laboratory test. Criterion 14 was updated to add following text: "male participants should consider preservation of sperm prior to treatment with pemetrexed or carboplatin, as these agents may impair fertility."	
5.2 Exclusion Criteria	Criterion 6 was updated to clarify that participants with history of or current evidence of leptomeningeal disease will be excluded.	To provide more clarification.
	Criterion 13 was updated to add the text to exclude participants with uncontrolled hypokalemia.	To incorporate request from health authorities.
5.3 Lifestyle Considerations	Criterion 3 was updated to indicate use of sun protective measures for additional 2 months: changed from 'until the last dose' to 'until at least 2 months after the last dose' of study treatment. Additionally, Arm C, which also contains amivantamab, has been added to this criterion for completeness.	To align criterion language with the amivantamab USPI. To correct the error in prior versions of the protocol.
1.3 Schedule of Activities; 6.5.1 Dose Delay Guidance; 6.7.2.2 Pre-and Post-Infusion Medications for Amivantamab (Arm A and Arm C)	Text was added to indicate that the total number of carboplatin administration cycles cannot exceed 4 cycles.	To align with clinical practice.
6.3 Measures to Minimize Bias: Randomization and Blinding	Following text was added: "participants who have adequate treatment for metastatic brain lesions, including a complete response or resection, must be identified as having a history of brain metastases."	To provide more clarification.
6.5.1 Dose Delay Guidance	'If chemotherapy is delayed twice' is replaced by 'If chemotherapy is delayed by 2 weeks' for Arm A and Arm C. Window period was added for chemotherapy dosing, Cycle 2 onwards.	To provide more clarification. To align with clinical practice.
6.7.2.1 Pre- and Post-Infusion Medications for Chemotherapy Table 16	Footnote 'a' updated to indicate oral dexamethasone can be skipped on Cycle 1 Day 1 and Day 2, at the discretion of the investigator. Of note, IV dexamethasone is administered as a pre-infusion medication for amivantamab on those days.	To correct the error in prior versions of the protocol.
6.7.2.2 Pre-and Post-Infusion Medications for Amivantamab (Arm A and Arm C)	The recommended dosing windows before amivantamab for pre-infusion medications in Table 17 were updated. Table 17 footnote 'e', indicating that the dose of paracetamol may be split, was removed. Footnote 'f' was re-lettered as footnote 'e'. Text was added to indicate that if required amivantamab pre-infusion medication is already given as chemotherapy prophylaxis, it does not	To align with clinical practice. To align with clinical practice. To provide more clarification.

Section number and Name	Description of Changes	Brief Rationale
	need to be re-administered prior to amivantamab infusion if dosed within recommended window. Arm A and C were mentioned for amivantamab.	
6.7.3 Prohibited or Restricted Medications and Therapies	In the list of prohibited medications and therapies, the prohibition of live or live attenuated vaccines was extended until at least 90 days after the last dose of study treatment.	To eliminate risk associated with concomitant administration of live or live attenuated vaccines with pemetrexed and carboplatin.
	The list of restricted medications and therapies was updated to indicate that nephrotoxic drugs should also be used cautiously with pemetrexed.	To eliminate risk associated with concomitant administration of nephrotoxic drugs and pemetrexed.
7.1 Discontinuation of Study Treatment	Added guidelines for treatment of participants after disease progression.	To incorporate request from health authority.
8. Study Assessments and Procedures	The total estimated blood volume to be collected during the study was updated.	To be consistent with ICF language.
1.3 Schedule of Activities; 8.2.1 Physical Examinations	Text was added to indicate that a physical examination is also required at the end of treatment visit.	To correct the error in prior versions of the protocol.
8.2.3 Electrocardiograms	Text was added to clarify that the order for blood sampling, vital sign measurement, and ECG to follow if procedures are less than 1 hour apart.	To provide more clarification.
8.2.3 Electrocardiograms	Text was added to specify ECG can be collected in triplicate at other times in addition to screening visit if clinically indicated.	For consistency with other sections
1.3 Schedule of Activities; 8.2.5 Pregnancy Testing	Requirement for monthly pregnancy testing for 6 months after last dose for participants in Arm A and Arm C was added.	For consistency with clinical trial facilitation group (CTFG) contraception recommendations.
10.5 Appendix 5: Contraceptive Guidance	Footnote b, which stated 'The study treatment may interact with hormonal contraception, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study treatment.' has been deleted. Footnote c was renumbered to footnote b.	To update contraceptive guidance as no interaction is expected between study treatments and hormonal contraception.
Appendix 14: Dosing Synchronization for Arms A and C	Figure was updated with cycle numbers, days, and visit windows. New explanatory text was added.	To provide more clarification.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 (06 August 2021)

Overall Rationale for the Amendment: The requirement to review each assessment with the Medical Monitor when a participant is treated beyond BICR-confirmed disease progression was removed. Text was added to clarify timing of the first Independent Data Monitoring Committee (IDMC) meeting.

Section number and Name	Description of Change	Brief Rationale
Table 1; 8.1 Efficacy Assessments	Removed the requirement to review clinical benefit with the Medical Monitor at each assessment when a participant is treated beyond BICR-confirmed disease progression.	Per Section 4.1.2, continuation of study treatment after disease progression requires approval from the Medical Monitor; reapproval is not required at each subsequent assessment.
Table 1; 8.2.5 Pregnancy Testing	Added pregnancy testing (serum or urine) within 72 hours before Day 1 of each cycle.	Other studies of amivantamab (with or without lazertinib or chemotherapy) have similar requirements.
10.2.6 Committees Structure	Added timing of the first IDMC meeting as occurring after 50 participants are randomized and complete at least 2 cycles of treatment.	The original protocol did not specify timing of the first IDMC meeting.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

11. REFERENCES

Ahn MJ (2019), Han JY, Lee KH, et al. Lazertinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: results from the dose escalation and dose expansion parts of a first-in-human, open-label, multicentre, phase 1-2 study. Lancet Oncol. 2019;20(12):1681-1690.

ALIMTA (pemetrexed) [package insert]. Indianapolis IN: Lilly USA, LLC; 2019. Available at: https://uspl.lilly.com/alimta/alimta.html#pi. Accessed 04 June 2020.

American Red Cross (2020). Available at https://www.redcrossblood.org/faq.html. Accessed 18 April 2020.

Bauml J (2020), Cho BC, Park K, et al. Amivantamab in combination with lazertinib for the treatment of osimertinib-relapsed, chemotherapy-naïve EGFR mutant (EGFRm) non-small cell lung cancer (NSCLC) and potential biomarkers for response [abstract]. J Clin Oncol 2021;39(15Suppl):9006.

Blackwell KL (2010), Burstein HJ, Storniolo AM et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 2010;28:1124–30. 10.1200/JCO.2008.21.4437.

Bray F (2018), Ferlay J, Soerjomataram I, Siegal RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA J Clin. 2018;68(6):394–424.

Carboplatin (2018) [package insert]. Lake Forest IL: Hospira, Inc.; 2018. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=4379. Accessed 04 June 2020.

Carrier M (2019), Abou-Nassar K, Mallick R, et al, AVERT Investigators. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med. 2019;380(8):711-719.

Cho BC (2020), Lee KH, Cho EK, et al. Amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in combination with lazertinib, a 3rd-generation tyrosine kinase inhibitor (TKI), in advanced EGFR NSCLC. Annals Oncol. 2020;31(suppl_4):S754-S840.

Ciuleanu T (2009), Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet. 2009;374:1432-1440.

European Society for Medical Oncology (ESMO 2020). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Available at: https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer. Accessed 13 January 2021.

Fischer A, Rosen AC, Ensslin CJ, Wu S, Lacouture ME. Pruritus to anticancer agents targeting the EGFR, BRAF, and CTLA-4. Dermatol Ther. 2013;26(2):135-148.

Globocan (2012): Estimated cancer incidence, mortality and prevalence worldwide in 2012. World Health Organization International Agency for Research on Cancer. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx?cancer=lung. Accessed 07 September 2015.

Galluzzi L (2015), Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell. 2015;28(6):690-714.

Griesinger F (2019), Korol EE, Kayaniyil S, Varol N, Ebner T, Goring SM. Efficacy and safety of first-line carboplatin-versus cisplatin-based chemotherapy for non-small cell lung cancer: A meta-analysis. Lung Cancer. 2019;135:196-204.

Harrison PT (2020), Vyse S, Huang PH. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. Semin Cancer Biol. 2020;61:167-179.

Haura EB (2019), Cho BC, Lee JS, et al. JNJ-61186372 (JNJ-372), an EGFR-cMet bispecific antibody, in EGFR-driven advanced non-small cell lung cancer (NSCLC). J Clin Oncol. 2019;37(Suppl15):9009 [abstract].

Herbst RS (2018), Morgensztern D, Boshoff C. The biology and management of non-small-cell lung cancer. Nature. 2018;553(7689):446-454.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of the EQ-5D (EQ-5D-5L). Qual Lif Res. 2011;1727-1736.

Hosomi Y (2020), Morita S, Sugawara S, et al. Gefitinib alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated epidermal growth factor receptor: NEJ009 Study. J Clin Oncol. 2020;38(2):115-123.

Investigator's Brochure: Amivantamab (JNJ-61186372). Janssen Research & Development, LLC.

Investigator's Brochure: Lazertinib (JNJ-73841937) . Janssen Research & Development, LLC .

Jang SB (2021), Kim KB, Sim S, et al. Cardiac safety assessment of lazertinib: findings from patients with EGFR mutation-positive advanced NSCLC and preclinical studies. JTO Clinical and Research Reports. 2021;2(10):1-11.

Janjigian YY (2014), Smit EF, Groen HJM, et al. Dual Inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. Cancer Discovery. 2014;4(9): 1036–1045.

Jänne PA (2006), Johnson BE. Effect of Epidermal Growth Factor Receptor Tyrosine Kinase Domain Mutations on the Outcome of Patients with Non–Small Cell Lung Cancer Treated with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors. Clinical Cancer Research. 2006;12(14):4416s-4420s.

Jänne PA (2015), Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med. 2015;372(18):1689-1699.

Kluetz PG (2016), Slagle A, Papadopoulos EJ, et al. Focusing on core patient-reported outcomes in cancer clinical trials: symptomatic adverse events, physical function, and disease-related symptoms. Clin Cancer Res. 2016:22(7);1553-1558.

Leighl NB (2020), Karaseva N, Nakagawa K, et al. Patient-reported outcomes from FLAURA: Osimertinib versus erlotinib or gefitinib in patients with EGFR-mutated advanced non-small-cell lung cancer. Eur J Cancer. 2020;125:49-57.

Leonetti A (2019), Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. Br J Cancer. 2019;121(9):725-737.

Li M (2012), Zhang Q, Fu P, et al. Pemetrexed plus platinum as the first-line treatment option for advanced non-small cell lung cancer: a meta-analysis of randomized controlled trials. PLoS One 2012;7:e37229.

Maurer W(2013), Bretz F. Multiple testing in group sequential trials using graphical approaches. Statistics in Biopharmaceutical Research. 2013;5(4):311-320.

McCarrier KP (2016), Atkinson TM, Debusk K, Coons SJ, on behalf of the small cell lung cancer working group. Qualitative development and content validity of the non-small cell lung cancer symptom assessment questionnaire (NSCLC-SAQ), a patient-reported outcome instrument. Clin Therapeutics. 2016;38(4):794-810.

Mok TS (2017), Wu Y-L, Ahn M-J, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. 2017;376(7):629-640.

Montazeri A (1998), Gillis CR, McEwen J. Quality of life in patients with lung cancer: a review of literature from 1970 to 1995. Chest. 1998;113(2):467-481.

National Comprehensive Cancer Network (NCCN 2021). Non-Small Cell Lung Cancer (Version 3.2021). Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 01 March 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines). Cancer-Associated Venous Thromboembolic Disease. Version 1.2022. https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1423. Accessed 02 August 2022.

National Institutes of Health (NIH 2021). The PRO-CTCAE Measurement System. Available at: https://healthcaredelivery.cancer.gov/pro-ctcae/measurement html. Accessed 27 May 2021.

Noronha V (2020), Patil VM, Joshi A, et al. Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in *EGFR*-mutated lung cancer. J Clin Oncol. 2020;38(2):124-136.

Oken MM (1982), Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-656.

Pao W (2011), Girard N. New driver mutations in non-small-cell lung cancer. Lancet Oncol. 2011;12(2):175-180.

Pakzad R (2015), Mohammadian-Hafshejani A, Ghoncheh M, Pakzad I, Salehiniya H. The incidence and mortality of lung cancer and their relationship to development in Asia. Transl Lung Cancer Res. 2015;4(6):763-774.

Park K (2020), John T, Kim S, et. al. Amivantamab (JNJ-61186372), an anti-EGFR-MET bispecific antibody, in patients with EGFR exon 20 insertion (exon20ins)-mutated non-small cell lung cancer (NSCLC). J Clin Oncol. 2020;38:Abstract 9512.

Peeters M (2010), Price TJ, Cervantes, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010;28:4706-4713.

Planchard D (2018), Popat S, Kerr K, et al; ESMO Guidelines Committee. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl4):iv192-iv237.

Ramalingam SS (2020), Vansteenkiste J, Planchard D, et al; FLAURA Investigators. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med. 2020;382(1):41-50.

Reungwetwattana T (2018), Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. J Clin Oncol. 2018;36(33):3290-3297.

Rutges AWS (2022), Porreca E, Candeloro M, Valeriani E, Di Nisio M. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008500.pub5/full. Accessed 02 August 2022

Soria JC (2015), Wu YL, Nakagawa K, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol. 2015;16:990-998.

Soria JC (2018), Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018;378(2):113-125.

Surveillance, Epidemiology, and End Results Program (SEER) (2021). Cancer Stat Facts: lung and bronchus cancer. Available at: http://seer.cancer.gov/statfacts/html/lungb.html. Accessed 24 June 2021.

Tanaka K (2021), Asahina H, Kishimoto J, et al. Osimertinib versus osimertinib plus chemotherapy for non-small cell lung cancer with EGFR (T790M)-associated resistance to initial EGFR inhibitor treatment: An open-label, randomised phase 2 clinical trial. Eur J Cancer. 2021;149:14-22.

Treat J (2012), Scagliotti GV, Peng G, et al: Comparison of pemetrexed plus cisplatin with other first-line doublets in advanced non-small cell lung cancer (NSCLC): a combined analysis of three phase 3 trials. Lung Cancer. 2012;76(2):222-227.

US FDA. Drug development and drug interactions: Table of Substrates, Inhibitors and Inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed 02 May 2022.

World Health Organization (2012). Blood Donor Selection: Guidelines on Assessing Donor Suitability for Blood Donation: 4, General donor assessment. Geneva. Available from: https://www.ncbi nlm nih.gov/books/NBK138219/

Xu JL (2015), Jin B, Ren ZH, et al. Chemotherapy plus erlotinib versus chemotherapy alone for treating advanced non-small cell lung cancer: a meta-analysis. PLoS One. 2015;10(7):e0131278.

INVESTIGATOR AGREEMENT

JNJ-61186372 (amivantamab) and JNJ-73841937 (lazertinib) Clinical Protocol 61186372NSC3002 Amendment 7

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD _____

Institution PPD velopment _____

Signature _____ Date: PPD

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 05 April 2024

Janssen Research & Development *

Clinical Protocol

GUIDANCE ON STUDY CONDUCT DURING NATURAL DISASTER /MAJOR DISRUPTION/PANDEMIC

Protocol Title

A Phase 3, Open-Label, Randomized Study of Amivantamab and Lazertinib in Combination with Platinum-Based Chemotherapy Compared with Platinum-Based Chemotherapy in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer After Osimertinib Failure

MARIPOSA-2

Protocol 61186372NSC3002; Phase 3

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

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312). Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation [EU] No 536/2014.

Regulatory Agency Identifier Number(s):
IND: 146319
EU Trial NUMBER: 2023-506518-33

Status:	Approved
Date:	05 April 2024
Prepared by:	Janssen Research & Development, LLC
EDMS number:	EDMS-RIM-1251528, 1.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

Study Conduct During a Natural Disaster/Major Disruption/Pandemic

GUIDANCE ON STUDY CONDUCT DURING NATURAL DISASTER/ MAJOR DISRUPTION/PANDEMIC

It is recognized that the natural disaster/major disruption/pandemic may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the natural disaster/major disruption/pandemic scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "Natural Disaster-related"/Major Disruption-related/Pandemic-related" (eg, "Regional crisis", "COVID-19-related") in the eCRF

NATURAL DISASTER/MAJOR DISRUPTION (eg, regional crisis): The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. Modifications made to the study conduct as a result of the natural disaster/major disruption should be summarized in the clinical study report.

PANDEMIC (eg, COVID-19): If the participant has tested positive for the pandemic (eg, COVID-19), the investigator should contact the sponsor's responsible medical officer to discuss plans for administration of study intervention, performing. study assessments, and follow-up. Modifications made to the study conduct as a result of the pandemic (eg, COVID-19) should be summarized in the clinical study report.

Consent/Screening

- Consenting of participants for study screening can be performed remotely by telephone or video conferencing per local policies and regulations. Re-consenting of active participants due to new safety information or updated study design should also be assessed for its feasibility to be conducted remotely per local policies and regulations.
- All screening procedures and assessments must be conducted per protocol at the investigative site.
- During screening of participants, the investigator should evaluate the feasibility of participants returning for scheduled dosing visits per protocol based on history of exposure to a pandemic and local travel restrictions due to a natural disaster or major disruption. If the situation suggests that this is not possible, the participant may be screen failed and re-screened when conditions improve.
- Screening procedures to a pandemic that may be mandated by local healthcare systems do not need to be reported as an amendment to the protocol even if done during clinical study visits.
- As SARS-CoV-2 represents a new infectious agent, and COVID-19 a new clinical syndrome, it is unclear how infection with this virus will impact the benefit/risk assessment with regards to study treatment, particularly given its association with the risk of severe viral pneumonia. As per the study exclusion criteria, participants with active infection, including viral illnesses such as COVID-19, should be excluded from study participation.

Study Treatment

Study treatment should continue to be administered at the investigative site in accordance with the protocol. Potential interruptions to therapy should be assessed on a case-by-case basis and include consideration of potential impact on participant's safety. If doses are missed or delayed due to natural disaster, major disruption or pandemic related circumstances, these deviations should be noted in the appropriate eCRF page, as "missed or delayed due to natural disaster/major disruption/pandemic", as applicable. The sponsor's medical monitor should be alerted to any anticipated interruption in study treatment.

Study treatment should be held for all participants with suspected (symptomatic) or documented SARS-CoV-2 positive disease, until recovery from all infection-related symptoms. The latest official guidance (eg, United States Food and Drug Administration, American Society of Clinical Oncology, European Society of Medical Oncology) should be followed and treatment decisions should be made in consultation with the medical monitor. Given the unmet medical need of this study population, and the unknown impact of prior COVID-19 infection on the risk of study treatment, re-initiation of study treatments should be evaluated with the medical monitor on a case-by-case basis, taking into account the severity of the COVID-19 related symptoms, and the observed clinical benefit from study treatment. Please report the event to the sponsor, following usual adverse event (AE) reporting requirements.

Note: Administration of non-live vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed before or during this study.

Treatment and Follow-up Visits

All study visits and assessments specified in the Schedule of Activities including key efficacy endpoint assessments should be followed in accordance to the protocol, unless natural disaster, major disruption, or pandemic related staffing shortages, site policies, or travel restrictions render these infeasible. In such cases, the following modifications may be implemented:

- If study imaging procedures cannot be performed at the active clinical study site, participants will be permitted to use other local imaging facilities (eg, at hospitals that are not the active study site). In these cases, digital copies should be made available to the investigator for submission to the central imaging vendor.

- Safety evaluations (eg, laboratory assessments) may be conducted at certified testing and triage facilities or at other local hospitals. Records for these evaluations must be available for the investigator to review prior to dosing and copies of the results should be included in the participant's study chart as a source document.

Audits

- During the natural disaster/major disruption/pandemic (eg, COVID-19) at the impacted sites, clinical site Good Clinical Practice (GCP) audits with direct impact/engagement with the clinical Investigator team will not be conducted to comply with national, local and/or organizational restrictions. Additional quality assurance activities such as remote audits or focused review of study-related documents may take place with limited impact/engagement, if possible.

Telemedicine/Teleconferencing/Videoconferencing:

If the participant is doing well and has no safety concerns, scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually (eg, conducted via phone or computer), where feasible, or delayed until such time which access is determined to be appropriate by the Investigator and Sponsor. At each telephone or telemedicine contact:

- Review of new, and follow-up of existing, AEs and concomitant medications between regularly scheduled on-site visits (eg, weekly assessments of AEs leading to treatment delay).

- The participant can complete any scheduled patient-reported outcome (PRO) assessments.
- Review of body systems and collection of general health status (to be followed up with in-person examination if indicated) prior to dosing days, if consistent with site's typical practice.

- Study assessments requiring investigator judgement should be conducted by the investigator.

Home Health Care

Blood sample collection may be done at the participant's home by mobile study personnel (ie, nurse or mobile phlebotomist) or at a commercial laboratory (eg, LabCorp). Other programs may be implemented with approval from the sponsor, such as Home Health Care Visits on a case-by-case basis for study assessments and procedures (eg, physical exam), where feasible and permissible by local policy and regulations. Study treatment with amivantamab and/or chemotherapy will only be administered at the study site and will not be administered at Home Health Care Visits.

Flexibility for all protocol-required assessments will be provided on a case-by-case basis, and with agreement between the sponsor and investigator. However, every effort should be made to adhere to protocol-specified assessments, including follow-up, if it is in the best interest of the participant.

Monitoring Visits

When on-site monitoring by the sponsor is not feasible due to changes in hospital or clinic's visitation policies, the sponsor's site monitor will contact the study site to schedule remote visits. In such cases, on-site monitoring visits will resume when feasible, with increased frequency to address the source data verification backlog.

Even with staffing limitations during a natural disaster, major disruption, or pandemic, all routine operations related to clinical trials should be well-documented and archived as part of standard process. When conditions permit, all parties involved in this clinical trial should communicate relevant information in a timely manner so that all relevant parties remain sufficiently informed to take any necessary measures in a timely manner.

Transfer of study subjects:

For regions significantly impacted by the major disruption, the investigator and sponsor may explore the possibility of transferring subjects to nearby, less impacted study sites (if warranted). In addition, for subjects relocating to other countries, on either a temporary or permanent basis, transfer to existing study sites in these countries may be explored. The sponsor should be informed of any decisions related to the transfer of subjects to other study sites prior to their transfer. In case there is an urgent need to open new trial site(s) for clinical trial visits, for example outside the hospital, this may be implemented by the sponsor per local Health Authority.

INVESTIGATOR AGREEMENT

Guidance on Study Conduct During Natural Disaster/Major Disruption/Pandemic
JNJ-61186372 (amivantamab) and JNJ-73841937 lazertinib Clinical Protocol 61186372NSC3002

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: PPD

PPD

Signature: _____ Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 05 April 2024