

METHODS OF TREATING NON-SMALL CELL LUNG CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/536,575, filed on September 5, 2023, and U.S. Provisional Application No. 63/564,664, filed on March 13, 2024, the disclosures of each of which are herein incorporated by reference in their entireties.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. The XML copy, created on September 3, 2024, is named JBI6835_SeqListing.xml and is 20,480 bytes in size.

FIELD

[0003] The present disclosure provides methods for treating Epidermal Growth Factor Receptor (EGFR)-positive non-small cell lung cancer (NSCLC) in a subject that had disease progression on or after treatment with at least one prior tyrosine kinase inhibitor (TKI).

BACKGROUND

[0004] Stratification of advanced non-small cell lung cancer (NSCLC) based on oncogenic driver mutations has improved the overall survival and quality of life for patients with actionable driver mutations and effectiveness of solid tumor targeted therapy. In NSCLC, specific mutations in the EGFR gene are associated with high response rates to EGFR tyrosine kinase inhibitors (EGFR-TKIs). Although the majority of NSCLC patients with EGFR mutations initially respond to EGFR TKI therapy, virtually all acquire resistance that prevents a durable response. Nearly 60% of all tumors that become resistant to EGFR tyrosine kinase inhibitors increase Hepatocyte Growth Factor Receptor (c-Met) expression, amplify the c-Met gene, or increase its only known ligand, Hepatocyte Growth Factor (Turke et al., Cancer Cell, 17:77-88, 2010).

[0005] Progression of acquired resistance to EGFR-TKI such as osimertinib in epidermal growth factor receptor mutant (EGFRm) NSCLC likely arises from complex and heterogenous patterns of resistance together with co-occurrence of multiple resistance mechanisms, and as such the details of such mechanisms remain elusive. Thus, duration and

durability of response with targeted therapies pose unique challenges, and there remains a need for new treatment paradigms for patients with NSCLC that had disease progression on or after treatment with at least one prior tyrosine kinase inhibitor (TKI).

SUMMARY

[0006] In one aspect, provided herein is a method of improving median progression free survival (PFS) in a population of subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring one or more epidermal growth factor receptor (EGFR) mutations whose NSCLC progressed on or after treatment with at least one prior tyrosine kinase inhibitor (TKI), said method comprising administering to the population of subjects a combination therapy comprising: (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody, (ii) a therapeutically effective amount of carboplatin, and (iii) a therapeutically effective amount of pemetrexed, wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with the at least one prior TKI, said reference population having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody.

[0007] In another aspect, provided herein is a method of improving median progression free survival (PFS) in a population of subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring one or more epidermal growth factor receptor (EGFR) mutations whose NSCLC progressed on or after treatment with at least one prior tyrosine kinase inhibitor (TKI), said method comprising administering to the population of subjects a combination therapy comprising: (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody, (ii) a therapeutically effective amount of lazertinib, or a pharmaceutically acceptable salt or hydrate thereof, (iii) a therapeutically effective amount of carboplatin, and (iv) a therapeutically effective amount of pemetrexed, wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with the at least one prior TKI, said reference population having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody nor said lazertinib or pharmaceutically acceptable salt or hydrate thereof. In some embodiments, the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, is lazertinib mesylate. In some embodiments, the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, is

lazertinib mesylate monohydrate. In some embodiments, the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, is administered at a dose of about 240 mg orally, once daily.

[0008] In some embodiments of any of the above methods of this disclosure, the bispecific anti-EGFR/c-Met antibody comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6, and wherein the second domain that binds c-Met comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.

[0009] In some embodiments of any of the above methods of this disclosure, the one or more EGFR mutations comprise one or more exon 19 deletions, or exon 21 L858R substitution, or any combination thereof. In some embodiments of any of the above methods of this disclosure, the one or more EGFR mutations comprise one or more exon 19 deletions. In some embodiments of any of the above methods of this disclosure, the one or more EGFR mutations comprise exon 21 L858R substitution.

[0010] In some embodiments of any of the above methods of this disclosure, said at least one prior TKI comprises a 1st generation EGFR TKI. In some embodiments of any of the above methods of this disclosure, said at least one prior TKI comprises a 2nd generation EGFR TKI. In some embodiments of any of the above methods of this disclosure, said at least one prior TKI comprises a 3rd generation EGFR TKI. In some embodiments of any of the above methods of this disclosure, said at least one prior TKI comprises osimertinib.

[0011] In some embodiments of any of the above methods of this disclosure, administration of the combination therapy begins on Cycle 1 Day 1 of the first 21-day cycle, and continues in subsequent 21-day cycles.

[0012] In some embodiments of any of the above methods of this disclosure, the bispecific anti-EGFR/c-Met antibody is administered intravenously. In some embodiments of any of the above methods of this disclosure, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.

[0013] In some embodiments of any of the above methods of this disclosure, the method comprises administering the bispecific anti-EGFR/c-Met antibody in an amount of between about 140 mg and about 2240 mg. In some embodiments of any of the above methods of this disclosure, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 700 mg,

about 750 mg, about 800 mg, about 850 mg, 900 mg, 950 mg, 1000 mg, 1050 mg, 1100 mg, 1150 mg, 1200 mg, 1250 mg, 1300 mg, 1350 mg, 1400 mg, 1575 mg, 1600 mg, 1750 mg, 2100 mg, or 2240 mg.

[0014] In some embodiments of any of the above methods of this disclosure, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg. In some embodiments of any of the above methods of this disclosure wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.

[0015] In some embodiments of any of the above methods of this disclosure, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg.

[0016] In some embodiments of any of the above methods of this disclosure, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg. In some embodiments of any of the above methods of this disclosure wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.

[0017] In some embodiments of any of the above methods of this disclosure, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg.

[0018] In some embodiments of any of the above methods of this disclosure, the method comprises administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles.

[0019] In some embodiments of any of the above methods of this disclosure, the method comprises administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression.

[0020] In some embodiments of any of the above methods of this disclosure, the method comprises: a) (i) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg; or (ii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg; or (iii) administering the bispecific anti-EGFR/c-Met antibody at a

dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg; or (iv) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg; and b) administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles; and c) administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression. In some embodiments of any of the above methods of this disclosure wherein the dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.

[0021] In some embodiments of any of the above methods of this disclosure, the combination therapy achieves an improvement in the median PFS of at least two weeks. In some embodiments of any of the above methods of this disclosure, the combination therapy achieves an improvement in the median PFS of at least 1 month. In some embodiments of any of the above methods of this disclosure, the combination therapy achieves an improvement in the median PFS of at least 1.5 months. In some embodiments of any of the above methods of this disclosure, the combination therapy achieves an improvement in the median PFS of at least 2 months. In some embodiments of any of the above methods of this disclosure, the subject exhibits PFS for at least 4.5 months. In some embodiments of any of the above methods of this disclosure, the subject exhibits PFS for at least 5 months. In some embodiments of any of the above methods of this disclosure, the subject exhibits progression-free survival for at least 5.5 months. In some embodiments of any of the above methods of this disclosure, the subject exhibits PFS for at least 6 months. In some embodiments of any of the above methods of this disclosure, the subject exhibits progression-free survival for at least 10 months. In some embodiments of any of the above methods of this disclosure, the subject exhibits PFS for at least 12 months. In some embodiments of any of the above methods of this disclosure, the subject exhibits PFS for at least 14 months.

[0022] In some embodiments of any of the above methods of this disclosure, the combination therapy further achieves an improvement in objective response relative to said reference population. In some embodiments of any of the above methods of this disclosure, the combination therapy further achieves an improvement in overall survival (OS) relative to said reference population. In some embodiments of any of the above methods of this disclosure, the combination therapy further achieves an improvement in duration of response (DoR) relative to said reference population. In some embodiments of any of the above methods of this disclosure, the combination therapy further achieves an improvement in time to subsequent

therapy relative to said reference population. In some embodiments of any of the above methods of this disclosure, the combination therapy further achieves an improvement in PFS after first subsequent therapy (PFS2) relative to said reference population. In some embodiments of any of the above methods of this disclosure, the combination therapy further achieves an improvement in intracranial median PFS relative to said reference population.

[0023] In one aspect, provided herein is a method of improving median overall survival (OS) in a population of subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring one or more epidermal growth factor receptor (EGFR) mutations whose NSCLC progressed on or after treatment with at least one prior tyrosine kinase inhibitor (TKI), said method comprising administering to the population of subjects a combination therapy comprising: (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody, (ii) a therapeutically effective amount of carboplatin, and (iii) a therapeutically effective amount of pemetrexed, wherein the improvement in median OS is relative to median OS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with the at least one prior TKI, said reference population having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody.

[0024] In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6, and wherein the second domain that binds c-Met comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.

[0025] In some embodiments, the one or more EGFR mutations comprise one or more exon 19 deletions, or exon 21 L858R substitution, or any combination thereof.

[0026] In some embodiments, the one or more EGFR mutations comprise one or more exon 19 deletions. In some embodiments, the one or more EGFR mutations comprise exon 21 L858R substitution.

[0027] In some embodiments, said at least one prior TKI comprises a 1st generation EGFR TKI. In some embodiments, said at least one prior TKI comprises a 2nd generation EGFR TKI.

In some embodiments, said at least one prior TKI comprises a 3rd generation EGFR TKI. In some embodiments, said at least one prior TKI comprises osimertinib.

[0028] In some embodiments, administration of the combination therapy begins on Cycle 1 Day 1 of the first 21-day cycle, and continues in subsequent 21-day cycles.

[0029] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered intravenously. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.

[0030] In some embodiments, the method comprises administering the bispecific anti-EGFR/c-Met antibody in an amount of between about 140 mg and about 2240 mg.

[0031] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 700 mg, about 750 mg, about 800 mg, about 850 mg, 900 mg, 950 mg, 1000 mg, 1050 mg, 1100 mg, 1150 mg, 1200 mg, 1250 mg, 1300 mg, 1350 mg, 1400 mg, 1575 mg, 1600 mg, 1750 mg, 2100 mg, or 2240 mg.

[0032] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg.

[0033] In some embodiments, the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.

[0034] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg.

[0035] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg.

[0036] In some embodiments, the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.

[0037] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg.

[0038] In some embodiments, the method comprises administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles.

[0039] In some embodiments, the method comprises administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression.

[0040] In some embodiments, the method comprises:

- a) (i) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg; or
- (ii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg; or
- (iii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg; or
- (iv) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg;

[0041] and

- b) administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles;

and

- c) administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression.

[0042] In some embodiments, the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.

[0043] In some embodiments, the combination therapy achieves an improvement in the median OS of at least two months.

[0044] In some embodiments, the combination therapy achieves an improvement in the median OS of at least 2.4 months.

[0045] In some embodiments, the combination therapy achieves an improvement in the median OS of about 2.4 months.

[0046] In some embodiments, the subject exhibits overall survival for at least 17 months.

[0047] In some embodiments, the subject exhibits overall survival for at least about 17.7 months.

[0048] In some embodiments, the subject exhibits overall survival for about 17.7 months.

[0049] In some embodiments, the combination therapy further achieves an improvement in time to symptomatic progression (TTSP) relative to said reference population.

[0050] In some embodiments, the combination therapy further achieves an improvement in time to subsequent therapy (TTST) relative to said reference population.

[0051] In some embodiments, the combination therapy further achieves an improvement in PFS after first subsequent therapy (PFS2) relative to said reference population.

[0052] In some embodiments, the combination therapy further achieves an improvement in time to treatment discontinuation (TTD) relative to said reference population.

BRIEF DESCRIPTION OF THE DRAWINGS

[0053] FIG. 1 shows an exemplary schematic overview of the study.

[0054] FIG. 2 shows MARIPOSA-2 Study Design. *a* - Analyses were further stratified based on osimertinib line of therapy, history of brain metastases, and race (Asian vs non-Asian). ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; OS, overall survival.

[0055] FIG. 3 shows Overall Survival. Ami, amivantamab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival.

[0056] FIG. 4 shows Time to Symptomatic Progression (TTSP). Ami, amivantamab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; TTSP, time to symptomatic progression.

[0057] FIG. 5 shows Time to Treatment Discontinuation. Ami, amivantamab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; PD, progressive disease; TTD, time to treatment discontinuation.

[0058] FIG. 6 shows Time to Subsequent Therapy. Ami, amivantamab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; TTST, time to subsequent therapy.

[0059] FIG. 7 shows PFS After First Subsequent Therapy. Ami, amivantamab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; PFS2, progression-free survival after first subsequent therapy.

DETAILED DESCRIPTION

Definitions

[0060] All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

[0061] It is to be understood that the terminology used herein is for describing particular embodiments only and is not intended to be limiting. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

[0062] Although any methods and materials similar or equivalent to those described herein may be used in the practice for testing of the present invention, exemplary materials and methods are described herein. In describing and claiming the present invention, the following terminology will be used.

[0063] When a list is presented, unless stated otherwise, it is to be understood that each individual element of that list, and every combination of that list, is a separate embodiment. For example, a list of embodiments presented as “A, B, or C” is to be interpreted as including the embodiments, “A,” “B,” “C,” “A or B,” “A or C,” “B or C,” or “A, B, or C.”

[0064] As used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to “a cell” includes a combination of two or more cells, and the like.

[0065] The conjunctive term “and/or” between multiple recited elements is understood as encompassing both individual and combined options. For instance, where two elements are conjoined by “and/or,” a first option refers to the applicability of the first element without the second. A second option refers to the applicability of the second element without the first. A third option refers to the applicability of the first and second elements together. Any one of these options is understood to fall within the meaning, and therefore satisfy the requirement of the term “and/or” as used herein. Concurrent applicability of more than one of the options is also understood to fall within the meaning, and therefore satisfy the requirement of the term “and/or.”

[0066] The transitional terms “**comprising**,” “**consisting essentially of**,” and “**consisting of**” are intended to connote their generally accepted meanings in the patent vernacular; that is, (i) “comprising,” which is synonymous with “including,” “containing,” or “characterized by,” is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; (ii) “consisting of” excludes any element, step, or ingredient not specified in the claim; and (iii) “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. Embodiments described in terms of the phrase “comprising” (or its equivalents) also provide as embodiments those independently described in terms of “consisting of” and “consisting essentially of.”

[0067] “Co-administration,” “administration with,” “administration in combination with,” “in combination with” or the like, encompass administration of the selected therapeutics or drugs to a single patient, and are intended to include treatment regimens in which the therapeutics or drugs are administered by the same or different route of administration or at the same or different time.

[0068] “Isolated” refers to a homogenous population of molecules (such as synthetic polynucleotides, polypeptides vectors or viruses) which have been substantially separated and/or purified away from other components of the system the molecules are produced in, such as a recombinant cell, as well as a protein that has been subjected to at least one purification or isolation step. “Isolated” refers to a molecule that is substantially free of other cellular material and/or chemicals and encompasses molecules that are isolated to a higher purity, such as to 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% purity.

[0069] “Treat,” “treating” or “treatment” of a disease or disorder such as cancer refers to accomplishing one or more of the following: reducing the severity and/or duration of the disorder, inhibiting worsening of symptoms characteristic of the disorder being treated, limiting or preventing recurrence of the disorder in subjects that have previously had the disorder, or limiting or preventing recurrence of symptoms in subjects that were previously symptomatic for the disorder.

[0070] “Prevent,” “preventing,” “prevention”, or “prophylaxis” of a disease or disorder means preventing that a disorder occurs in subject.

[0071] “Diagnosing” or “diagnosis” refers to methods to determine if a subject is suffering from a given disease or condition or may develop a given disease or condition in the future or is likely to respond to treatment for a prior diagnosed disease or condition, i.e., stratifying a patient population on likelihood to respond to treatment. Diagnosis is typically performed by a physician based on the general guidelines for the disease to be diagnosed or other criteria that indicate a subject is likely to respond to a particular treatment.

[0072] “Responsive”, “responsiveness” or “likely to respond” refers to any kind of improvement or positive response, such as alleviation or amelioration of one or more symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable.

[0073] “**Therapeutically effective amount**” refers to an amount effective, at doses and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount may vary depending on factors such as the disease state, age, sex, and weight of the individual, and the ability of a therapeutic or a combination of therapeutics to elicit a desired response in the individual. Exemplary indicators of an effective therapeutic or combination of therapeutics that include, for example, improved well-being of the patient.

[0074] “**Subject**” includes any human or nonhuman animal. “**Nonhuman animal**” includes all vertebrates, e.g., mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, etc. The terms “subject” and “patient” are used interchangeably herein.

[0075] “**About**” means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. Unless explicitly stated otherwise within the Examples or elsewhere in the Specification in the context of a particular assay, result or embodiment, “about” means within one standard deviation per the practice in the art, or a range of up to 5%, whichever is larger.

[0076] “**Cancer**” refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread) to other areas of a patient’s body.

[0077] “**EGFR or c-Met expressing cancer**” refers to cancer that has detectable expression of EGFR or c-Met or has EGFR or c-Met mutation or amplification. EGFR or c-Met expression, amplification and mutation status can be detected using known methods, such as sequencing, fluorescent in situ hybridization, immunohistochemistry, flow cytometry or western blotting.

[0078] “**Epidermal growth factor receptor**” or “**EGFR**” refers to the human EGFR (also known as HER1 or ErbB1 (Ullrich et al., Nature 309:418-425, 1984)) having the amino acid sequence shown in GenBank accession number NP_005219, as well as naturally-occurring variants thereof.

[0079] “**Hepatocyte growth factor receptor**” or “**c-Met**” as used herein refers to the human c-Met having the amino acid sequence shown in GenBank Accession No: NP_001120972 and natural variants thereof.

[0080] “**Bispecific anti-EGFR/c-Met antibody**” or “**bispecific EGFR/c-Met antibody**” refers to a bispecific antibody having a first domain that specifically binds EGFR and a second domain that specifically binds c-Met. The domains specifically binding EGFR and c-

Met are typically VH/VL pairs, and the bispecific anti-EGFR/c-Met antibody is monovalent in terms of binding to EGFR and c-Met.

[0081] “Specific binding” or “specifically binds” or “specifically binding” or “binds” refer to an antibody binding to an antigen or an epitope within the antigen with greater affinity than for other antigens. Typically, the antibody binds to the antigen or the epitope within the antigen with an equilibrium dissociation constant (K_D) of about 5×10^{-8} M or less, for example about 1×10^{-9} M or less, about 1×10^{-10} M or less, about 1×10^{-11} M or less, or about 1×10^{-12} M or less, typically with the K_D that is at least one hundred-fold less than its K_D for binding to a non-specific antigen (e.g., BSA, casein). The dissociation constant may be measured using known protocols. Antibodies that bind to the antigen or the epitope within the antigen may, however, have cross-reactivity to other related antigens, for example to the same antigen from other species (homologs), such as human or monkey, for example *Macaca fascicularis* (cynomolgus, cyno) or *Pan troglodytes* (chimpanzee, chimp). While a monospecific antibody binds one antigen or one epitope, a bispecific antibody binds two distinct antigens or two distinct epitopes.

[0082] “Antibodies” is meant in a broad sense and includes immunoglobulin molecules including monoclonal antibodies including murine, human, humanized and chimeric monoclonal antibodies, antigen binding fragments, multispecific antibodies, such as bispecific, trispecific, tetraspecific etc., dimeric, tetrameric or multimeric antibodies, single chain antibodies, domain antibodies and any other modified configuration of the immunoglobulin molecule that comprises an antigen binding site of the required specificity. “Full length antibodies” are comprised of two heavy chains (HC) and two light chains (LC) inter-connected by disulfide bonds as well as multimers thereof (e.g., IgM). Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region (comprised of domains CH1, hinge, CH2 and CH3). Each light chain is comprised of a light chain variable region (VL) and a light chain constant region (CL). The VH and the VL regions may be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with framework regions (FR). Each VH and VL is composed of three CDRs and four FR segments, arranged from amino-to-carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4.

[0083] “Biosimilar” (of an approved reference product/biological drug, i.e., reference listed drug) refers to a biological drug that is highly similar to the reference drug with no clinically meaningful differences between the biosimilar and the reference drug in terms of safety, purity and potency, based upon data derived from (a) analytical studies that demonstrate that

the biological product is highly similar to the reference drug; (b) animal studies (including the assessment of toxicity); and/or (c) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biosimilar. The biosimilar may be an interchangeable product that may be substituted for the reference product at the pharmacy without the intervention of the prescribing healthcare professional. To meet the additional standard of “interchangeability,” the biosimilar is to be expected to produce the same clinical result as the reference product in any given patient and, if the biosimilar is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biosimilar and the reference product is not greater than the risk of using the reference product without such alternation or switch. The biosimilar utilizes the same mechanisms of action for the proposed conditions of use to the extent the mechanisms are known for the reference product. The condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biosimilar have been previously approved for the reference product. The route of administration, the dosage form, and/or the strength of the biosimilar are the same as those of the reference product and the biosimilar is manufactured, processed, packed or held in a facility that meets standards designed to assure that the biosimilar continues to be safe, pure and potent. The biosimilar may include minor modifications in the amino acid sequence when compared to the reference product, such as N- or C-terminal truncations that are not expected to change the biosimilar performance.

[0084] “Complementarity determining regions” (CDR) are antibody regions that bind an antigen. CDRs may be defined using various delineations such as Kabat (Wu et al. (1970) J Exp Med 132: 211-50) (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991), Chothia (Chothia et al. (1987) J Mol Biol 196: 901-17), IMGT (Lefranc et al. (2003) Dev Comp Immunol 27: 55-77) and AbM (Martin and Thornton (1996) J Biol Chem 271: 800-15). The correspondence between the various delineations and variable region numbering are described (see e.g., Lefranc et al. (2003) Dev Comp Immunol 27: 55-77; Honegger and Pluckthun, (2001) J Mol Biol 309:657-70; International Immunogenetics (IMGT) database; Web resources, <http://imgt.org>). Available programs such as abYsis by UCL Business PLC may be used to delineate CDRs. The term “CDR”, “HCDR1”, “HCDR2”, “HCDR3”, “LCDR1”, “LCDR2” and “LCDR3” as used herein includes CDRs defined by any of the

methods described supra, Kabat, Chothia, IMGT or AbM, unless otherwise explicitly stated in the specification.

[0085] Immunoglobulins may be assigned to five major classes, IgA, IgD, IgE, IgG and IgM, depending on the heavy chain constant domain amino acid sequence. IgA and IgG are further sub-classified as the isotypes IgA1, IgA2, IgG1, IgG2, IgG3 and IgG4. Antibody light chains of any vertebrate species may be assigned to one of two clearly distinct types, namely kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

[0086] “**Antigen binding fragment**” refers to a portion of an immunoglobulin molecule that binds an antigen. Antigen binding fragments may be synthetic, enzymatically obtainable or genetically engineered polypeptides and include the VH, the VL, the VH and the VL, Fab, F(ab')₂, Fd and Fv fragments, domain antibodies (dAb) consisting of one VH domain or one VL domain, shark variable IgNAR domains, camelized VH domains, minimal recognition units consisting of the amino acid residues that mimic the CDRs of an antibody, such as FR3-CDR3-FR4 portions, the HCDR1, the HCDR2 and/or the HCDR3 and the LCDR1, the LCDR2 and/or the LCDR3. VH and VL domains may be linked together via a synthetic linker to form various types of single chain antibody designs where the VH/VL domains may pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate single chain antibody constructs, to form a monovalent antigen binding site, such as single chain Fv (scFv) or diabody; described for example in Int. Patent Publ. Nos. WO1998/44001, WO1988/01649, WO1994/13804 and WO1992/01047.

[0087] “**Monoclonal antibody**” refers to an antibody obtained from a substantially homogenous population of antibody molecules, i.e., the individual antibodies comprising the population are identical except for possible well-known alterations such as removal of C-terminal lysine from the antibody heavy chain or post-translational modifications such as amino acid isomerization or deamidation, methionine oxidation or asparagine or glutamine deamidation. Monoclonal antibodies typically bind one antigenic epitope. A bispecific monoclonal antibody binds two distinct antigenic epitopes. Monoclonal antibodies may have heterogeneous glycosylation within the antibody population. Monoclonal antibody may be monospecific or multispecific such as bispecific, monovalent, bivalent or multivalent.

[0088] “**Recombinant**” refers to DNA, antibodies and other proteins that are prepared, expressed, created or isolated by recombinant means when segments from different sources are joined to produce recombinant DNA, antibodies or proteins.

[0089] “**Bispecific**” refers to an antibody that specifically binds two distinct antigens or two distinct epitopes within the same antigen. The bispecific antibody may have cross-reactivity to other related antigens, for example to the same antigen from other species (homologs), such as human or monkey, for example *Macaca cynomolgus* (*cynomolgus*, *cyno*) or *Pan troglodytes*, or may bind an epitope that is shared between two or more distinct antigens.

[0090] “**Antagonist**” or “**inhibitor**” refers to a molecule that, when bound to a cellular protein, suppresses at least one reaction or activity that is induced by a natural ligand of the protein. A molecule is an antagonist when the at least one reaction or activity is suppressed by at least about 20%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% more than the at least one reaction or activity suppressed in the absence of the antagonist (e.g., negative control), or when the suppression is statistically significant when compared to the suppression in the absence of the antagonist.

[0091] “**Biological sample**” refers to a collection of similar fluids, cells, or tissues isolated from a subject, as well as fluids, cells, or tissues present within a subject. Exemplary samples are biological fluids such as blood, serum and serosal fluids, plasma, lymph, urine, saliva, cystic fluid, tear drops, feces, sputum, mucosal secretions of the secretory tissues and organs, vaginal secretions, ascites fluids, fluids of the pleural, pericardial, peritoneal, abdominal and other body cavities, fluids collected by bronchial lavage, synovial fluid, liquid solutions contacted with a subject or biological source, for example, cell and organ culture medium including cell or organ conditioned medium, lavage fluids and the like, tissue biopsies, tumor tissue biopsies, tumor tissue samples, fine needle aspirations, surgically resected tissue, organ cultures or cell cultures. As a non-limiting example, the biological sample is a blood sample. As another non-limiting example, the biological sample is a plasma sample. As yet another non-limiting example, the biological sample is a tumor sample. In some embodiments, the biological sample is circulating tumor DNA (ctDNA) that may be isolated from various other biological samples disclosed herein such as, but not limited to, a blood or plasma sample. In some embodiments, the biological sample is tumor DNA that may be isolated from, e.g., a tumor sample.

[0092] “**Low fucose**” or “**low fucose content**” as used in the application refers to antibodies with fucose content of about between 1%-15%.

[0093] “**Normal fucose**” or “**normal fucose content**” as used herein refers to antibodies with fucose content of about over 50%, typically about over 80% or over 85%.

[0094] As used herein, “**treatment naïve**” refers to a subject that has been diagnosed with locally advanced or metastatic NSCLC and has not yet received anti-cancer treatment for the NSCLC; the subject is therefore chemotherapy naïve and TKI naïve, e.g., has not received chemotherapy, or a tyrosine kinase inhibitor (including 1st generation TKI, 2nd generation TKI or 3rd generation TKI), or other anti-NSCLC treatment. A method of treating a treatment naïve subject may also be referred to as first-line or front line treatment.

[0095] As used herein, RECIST v1.1 criteria refer to publicly available guidelines for response evaluation criteria in solid tumors as described by Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247, which is incorporated by reference herein. Eisenhauer et al., provide the following definitions of criteria used to determine objective tumor response for target lesions:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

As used herein, a partial response or better refers to a partial response (PR) or complete response (CR).

As used herein, progression-free survival (PFS) refers to the time from randomization in a clinical trial until the date of objective disease progression or death, whichever comes first, based on blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

As used herein, overall response (OR) is defined as those participants in a clinical trial who achieve either a PR or CR as their best response, as defined by BICR using RECIST v1.1.

As used herein, overall survival (OS) is defined as the time from the date of randomization in a clinical trial until the date of death due to any cause.

As used herein, the duration of response (DoR) is defined as the time from the date of first documented response (PR or CR) in a clinical trial until the date of documented progression or death, whichever comes first, for participants who have PR or CR.

As used herein, the Time to Subsequent Therapy (TTST) is defined as the time from the date of randomization in a clinical trial to the start date of the subsequent anticancer therapy following study treatment discontinuation or death, whichever comes first.

As used herein, the Progression-free Survival After the First Subsequent Therapy (PFS2) is defined as the time from randomization in a clinical trial 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.

As used herein, the Time to Symptomatic Progression (TTSP) is defined as the time from randomization in a clinical trial to documentation 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.

As used herein, Intracranial Progression-Free Survival (Intracranial PFS) is defined as the time from randomization in a clinical trial 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.

Methods of the disclosure

[0096] Resistance to osimertinib is diverse, polyclonal, and difficult to treat. There are currently no targeted therapies approved in the post-osimertinib setting. Two studies of immunotherapy-chemotherapy regimens have recently failed to show efficacy in the TKI-resistant setting. Currently, there are 6 other phase 3 studies (NCT05261399, NCT04765059, NCT05089734, NCT05338970, NCT04656652, NCT05184712) investigating targeted therapy combinations versus chemotherapy as second-line (or later) treatment in EGFR-mutated advanced NSCLC, highlighting the unmet need in this patient population.

[0097] The present invention is directed to novel regimens for the treatment of patients with EGFR-mutated advanced NSCLC whose disease had progressed on or after a TKI therapy, such as osimertinib. Embodiments of the present invention provide methods of significantly improving progression-free survival with amivantamab- chemotherapy and amivantamab-

lazertinib-chemotherapy compared with chemotherapy in patients with EGFR-mutated advanced NSCLC whose disease had progressed on or after osimertinib monotherapy.

[0098] According to an embodiment of the present invention, a method of improving median PFS in a population of subjects with locally advanced or metastatic (NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with at least one prior TKI (i.e., the subjects are not treatment naïve but have previously received TKI therapy), comprises administering to the population of subjects a combination therapy comprising: (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody, (ii) a therapeutically effective amount of carboplatin, and (iii) a therapeutically effective amount of pemetrexed wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with the prior TKI, said reference population having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody.

[0099] According to another embodiment of the present invention, a method of improving median PFS in a population of subjects with locally advanced or metastatic NSCLC harboring one or more epidermal growth factor receptor (EGFR) mutations whose NSCLC progressed on or after treatment with a prior TKI (i.e., the subjects are not treatment naïve but have previously received TKI therapy), comprises administering to the population of subjects a combination therapy comprising: (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody, (ii) a therapeutically effective amount of lazertinib, or a pharmaceutically acceptable salt or hydrate thereof, (iii) a therapeutically effective amount of carboplatin, and (iv) a therapeutically effective amount of pemetrexed, wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with a third-generation TKI, said reference population having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody nor said lazertinib or pharmaceutically acceptable salt or hydrate thereof.

[00100] According to an embodiment of the present invention, a method of improving median intracranial PFS in a population of subjects with locally advanced or metastatic NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with at least one prior TKI (i.e., the subjects are not treatment naïve but have previously received TKI therapy), comprises administering to the population of subjects a combination therapy comprising: (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody, (ii) a therapeutically effective amount of carboplatin, and (iii) a therapeutically effective

amount of pemetrexed wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with the prior TKI, said reference population having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody.

[00101] According to another embodiment of the present invention, a method of improving median intracranial PFS in a population of subjects with locally advanced or metastatic NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with a prior TKI (i.e., the subjects are not treatment naïve but have previously received TKI therapy), comprises administering to the population of subjects a combination therapy comprising: (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody, (ii) a therapeutically effective amount of lazertinib, or a pharmaceutically acceptable salt or hydrate thereof, (iii) a therapeutically effective amount of carboplatin, and (iv) a therapeutically effective amount of pemetrexed, wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with a third-generation TKI, said reference population having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody nor said lazertinib or pharmaceutically acceptable salt or hydrate thereof.

[00102] According to another embodiment of the present invention, a method of treating a subject with locally advanced or metastatic NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with a prior TKI (i.e., the subjects are not treatment naïve but have previously received TKI therapy), comprises administering to the subject a combination therapy comprising: (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody, (ii) a therapeutically effective amount of lazertinib, or a pharmaceutically acceptable salt or hydrate thereof, (iii) a therapeutically effective amount of carboplatin, and (iv) a therapeutically effective amount of pemetrexed, wherein administration of the combination therapy begins on Cycle 1 Day 1 of a first 21-day cycle, and continues in subsequent 21-day cycles, and wherein the method comprises administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, after administration of the carboplatin is completed (e.g., wherein the method comprises: (a) administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles, and (b) administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, at a dose of about 240 mg orally, once daily starting Cycle 5 Day 1 or sooner if said carboplatin is discontinued earlier).

[00103] In some embodiments, the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, is lazertinib mesylate. In some embodiments, the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, is lazertinib mesylate monohydrate.

[00104] In some embodiments, the method comprises administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, at a dose of about 240 mg orally, once daily.

[00105] In some embodiments, the method comprises administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, at a dose of about 240 mg orally, once daily starting Cycle 5 Day 1 or sooner if said carboplatin is discontinued earlier.

[00106] In some embodiments, the one or more EGFR mutations comprise one or more exon 19 deletions, or exon 21 L858R substitution, or any combination thereof. In some embodiments, the one or more EGFR mutations comprise one or more exon 19 deletions. In some embodiments, the one or more EGFR mutations comprise exon 21 L858R substitution.

[00107] In some embodiments, the at least one prior TKI comprises a 1st generation EGFR TKI. In some embodiments, the at least one prior TKI comprises a 2nd generation EGFR TKI. In some embodiments, the at least one prior TKI comprises a 2nd generation EGFR TKI. In some embodiments, the at least one prior TKI comprises osimertinib. EGFR-TKIs are EGFR-targeted agents that interfere with EGFR signaling. To date, three different generations of EGFR-TKIs are available, though all remain subject to development of resistance mechanisms. The mechanism of action of first-generation TKIs (e.g., Erlotinib, Gefinitib, and Icotinib) causes a reversible ATP-binding sites blockade, stopping downstream signaling. Second-generation TKIs (e.g., Afatinib and Dacominitib) provide an alternative for patients with acquired resistance to first-generation TKIs. Third generation TKIs (e.g., Osimertinib, Rociletinib, Olmutinib, Lazertinib) offer a treatment for patients with acquired resistance to first and second-generation TKIs. *See, e.g., Caponnetto et al., J. Mol. Pathol.* 2021, 2(1), 1-10.

[00108] In some embodiments, the method comprises administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, in an amount of about 80 mg to about 320 mg orally once daily. In some embodiments, the method comprises administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, in an amount of about 240 mg orally once daily. In some embodiments, the method comprises administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, at a dose in an amount of about 240 mg orally, once daily starting Cycle 5 Day 1 or sooner if said carboplatin is discontinued earlier.

[00109] In some embodiments, administration of the combination therapy begins on Cycle 1 Day 1 of the first 21-day cycle, and continues in subsequent 21-day cycles.

[00110] In some embodiments, the method elicits a clinical response in the subject according to RECIST v1.1 criteria. In some embodiments, the method achieves a partial response or better in the subject according to RECIST v1.1 criteria. In some embodiments, the combination therapy achieves an improvement in the median PFS of at least two weeks. In some embodiments, the combination therapy achieves an improvement in the median PFS of at least 1 month. In some embodiments, the combination therapy achieves an improvement in the median PFS of at least 1.5 months. In some embodiments, the combination therapy achieves an improvement in the median PFS of at least 2 months. In some embodiments, the subject exhibits PFS for at least 4.5 months. In some embodiments, the subject exhibits PFS for at least 5 months. In some embodiments, the subject exhibits PFS for at least 5.5 months. In some embodiments, the subject exhibits PFS for at least 6 months, or at least 10 months, or at least 12 months, or at least 14 months. In some embodiments, the combination therapy further achieves an improvement in objective response relative to said reference population. In some embodiments, the combination therapy further achieves an improvement in OS relative to said reference population. In some embodiments, the improvement in OS is at least two months relative to said reference population. In some embodiments, the improvement in OS is at least about 2.4 months relative to said reference population. In some embodiments, the improvement in OS is about 2.2 months relative to said reference population. In some embodiments, the improvement in OS is about 2.3 months relative to said reference population. In some embodiments, the improvement in OS is about 2.4 months relative to said reference population. In some embodiments, the improvement in OS is about 2.5 months relative to said reference population. In some embodiments, the improvement in OS is about 2.6 months relative to said reference population. In some embodiments, the combination therapy further achieves an improvement in duration of response (DoR) relative to said reference population. In some embodiments, the combination therapy further achieves an improvement in time to subsequent therapy relative to said reference population. In some embodiments, the combination therapy further achieves an improvement in PFS after first subsequent therapy (PFS2) relative to said reference population. In some embodiments, the combination therapy further achieves an improvement in intracranial median PFS relative to said reference population. In some embodiments, the improvement in PFS2 is at least two months relative to said reference population. In some embodiments, the improvement in PFS2 is at least about 4.4 months relative to said reference population. In some embodiments, the improvement in PFS2 is about 4.5 months relative to said reference population. In some embodiments, the improvement in PFS2 is about 5 months relative to said reference population. In some embodiments, the

combination therapy further achieves an improvement in time to symptomatic progression (TTSP) relative to said reference population. In some embodiments, the improvement in TTSP is at least about 4 months relative to said reference population. In some embodiments, the improvement in TTSP is at least about 4.2 months relative to said reference population. In some embodiments, the improvement in TTSP is at least about 4.5 months relative to said reference population. In some embodiments, the combination therapy further achieves an improvement in time to treatment discontinuation (TTD) relative to said reference population. In some embodiments, the improvement in TTD is at least about 5.5 months relative to said reference population. In some embodiments, the improvement in TTD is at least about 5.9 months relative to said reference population. In some embodiments, the improvement in TTD is at least about 6 months relative to said reference population. In some embodiments, the combination therapy further achieves an improvement in time to subsequent therapy (TTST) relative to said reference population. In some embodiments, the improvement in TTST is at least about 5 months relative to said reference population. In some embodiments, the improvement in TTST is at least about 5.5 months relative to said reference population. In some embodiments, the improvement in TTST is at least about 5.6 months relative to said reference population. In some embodiments, the improvement in TTST is at least about 6 months relative to said reference population.

[00111] In some embodiments, the subject is progression-free after at least 20 months. In some embodiments, the subject is progression-free after at least 30 months. In some embodiments, the method achieves a PFS rate of 85% at 12 months, 65% at 24 months, and/or 51% at 36 months in a population of the treatment naïve subjects diagnosed with locally advanced or metastatic NSCLC harboring one or more EGFR mutations.

[00112] In some embodiments, the subject's overall survival (OS) is at least 17 months. In some embodiments, the subject's overall survival (OS) is at least 17.7 months. In some embodiments, the subject's overall survival (OS) is about 17 months. In some embodiments, the subject's overall survival (OS) is at least 17.5 months. In some embodiments, the subject's overall survival (OS) is at least 18 months.

[00113] In some embodiments, the subject's time to subsequent therapy (TTST) is at least 12 months. In some embodiments, the subject's time to subsequent therapy (TTST) is at least 12.2 months.

[00114] In some embodiments, the subject's time to symptomatic progression (TTSP) is at least 16 months. In some embodiments, the subject's time to symptomatic progression (TTSP) is about 16 months.

[00115] In some embodiments, the subject's time to treatment discontinuation (TTD) is at least 10 months. In some embodiments, the subject's time to treatment discontinuation (TTD) is at least 10.4 months. In some embodiments, the subject's time to treatment discontinuation (TTD) is about 10.4 months.

[00116] In some embodiments, the subject's progression-free survival after first subsequent therapy (PFS2) is at least 16 months. In some embodiments, the subject's progression-free survival after first subsequent therapy (PFS2) is about 16 months.

[00117] In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6, and wherein the second domain that binds c-Met comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12. In some embodiments, the first domain that specifically binds EGFR comprises a heavy chain variable region (VH) of SEQ ID NO: 13 and a light chain variable region (VL) of SEQ ID NO: 14, and the second domain that specifically binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16. In some embodiments, the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a first heavy chain (HC1) of SEQ ID NO: 17, a first light chain (LC1) of SEQ ID NO: 18, a second heavy chain (HC2) of SEQ ID NO: 19 and a second light chain (LC2) of SEQ ID NO: 20. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about between 1% to about 15%.

[00118] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered intravenously to the subject. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of between about 140 mg to about 2240 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 700 mg, about 750 mg, about 800 mg, about 850 mg, 900 mg, 950 mg, 1000 mg, 1050 mg, 1100 mg, 1150 mg, 1200 mg, 1250 mg, 1300 mg, 1350 mg, 1400 mg, 1575 mg, 1600 mg, 1750 mg, 2100 mg, or 2240 mg. According to certain embodiments, the method comprises administering the dose weekly for 4 weeks, then administering the dose every 2 weeks starting at Week 5, wherein, for body weight at baseline that is less than 80 kg, the dose is 1050 mg; and for body weight at

baseline that is greater than or equal to 80 kg, the dose is 1400 mg. In some embodiments, the initial dose is administered as a split infusion in Week 1 on Day 1 and Day 2. In some embodiments, the initial dose is administered in Week 1 on Day 1.

[00119] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg. In some embodiments, the initial dose is administered as a split infusion in Week 1 on Day 1 and Day 2. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg. In some embodiments, the initial dose is administered as a split infusion in Week 1 on Day 1 and Day 2. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg.

[00120] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered twice a week, once a week, once in two weeks, once in three weeks or once in four weeks.

[00121] In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6, and wherein the second domain that binds c-Met comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12. In some embodiments, the first domain that specifically binds EGFR comprises a heavy chain variable region (VH) of SEQ ID NO: 13 and a light chain variable region (VL) of SEQ ID NO: 14, and the second domain that specifically binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.

[00122] In some embodiments, the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

[00123] In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a first heavy chain (HC1) of SEQ ID NO: 17, a first light chain (LC1) of SEQ ID NO: 18, a second heavy chain (HC2) of SEQ ID NO: 19 and a second light chain (LC2) of SEQ ID NO: 20.

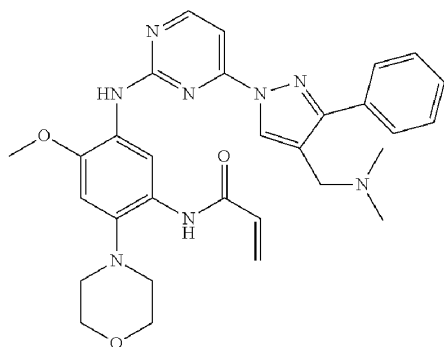
[00124] In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about between 1% to about 15%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about between 2% to about 14%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about between 3% to about 13%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about between 4% to about 12%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about between 5% to about 11%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 1%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 2%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 3%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 4%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 5%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 6%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 7%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 8%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 9%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 10%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 11%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 12%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 13%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 14%. In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about 15%.

[00125] In some embodiments, the bispecific anti-EGFR/c-Met antibody disclosed herein may be administered in combination with a tyrosine kinase inhibitor (TKI) such as, but not

limited to an epidermal growth factor receptor (EGFR TKI). Non-limiting examples of TKI are erlotinib, gefitinib, lapatinib, vandetanib, afatinib, osimertinib, lazertinib, poziotinib, criotinib, cabozantinib, capmatinib, axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib or sunitinib. In some embodiments, the bispecific anti-EGFR/c-Met antibody disclosed herein may be administered in combination with lazertinib.

[00126] Lazertinib is an oral, third-generation, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) in development for the treatment of non-small cell lung cancer (NSCLC).

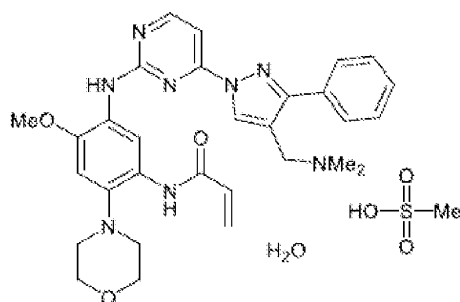
[00127] Lazertinib is described in WO 2016/060443 as N-(5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide, depicted below as a compound of Formula I.



Formula I

[00128] In addition, WO2018/194356 describes salts, hydrates and crystalline forms thereof; and WO2019/022485, WO2019/022486 and WO2019/022487 disclose processes for the production of lazertinib.

[00129] Lazertinib mesylate monohydrate is depicted below as a compound of Formula Ia,



Formula Ia,

which may be referred to as N-[5-[[4-[4-[(dimethylamino)methyl]-3-phenyl-1H-pyrazol-1-yl]pyrimidin-2-yl]amino]-4-methoxy-2-(morpholin-4-yl)phenyl]acrylamide methanesulfonate hydrate.

[00130] In some embodiments, the method comprises administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles. Carboplatin may be administered at a dose of AUC 5 in accordance with commercially available methods that are approved by health authorities.

[00131] In some embodiments, the method comprises administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression.

Administration

[00132] The bispecific anti-EGFR/c-Met antibody may be administered in a pharmaceutically acceptable carrier. "Carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the antibody of the invention is administered. Such vehicles may be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. For example, 0.4% saline and 0.3% glycine may be used to formulate the bispecific anti-EGFR/c-Met antibody. These solutions are sterile and generally free of particulate matter. They may be sterilized by conventional, well-known sterilization techniques (e.g., filtration). For parenteral administration, the carrier may comprise sterile water and other excipients may be added to increase solubility or preservation. Injectable suspensions or solutions may also be prepared utilizing aqueous carriers along with appropriate additives. Suitable vehicles and formulations, inclusive of other human proteins, e.g., human serum albumin, are described, for example, in e.g., Remington: The Science and Practice of Pharmacy, 21st Edition, Troy, D.B. ed., Lipincott Williams and Wilkins, Philadelphia, PA 2006, Part 5, Pharmaceutical Manufacturing pp 691-1092, See especially pp. 958-989.

[00133] The mode of administration may be any suitable route that delivers the bispecific anti-EGFR-c-Met antibody to the host, such as parenteral administration, e.g., intradermal, intramuscular, intraperitoneal, intravenous or subcutaneous, pulmonary, transmucosal (oral, intranasal, intravaginal, rectal), using a formulation in a tablet, capsule, solution, powder, gel, particle; and contained in a syringe, an implanted device, osmotic pump, cartridge, micropump; or other means appreciated by the skilled artisan, as well known in the art. Site specific administration may be achieved by for example intratumoral, intra-articular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelical, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic,

intracardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravascular, intravesical, intralesional, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery.

[00134] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered intravenously.

[00135] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously or intradermally to the subject. The bispecific anti-EGFR/c-Met antibody may be administered subcutaneously or intradermally at a dose sufficient to achieve a therapeutic effect in the subject.

[00136] In some embodiments, the bispecific anti-EGFR/c-Met antibody is formulated as a subcutaneous formulation as disclosed in PCT International Publication No. WO 2022/224187A1.

[00137] In some embodiments, the method comprises administering the dose weekly for 4 weeks, then administering the dose every 2 weeks starting at Week 5, wherein, for body weight at baseline that is less than 80 kg, the dose is 1050 mg; and for body weight at baseline that is greater than or equal to 80 kg, the dose is 1400 mg. In some embodiments, the initial dose is administered as a split infusion in Week 1 on Day 1 and Day 2.

[00138] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of between about 140 mg and about 2240 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of between about 1400 mg to about 3360 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of between about 1400 mg to about 1750 mg.

[00139] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, about 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg,

about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 980 mg, about 990 mg, about 1000 mg, about 1010 mg, about 1020 mg, about 1030 mg, about 1040 mg, about 1050 mg, about 1060 mg, about 1070 mg, about 1080 mg, about 1090 mg, about 1100 mg, about 1110 mg, about 1120 mg, about 1130 mg, about 1140 mg, about 1150 mg, about 1160 mg, about 1170 mg, about 1180 mg, about 1190 mg, about 1200 mg, about 1210 mg, about 1220 mg, about 1230 mg, about 1240 mg, about 1250 mg, about 1260 mg, about 1270 mg, about 1280 mg, about 1290 mg, about 1300 mg, about 1310 mg, about 1320 mg, about 1330 mg, about 1340 mg, about 1350 mg, about 1360 mg, about 1370 mg, about 1380 mg, about 1390 mg, about 1400 mg, about 1410 mg, about 1420 mg, about 1430 mg, about 1440 mg, about 1450 mg, about 1460 mg, about 1470 mg, about 1480 mg, about 1490 mg, about 1500 mg, about 1510 mg, about 1520 mg, about 1530 mg, about 1540 mg, about 1550 mg, about 1560 mg, about 1570 mg, 1575 mg, about 1580 mg, about 1590 mg, about 1600 mg, about 1610 mg, 1620 mg, about 1630 mg, about 1640 mg, about 1650 mg, about 1660 mg, about 1670 mg, about 1680 mg, about 1690 mg, about 1700 mg, about 1710 mg, about 1720 mg, about 1730 mg, about 1740 mg, about 1750 mg, about 1760 mg, about 1770 mg, about 1780 mg, about 1790 mg, about 1800 mg, about 1810 mg, about 1820 mg, about 1830 mg, about 1840 mg, about 1850 mg, about 1860 mg, about 1870 mg, about 1880 mg, 1890 mg, about 1900 mg, about 1910 mg, about 1920 mg, about 1930 mg, about 1940 mg, about 1950 mg, about 1960 mg, about 1970 mg, about 1980 mg, about 1990 mg, about 2000 mg, 2100 mg, 2110 mg, 2120 mg, 2130 mg, 2140 mg, 2150 mg, 2160 mg, 2170 mg, 2180 mg, 2190 mg, 2200 mg, 2210 mg, 2220 mg, 2230 mg, 2240 mg, 2250 mg, 2260 mg, 2270 mg, 2280 mg, 2290 mg, 2300 mg, 2310 mg, 2320 mg, 2330 mg, 2340 mg, 2350 mg, 2360 mg, 2370 mg, 2380 mg, 2390 mg, 2400 mg or 2410 mg.

[00140] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 350 mg, about 700 mg, about 1050 mg, about 1400 mg, about 1750 mg or about 2100mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 350 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 700 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 750 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 800 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 850 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is

administered at a dose of about 900 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 950 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1000 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1050 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1100 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1150 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1200 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1250 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1300 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1350 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1400 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 2100 mg.

[00141] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered is administered at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered is administered at a dose of about 1400 mg on Cycle 1 Days 1/2 (split dosing), 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg.

[00142] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg.

[00143] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Cycle 1 Days 1/2 (split dosing), 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg.

[00144] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg.

[00145] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered twice a week. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered once a week. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered once in two weeks. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered once in three weeks. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered once in four weeks.

[00146] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered twice a week, once a week, once in two weeks, once in three weeks or once in four weeks.

[00147] In some embodiments, the mode of administration that may be the suitable route that delivers lazertinib to the subject may be oral administration, such as oral administration of a tablet. Lazertinib tablet formulations suitable for oral administration in accordance with the present invention are described, for example, in WO2021/209893 and WO2020/079637, which are incorporated by reference herein.

[00148] In some embodiments, lazertinib is administered at a dose of between about 10 mg to about 400 mg. In some embodiments, lazertinib is administered at a dose of between about 20 mg to about 320 mg. In some embodiments, lazertinib is administered at a dose of between about 50 mg to about 300 mg. In some embodiments, lazertinib is administered at a dose of between about 100 mg to about 300 mg. In some embodiments, lazertinib is administered at a dose of between about 150 mg to about 280 mg. In some embodiments, lazertinib is administered at a dose of between about 200 mg to about 250 mg. In some embodiments, lazertinib is administered at a dose of between about 220 mg to about 250 mg.

[00149] In some embodiments, lazertinib is administered at a dose of about 20 mg, about 50 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, or about 400 mg. In some embodiments, lazertinib is administered at a dose of about 240 mg.

[00150] In some embodiments, lazertinib is administered daily. In some embodiments, lazertinib is administered twice a week. In some embodiments, lazertinib is administered once a week. In some embodiments, lazertinib is administered once in two weeks. In some embodiments, lazertinib is administered once in three weeks. In some embodiments, lazertinib is administered once in four weeks.

[00151] In some embodiments, the bispecific anti-EGFR/c-Met antibody disclosed herein may be administered in combination with lazertinib, which may be administered using any of the doses and dosages disclosed herein. In some embodiments, lazertinib is administered at a dose of between about 10 mg to about 400 mg. In some embodiments, lazertinib is administered at a dose of between about 20 mg to about 320 mg. In some embodiments, lazertinib is administered at a dose of about 20 mg, about 50 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, or about 400 mg. In some embodiments, lazertinib is administered at a dose of about 240 mg.

[00152] In some embodiments, the bispecific anti-EGFR/c-Met antibody disclosed herein may be administered in any of these doses and dosages disclosed herein in combination with lazertinib, which may be administered in any of these doses and dosages disclosed herein. As a non-limiting example, 1400 mg amivantamab may be administered in combination with 240 mg lazertinib. As a non-limiting example, 1750 mg amivantamab may be administered in combination with 240 mg lazertinib. As a non-limiting example, 2100 mg amivantamab may be administered in combination with 240 mg lazertinib.

[00153] In some embodiments, the bispecific anti-EGFR/c-Met antibody disclosed herein may be administered in combination with lazertinib, wherein lazertinib is administered daily, every other day, twice a week, or once a week. In some embodiments, the bispecific anti-EGFR/c-Met antibody disclosed herein may be administered in combination with lazertinib, wherein lazertinib is administered daily. In some embodiments, the bispecific anti-EGFR/c-Met antibody disclosed herein may be administered in combination with lazertinib, wherein lazertinib is administered orally.

[00154] In some embodiments, the bispecific anti-EGFR/c-Met antibody disclosed herein may be administered in combination with carboplatin.

[00155] In some embodiments, the bispecific anti-EGFR/c-Met antibody disclosed herein may be administered in combination with pemetrexed.

[00156] In some embodiments, the bispecific anti-EGFR/c-Met antibody disclosed herein may be administered in combination with Lazertinib, carboplatin and pemetrexed.

[00157] In some embodiments, the combination therapy comprising a bispecific anti-EGFR/c-Met bispecific antibody and an EGFR TKI may further include one or more additional anti-cancer therapies.

[00158] In some embodiments, the methods of the present disclosure comprise administering to a subject a cancer therapy which does not include the combination therapy comprising a bispecific anti-EGFR/c-Met bispecific antibody and an EGFR TKI disclosed herein. In some embodiments, the cancer therapy may include any one of those described herein. As a non-limiting example, the cancer therapy that may be administered in the methods of the disclosure may comprise any number of various platinum-based chemotherapies or combinations thereof. As a non-limiting example, the platinum-based chemotherapy comprises carboplatin, cisplatin, or a combination thereof.

[00159] Additional anti-cancer therapies that may be administered in the methods of the disclosure may include any one or more of the chemotherapeutic drugs or other anti-cancer therapeutics known to those of skill in the art. Chemotherapeutic agents are chemical compounds useful in the treatment of cancer and include growth inhibitory agents or other cytotoxic agents and include alkylating agents, anti-metabolites, anti-microtubule inhibitors, topoisomerase inhibitors, receptor tyrosine kinase inhibitors, angiogenesis inhibitors and the like. Examples of chemotherapeutic agents include alkylating agents such as thiopeta and cyclophosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabycin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-FU; folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogues such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine

analogues such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitio stanol, mepitio stanane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; members of taxoid or taxane family, such as paclitaxel (TAXOL®) docetaxel (TAXOTERE®) and analogues thereof; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogues such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; inhibitors of receptor tyrosine kinases and/or angiogenesis, including sorafenib (NEXAVAR®), sunitinib (SUTENT®), pazopanib (VOTRIENT™), toceranib (PALLADIA™), vandetanib (ZACTIMA™), cediranib (RECENTIN®), regorafenib (BAY 73-4506), axitinib (AG013736), lestaurtinib (CEP-701), erlotinib (TARCEVA®), gefitinib (IRESSA®), afatinib (BIBW 2992), lapatinib (TYKERB®), neratinib (HKI-272), and the like, and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (FARESTON®); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Other conventional cytotoxic chemical compounds as those disclosed in Wiemann et al., 1985, in Medical Oncology (Calabresi et al., eds.), Chapter 10, McMillan Publishing, are also applicable to the methods of the present invention.

Generation of bispecific anti-EGFR/c-Met antibodies used in the methods of the disclosure

[00160] An exemplary bispecific anti-EGFR/c-Met antibody that can be used in the methods of the disclosures is amivantamab. Amivantamab is an IgG1 anti-EGFR/c-Met bispecific antibody described in U.S. Pat. No. 9,593,164, which is incorporated herein by reference in its entirety. Amivantamab is characterized by following amino acid sequences:
EGFR binding arm

>SEQ ID NO: 1 (HCDR1, EGFR binding arm)
TYGMH

>SEQ ID NO: 2 (HCDR2, EGFR binding arm)
VIWDDGSYKYYGDSVKG

>SEQ ID NO: 3 (HCDR3, EGFR binding arm)
DGITMVRGVMKDYFDY

>SEQ ID NO: 4 (LCDR1, EGFR binding arm)
RASQDISSALV

>SEQ ID NO: 5 (LCDR2, EGFR binding arm)
DASSLES

>SEQ ID NO: 6 (LCDR3, EGFR binding arm)
QQFNSYPLT

>SEQ ID NO: 7 (HCDR1, c-Met binding arm)
SYGIS

>SEQ ID NO: 8 (HCDR2, c-Met binding arm)
WISAYNGYTNYAQKLQG

>SEQ ID NO: 9 (HCDR3, c-Met binding arm)

DLRGTNYFDY

>SEQ ID NO: 10 (LCDR1, c-Met binding arm)

RASQGISNWL

>SEQ ID NO: 11 (LCDR2, c-Met binding arm)

AASSLLS

>SEQ ID NO: 12 (LCDR3, c-Met binding arm)

QQANSFPIT

>SEQ ID NO: 13 (VH, EGFR binding arm)

QVQLVESGGGVVQPGRLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVAVIWDDG
SYKYYGDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDGITMVRGVMKD
YFDYWGQGTLVTVSS

>SEQ ID NO: 14 (VL, EGFR binding arm)

AIQLTQSPSSLSASVGDRVITTCRASQDISSALVWYQQKPGKAPKLLIYDASSLESGVP
SRFSGSESGTDFTLTISLQPEDFATYYCQQFNSYPLTFGGGTKVEIK

>SEQ ID NO: 15 (VH, c-Met binding arm)

QVQLVQSGAEVKKPGASVKVSCETSGYTFTSYGISWVRQAPGHGLEWMGWISAYN
GYTNYAQKLQGRVTMTDTSTSTAYMELRSLRSDDTAVYYCARDLRGTNYFDYWG
QGTLVTVSS

>SEQ ID NO: 16 (VL, c-Met binding arm)

DIQMTQSPSSVSASVGDRVITTCRASQGISNWLAWFQHKPGKAPKLLIYAASSLLSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQQANSFPITFGQGTRLEIK

>SEQ ID NO: 17 HC1

QVQLVESGGGVVQPGRLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVAVIWDDG
SYKYYGDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDGITMVRGVMKD
YFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV

KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFLLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSL
SPGK

>SEQ ID NO: 18 LC1

AIQLTQSPSSLSASVGDRVTITCRASQDISSALVWYQQKPGKAPKLLIYDASSLESGVP
SRFSGSESGTDFTLTISSLQPEDFATYYCQQFNSYPLTFGGGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSL
SSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

>SEQ ID NO: 19 HC2

QVQLVQSGAEVKKPGASVKVSCETSGYTFTSYGISWVRQAPGHGLEWMGWISAYN
GYTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDLRGTNYFDYWG
QGTLVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDK
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFLLYSRLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

>SEQ ID NO: 20 LC2

DIQMTQSPSSVSASVGDRVTITCRASQGISNWLAWFQHKPGKAPKLLIYAASSLLSGV
PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPITFGQGTRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSL
LSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

[00161] In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6; and the second domain comprises the

HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.

[00162] In some embodiments, the first domain that specifically binds EGFR comprises a heavy chain variable region (VH) of SEQ ID NO: 13 and a light chain variable region (VL) of SEQ ID NO: 14; and the second domain that specifically binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.

[00163] In some embodiments, the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

[00164] In some embodiments, the bispecific anti-EGFR/c-Met antibody comprises a first heavy chain (HC1) of SEQ ID NO: 17, a first light chain (LC1) of SEQ ID NO: 18, a second heavy chain (HC2) of SEQ ID NO: 19 and a second light chain (LC2) of SEQ ID NO: 20.

[00165] In some embodiments, the bispecific anti-EGFR/c-Met antibody is amivantamab.

[00166] In some embodiments, the bispecific anti-EGFR/c-Met antibody is a biosimilar of amivantamab.

[00167] In some embodiments, a non-limiting example of a biosimilar of amivantamab can be found in publicly available Web resource:

https://us.proteogenix_science/product/amivantamab-biosimilar-anti-egfr-me-rccp2-mab-research-grade/.

[00168] In some embodiments, a non-limiting example of a biosimilar of amivantamab can be found in publicly available Web resource:

<https://www.thermofisher.com/antibody/product/Amivantamab-Antibody-Recombinant-Monoclonal/MA5-42260>.

[00169] In some embodiments, a non-limiting example of a biosimilar of amivantamab can be found in publicly available Web resource: <https://www.genemedi.net/i/biologics-biosimilar-GMP-Bios-ab-021>.

[00170] In some embodiments, a non-limiting example of a biosimilar of amivantamab can be found in publicly available Web resource: <https://www.prosci-inc.com/product/amivantamab-egfr-me-rccp2-research-grade-biosimilar-10-966/>.

[00171] In some embodiments, a non-limiting example of a biosimilar of amivantamab can be found in publicly available Web resource: <https://www.antibodysystem.com/product/6201.html>.

[00172] In some embodiments, a non-limiting example of a biosimilar of amivantamab can be found in publicly available Web resource: <https://www.biorbyt.com/amivantamab-biosimilar-antibody-orb1140752.html>.

[00173] In one embodiment, the bispecific anti-EGFR/c-Met antibody comprises one or more Fc silencing mutations.

[00174] In one embodiment, the one or more Fc silencing mutations decrease affinity to Fc γ receptors.

[00175] In one embodiment, the one or more Fc silencing mutations comprise V234A/G237A/P238S/H268A/V309L/A330S/P331S.

[00176] In one embodiment, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content between about 1% to about 15%. Antibodies with reduced fucose content can be made using different methods reported to lead to the successful expression of relatively high defucosylated antibodies bearing the biantennary complex-type of Fc oligosaccharides such as control of culture osmolality (Konno et al., *Cytotechnology* 64(249-65, 2012), application of a variant CHO line Lec13 as the host cell line (Shields et al., *J Biol Chem* 277:26733-26740, 2002), application of a variant CHO line EB66 as the host cell line (Olivier et al., *MAbs* ;2(4), 2010; Epub ahead of print; PMID:20562582), application of a rat hybridoma cell line YB2/0 as the host cell line (Shinkawa et al., *J Biol Chem* 278:3466-3473, 2003), introduction of small interfering RNA specifically against the α 1,6-fucosyltransferase (FUT8) gene (Mori et al., *Biotechnol Bioeng*88:901-908, 2004), or coexpression of β -1,4-N-acetylglucosaminyltransferase III and Golgi α -mannosidase II or a potent alpha-mannosidase I inhibitor, kifunensine (Ferrara et al., *J Biol Chem*281:5032-5036, 2006, Ferrara et al., *Biotechnol Bioeng* 93:851-861, 2006; Xhou et al., *Biotechnol Bioeng* 99:652-65, 2008). In general, lowering fucose content in the glycan of the antibodies potentiates antibody-mediated cellular cytotoxicity (ADCC).

[00177] Other bispecific anti-EGFR/c-Met antibodies publicly available may also be used in the methods of the disclosure as long as they demonstrate similar characteristics when compared to amivantamab as described in U.S. Pat. No. 9,593,164. Bispecific anti-EGFR/c-Met antibodies that may be used in the methods of the disclosure may also be generated by combining EGFR binding VH/VL domains and c-Met binding VH/VL domains that are publicly available and testing the resulting bispecific antibodies for their characteristics as described in U.S. Pat. No. 9,593,164. In some embodiments, the anti-EGFR/c-Met antibodies are biosimilar of anti-EGFR/c-Met antibodies as described in U.S. Pat. No. 9,593,164.

[00178] Bispecific anti-EGFR/c-Met antibodies used in the methods of the disclosure may be generated for example using Fab arm exchange (or half molecule exchange) between two monospecific bivalent antibodies by introducing substitutions at the heavy chain CH3

interface in each half molecule to favor heterodimer formation of two antibody half molecules having distinct specificity either in vitro in cell-free environment or using co-expression. The Fab arm exchange reaction is the result of a disulfide-bond isomerization reaction and dissociation-association of CH3 domains. The heavy chain disulfide bonds in the hinge regions of the parental monospecific antibodies are reduced. The resulting free cysteines of one of the parental monospecific antibodies form an inter heavy-chain disulfide bond with cysteine residues of a second parental monospecific antibody molecule and simultaneously CH3 domains of the parental antibodies release and reform by dissociation-association. The CH3 domains of the Fab arms may be engineered to favor heterodimerization over homodimerization. The resulting product is a bispecific antibody having two Fab arms or half molecules which each bind a distinct epitope, i.e., an epitope on EGFR and an epitope on c-Met. For example, the bispecific antibodies of the invention may be generated using the technology described in Int.Pat. Publ. No. WO2011/131746. Mutations F405L in one heavy chain and K409R in the other heavy chain may be used in case of IgG1 antibodies. For IgG2 antibodies, a wild-type IgG2 and a IgG2 antibody with F405L and R409K substitutions may be used. For IgG4 antibodies, a wild-type IgG4 and a IgG4 antibody with F405L and R409K substitutions may be used. To generate bispecific antibodies, first monospecific bivalent antibody and the second monospecific bivalent antibody are engineered to have the aforementioned mutation in the Fc region, the antibodies are incubated together under reducing conditions sufficient to allow the cysteines in the hinge region to undergo disulfide bond isomerization; thereby generating the bispecific antibody by Fab arm exchange. The incubation conditions may optimally be restored to non-reducing. Exemplary reducing agents that may be used are 2- mercaptoethylamine (2-MEA), dithiothreitol (DTT), dithioerythritol (DTE), glutathione, tris(2-carboxyethyl)phosphine (TCEP), L-cysteine and beta- mercaptoethanol. For example, incubation for at least 90 min at a temperature of at least 20°C in the presence of at least 25 mM 2-MEA or in the presence of at least 0.5 mM dithiothreitol at a pH of from 5-8, for example at pH of 7.0 or at pH of 7.4 may be used.

[00179] Bispecific anti-EGFR/c-Met antibodies used in the methods of the disclosure may also be generated using designs such as the Knob-in-Hole (Genentech), CrossMAbs (Roche) and the electrostatically-matched (Chugai, Amgen, NovoNordisk, Oncomed), the LUZ-Y (Genentech), the Strand Exchange Engineered Domain body (SEEDbody)(EMD Serono), and the Biclonic (Merus).

[00180] In the “knob-in-hole” strategy (see, e.g., Intl. Publ. No. WO 2006/028936) select amino acids forming the interface of the CH3 domains in human IgG can be mutated at positions affecting CH3 domain interactions to promote heterodimer formation. An amino acid with a small side chain (hole) is introduced into a heavy chain of an antibody specifically binding a first antigen and an amino acid with a large side chain (knob) is introduced into a heavy chain of an antibody specifically binding a second antigen. After co-expression of the two antibodies, a heterodimer is formed as a result of the preferential interaction of the heavy chain with a “hole” with the heavy chain with a “knob”. Exemplary CH3 substitution pairs forming a knob and a hole are (expressed as modified position in the first CH3 domain of the first heavy chain/ modified position in the second CH3 domain of the second heavy chain): T366Y/F405A, T366W/F405W, F405W/Y407A, T394W/Y407T, T394S/Y407A, T366W/T394S, F405W/T394S and T366W/T366S_L368A_Y407V.

[00181] CrossMAb technology, in addition to utilizing the “knob-in-hole” strategy to promoter Fab arm exchange utilizes CH1/CL domain swaps in one half arm to ensure correct light chain pairing of the resulting bispecific antibody (see e.g., U.S. Patent No. 8,242,247).

[00182] Other cross-over strategies may be used to generate full length bispecific antibodies of the invention by exchanging variable or constant, or both domains between the heavy chain and the light chain or within the heavy chain in the bispecific antibodies, either in one or both arms. These exchanges include for example VH-CH1 with VL-CL, VH with VL, CH3 with CL and CH3 with CH1 as described in Int. Patent Publ. Nos. WO2009/080254, WO2009/080251, WO2009/018386 and WO2009/080252.

[00183] Other strategies such as promoting heavy chain heterodimerization using electrostatic interactions by substituting positively charged residues at one CH3 surface and negatively charged residues at a second CH3 surface may be used, as described in US Patent Publ. No. US2010/0015133; US Patent Publ. No. US2009/0182127; US Patent Publ. No. US2010/028637 or US Patent Publ. No. US2011/0123532. In other strategies, heterodimerization may be promoted by following substitutions (expressed as modified positions in the first CH3 domain of the first heavy chain/ modified position in the second CH3 domain of the second heavy chain): L351Y_F405A_Y407V/T394W, T366I_K392M_T394W/F405A_Y407V, T366L_K392M_T394W/F405A_Y407V, L351Y_Y407A/T366A_K409F, L351Y_Y407A/T366V_K409F, Y407A/T366A_K409F, or T350V_L351Y_F405A_Y407V/T350V_T366L_K392L_T394W as described in U.S. Patent Publ. No. US2012/0149876 or U.S. Patent Publ. No. US2013/0195849.

[00184] SEEDbody technology may be utilized to generate bispecific antibodies of the invention. SEEDbodies have, in their constant domains, select IgG residues substituted with IgA residues to promote heterodimerization as described in U.S. Patent No. US20070287170.

[00185] Mutations are typically made at the DNA level to a molecule such as the constant domain of the antibody using standard methods.

Exemplary Embodiments

1. A method of improving median progression free survival (PFS) in a population of subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring one or more epidermal growth factor receptor (EGFR) mutations whose NSCLC progressed on or after treatment with at least one prior tyrosine kinase inhibitor (TKI), said method comprising administering to the population of subjects a combination therapy comprising:

- (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody,
- (ii) a therapeutically effective amount of carboplatin, and
- (iii) a therapeutically effective amount of pemetrexed,

wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with the at least one prior TKI, said reference population having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody.

2. The embodiment of claim 1, wherein the bispecific anti-EGFR/c-Met antibody comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6, and wherein the second domain that binds c-Met comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.

3. The method of embodiment 1 or embodiment 2, wherein the one or more EGFR mutations comprise one or more exon 19 deletions, or exon 21 L858R substitution, or any combination thereof.
4. The method of embodiment 3, wherein the one or more EGFR mutations comprise one or more exon 19 deletions.
5. The method of embodiment 3, wherein the one or more EGFR mutations comprise exon 21 L858R substitution.
6. The method of any one of embodiments 1-5, wherein said at least one prior TKI comprises a 1st generation EGFR TKI.
7. The method of any one of embodiments 1-5, wherein said at least one prior TKI comprises a 2nd generation EGFR TKI.
8. The method of any one of embodiments 1-5, wherein said at least one prior TKI comprises a 3rd generation EGFR TKI.
9. The method of any one of embodiments 1-5, wherein said at least one prior TKI comprises osimertinib.
10. The method of any one of embodiments 1-9, wherein administration of the combination therapy begins on Cycle 1 Day 1 of the first 21-day cycle, and continues in subsequent 21-day cycles.
11. The method of any one of embodiments 1-10, wherein the bispecific anti-EGFR/c-Met antibody is administered intravenously.
12. The method of any one of embodiments 1-10, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.
13. The method of embodiments 1-12, wherein the method comprises administering the bispecific anti-EGFR/c-Met antibody in an amount of between about 140 mg and about 2240 mg.
14. The method of embodiment 13, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 700 mg, about 750 mg, about 800 mg, about 850 mg, 900 mg, 950 mg, 1000 mg, 1050 mg, 1100 mg, 1150 mg, 1200 mg, 1250 mg, 1300 mg, 1350 mg, 1400 mg, 1575 mg, 1600 mg, 1750 mg, 2100 mg, or 2240 mg.

15. The method of embodiment 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg.
16. The method of embodiment 15, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
17. The method of embodiment 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg.
18. The method of embodiment 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg.
19. The method of embodiment 18, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
20. The method of embodiment 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg.
21. The method of any one of embodiments 1-20, wherein the method comprises administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles.
22. The method of any one of embodiments 1-21, wherein the method comprises administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression.
23. The method of claim 22, wherein the method comprises:
 - a) (i) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg; or
 - (ii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg; or
 - (iii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750

mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg; or

(iv) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg;

and

b) administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles;

and

c) administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression.

24. The method of embodiment 23, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
25. The method of any one of embodiments 1-24, wherein the combination therapy achieves an improvement in the median PFS of at least two weeks.
26. The method of embodiment 25, wherein the combination therapy achieves an improvement in the median PFS of at least 1 month.
27. The method of embodiment 26, wherein the combination therapy achieves an improvement in the median PFS of at least 1.5 months.
28. The method of embodiment 27, wherein the combination therapy achieves an improvement in the median PFS of at least 2 months.
29. The method of embodiment 28, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 4.5 months.
30. The method of embodiment 29, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 5 months.
31. The method of embodiment 30, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 5.5 months.
32. The method of embodiment 31, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 6 months.

33. The method of embodiment 32, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 10 months.
34. The method of embodiment 33, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 12 months.
35. The method of embodiment 34, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 14 months.
36. The method of any one of embodiments 1-35, wherein the combination therapy further achieves an improvement in objective response relative to said reference population (e.g., wherein the combination therapy achieves an ORR of at least about 60%, or at least about 61%, or at least about 62%).
37. The method of any one of embodiments 1-36, wherein the combination therapy further achieves an improvement in overall survival (OS) relative to said reference population.
38. The method of any one of embodiments 1-37, wherein the combination therapy further achieves an improvement in duration of response (DoR) relative to said reference population (e.g., wherein the combination therapy achieves a median DoR of at least about 6 months, or at least about 7 months, or at least about 8 months, or at least about 9 months).
39. The method of any one of embodiments 1-38, wherein the combination therapy further achieves an improvement in time to subsequent therapy (TTST) relative to said reference population (e.g., wherein the combination therapy achieves a median TTST of at least about 7 months, or at least about 8 months, or at least about 9 months, or at least about 10 months, or at least about 11 months, or at least about 12 months).
40. The method of any one of embodiments 1-39, wherein the combination therapy further achieves an improvement in PFS after first subsequent therapy (PFS2) relative to said reference population (e.g., wherein the combination therapy achieves a median PFS2 of at least about 12 months, or at least about 13 months, or at least about 14 months).
41. The method of any one of embodiments 1-40, wherein the combination therapy further achieves an improvement in intracranial median PFS relative to said reference

population (e.g., wherein the combination therapy achieves a median intracranial PFS of at least about 9 months, or at least about 10 months, or at least about 11 months, or at least about 12 months).

42. A method of improving median progression free survival (PFS) in a population of subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring one or more epidermal growth factor receptor (EGFR) mutations whose NSCLC progressed on or after treatment with at least one prior tyrosine kinase inhibitor (TKI), said method comprising administering to the population of subjects a combination therapy comprising:

- (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody,
- (ii) a therapeutically effective amount of lazertinib, or a pharmaceutically acceptable salt or hydrate thereof,
- (iii) a therapeutically effective amount of carboplatin, and
- (iv) a therapeutically effective amount of pemetrexed,

wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with the at least one prior TKI, said reference population having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody nor said lazertinib or pharmaceutically acceptable salt or hydrate thereof.

43. The method of embodiment 42, wherein the bispecific anti-EGFR/c-Met antibody comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6, and wherein the second domain that binds c-Met comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.

44. The method of embodiment 42 or embodiment 43, wherein the one or more EGFR mutations comprise one or more exon 19 deletions, or exon 21 L858R substitution, or any combination thereof.
45. The method of embodiment 44, wherein the one or more EGFR mutations comprise one or more exon 19 deletions.
46. The method of embodiment 44, wherein the one or more EGFR mutations comprise exon 21 L858R substitution.
47. The method of any one of embodiments 42-46, wherein said at least one prior TKI comprises a 1st generation EGFR TKI.
48. The method of any one of embodiments 42-46, wherein said at least one prior TKI comprises a 2nd generation EGFR TKI.
49. The method of any one of embodiments 42-46, wherein said at least one prior TKI comprises a 3rd generation EGFR TKI.
50. The method of any one of embodiments 42-46, wherein said at least one prior TKI comprises osimertinib.
51. The method of any one of embodiments 42-50, wherein administration of the combination therapy begins on Cycle 1 Day 1 of the first 21-day cycle, and continues in subsequent 21-day cycles.
52. The method of any one of embodiments 42-51 wherein the bispecific anti-EGFR/c-Met antibody is administered intravenously.
53. The method of any one of embodiments 42-51, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.
54. The method of any one of embodiments 42-53, wherein the method comprises administering the bispecific anti-EGFR/c-Met antibody in an amount of between about 140 mg and about 2240 mg.
55. The method of embodiment 54, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 700 mg, about 750 mg, about 800 mg, about 850 mg, 900 mg, 950 mg, 1000 mg, 1050 mg, 1100 mg, 1150 mg, 1200 mg, 1250 mg, 1300 mg, 1350 mg, 1400 mg, 1575 mg, 1600 mg, 1750 mg, 2100 mg, or 2240 mg.

56. The method of embodiment 55, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg.
57. The method of embodiment 56, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
58. The method of embodiment 55, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg.
59. The method of embodiment 55, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg.
60. The method of embodiment 59, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
61. The method of embodiment 55, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg.
62. The method of any one of embodiments 42-61, wherein the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, is lazertinib mesylate.
63. The method of any one of embodiments 42-61, wherein the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, is lazertinib mesylate monohydrate.
64. The method of any one of embodiments 42-63, wherein the method comprises administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, at a dose of about 240 mg orally, once daily.
65. The method of embodiment 64, wherein the method comprises administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, at a dose of about 240 mg orally, once daily starting Cycle 5 Day 1 or sooner if said carboplatin is discontinued earlier.
66. The method of any one of embodiments 42-65, wherein the method comprises administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles.

67. The method of any one of embodiments 42-66, wherein the method comprises administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with carboplatin for up to 4 cycles, and then as maintenance until disease progression.
68. The method of embodiment 67, wherein the method comprised:
- a) (i) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg; or
 - (ii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg; or
 - (iii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg; or
 - (iv) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg;
- and
- b) (i) administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, at a dose of about 240 mg orally, once daily; or
 - (ii) administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, at a dose of about 240 mg orally, once daily starting Cycle 5 Day 1 or sooner if the carboplatin is discontinued earlier;
- and
- c) administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles;
- and
- d) administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with carboplatin for up to 4 cycles, and then as maintenance until disease progression.
69. The method of embodiment 68, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.

70. The method of any one of embodiments 42-69, wherein the combination therapy achieves an improvement in the median PFS of at least two weeks.
71. The method of embodiment 70, wherein the combination therapy achieves an improvement in the median PFS of at least 1 month.
72. The method of embodiment 71, wherein the combination therapy achieves an improvement in the median PFS of at least 1.5 months.
73. The method of embodiment 72, wherein the combination therapy achieves an improvement in the median PFS of at least 2 months.
74. The method of embodiment 73, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 4.5 months.
75. The method of embodiment 74, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 5 months.
76. The method of embodiment 75, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 5.5 months.
77. The method of embodiment 76, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 6 months.
78. The method of embodiment 77, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 10 months.
79. The method of embodiment 78, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 12 months.
80. The method of embodiment 79, wherein at least one subject within the population of subjects exhibits progression-free survival for at least 14 months.
81. The method of any one of embodiments 42-80, wherein the combination therapy further achieves an improvement in objective response relative to of said reference population (e.g., wherein the combination therapy achieves an ORR of at least about 60%, or at least about 61%, or at least about 62%).
82. The method of any one of embodiments 42-81, wherein the combination therapy further achieves an improvement in overall survival (OS) relative to of said reference population.

83. The method of any one of embodiments 42-82, wherein the combination therapy further achieves an improvement in duration of response (DoR) relative to of said reference population (e.g., wherein the combination therapy achieves a median DoR of at least about 6 months, or at least about 7 months, or at least about 8 months, or at least about 9 months).
84. The method of any one of embodiments 42-83, wherein the combination therapy further achieves an improvement in time to subsequent therapy (TTST) relative to of said reference population (e.g., wherein the combination therapy achieves a median TTST of at least about 7 months, or at least about 8 months, or at least about 9 months, or at least about 10 months, or at least about 11 months, or at least about 12 months).
85. The method of any one of embodiments 42-84, wherein the combination therapy further achieves an improvement in PFS after first subsequent therapy (PFS2) relative to of said reference population (e.g., wherein the combination therapy achieves a median PFS2 of at least about 12 months, or at least about 13 months, or at least about 14 months).
86. The method of any one of embodiments 42-85, wherein the combination therapy further achieves an improvement in intracranial median PFS relative to of said reference population (e.g., wherein the combination therapy achieves a median intracranial PFS of at least about 9 months, or at least about 10 months, or at least about 11 months, or at least about 12 months).
87. The method of any one of embodiments 1-86, wherein the bispecific anti-EGFR/c-Met antibody is amivantamab.
88. The method of any one of embodiments 1-86, wherein the bispecific anti-EGFR/c-Met antibody is a biosimilar of amivantamab.
89. The method of any of embodiments 1-41, wherein the combination therapy further achieves an improvement in TTD, TTST, and PFS2 relative to said reference population (e.g., wherein the combination therapy achieves a median TTD of greater than 4.5 months, or at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, or at least about 11 months; and wherein the combination therapy achieves a median TTST of greater than 6.6 months, or at least about 7 months, at least about 8 months,

at least about 9 months, at least about 10 months, at least about 11 months, or at least about 12 months; and wherein the combination therapy achieves a median PFS2 of greater than 11.3 months, or at least about 12 months, or at least about 13 months).

90. The method of any of embodiments 1-41, wherein the combination therapy further achieves an improvement in time to symptomatic progression (TTSP) relative to said reference population (e.g., greater than 13 months, or at least 13.5 months, or at least 14 months).
91. A method of improving median overall survival (OS) in a population of subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring one or more epidermal growth factor receptor (EGFR) mutations whose NSCLC progressed on or after treatment with at least one prior tyrosine kinase inhibitor (TKI), said method comprising administering to the population of subjects a combination therapy comprising:
- (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody,
 - (ii) a therapeutically effective amount of carboplatin, and
 - (iii) a therapeutically effective amount of pemetrexed,

wherein the improvement in median OS is relative to median OS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with the at least one prior TKI, said reference population having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody.

92. The method of embodiment 91, wherein the bispecific anti-EGFR/c-Met antibody comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6, and wherein the second domain that binds c-Met comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.

93. The method of embodiment 91 or embodiment 92, wherein the one or more EGFR mutations comprise one or more exon 19 deletions, or exon 21 L858R substitution, or any combination thereof.
94. The method of embodiment 93, wherein the one or more EGFR mutations comprise one or more exon 19 deletions.
95. The method of embodiment 93, wherein the one or more EGFR mutations comprise exon 21 L858R substitution.
96. The method of any one of embodiments 91-95, wherein said at least one prior TKI comprises a 1st generation EGFR TKI.
97. The method of any one of embodiments 91-95, wherein said at least one prior TKI comprises a 2nd generation EGFR TKI.
98. The method of any one of embodiments 91-95, wherein said at least one prior TKI comprises a 3rd generation EGFR TKI.
99. The method of any one of embodiments 91-95, wherein said at least one prior TKI comprises osimertinib.
100. The method of any one of embodiments 91-99, wherein the improvement in median OS at 18 months was greater in the population of subjects administered the combination therapy than the reference population.
101. The method of any one of embodiments 91-100, wherein administration of the combination therapy begins on Cycle 1 Day 1 of the first 21-day cycle, and continues in subsequent 21-day cycles.
102. The method of any one of embodiments 91-101, wherein the bispecific anti-EGFR/c-Met antibody is administered intravenously.
103. The method of any one of embodiments 91-101, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.
104. The method of any one of embodiments 91-103, wherein the method comprises administering the bispecific anti-EGFR/c-Met antibody in an amount of between about 140 mg and about 2240 mg.
105. The method of embodiment 104, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 700 mg, about 750 mg, about 800 mg,

about 850 mg, 900 mg, 950 mg, 1000 mg, 1050 mg, 1100 mg, 1150 mg, 1200 mg, 1250 mg, 1300 mg, 1350 mg, 1400 mg, 1575 mg, 1600 mg, 1750 mg, 2100 mg, or 2240 mg.

106. The method of embodiment 105, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg.
107. The method of embodiment 106, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
108. The method of embodiment 105, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg.
109. The method of embodiment 105, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg.
110. The method of embodiment 109, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
111. The method of embodiment 105, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg.
112. The method of any one of embodiments 91-111, wherein the method comprises administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles.
113. The method of any one of embodiments 91-112, wherein the method comprises administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression.
114. The method of embodiment 113, wherein the method comprises:
 - a) (i) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg; or

- (ii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg; or
- (iii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg; or
- (iv) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg;

and

- b) administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles;

and

- c) administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression.

- 115. The method of embodiment 114, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
- 116. The method of any one of embodiments 91-115, wherein the population of subjects administered the combination therapy achieves an improvement in the median OS of at least two months, relative to said reference population.
- 117. The method of embodiment 116, wherein the population of subjects administered the combination therapy achieves an improvement in the median OS of at least about 2.2 months, 2.3 months, 2.4 months, 2.5 months, or 2.6 months, relative to said reference population.
- 118. The method of embodiment 116, wherein the population of subjects administered the combination therapy achieves an improvement in the median OS of about 2.4 months, relative to said reference population.
- 119. The method of embodiment 116, wherein the population of subjects administered the combination therapy exhibits overall survival for at least 17 months.

120. The method of embodiment 119, wherein the subject exhibits overall survival for at least about 17.2 months, about 17.4 months, about 17.6 months, about 17.7 months, about 17.8 months, or about 18 months.
121. The method of embodiment 119, wherein the subject exhibits overall survival for about 17.7 months.
122. The method of any one of embodiments 91-121, wherein the population of subjects administered the combination therapy further achieves an improvement in time to subsequent therapy (TTST) relative to said reference population.
123. The method of any one of embodiments 91-121, wherein the the population of subjects administered the combination therapy further achieves an improvement in time to symptomatic progression (TTSP) relative to said reference population.
124. The method of any one of embodiments 91-121, wherein the population of subjects administered the combination therapy further achieves an improvement in PFS after first subsequent therapy (PFS2) relative to said reference population.
125. The method of any one of embodiments 91-121, wherein the population of subjects administered the combination therapy further achieves an improvement in time to treatment discontinuation (TTD) relative to said reference population.
126. The method of embodiment 122, wherein the population of subjects administered the combination therapy achieves the improvement of at least about 5 months, about 5.5 months, about 5.6 months, about 6 months, about 6.5, or about 7 months TTST relative to said reference population.
127. The method of embodiment 122, wherein the population of subjects administered the combination therapy exhibits TTST of at least about 12 months.
128. The method of embodiment 122, wherein the population of subjects administered the combination therapy exhibits TTST of about 12 months, about 12.2 months, or about 12.5 months.
129. The method of embodiment 122, wherein the population of subjects administered the combination therapy exhibits TTST of about 12.2 months.
130. The method of embodiment 122, wherein the population of subjects administered the combination therapy exhibits TTST of about 2-fold longer at 18 months than the reference population.

131. The method of embodiment 123, wherein the population of subjects administered the combination therapy achieves an improvement of at least about 4 months TTSP relative to said reference population.
132. The method of embodiment 123, wherein the population of subjects administered the combination therapy achieves an improvement of about 4 months, about 4.2 months, or about 4.5 months in TTSP relative to said reference population.
133. The method of embodiment 123, wherein the population of subjects administered the combination therapy achieves an improvement of about 4 months, in TTSP relative to said reference population.
134. The method of embodiment 123, wherein the population of subjects administered the combination therapy achieves an improvement of about 4.2 months in TTSP relative to said reference population.
135. The method of embodiment 123, wherein the population of subjects administered the combination therapy exhibits TTSP of at least about 16 months.
136. The method of embodiment 123, wherein the population of subjects administered the combination therapy exhibits TTSP of about 16 months.
137. The method of embodiment 123, wherein the population of subjects administered the combination therapy achieves a reduction of about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, or about 30% in TTSP relative to said reference population.
138. The method of embodiment 123, wherein the population of subjects administered the combination therapy achieves a reduction of about 27% in TTSP at 18 months relative to said reference population.
139. The method of embodiment 124, wherein the population of subjects administered the combination therapy achieves an improvement in PFS2 of at least about 4 months, about 4.2 months, about 4.4 months, about 4.5 months, about 4.6 months, about 4.8 months, or about 5 months relative to said reference population.
140. The method of embodiment 124, wherein the population of subjects administered the combination therapy achieves an improvement in PFS2 of about 4 months, about 4.2 months, about 4.4 months, about 4.5 months, about 4.6 months, about 4.8 months, or about 5 months relative to said reference population.

141. The method of embodiment 124, wherein the population of subjects administered the combination therapy achieves an improvement in PFS2 of about 4.4 months relative to said reference population.
142. The method of embodiment 124, wherein the subject exhibits PFS2 of at least about 16 months.
143. The method of embodiment 124, wherein the subject exhibits PFS2 of about 16 months.
144. The method of embodiment 124, wherein the population of subjects administered the combination therapy exhibits a greater PFS2 at 18 months relative to said reference population.
145. The method of embodiment 125, wherein the population of subjects administered the combination therapy achieves an improvement in TTD of at least about 5 months, about 5.3 months, about 5.5 months, about 5.7, about 5.9 months, or about 6 months, relative to said reference population.
146. The method of embodiment 125, wherein the population of subjects administered the combination therapy achieves an improvement in TTD of about 5 months, about 5.3 months, about 5.5 months, about 5.7, about 5.9 months, or about 6 months, relative to said reference population.
147. The method of embodiment 125, wherein the population of subjects administered the combination therapy exhibits TTD of at least about 10 months, about 10.2 months, about 10.4 months, about 10.6 months, about 10.8 months, or about 11 months.
148. The method of embodiment 125, wherein the population of subjects administered the combination therapy exhibits TTD of about 10 months, about 10.2 months, about 10.4 months, about 10.6 months, about 10.8 months, or about 11 months.
149. The method of embodiment 125, wherein the population of subjects administered the combination therapy has about 5-fold greater subjects on treatment at 18 months than the reference population.

EXAMPLES

[00186] The following examples are provided to further describe some of the embodiments disclosed herein. The examples are intended to illustrate, not to limit, the disclosed embodiments.

[00187] Example 1. CHRYSALIS-2 Clinical Trial

[00188] CHRYSALIS-2 (NCT04077463) is an open-label Phase 1/1b study to evaluate the safety and pharmacokinetics of Lazertinib as monotherapy or in combinations with amivantamab in participants with advanced non-small cell lung cancer. The study includes multiple cohorts. Provided below are results for the LACP (lazertinib, amivantamab, carboplatin, pemetrexed) cohort of 20 patients.

[00189] Methods:

[00190] The LACP cohort of the CHRYSALIS-2 study enrolled patients with relapsed/refractory EGFR-mutated advanced NSCLC whose disease progressed on or after treatment with an EGFR TKI as last line of therapy (maximum of 3 prior lines). Patients received intravenous amivantamab 1400 mg (1750 mg, ≥ 80 kg) weekly for the first 4 weeks and 1750 mg (2100 mg, ≥ 80 kg) every 3 weeks starting at cycle 3 plus 240 mg oral lazertinib daily, and pemetrexed (500 mg/m²) with carboplatin (AUC5 for the first 4 cycles) on a 21-day cycle. Response was assessed by the investigator per RECIST v1.1.

[00191] Results:

[00192] Of the 20 patients enrolled, median age was 61 years (range, 38-76), 55% female, 55% Asian and 40% White, and a median of 2 prior lines (70% prior osimertinib, 45% prior 1st/2nd-generation EGFR TKIs). The objective response rate was 50%, with median duration of response not estimable (median follow-up was 13.1 [range, 2.4-17.5] months). Eight of 10 responders have a response duration ≥ 6 months. Eleven (55%) patients are ongoing treatment; median progression-free survival (PFS) was 14.0 (95% CI, 4.3-not estimable) months. A total of 5 patients were treated beyond progression, with an incremental median treatment duration of 4.2 (range, 3.1-7.1) months. Of the 12 patients with history of brain metastases, median PFS was 6.7 (95% CI, 1.4-not estimable) months. The most frequent treatment-emergent adverse events (TEAEs) were rash (100%), neutropenia (90%), and infusion-related reactions (65%). Most common grade ≥ 3 TEAEs were neutropenia (70%), thrombocytopenia (25%), and fatigue (25%). For grade ≥ 3 neutropenia, febrile neutropenia, and thrombocytopenia TEAEs, all but two cases of neutropenia had fully resolved by Day 1 of the subsequent cycle. Fifteen of 20 patients (75%) experienced cytopenia events during the

first 4 cycles versus 2 of 17 patients (12%) during cycle 5 or onwards. Five of 7 patients who were given colony stimulating factors for neutropenia had no recurrent episodes of neutropenia. Treatment-related dose interruptions, reductions, and discontinuations of any study agent occurred in 18 (90%), 14 (70%), and 8 (40%) patients, respectively; no patient discontinued all study agents due to TEAEs.

[00193] Conclusions: Among patients with EGFR-mutated advanced NSCLC who experienced disease progression on EGFR TKIs, amivantamab, lazertinib plus chemotherapy demonstrated meaningful and durable response rates.

Example 2. MARIPOSA-2 Clinical Study

[00194] MARIPOSA-2 is a randomized, open-label, active-controlled, parallel, multicenter, Phase 3 study to compare the efficacy and safety of Arm A (lazertinib, amivantamab, carboplatin, and pemetrexed “LACP/ACP-L”) versus Arm B (carboplatin and pemetrexed, “CP”) and Arm C (amivantamab, carboplatin, and pemetrexed, “ACP”) versus Arm B (CP) in participants with EGFR-mutated locally advanced or metastatic nonsquamous NSCLC who have progressed on or after treatment with osimertinib. Study ID numbers include: NCT04988295, CR109061, 2021-001825-33 (EudraCT) and 61186372NSC3002.

[00195] The purpose of this study is to assess the efficacy of adding lazertinib to amivantamab, carboplatin, and pemetrexed (LACP/ACP-L dosing strategies) and amivantamab, carboplatin and pemetrexed (ACP) compared with carboplatin and pemetrexed (CP) in participants with locally advanced or metastatic epidermal growth factor receptor (EGFR) Exon 19del or Exon 21 L858R substitution non-small cell lung cancer (NSCLC) after osimertinib failure. The purpose of the extension cohort is to further describe the safety and efficacy for the ACP-L dosing schedule versus ACP with additional data.

[00196] Study Design

[00197] The original study design of MARIPOSA-2 had 3 arms with a randomization ratio of 2:2:1 for LACP, CP and ACP respectively, for the primary objective of comparing LACP and CP, with an ACP arm in the study to demonstrate the contribution of lazertinib. A decision was made to amend MARIPOSA-2 to implement the dual primary hypotheses of comparing ACP versus CP and LACP versus CP.

[00198] Arm A was eventually modified to withhold lazertinib during administration of carboplatin. The modified dosing schedule whereby lazertinib was started after treatment with carboplatin was completed is referred to as ACP-L; the prior dosing schedule before modification (i.e., participants started lazertinib from the beginning of treatment) is referred

to as LACP. The primary statistical analyses compared all participants randomized between Arm A and Arm B, regardless of dosing schedule, and between Arm C and Arm B on an intent to treat basis.

[00199] To further characterize the safety and efficacy of the modified ACP-L dosing schedule versus ACP, a separate open-label, randomized extension cohort was added to the study. Enrollment of participants into the extension cohort began after enrollment into the main study was complete. The extension cohort had the same eligibility criteria and study procedures, and operated within the same investigational sites as the main study. Participants were planned to be randomly assigned to study treatment arms in 2:1 ratio (Arms A2 and C2 respectively) in the extension cohort.

[00200] Data from the extension cohort were not included in the primary analysis. The primary analysis for Arm A as pre-specified in statistical analysis plan (SAP) pools data from participants treated with LACP and ACP-L. As a result of the limited follow-up of participants receiving ACP-L in the main study and extension cohort, the full comparison of ACP-L with CP is not in scope of this analysis. A diagram of the study design is provided in Figure 1.

[00201] **Inclusion/Exclusion Criteria.**

[00202] Eligible patients were 18 years of age or older, had locally advanced or metastatic NSCLC with disease progression on or after osimertinib monotherapy (as the most recent line of treatment), and had *EGFR* Ex19del or L858R mutations. Patients with brain metastases were eligible provided intracranial disease was stable, asymptomatic, and on unchanged doses of steroids. Additional information about the criteria is provided below.

[00203] **Inclusion Criteria:**

- Participant must have at least 1 measurable lesion, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, that has not been previously irradiated;
- Participant must have histologically or cytologically confirmed, locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC), characterized at or after the time of locally advanced or metastatic disease diagnosis by either epidermal growth factor receptor (EGFR) Exon 19del or Exon 21 L858R mutation;
- A participant with a history of brain metastases must have had all lesions treated as clinically indicated (that is, 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 milligrams (mg) prednisone or equivalent daily for the treatment of intracranial disease;

- Participant must have Eastern Cooperative Oncology Group (ECOG) status of 0 or 1;
- 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 $\leq$ 2 peripheral neuropathy, or Grade $\leq$ 2 hypothyroidism stable on hormone replacement);
- A woman 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;
- 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 tyrosine kinase inhibitor (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 (that is last dose no later than Day -8).

[00204] Exclusion Criteria:

- Participant received radiotherapy for palliative treatment of NSCLC less than 14 days prior to randomization;
- Participant with symptomatic or progressive brain metastases;
- Participant has history of or current evidence of leptomeningeal disease, or participant has spinal cord compression not definitively treated with surgery or radiation;
- Participant has known small cell transformation;
- Participant has a medical history of interstitial lung disease (ILD), including drug-induced ILD or radiation pneumonitis;
- Participant has a history of clinically significant cardiovascular disease including, but not limited to diagnosis of deep vein thrombosis or pulmonary embolism within 4 weeks prior to randomization; myocardial infarction; unstable angina; stroke; transient ischemic attack; coronary/peripheral artery bypass graft; or acute coronary syndrome. Participant has a significant genetic predisposition to venous thromboembolic events. Participant has a prior history of venous thromboembolic events and is not on appropriate therapeutic anticoagulation as per National Comprehensive Cancer Network or local guidelines.

[00205] Treatment duration/Trial duration:

[00206] The study included a Screening Phase, a Treatment Phase, and a Follow-up Phase. Participants were to complete screening procedures within 28 days before randomization. The Treatment Phase began on Cycle 1 Day 1 and continued in 21-day cycles until the End of

Treatment visit, that was to occur within 30 days after discontinuation of study treatment or prior to starting subsequent systemic therapy, whichever occurred first. Participants who discontinued study treatment for any reason were to be followed for survival and symptomatic progression in the Follow-up Phase. The Follow-up Phase starts after the End of Treatment Visit and continues until death, lost to follow-up, or withdrawal of consent, whichever comes first.

[00207] Main Study Arms:

Arm A

Dosing Schedule 1 (LACP):

- 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(split dosing), 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.

Dosing Schedule 2 (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(split dosing), 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/m² on Day 1 of each 21-day cycle, with carboplatin for up to 4 cycles, and then as maintenance until disease progression

Arm C (ACP):

- Amivantamab administered as per schedule in Arm A
- Carboplatin and pemetrexed as in Arm B

[00208] Primary and Secondary Endpoints:

Objectives of the Study	Endpoints
Dual Primary	
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 criteria, as assessed by BICR (Blinded Independent Central review)
To assess the efficacy of LACP/ACP-L, compared with CP, in participants with locally	- PFS using RECIST v1.1 criteria, as assessed by BICR

advanced or metastatic EGFR Exon 19del or Exon 21 L858R substitution NSCLC	
Secondary	
To further assess the clinical benefit of: - ACP vs CP - LACP/ACP-L vs CP	- Objective response (by BICR) - Overall survival - Duration of response (by BICR) - Time to subsequent therapy (PFS2) - Time to symptomatic progression - Intracranial PFS (by BICR)
To assess the safety of: - ACP vs CP - LACP/ACP-L 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: - ACP vs CP - LACP/ACP-L 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)

[00209] Results:

[00210] As noted above, MARIPOSA-2 (NCT04988295) is a randomized, open-label Phase 3 study evaluating the efficacy and safety of two dosing regimens of RYBREVANT® (amivantamab) and chemotherapy. Patients with locally advanced or metastatic EGFR ex19del or L858R substitution NSCLC who had disease progression on or after osimertinib were randomized to treatment with RYBREVANT® plus chemotherapy, RYBREVANT® plus chemotherapy with lazertinib or chemotherapy alone. Dual primary endpoints were used to compare the PFS (using RECIST v1.1 guidelines) as assessed by blinded independent

central review (BICR) for each experimental arm to chemotherapy alone. Secondary endpoints included objective response as assessed by BICR, overall survival (OS), duration of response (DoR), time to subsequent therapy, PFS after first subsequent therapy (PFS2) and intracranial PFS. All study participants underwent serial brain imaging to allow for the robust assessment of intracranial endpoints, and to assess the central nervous system (CNS) activity of RYBREVANT® with and without lazertinib. As brain metastases can lead to significant burden and poor outcomes for patients, this aspect of the study design provides critical information in an area of high unmet need. The study enrolled 657 participants with locally advanced or metastatic EGFR exon 19 deletions (ex19del) or L858R substitution non-small cell lung cancer (NSCLC) after disease progression on or after osimertinib.

[00211] Summarized below are positive topline results from the Phase 3 MARIPOSA-2 study evaluating RYBREVANT® (amivantamab) given with and without lazertinib, combined with chemotherapy (carboplatin and pemetrexed). The study met its dual primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS versus chemotherapy alone in both experimental treatment arms. No new safety signals were found for the addition of RYBREVANT® to chemotherapy.

[00212] A total of 657 participants (ACP: 131; LACP/ACP-L: 263; CP: 263) were randomized in the main study and included in this primary analysis. The key efficacy results are summarized in the Table 1A. At the clinical cut-off (CCO), with a median study follow-up of 8.74 months, there were 371 PFS events by BICR observed.

Table 1A: Key Efficacy Results

	CP (N=263)	ACP (N=131)	LACP/ACP-L (N=263)
Progression-free survival (PFS) by BICR			
Number of events (%)	171 (65.0%)	74 (56.5%)	126 (47.9%)
Median, months (95% CI)	4.17 (4.04, 4.44)	6.28 (5.55, 8.41)	8.31 (6.77, 9.10)
HR (95% CI); p-value		0.48 (0.36, 0.64); <0.0001	0.44 (0.35, 0.56); <0.0001
Objective response rate (ORR) by BICR			
ORR, % (95% CI)	36.2% (30.3, 42.3)	63.8% (55.0, 72.1)	62.9% (56.7, 68.8)
Complete response, %	0.4%	1.5%	2.3%
Partial response, %	35.8%	62.3%	60.6%
Odds ratio (95% CI); p-value		3.10 (2.00, 4.80); <0.0001	2.97 (2.08, 4.24); <0.0001
Duration of response (DOR) by BICR for confirmed responders			
Median (95% CI), months	5.55 (4.17, 9.56)	6.90 (5.52, NE)	9.43 (6.93, NE)

Subjects% with DOR $\geq$ 6 months	20.0%	31.9%	34.5%
Overall survival (OS)			
Number of events (%)	65 (24.7%)	27 (20.6%)	69 (26.2%)
Median, months (95% CI)	15.18 (13.01, NE)	14.19 (13.90, NE)	15.11 (13.24, NE)
HR (95% CI); p-value		0.77 (0.49, 1.21); 0.2531	0.96 (0.67, 1.35); 0.7972
Intracranial PFS by BICR			
Number of events (%)	102 (38.8%)	41 (31.3%)	86 (32.7%)
Median, months (95% CI)	8.31 (7.29, 11.27)	12.45 (10.84, NE)	12.81 (11.07, 14.26)
HR (95% CI); p-value		0.55 (0.38, 0.79); 0.0011	0.58 (0.44, 0.78); 0.0003
Time to subsequent therapy (TTST)			
Number of events (%)	138 (52.5%)	46 (35.1%)	100 (38.0%)
Median, months (95% CI)	6.60 (6.24, 8.11)	12.06 (11.04, 14.88)	12.58 (9.63, NE)
HR (95% CI); p-value		0.42 (0.30, 0.59); <0.0001	0.53 (0.40, 0.68); 0.0001
PFS after first subsequent therapy (PFS2)			
Number of events (%)	80 (30.4%)	33 (25.2%)	72 (27.4%)
Median, months (95% CI)	11.27 (9.07, 13.83)	13.90 (11.40, NE)	14.26 (13.24, NE)
HR (95% CI); p-value		0.60 (0.40, 0.92); 0.0167	0.70 (0.50, 0.97); 0.0287
Key: BICR=Blinded Independent Central review; HR=Hazard ratio; CI = Confidence Interval; NE=not estimable			

[00213] Efficacy Results:

[00214] The median progression-free survival by blinded independent central review was 6.3 months (95% CI, 5.55 to 8.4) with amivantamab-chemotherapy, 8.3 months (95% CI, 6.8 to 9.1) with amivantamab-lazertinib-chemotherapy, and 4.2 months (95% CI, 4.0 to 4.4) with chemotherapy. The hazard ratio for disease progression or death was 0.48 (95% CI, 0.36 to 0.64; $P < 0.001$) for amivantamab-chemotherapy versus chemotherapy and similar in magnitude to amivantamab-lazertinib-chemotherapy versus chemotherapy (0.44; 95% CI, 0.35 to 0.56; $P < 0.001$).

[00215] The median investigator-assessed progression-free survival was 8.2 months (95% CI, 6.8 to 10.9) for amivantamab-chemotherapy and 8.3 months (95% CI, 7.1 to 9.9) for amivantamab-lazertinib-chemotherapy versus 4.2 months (95% CI, 4.0 to 4.5) for chemotherapy, corresponding to similar hazard ratios for disease progression or death of 0.41 and 0.38, respectively ($P < 0.001$ for both versus chemotherapy).

[00216] The progression-free survival benefit was consistent across predefined subgroups for amivantamab-chemotherapy and similar in magnitude to amivantamab-lazertinib-chemotherapy, including subgroups based on history of brain metastases, osimertinib line of therapy, and EGFR mutation type.

[00217] The objective response rate was 64% (95% CI, 55 to 72) for amivantamab-chemotherapy, 63% (95% CI, 57 to 69) for amivantamab-lazertinib-chemotherapy, and 36% (95% CI, 30 to 42) for chemotherapy, with similar significant improvements versus chemotherapy for amivantamab-chemotherapy (odds ratio, 3.10; 95% CI, 2.00 to 4.80; $P<0.001$) and amivantamab-lazertinib-chemotherapy (odds ratio, 2.97; 95% CI, 2.08 to 4.24; $P<0.001$). Among patients with a confirmed response, median duration of response was 6.9 months (95% CI, 5.5 to not estimable) for amivantamab-chemotherapy, 9.4 months (95% CI, 6.9 to not estimable) for amivantamab-lazertinib-chemotherapy, and 5.55 months (95% CI, 4.2 to 9.6) for chemotherapy.

[00218] With 161 deaths observed in the study, there was a trend favoring improved overall survival for amivantamab-chemotherapy versus chemotherapy (hazard ratio for death, 0.77; 95% CI, 0.49 to 1.21). A non-detrimental effect was seen for amivantamab-lazertinib-chemotherapy versus chemotherapy (hazard ratio for death, 0.96; 95% CI, 0.67 to 1.35).

[00219] Median intracranial progression-free survival was 12.45 months (95% CI, 10.8 to not estimable) for amivantamab-chemotherapy, 12.8 months (95% CI, 11.1 to 14.3) for amivantamab-lazertinib-chemotherapy, and 8.3 months (95% CI, 7.3 to 11.3) for chemotherapy. The improvement versus chemotherapy was significant for amivantamab-chemotherapy (hazard ratio for disease progression or death, 0.55; 95% CI, 0.38 to 0.79; $P=0.001$) and similar in magnitude to amivantamab-lazertinib-chemotherapy versus chemotherapy (hazard ratio for disease progression or death, 0.58; 95% CI, 0.44 to 0.78; $P<0.001$).

[00220] As a result of the limited follow-up of participants receiving ACP-L in the main study and extension cohort to date, the comparison of ACP-L with CP is not in scope for this analysis and will be further evaluated when additional data is available.

[00221] Discussion

[00222] Amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy significantly prolonged progression-free survival versus chemotherapy, with a 52% and 56% reduction in the risk of disease progression or death, respectively. Early separation of curves was observed between both amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy versus chemotherapy. The progression-free survival benefit was consistent

across predefined subgroups. The magnitude of improvement over chemotherapy was similar for amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy.

[00223] Amivantamab is a large molecule and was not expected to readily cross the blood-brain barrier. This was one of the key drivers for including lazertinib, a known CNS-active TKI, in the amivantamab-lazertinib-chemotherapy arm. It is thus notable that amivantamab-chemotherapy demonstrated similar intracranial progression-free survival advantages over chemotherapy as amivantamab-lazertinib-chemotherapy. These findings suggest that amivantamab exerts an antitumor effect intracranially, whether this occurs through direct engagement with intracranial metastases or indirectly through an immune-based mechanism is unclear. Despite the frequent utilization of TKI continuation out of concern for CNS progression, no prior prospective trial has shown improved clinical outcomes with this approach.

[00224] Resistance to osimertinib is diverse, polyclonal, and difficult to treat. There are currently no targeted therapies approved in the post-osimertinib setting. Two studies of immunotherapy-chemotherapy regimens have recently failed to show efficacy in the TKI-resistant setting. Currently, there are 6 other phase 3 studies (NCT05261399, NCT04765059, NCT05089734, NCT05338970, NCT04656652, NCT05184712) investigating targeted therapy combinations versus chemotherapy as second-line (or later) treatment in EGFR-mutated advanced NSCLC, highlighting the unmet need in this patient population.

[00225] In summary, progression-free survival was significantly longer with amivantamab- chemotherapy and amivantamab-lazertinib-chemotherapy compared with chemotherapy in patients with EGFR-mutated advanced NSCLC whose disease had progressed on or after osimertinib monotherapy.

[00226] Updated Data: post-progression outcomes and additional safety data from MARIPOSA-2

[00227] Post-progression outcomes and additional safety data from MARIPOSA-2 were assessed, as described below.

[00228] **Methods:** The following analyses focus on the 131 pts randomized to ami-chemo (safety set: n=130) and 263 to chemo (safety set: n=243). A third arm (ami-lazertinib-chemo) was modified during the study and will be reported in the future. Post-progression endpoints were time to treatment discontinuation (TTD), time to subsequent therapy (TTST), and PFS after first subsequent therapy (PFS2).

[00229] **Results:** At a median follow-up of 8.7 months (mo), 55/130 (42%) pts in the ami-chemo arm and 173/243 (71%) in the chemo arm had progressive disease (PD). Among those

with PD, 19/55 (35%) in the ami-chemo arm and 28/173 (16%) in the chemo arm were treated beyond progression for >4 weeks with a median (95% CI) post-progression treatment duration of 18.3 (9.0–NE) and 9.0 (6.0–16.4) weeks, respectively. Compared to chemo, ami-chemo significantly prolonged TTD (median, 11.0 vs 4.5 mo for chemo; HR, 0.37 [95% CI, 0.28–0.50]; $P<0.0001$), TTST (median, 12.1 vs 6.6 mo for chemo; HR, 0.42 [95% CI, 0.30–0.59]; $P<0.0001$), and PFS2 (median, 13.9 vs 11.3 mo for chemo; HR, 0.60 [95% CI, 0.40–0.92]; $P=0.017$). Among pts with PD, 75% (41/55) in the ami-chemo arm discontinued treatment after progression vs 93% (161/173) for chemo. First subsequent systemic therapy was initiated by 63% (26/41) of pts after ami-chemo and 63% (101/161) after chemo. Most common subsequent therapies were osimertinib and docetaxel for both arms. Among ami-chemo pts, first onset of cytopenic, cutaneous, and fatigue adverse events was highest in the first 4 mo and decreased over time.

[00230] Conclusions: Ami-chemo significantly prolonged TTD, TTST, and PFS2 vs chemo. Ami-chemo represents the new standard of care for pts with *EGFR*-mutant advanced NSCLC after disease progression on osimertinib.

[00231] Updated Data: Secondary Analyses of Patient-relevant Endpoints from MARIPOSA-2

[00232] Provided below is an evaluation of time to symptomatic progression (TTSP) and patient-reported outcomes (PROs) from MARIPOSA-2.

[00233] Methods: The following analyses included 131 pts randomized to ami-chemo and 263 pts to chemo (intent-to-treat population [ITT]). TTSP was defined as time from randomization to onset of new/worsening lung cancer symptoms requiring change in anticancer therapy or death, whichever occurred first. Patient-reported outcomes (PROs) were measured using the EORTC-QLQ-C30, NSCLC-SAQ, and PROMIS-PF 8c instruments.

[00234] Results: At a median follow-up of 8.7 mo, a trend towards improvement in median TTSP was observed for ami-chemo vs chemo (14.9 vs 13.0 mo; HR, 0.74 [95% CI, 0.51–1.07]; $P=0.10$).

[00235] Median treatment duration was 6.3 mo for ami-chemo vs 3.7 mo for chemo. At 6 mo (189 days), the percentage of ITT pts who remained on treatment and had improved or stable physical functioning relative to baseline was 37% for ami-chemo vs 21% for chemo. There were higher percentages of pts with improved or stable emotional functioning (38% vs 21%), cognitive functioning (38% vs 20%), role functioning (30% vs 19%), and global health status (40% vs 19%) for ami-chemo vs chemo, respectively.

[00236] Based on data from EORTC-QLQ-C30, at 6 mo 28% vs 13% pts reported no dyspnea, 23% vs 15% reported no pain, and 10% vs 5% reported no fatigue for ami-chemo vs chemo, respectively. Per the EORTC-QLQ-C30, more patients in the amivantamab-chemotherapy arm reported improved/stable functioning or absence of key symptoms vs chemotherapy.

[00237] Per the NSCLC-SAQ, amivantamab-chemotherapy substantially prolonged time to sustained deterioration in lung cancer symptoms vs chemotherapy (11.6 vs 8.5 mo).

[00238] Per the PROMIS-PF 8c, amivantamab-chemotherapy numerically prolonged time to sustained deterioration in physical functioning vs chemotherapy (11.6 vs 9.4 mo).

[00239] **Conclusions:** Ami-chemo numerically prolonged time to symptomatic progression vs chemo. More pts in the ITT population reported improved or stable functioning and absence of lung cancer-related symptoms for ami-chemo vs chemo. The PFS benefit of ami-chemo was achieved while maintaining low disease symptom burden and high levels of functioning in pts with *EGFR*-mutant advanced NSCLC after progression on osimertinib.

Example 3. Amivantamab Plus Chemotherapy vs Chemotherapy in *EGFR*-mutated, Advanced Non-small Cell Lung Cancer After Disease Progression on Osimertinib: 2nd Interim Overall Survival From MARIPOSA-2

[00240] **Background:** In the phase 3 MARIPOSA-2 study (NCT04988295), amivantamab (ami)-chemotherapy (chemo; carboplatin/pemetrexed) showed superior progression-free survival (PFS) vs chemo in patients (pts) with *EGFR*-mutant, advanced non-small cell lung cancer (NSCLC) after progression on osimertinib (osi; HR, 0.48; 95% CI, 0.36–0.64; $P < 0.001$). At the first interim analysis (IA) of overall survival (OS; median follow-up: 8.7 mo), a favorable trend was seen for ami-chemo vs chemo (HR, 0.77; 95% CI, 0.49–1.21). Second IA (IA2) of OS and post-progression results are reported.

[00241] **Methods:** MARIPOSA-2 enrolled pts with *EGFR*-mutant (Ex19del/L858R) advanced NSCLC post-osi. The primary endpoint was PFS. IA2 of OS was prespecified to occur when ~75% of total OS events were observed. OS was to be evaluated at a 2-sided alpha of 0.0142 (O'Brien-Fleming alpha spending approach as implemented by the Lan-DeMets method). Other endpoints were time to treatment discontinuation (TTD), time to subsequent therapy (TTST), and PFS after first subsequent therapy (PFS2).

[00242] **Results:** At IA2, 208 OS events were observed across both arms. After a median follow-up of 18.1 mo, OS was numerically improved for ami-chemo vs chemo (median, 17.7

vs 15.3 mo; HR, 0.73; 95% CI, 0.54–0.99; P=0.039), but did not reach the prespecified significance threshold. At 18 mo, 50% vs 40% of pts were alive with ami-chemo vs chemo. The OS benefit of ami-chemo vs chemo was generally consistent among pre-defined subgroups. PFS2 was significantly prolonged for ami-chemo vs chemo (median, 16.0 vs 11.6 mo; HR, 0.64; 95% CI, 0.48–0.85; P=0.002) and improved over time, supporting the OS findings. TTD and TTST were significantly prolonged in favor of ami-chemo (Table 2).

Table 2. Efficacy outcomes

Endpoint	Ami-chemo (n=131)	Chemo (n=263)
Median follow-up, mo	18.6	17.8
OS events, n (%)	65 (50)	143 (54)
Median OS, mo (95% CI)	17.7 (16.0–22.4)	15.3 (13.7–16.8)
HR for OS (95% CI)	0.73 (0.54–0.99); P=0.039	
18-mo OS rate, % (95% CI)	50 (40–59)	40 (33–46)
Median TTD, mo (95% CI)	10.4 (7.9–11.6)	4.5 (4.2–5.0)
HR for TTD (95% CI)	0.42 (0.33–0.53); P<0.0001	
Median TTST, mo (95% CI)	12.2 (10.7–14.3)	6.6 (6.1–7.4)
HR for TTST (95% CI)	0.51 (0.39–0.65); P<0.0001	
Median PFS2, mo (95% CI)	16.0 (13.9–17.6)	11.6 (10.1–13.0)
HR for PFS2 (95% CI)	0.64 (0.48–0.85); P=0.002	

[00243] FIG. 2 shows the MARIPOSA-2 Study Design. Secondary/Exploratory efficacy endpoints reported: overall survival (OS); time to symptomatic progression (TTSP); time to treatment discontinuation (TTD); time to subsequent therapy (TTST); and PFS after first subsequent therapy (PFS2). The second interim analysis of OS was prespecified for when ~75% of the planned OS events were observed. The significance level at the second interim analysis for OS was determined based on the O’Brien-Fleming alpha spending approach (2-sided alpha: 0.0142) as implemented by the Lan-DeMets method.

[00244] FIG. 3 shows overall survival. Amivantamab-chemotherapy demonstrated a clear and improving OS trend vs chemotherapy. P-value was calculated using a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no). OS was evaluated at a 2-sided alpha of 0.0142.

[00245] FIG. 4 shows Time to Symptomatic Progression (TTSP, time from randomization to onset of new symptoms or symptom worsening that was considered by the investigator to be related to lung cancer and required either a change in anticancer treatment and/or clinical intervention to manage symptoms). TTSP was significantly improved with amivantamab-

chemotherapy vs chemotherapy. b - In a prior analysis, ami-chemo numerically improved TTSP vs chemo (HR, 0.74; 95% CI, 0.51–1.07; $P=0.10$). *P-value* was calculated using a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no).

[00246] FIG. 5 shows Time to Treatment Discontinuation (TTD, time from randomization to discontinuation of all study treatments for any reason, including disease progression, treatment toxicity, or death). b - In a prior analysis, ami-chemo significantly prolonged TTD vs chemo (HR, 0.37; 95% CI, 0.28–0.50; $P<0.0001$).¹ *cP-value* is from a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no).

[00247] FIG. 6 shows Time to Subsequent Therapy (Time from the date of randomization to the start date of the subsequent anticancer therapy following study treatment discontinuation, or death, whichever occurred first). TTST was significantly prolonged with amivantamab-chemotherapy vs chemotherapy. b - In a prior analysis, ami-chemo significantly prolonged TTST vs chemo (HR, 0.42; 95% CI, 0.30–0.59; $P<0.0001$).¹ *P-value* was determined using a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no).

[00248] FIG. 7 shows PFS After First Subsequent Therapy (PFS2, 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 occurred first). PFS2 was significantly prolonged with amivantamab-chemotherapy vs chemotherapy. b - In a prior analysis, ami-chemo significantly prolonged PFS2 vs chemo (HR, 0.60; 95% CI, 0.40–0.92; $P=0.017$). *P-value* was calculated using a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no). No single therapy class was identified as the most prominent subsequent therapy, highlighting the limited options in the third-line setting.

[00249] **Conclusions:** Ami-chemo numerically improved OS and significantly prolonged post-progression outcomes vs chemo in *EGFR*-mutant, advanced NSCLC post-osimertinib. At median follow-up time of 18.1 months data continued to favor amivantamab-chemotherapy over chemotherapy, with a promising OS trend in the post-osimertinib setting (median, 17.7 vs 15.3 mo; HR, 0.73; $P=0.039$).

[00250] Post-progression endpoints showed significant and sustained improvement for amivantamab-chemotherapy vs chemotherapy:

- Time to symptomatic progression (HR, 0.73; P=0.026)
- Time to treatment discontinuation (HR, 0.42; P<0.0001)
- Time to subsequent therapy (HR, 0.51; P<0.0001)
- Progression-free survival after first subsequent therapy (HR, 0.64; P=0.002).

[00251] Amivantamab's multi-targeted MoA and immune cell-directing activity combined with chemotherapy's antitumor effects is likely contributing to the observed durability.

[00252] These MARIPOSA-2 follow-up results confirm the superior outcomes of amivantamab-chemotherapy vs chemotherapy in EGFR-mutant advanced NSCLC after disease progression on osimertinib.

* * *

[00253] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

[00254] All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference in their entirety as if physically present in this specification.

Claims

1. A method of improving median progression free survival (PFS) in a population of subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring one or more epidermal growth factor receptor (EGFR) mutations whose NSCLC progressed on or after treatment with at least one prior tyrosine kinase inhibitor (TKI), said method comprising administering to the population of subjects a combination therapy comprising:

- (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody,
- (ii) a therapeutically effective amount of carboplatin, and
- (iii) a therapeutically effective amount of pemetrexed,

wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with the at least one prior TKI, said reference population having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody.

2. The method of claim 1, wherein the bispecific anti-EGFR/c-Met antibody comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6, and wherein the second domain that binds c-Met comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.
3. The method of claim 1 or claim 2, wherein the one or more EGFR mutations comprise one or more exon 19 deletions, or exon 21 L858R substitution, or any combination thereof.
4. The method of claim 3, wherein the one or more EGFR mutations comprise one or more exon 19 deletions.

5. The method of claim 3, wherein the one or more EGFR mutations comprise exon 21 L858R substitution.
6. The method of any one of claims 1-5, wherein said at least one prior TKI comprises a 1st generation EGFR TKI.
7. The method of any one of claims 1-5, wherein said at least one prior TKI comprises a 2nd generation EGFR TKI.
8. The method of any one of claims 1-5, wherein said at least one prior TKI comprises a 3rd generation EGFR TKI.
9. The method of any one of claims 1-5, wherein said at least one prior TKI comprises osimertinib.
10. The method of any one of claims 1-9, wherein administration of the combination therapy begins on Cycle 1 Day 1 of the first 21-day cycle, and continues in subsequent 21-day cycles.
11. The method of any one of claims 1-10, wherein the bispecific anti-EGFR/c-Met antibody is administered intravenously.
12. The method of any one of claims 1-10, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.
13. The method of claim 1-12, wherein the method comprises administering the bispecific anti-EGFR/c-Met antibody in an amount of between about 140 mg and about 2240 mg.
14. The method of claim 13, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 700 mg, about 750 mg, about 800 mg, about 850 mg, 900 mg, 950 mg, 1000 mg, 1050 mg, 1100 mg, 1150 mg, 1200 mg, 1250 mg, 1300 mg, 1350 mg, 1400 mg, 1575 mg, 1600 mg, 1750 mg, 2100 mg, or 2240 mg.
15. The method of claim 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg.
16. The method of claim 15, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.

17. The method of claim 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg.
18. The method of claim 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg.
19. The method of claim 18, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
20. The method of claim 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg.
21. The method of any one of claims 1-20, wherein the method comprises administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles.
22. The method of any one of claims 1-21, wherein the method comprises administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression.
23. The method of claim 22, wherein the method comprises:
 - a) (i) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg; or
 - (ii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg; or
 - (iii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg; or
 - (iv) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg;and
 - b) administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles;

and

c) administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression.

24. The method of claim 23, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
25. The method of any one of claims 1-24, wherein the combination therapy achieves an improvement in the median PFS of at least two weeks.
26. The method of claim 25, wherein the combination therapy achieves an improvement in the median PFS of at least 1 month.
27. The method of claim 26, wherein the combination therapy achieves an improvement in the median PFS of at least 1.5 months.
28. The method of claim 27, wherein the combination therapy achieves an improvement in the median PFS of at least 2 months.
29. The method of claim 28, wherein the subject exhibits progression-free survival for at least 4.5 months.
30. The method of claim 29, wherein the subject exhibits progression-free survival for at least 5 months.
31. The method of claim 30, wherein the subject exhibits progression-free survival for at least 5.5 months.
32. The method of claim 31, wherein the subject exhibits progression-free survival for at least 6 months.
33. The method of claim 32, wherein the subject exhibits progression-free survival for at least 10 months.
34. The method of claim 33, wherein the subject exhibits progression-free survival for at least 12 months.
35. The method of claim 34, wherein the subject exhibits progression-free survival for at least 14 months.
36. The method of any one of claims 1-35, wherein the combination therapy further achieves an improvement in objective response relative to said reference population.

37. The method of any one of claims 1-36, wherein the combination therapy further achieves an improvement in overall survival (OS) relative to said reference population.
38. The method of any one of claims 1-37, wherein the combination therapy further achieves an improvement in duration of response (DoR) relative to said reference population.
39. The method of any one of claims 1-38, wherein the combination therapy further achieves an improvement in time to subsequent therapy relative to said reference population.
40. The method of any one of claims 1-39, wherein the combination therapy further achieves an improvement in PFS after first subsequent therapy (PFS2) relative to said reference population.
41. The method of any one of claims 1-40, wherein the combination therapy further achieves an improvement in intracranial median PFS relative to said reference population.
42. A method of improving median progression free survival (PFS) in a population of subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring one or more epidermal growth factor receptor (EGFR) mutations whose NSCLC progressed on or after treatment with at least one prior tyrosine kinase inhibitor (TKI), said method comprising administering to the population of subjects a combination therapy comprising:
- (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody,
 - (ii) a therapeutically effective amount of lazertinib, or a pharmaceutically acceptable salt or hydrate thereof,
 - (iii) a therapeutically effective amount of carboplatin, and
 - (iv) a therapeutically effective amount of pemetrexed,

wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with the at least one prior TKI, said reference population

having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody nor said lazertinib or pharmaceutically acceptable salt or hydrate thereof.

43. The method of claim 41, wherein the bispecific anti-EGFR/c-Met antibody comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6, and wherein the second domain that binds c-Met comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.
44. The method of claim 42 or claim 43, wherein the one or more EGFR mutations comprise one or more exon 19 deletions, or exon 21 L858R substitution, or any combination thereof.
45. The method of claim 44, wherein the one or more EGFR mutations comprise one or more exon 19 deletions.
46. The method of claim 44, wherein the one or more EGFR mutations comprise exon 21 L858R substitution.
47. The method of any one of claims 42-46, wherein said at least one prior TKI comprises a 1st generation EGFR TKI.
48. The method of any one of claims 42-46, wherein said at least one prior TKI comprises a 2nd generation EGFR TKI.
49. The method of any one of claims 42-46, wherein said at least one prior TKI comprises a 3rd generation EGFR TKI.
50. The method of any one of claims 42-46, wherein said at least one prior TKI comprises osimertinib.
51. The method of any one of claims 42-50, wherein administration of the combination therapy begins on Cycle 1 Day 1 of the first 21-day cycle, and continues in subsequent 21-day cycles.

52. The method of any one of claims 42-51 wherein the bispecific anti-EGFR/c-Met antibody is administered intravenously.
53. The method of any one of claims 42-51, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.
54. The method of any one of claims 42-53, wherein the method comprises administering the bispecific anti-EGFR/c-Met antibody in an amount of between about 140 mg and about 2240 mg.
55. The method of claim 54, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 700 mg, about 750 mg, about 800 mg, about 850 mg, 900 mg, 950 mg, 1000 mg, 1050 mg, 1100 mg, 1150 mg, 1200 mg, 1250 mg, 1300 mg, 1350 mg, 1400 mg, 1575 mg, 1600 mg, 1750 mg, 2100 mg, or 2240 mg.
56. The method of claim 55, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg.
57. The method of claim 56, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
58. The method of claim 55, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg.
59. The method of claim 55, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg.
60. The method of claim 59, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
61. The method of claim 55, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg.
62. The method of any one of claims 42-61, wherein the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, is lazertinib mesylate.

63. The method of any one of claims 42-61, wherein the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, is lazertinib mesylate monohydrate.
64. The method of any one of claims 42-63, wherein the method comprises administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, at a dose of about 240 mg orally, once daily.
65. The method of claim 64, wherein the method comprises administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, at a dose of about 240 mg orally, once daily starting Cycle 5 Day 1 or sooner if said carboplatin is discontinued earlier.
66. The method of any one of claims 42-65, wherein the method comprises administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles.
67. The method of any one of claims 42-66, wherein the method comprises administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with carboplatin for up to 4 cycles, and then as maintenance until disease progression.
68. The method of claim 67, wherein the method comprised:
- a) (i) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg; or
 - (ii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg; or
 - (iii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg; or
 - (iv) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg;
- and
- b) (i) administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, at a dose of about 240 mg orally, once daily; or
 - (ii) administering the lazertinib, or pharmaceutically acceptable salt or hydrate thereof, at a dose of about 240 mg orally, once daily starting Cycle 5 Day 1 or sooner

if the carboplatin is discontinued earlier;

and

c) administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles;

and

d) administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with carboplatin for up to 4 cycles, and then as maintenance until disease progression.

69. The method of claim 68, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
70. The method of any one of claims 42-69, wherein the combination therapy achieves an improvement in the median PFS of at least two weeks.
71. The method of claim 70, wherein the combination therapy achieves an improvement in the median PFS of at least 1 month.
72. The method of claim 71, wherein the combination therapy achieves an improvement in the median PFS of at least 1.5 months.
73. The method of claim 72, wherein the combination therapy achieves an improvement in the median PFS of at least 2 months.
74. The method of claim 73, wherein the subject exhibits progression-free survival for at least 4.5 months.
75. The method of claim 74, wherein the subject exhibits progression-free survival for at least 5 months.
76. The method of claim 75, wherein the subject exhibits progression-free survival for at least 5.5 months.
77. The method of claim 76, wherein the subject exhibits progression-free survival for at least 6 months.
78. The method of claim 77, wherein the subject exhibits progression-free survival for at least 10 months.
79. The method of claim 78, wherein the subject exhibits progression-free survival for at least 12 months.

80. The method of claim 79, wherein the subject exhibits progression-free survival for at least 14 months.
81. The method of any one of claims 42-80, wherein the combination therapy further achieves an improvement in objective response relative to of said reference population.
82. The method of any one of claims 42-81, wherein the combination therapy further achieves an improvement in overall survival (OS) relative to of said reference population.
83. The method of any one of claims 42-82, wherein the combination therapy further achieves an improvement in duration of response (DoR) relative to of said reference population.
84. The method of any one of claims 42-83, wherein the combination therapy further achieves an improvement in time to subsequent therapy relative to of said reference population.
85. The method of any one of claims 42-84, wherein the combination therapy further achieves an improvement in PFS after first subsequent therapy (PFS2) relative to of said reference population.
86. The method of any one of claims 42-85, wherein the combination therapy further achieves an improvement in intracranial median PFS relative to of said reference population.
87. A method of improving median overall survival (OS) in a population of subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring one or more epidermal growth factor receptor (EGFR) mutations whose NSCLC progressed on or after treatment with at least one prior tyrosine kinase inhibitor (TKI), said method comprising administering to the population of subjects a combination therapy comprising:
 - (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody,
 - (ii) a therapeutically effective amount of carboplatin, and
 - (iii) a therapeutically effective amount of pemetrexed,

wherein the improvement in median OS is relative to median OS of a reference population of subjects with NSCLC harboring one or more EGFR mutations whose NSCLC progressed on or after treatment with the at least one prior TKI, said reference population having been administered carboplatin and pemetrexed but not said bispecific anti-EGFR/c-Met antibody.

88. The method of claim 87, wherein the bispecific anti-EGFR/c-Met antibody comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6, and wherein the second domain that binds c-Met comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.
89. The method of claim 87 or claim 88, wherein the one or more EGFR mutations comprise one or more exon 19 deletions, or exon 21 L858R substitution, or any combination thereof.
90. The method of claim 89, wherein the one or more EGFR mutations comprise one or more exon 19 deletions.
91. The method of claim 89, wherein the one or more EGFR mutations comprise exon 21 L858R substitution.
92. The method of any one of claims 87-91, wherein said at least one prior TKI comprises a 1st generation EGFR TKI.
93. The method of any one of claims 87-91, wherein said at least one prior TKI comprises a 2nd generation EGFR TKI.
94. The method of any one of claims 87-91, wherein said at least one prior TKI comprises a 3rd generation EGFR TKI.
95. The method of any one of claims 87-91, wherein said at least one prior TKI comprises osimertinib.

96. The method of any one of claims 87-95, wherein administration of the combination therapy begins on Cycle 1 Day 1 of the first 21-day cycle, and continues in subsequent 21-day cycles.
97. The method of any one of claims 87-96, wherein the bispecific anti-EGFR/c-Met antibody is administered intravenously.
98. The method of any one of claims 87-96, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.
99. The method of any one of claims 87-98, wherein the method comprises administering the bispecific anti-EGFR/c-Met antibody in an amount of between about 140 mg and about 2240 mg.
100. The method of claim 99, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 700 mg, about 750 mg, about 800 mg, about 850 mg, 900 mg, 950 mg, 1000 mg, 1050 mg, 1100 mg, 1150 mg, 1200 mg, 1250 mg, 1300 mg, 1350 mg, 1400 mg, 1575 mg, 1600 mg, 1750 mg, 2100 mg, or 2240 mg.
101. The method of claim 100, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg.
102. The method of claim 101, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
103. The method of claim 100, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg.
104. The method of claim 100, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg.
105. The method of claim 104, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.
106. The method of claim 100 wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg.

107. The method of any one of claims 87-106, wherein the method comprises administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles.

108. The method of any one of claims 87-107, wherein the method comprises administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression.

109. The method of claim 108, wherein the method comprises:

a) (i) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1400 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of less than 80 kg; or

(ii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of less than 80 kg; or

(iii) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 1750 mg on Cycle 1 Days 1, 8, and 15, and Cycle 2 Day 1 if the subject has a body weight of greater than or equal to 80 kg; or

(iv) administering the bispecific anti-EGFR/c-Met antibody at a dose of about 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 if the subject has a body weight of greater than or equal to 80 kg;

and

b) administering the carboplatin at a dose of AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles;

and

c) administering the pemetrexed at a dose of about 500 mg/m² on Day 1 of each 21-day cycle, with the carboplatin for up to 4 cycles, and then as maintenance until disease progression.

110. The method of claim 109, wherein the bispecific anti-EGFR/c-Met antibody dose of Cycle 1 Day 1 is administered as a split dose over Day 1 and 2.

111. The method of any one of claims 87-110, wherein the population of subjects administered the combination therapy achieves an improvement in the median OS of at least two months, relative to the reference population.

112. The method of claim 111, wherein the population of subjects administered the combination therapy achieves an improvement in the median OS of at least 2.4 months, relative to the reference population.
113. The method of claim 111, wherein the population of subjects administered the combination therapy achieves an improvement in the median OS of about 2.4 months, relative to the reference population.
114. The method of claim 111, wherein the subject administered the combination therapy exhibits overall survival for at least 17 months.
115. The method of claim 114, wherein the subject administered the combination therapy exhibits overall survival for at least about 17.7 months.
116. The method of claim 114, wherein the subject administered the combination therapy exhibits overall survival for about 17.7 months.
117. The method of any one of claims 87-116, wherein the combination therapy further achieves an improvement in time to symptomatic progression (TTSP) relative to said reference population.
118. The method of any one of claims 87-116, wherein the combination therapy further achieves an improvement in time to subsequent therapy (TTST) relative to said reference population.
119. The method of any one of claims 87-116, wherein the combination therapy further achieves an improvement in PFS after first subsequent therapy (PFS2) relative to said reference population.
120. The method of any one of claims 87-116, wherein the combination therapy further achieves an improvement in time to treatment discontinuation (TTD) relative to said reference population.