

**FIRST LINE TREATMENT IN EGFR EXON 20 INSERTION-MUTATED
ADVANCED NON-SMALL CELL LUNG CANCER**

FIELD

[0001] The present disclosure provides methods for treating EGFR-positive non-small cell lung cancer (NSCLC) in a subject that is treatment naïve.

CROSS REFERENCE TO RELATED APPLICATIONS

[0002] This application claims priority to U.S. Provisional Application No. 63/543,778, filed October 12, 2023, and U.S. Provisional Application No. 63/564,670, filed March 13, 2024, which are hereby incorporated by reference herein in their entirety.

REFERENCE TO A "SEQUENCE LISTING," SUBMITTED AS AN XML FILE

[0003] The Sequence Listing written in the xml file titled: "JBI6845_SequenceListing.xml"; created on October 8, 2024, and 20,021 bytes in size, is hereby incorporated by reference.

BACKGROUND

[0004] Cancer is a leading cause of death worldwide. Lung cancer is one of the most common types of cancer and is the most common cause of death from cancer (almost 20% of cancer deaths); NSCLC accounts for 80% to 85% of lung cancers. Adenocarcinoma is a subset of NSCLC and the most common type of lung cancer, comprising 40% of lung cancers. Five-year survival rates for NSCLC depend on the stage at diagnosis, ranging from 57% for localized cancer to 5% for cancer that has spread to distant locations. In patients with metastatic NSCLC, clinical guidelines recommend testing for activating mutations, which are observed in approximately 50% of adenocarcinomas.

[0005] The identification of these "driver" activating mutations has provided an opportunity to specifically inhibit the constitutively activated pathway using targeted tyrosine kinase inhibitors (TKIs). Among patients with NSCLC adenocarcinoma, the most prevalent of these driver mutations are those that result in the activation of EGFR, which are identified in more than 15% of patients with adenocarcinoma and up to 50% of the corresponding Asian population. The most commonly occurring EGFR mutations, L858R and Exon 19del, are sensitive to approved EGFR TKIs, which are associated with high response rates

(approximately 60% to 80%), prolonged duration of response, and median progression free survival (PFS) of approximately 10-19 months. As a result, these EGFR TKIs are considered first-line therapy for patients with NSCLC and EGFR L858R or Exon 19del mutations.

[0006] In approximately 10% of EGFR-mutated NSCLC, EGFR is activated through one of a group of heterogenous, in-frame base pair insertions in EGFR Exon 20, collectively referred to as EGFR Exon 20ins mutations. Although EGFR Exon 20ins-mutated NSCLC is believed to share a similar biology with other EGFR-mutated NSCLC, the unique protein structure associated with this group of EGFR mutations prevents effective binding by approved EGFR TKIs, by sterically hindering access to the receptor active site. Thus, NSCLC arising from Exon 20ins mutations is distinguished by de novo resistance to currently approved EGFR TKIs, including third-generation TKIs such as osimertinib. Correspondingly, recently presented real-world evidence suggests inferior therapeutic outcomes with the non-standard use of EGFR TKI in the first-line setting, as compared to chemotherapy. As a result, no EGFR TKI or other targeted therapy is approved for the treatment of patients with EGFR Exon 20ins NSCLC.

[0007] In the absence of effective targeted therapies, platinum-based doublet chemotherapy remains the standard of care for first-line therapy in patients with EGFR Exon 20ins-mutated NSCLC. The efficacy of combination chemotherapy in patients with advanced NSCLC and EGFR L858R or Exon 19del mutations includes an objective response rate (ORR) of approximately 30% and median PFS of approximately 5 months. There is a need for better treatment regimens in the field of lung cancer treatment.

SUMMARY

[0008] In one aspect, provided herein is a method of improving median progression free survival (PFS) in a population of subjects with non-small cell lung cancer (NSCLC) having one or more epidermal growth factor receptor (EGFR) exon 20 insertion mutations who are treatment-naïve, the 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, and (ii) chemotherapy, wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC having one or more EGFR exon 20 insertion mutations who are treatment-naïve, the reference population having been administered chemotherapy only.

[0009] In another aspect, provided herein is a method of improving median overall survival (OS) in a population of subjects with non-small cell lung cancer (NSCLC) having one or more epidermal growth factor receptor (EGFR) exon 20 insertion mutations who are treatment-naïve, the 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, and (ii) chemotherapy, wherein the improvement in median OS is relative to median OS of a reference population of subjects with NSCLC having one or more EGFR exon 20 insertion mutations who are treatment-naïve, the reference population having been administered chemotherapy only.

[0010] In some embodiment, of any of the methods disclosed herein, the NSCLC is locally advanced or metastatic. In some embodiment, of any of the above methods, the NSCLC is nonsquamous NSCLC.

[0011] In some embodiment, of any of the methods disclosed herein, the chemotherapy comprises administration of pemetrexed and carboplatin.

[0012] In some embodiment, of any of the methods disclosed herein, pemetrexed is administered at a dose of 500 mg/m² on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression. In some embodiment, of any of the above methods, carboplatin is administered at a dose to achieve area under the concentration-time curve 5 mg/mL per minute (AUC 5) on Day 1 of each 21-day cycle, for up to 4 cycles.

[0013] In some embodiment, of any of the methods disclosed herein, the method elicits a clinical response in the subject according to RECIST v1.1 criteria. In some embodiment, of any of the above methods, the method achieves a partial response or better in the subject according to RECIST v1.1 criteria. In some embodiment, of any of the above methods, the clinical response comprises a median duration of response (DOR) of at least 9 months. In some embodiment, of any of the above methods, the subject is progression-free after at least 11 months.

[0014] In some embodiment, of any of the methods disclosed herein, 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 embodiment, of any of the above methods, 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 embodiment, of any of the above methods, the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype. In some embodiment, of any of the above methods, 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 embodiment, of any of the above methods, the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about between 1% to about 15%.

[0015] In some embodiment, of any of the methods disclosed herein, the bispecific anti-EGFR/c-Met antibody is administered intravenously to the subject.

[0016] In some embodiment, of any of the methods disclosed herein, the bispecific anti-EGFR/c-Met antibody is administered at a dose of between about 140 mg to about 2240 mg. In some embodiment, of any of the methods disclosed herein, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 350 mg, 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. In some embodiment, of any of the methods disclosed herein, the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1400 mg if the subject has a body weight of less than 80 kg. In some embodiment, of any of the above methods, the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1750 mg if the subject has a body weight of less than 80 kg. In some embodiment, of any of the above methods, the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1750 mg if the subject has a body weight of greater than or equal to 80 kg. In some embodiment, of any of the methods disclosed herein, the bispecific anti-EGFR/c-Met antibody is administered at a dose of 2100 mg if the subject has a body weight of greater than or equal to 80 kg.

[0017] In some embodiment, of any of the methods disclosed herein, the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1,400 mg (1,750 mg if body weight is ≥ 80 kg) once weekly up to Cycle 2 Day 1, then 1,750 mg (2,100 mg if body weight is ≥ 80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3.

[0018] In some embodiment, of any of the methods disclosed herein, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously or intradermally to the subject. In some embodiment, of any of the methods disclosed herein, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously or intradermally at a dose sufficient to achieve a therapeutic effect in the subject. In some embodiment, of any of the methods disclosed herein, 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. In some embodiment, the bispecific anti-EGFR/c-Met antibody is administered once per 21 day cycle.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0019] **Figure 1** shows an exemplary schematic overview of the study.
- [0020] **Figure 2** shows Progression-free survival (PFS) results.
- [0021] **Figure 3** shows consistent PFS benefit across predefined subgroups by BICR.
- [0022] **Figure 4** shows ORR and Best Response results.
- [0023] **Figure 5** shows Duration of Response (DoR) by BICR
- [0024] **Figure 6** shows PFS After First Subsequent Therapy (PFS2) results.
- [0025] **Figure 7** shows Interim Overall Survival results.
- [0026] **Figure 8** shows a Kaplan-Meier Curve of PFS in Previously Untreated NSCLC Patients by BICR Assessment. “R-CP”- RYBREVANT + carboplatin + pemetrexed; “CP”- carboplatin + pemetrexed.

DETAILED DESCRIPTION

Definitions

- [0027] 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.
- [0028] 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.
- [0029] 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.

[0030] 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.”

[0031] 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.

[0032] 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.”

[0033] 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.”

[0034] “**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.

[0035] “**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.

[0036] “**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.

[0037] “**Prevent**”, “**preventing**”, “**prevention**”, or “**prophylaxis**” of a disease or disorder means preventing that a disorder occurs in subject.

[0038] “**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.

[0039] “**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.

[0040] “**Newly diagnosed**” refers to a subject who has been diagnosed with cancer (e.g., EGFR or c-Met expressing cancer) but has not yet received treatment (e.g., treatment for lung cancer).

[0041] “**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.

[0042] **“Refractory”** refers to a disease that does not respond to a treatment. A refractory disease can be resistant to a treatment before or at the beginning of the treatment, or a refractory disease can become resistant during a treatment.

[0043] **“Relapsed”** refers to the return of a disease or the signs and symptoms of a disease after a period of improvement after prior treatment with a therapeutic.

[0044] **“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.

[0045] **“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.

[0046] **“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.

[0047] **“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.

[0048] **“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.

[0049] **“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.

[0050] “**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.

[0051] “**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.

[0052] “**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.

[0053] “**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.

[0054] “**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 Mol Biol 263: 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

[0055] 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.

[0056] “**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.

[0057] “**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.

[0058] “**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.

[0059] “**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.

[0060] “**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.

[0061] “**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.

[0062] “**Low fucose**” or “**low fucose content**” as used in the application refers to antibodies with fucose content of about between 1%-15%.

[0063] “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%.

[0064] 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.

[0065] 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); and progression-free refers to lack of disease progression.

Methods of the disclosure

[0066] New treatment options for patients that are newly diagnosed with EGFR mutation-positive advanced NSCLC represent a significant unmet medical need. The EGFR-TKI TAGRISSO® (osimertinib) is a standard of care in the front line patient population. Results of the FLAURA clinical trial showed that in patients with previously untreated EGFR

mutation-positive advanced NSCLC, osimertinib treatment resulted in a median progression-free survival (mPFS) of 18.9 months (Soria et al., N Engl J Med 2018; 378:113-125).

[0067] The present inventors have developed novel methods for treating EGFR mutation-positive advanced NSCLC in patients that are treatment naïve. Thus, embodiments of the present invention provide methods for treating patients with newly diagnosed EGFR-mutant non-small cell lung cancer (NSCLC).

[0068] In one aspect, provided herein is a method of improving median progression free survival (PFS) in a population of subjects with non-small cell lung cancer (NSCLC) having one or more epidermal growth factor receptor (EGFR) exon 20 insertion mutations who are treatment-naïve, the 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, and (ii) chemotherapy, wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC having one or more EGFR exon 20 insertion mutations who are treatment-naïve, the reference population having been administered chemotherapy only.

[0069] In another aspect, provided herein is a method of improving median overall survival (OS) in a population of subjects with non-small cell lung cancer (NSCLC) having one or more epidermal growth factor receptor (EGFR) exon 20 insertion mutations who are treatment-naïve, the 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, and (ii) chemotherapy, wherein the improvement in median OS is relative to median OS of a reference population of subjects with NSCLC having one or more EGFR exon 20 insertion mutations who are treatment-naïve, the reference population having been administered chemotherapy only.

[0070] In some embodiments, the subject has newly diagnosed, locally advanced NSCLC. In some embodiments, the subject has newly diagnosed metastatic NSCLC. In some embodiments, the subject has a treatment naïve NSCLC. In some embodiments, the NSCLC is not amenable to curative therapy including surgical resection or chemoradiation. In some embodiments, the curative therapy includes surgical resection or chemoradiation. In some embodiment, of any of the methods disclosed herein, the NSCLC is locally advanced or metastatic. In some embodiment, of any of the above methods, the NSCLC is nonsquamous NSCLC.

[0071] 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 clinical response comprises a duration of response (DOR) of at least 9 months, or at least 9.7 months, or at least 10 months, or at least 10.1 months, or at least 8 months, or at least 1 year, or at least 2 years, or at least 3 years.

[0072] In some embodiments, the subject is progression-free after at least 11 months. In some embodiments, the subject is progression-free after at least 11.4 months. In some embodiments, the subject is progression-free after at least 11.5 months. 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.

[0073] In some embodiments, the method achieves an overall response rate (ORR) in subjects of at least 60%, or at least 65%, or at least 67%, or at least 70%, or at least 73%.

[0074] 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%.

[0075] 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 between about 350 mg to about 2100 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is

administered at a dose of about 350 mg, 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, 1450 mg, 1500mg, 1550 mg, 1575 mg, 1600 mg, 1750 mg, 2100 mg, or 2240 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of 350 mg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered intravenously at a dose of 1050 mg if the subject has a body weight of less than 80 kg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered intravenously at a dose of 1400 mg 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 intravenously at a dose of 1400 mg if the subject has a body weight of less than 80 kg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered intravenously at a dose of 1750 mg 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 intravenously at a dose of 1750 mg if the subject has a body weight of less than 80 kg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered intravenously at a dose of 2100 mg 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 intravenously at a dose of 1750 mg once in three weeks. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered intravenously at a dose of 2100 mg once in three weeks. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered intravenously at a dose of 1,400 mg (1,750 mg if body weight is ≥ 80 kg) once weekly up to Cycle 2 Day 1; and at a dose of 1,750 mg (2,100 mg if body weight is ≥ 80 kg) on Day 1 of each 21-day cycle starting with Cycle 3. In some embodiments, the first dose of the bispecific anti-EGFR/c-Met antibody is administered as a split dose over Day 1 and Day 2.

[0076] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously or intradermally to the subject. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously or intradermally at a dose sufficient to achieve a therapeutic effect in the subject. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously at a dose of 1600 mg if the subject has a body weight of less than 80 kg or at a dose of 2240 mg if the subject has a body weight of greater than or equal to 80 kg. In some embodiments, the dosing can be once in two weeks. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously at a dose of 2400 mg if the subject has a body weight of less than 80 kg or at a dose of 3360 mg if the subject has a body weight of greater than or equal to 80 kg. In some embodiments, the

dosing can be once in three weeks. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously at a dose of 1400 mg if the subject has a body weight of less than 80 kg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously at a dose of 1750 mg 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 subcutaneously at a dose of 1750 mg if the subject has a body weight of less than 80 kg. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously at a dose of 2100 mg 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 subcutaneously at a dose of 1750 mg once in three weeks. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously at a dose of 2100 mg once in three weeks. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously at a dose of 1,400 mg (1,750 mg if body weight is ≥ 80 kg) once weekly up to Cycle 2 Day 1; and at a dose of 1,750 mg (2,100 mg if body weight is ≥ 80 kg) on Day 1 of each 21-day cycle starting with Cycle 3. 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.

[0077] 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.

[0078] In some embodiments, the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

[0079] 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.

[0080] 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%.

Therapeutic methods

[0081] In some embodiments, the methods of the present disclosure useful for treating a cancer in a subject in need thereof may comprise administering to a subject an effective amount of a combination therapy comprising a bispecific anti-epidermal growth factor receptor (EGFR)/hepatocyte growth factor receptor (c-Met) bispecific antibody and chemotherapy. 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%.

[0082] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered in combination with chemotherapy. In some embodiments, the chemotherapy is standard of care therapy for NSCLC. In some embodiments, the chemotherapy is first-line standard of care therapy for NSCLC. In some embodiments, the chemotherapy is platinum-based combination chemotherapy regimen. In some embodiments, the chemotherapy is a combination of carboplatin and pemetrexed. In some embodiments, the chemotherapy is a combination of cisplatin and pemetrexed. In some embodiments, the chemotherapy is pemetrexed. In some embodiments, pemetrexed is administered at a dose of 500 mg/m². In some embodiments, pemetrexed is administered at a dose of 500 mg/m² on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance pemetrexed

therapy until disease progression. In some embodiments, carboplatin is administered at a dose achieving the area under the concentration-time curve 5 mg/mL per minute (AUC 5) in the patient, on Day 1 of each 21-day cycle, for up to 4 cycles. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1,400 mg (1,750 mg if body weight is ≥ 80 kg) once weekly up to Cycle 2 Day 1, then 1,750 mg (2,100 mg if body weight is ≥ 80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3.

[0083] In some embodiments, pemetrexed is administered concomitantly with corticosteroids, folic acid, and vitamin B12. In some embodiments, corticosteroids comprise dexamethasone. In some embodiments, dexamethasone is administered at a dose of 4 mg orally twice daily or equivalent. In some embodiments, dexamethasone is administered one day before the administration of pemetrexed. In some embodiments, dexamethasone is administered on the same day as the administration of pemetrexed. In some embodiments, dexamethasone is administered one day after the administration of pemetrexed. In some embodiments, folic acid is administered at a dose of 350-1,000 μ g orally. In some embodiments, folic acid is administered daily beginning 7 days prior to first infusion and continuing until 21 days after the last dose of pemetrexed. In some embodiments, vitamin B12 is administered at a dose of 1,000 μ g intramuscularly. In some embodiments, vitamin B12 is administered as 1 dose within 7 days of Cycle 1 Day 1, then every 3 cycles afterwards. In some embodiments, vitamin B12 may be administered on the same day as pemetrexed.

Premedications

[0084] In some embodiments, the combination treatment, comprising an EGFR/ c-Met antibody, also comprises one or more premedications. In some embodiments, the premedication comprises antihistamines, antipyretics, or glucocorticoids. In some embodiments, the premedication comprises an antihistamine. In some embodiments, the premedication comprises an antipyretic. In some embodiments, the premedication comprises a glucocorticoid. In some embodiments, the one or more premedications are administered as described in Table 1.

Table 1.

Medication	Dose	Route of Administration
Antihistamine*	Diphenhydramine (25 to 50 mg) or equivalent	IV
		Oral
Antipyretic*	Acetaminophen (650 to 1,000 mg)	IV

		Oral
Glucocorticoid [‡]	Dexamethasone (10 mg) or Methylprednisolone (40 mg) or equivalent	IV
		Oral

* Required at all doses.

[‡] Required at initial dose (Week 1, Days 1 and 2); optional for subsequent doses.

Administration

[0085] 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.

[0086] 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, intracolonic, 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.

[0087] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered intravenously.

[0088] 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.

[0089] In some embodiments, the bispecific anti-EGFR/c-Met antibody is formulated as an intravenous formulation as disclosed in PCT International Publication No. WO 2022/043900 A1. 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.

[0090] In some embodiments, administration comprises administering a composition comprising the bispecific anti-EGFR/c-Met antibody at a concentration of 50 mg/mL.

[0091] In some embodiments, the bispecific anti-EGFR/c-Met antibody is formulated with EDTA disodium salt dihydrate, L histidine, L histidine hydrochloride monohydrate, L methionine, polysorbate 80, sucrose, and water. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered intravenously in a composition comprising EDTA disodium salt dihydrate, L histidine, L histidine hydrochloride monohydrate, L methionine, polysorbate 80, sucrose, and water.

[0092] In some embodiments, the bispecific anti-EGFR/c-Met antibody is formulated in a composition comprising the antibody at a concentration of 50 mg/mL, EDTA disodium salt dihydrate at a concentration of 0.02 mg/mL, L histidine at a concentration of 0.33 mg/mL, L histidine hydrochloride monohydrate at a concentration of 1.23 mg/mL, L methionine at a concentration of 1 mg/mL, polysorbate 80 at a concentration of 0.6 mg/mL, sucrose at a concentration of 85 mg/mL, and water. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered intravenously in a composition comprising the antibody at a concentration of 50 mg/mL, EDTA disodium salt dihydrate at a concentration of 0.02 mg/mL, L histidine at a concentration of 0.33 mg/mL, L histidine hydrochloride monohydrate at a concentration of 1.23 mg/mL, L methionine at a concentration of 1 mg/mL, polysorbate 80 at a concentration of 0.6 mg/mL, sucrose at a concentration of 85 mg/mL, and water.

[0093] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody comprises extracting a composition from a vial comprising 350 mg of the bispecific anti-

EGFR/c-Met antibody, 0.14 mg of EDTA disodium salt dihydrate, 2.3 mg of L histidine, 8.6 mg of L histidine hydrochloride monohydrate, 7 mg of L methionine, 4.2 mg of polysorbate 80, 595 mg of sucrose, and water. In some embodiments, intravenous administration of the bispecific anti- EGFR/c-Met antibody comprises extracting a composition from a vial comprising 350 mg of the bispecific anti- EGFR/c-Met antibody, 0.14 mg of EDTA disodium salt dihydrate, 2.3 mg of L histidine, 8.6 mg of L histidine hydrochloride monohydrate, 7 mg of L methionine, 4.2 mg of polysorbate 80, 595 mg of sucrose, and water.

[0094] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously to the subject at a dose between about 1600 mg to about 3360 mg. The subcutaneous administration can be once in two weeks (Q2W) or once in three weeks (Q3W). Q2W dosing is administered at 1600 mg (2240 mg if the subject is ≥ 80 kg). Q3W dosing is administered at 2400 mg (3360 mg if the subject is ≥ 80 kg).

[0095] 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.

[0096] 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.

[0097] 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 or about 1400 mg. 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.

[0098] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered is administered at a dose of 1050 mg 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 1400 mg if the subject has a body weight of greater than or equal to 80 kg.

[0099] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered is administered at a dose of 1400 mg 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 1750 mg 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 once weekly. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered once in three weeks.

[00100] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered is administered at a dose of 1750 mg 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 2100 mg 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 once in three weeks.

[00101] 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 about 1050 mg once a week. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered about 1400 mg once a week.

[00102] 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 about 1050 mg once in two weeks. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered about 1400 mg once in two weeks.

[00103] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1400 mg once in a 21 day cycle. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg once in a 21 day cycle.

In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 1750 mg once in a 21 day cycle. In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 2100 mg once in a 21 day cycle.

[00104] 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.

[00105] 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.

[00106] In some embodiments, the dose of the bispecific anti-EGFR/c-Met antibody is decreased upon detection of an adverse reaction in the subject. In some embodiments, the dose is reduced according to Table 11. In some embodiments, the dose is decreased from 1050 mg to 700 mg. In some embodiments, the dose is decreased from 1400 mg to 1050 mg. In some embodiments, the dose is decreased from 1750 mg to 1400 mg. In some embodiments, dose is decreased from 2100 mg to 1750 mg.

[00107] In some embodiments, the dose of the bispecific anti-EGFR/c-Met antibody is decreased upon detection of an adverse reaction in the subject, and further reduced upon continued detection of an adverse reaction in the subject. In some embodiments, the dose is further reduced according to Table 11. In some embodiments, the dose is further decreased from 700 mg to 350 mg. In some embodiments, the dose is further decreased from 1050 mg to 700 mg. In some embodiments, the dose is further decreased from 1400 mg to 1050 mg. In some embodiments, the dose is further decreased from 1750 mg to 1400 mg.

[00108] In some embodiments, the dose of the bispecific anti-EGFR/c-Met antibody is decreased upon detection of an adverse reaction in the subject, further reduced upon continued detection of an adverse reaction in the subject, and administration is discontinued upon further continued detection of an adverse reaction in the subject.

[00109] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is modified according to Table 12 upon detection of an adverse reaction. In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is interrupted if a grade 1 to 2 infusion-related reaction is detected until reaction symptoms resolve. In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is resumed at 50% of the infusion rate at which the reaction occurred. In some embodiments, the infusion rate is escalated

according to Table 13 or Table 14 upon detection of no additional symptoms after 30 minutes. In some embodiments, corticosteroids are included with pre-medications for the subsequent dose.

[00110] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is interrupted and supportive care medications are administered if a grade 3 infusion-related reaction is detected. In some embodiments, the administration of the bispecific anti-EGFR/c-Met antibody is resumed at 50% of the infusion rate at which the reaction occurred. In some embodiments, the infusion rate is escalated according to Table 13 or Table 14 upon detection of no additional symptoms after 30 minutes. In some embodiments, corticosteroids are included with pre-medications for the subsequent dose.

[00111] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is discontinued upon recurrent grade 3 infusion related reactions.

[00112] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is discontinued if a grade 4 infusion-related reaction is detected.

[00113] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is withheld if Interstitial Lung Disease (ILD)/pneumonitis is suspected. In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is discontinued if ILD/pneumonitis is confirmed.

[00114] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is continued upon detection of a grade 1 or grade 2 dermatologic adverse reaction, and supportive care management is initiated and symptoms are reassessed after 2 weeks. In some embodiments, the dose of the bispecific anti-EGFR/c-Met antibody is reduced if grade 2 reaction does not improve after 2 weeks.

[00115] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is withheld and supportive care is initiated upon detection of a grade 3 dermatologic adverse reaction. In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is resumed at reduced dose upon recovery to less than or equal to a grade 2 dermatologic adverse reaction. In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is discontinued if the reaction does not improve within 2 weeks.

[00116] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is discontinued upon detection of a grade 4 dermatologic adverse reaction or severe bullous, blistering or exfoliating skin conditions (including toxic epidermal necrolysis (TEN)).

[00117] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is withheld upon detection of a grade 3 adverse reaction until recovery to less than or equal to a

grade 1 reaction or baseline. In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is resumed if recovery occurs within 1 week. In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is resumed at a reduced dose if recovery occurs between 1 week and 4 weeks. In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is discontinued if recovery does not occur within 4 weeks.

[00118] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is withheld upon detection of a grade 4 adverse reaction until recovery to less than or equal to a grade 1 reaction or baseline. In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is resumed at a reduced dose if recovery occurs within 4 weeks. In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is discontinued if recovery does not occur within 4 weeks or if grade 4 reactions are recurrent.

[00119] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is continued upon detection of a grade 1 or grade 2 ocular toxicity, and supportive care management is initiated and symptoms are reassessed after 2 weeks. In some embodiments, the dose of the bispecific anti-EGFR/c-Met antibody is reduced if grade 2 reaction does not improve after 2 weeks. In some embodiments, ocular toxicity is selected from the group consisting of keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, uveitis, blepharitis, and eye pruritus.

[00120] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is withheld and supportive care is initiated upon detection of a grade 3 ocular toxicity. In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is resumed at reduced dose upon recovery to less than or equal to a grade 2 ocular toxicity. In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is discontinued if the reaction does not improve within 2 weeks. In some embodiments, ocular toxicity is selected from the group consisting of keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, uveitis, blepharitis, and eye pruritus.

[00121] In some embodiments, administration of the bispecific anti-EGFR/c-Met antibody is discontinued upon detection of a grade 4 ocular toxicity. In some embodiments, ocular toxicity is selected from the group consisting of keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, uveitis, blepharitis, and eye pruritus.

[00122] 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.

[00123] 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.

[00124] 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 frolic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestabucil; 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

[00125] An exemplary bispecific anti-EGFR/c-Met antibody that can be used in the methods of the disclosures is amivantamab. Amivantamab or JNJ-61186372 (JNJ-372) 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)

DLRGTTYFDY

>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)

QVQLVESGGGVVQPGRSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVAVIWDDG
SYKYYGDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDGITMVRGVMKD
YFDYWGQGTLVTVSS

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

AIQLTQSPSSLSASVGDRVTITCRASQDISALVWYQQKPGKAPKLLIYDASSLESGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPLTFGGGTKVEIK

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

QVQLVQSGAEVKKPGASVKVSCETSGYTFTSYGISWVRQAPGHGLEWMGWISAYN
GYTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDLRGTTYFDYWG
QGTLVTVSS

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

DIQMTQSPSSVSASVGDRVTITCRASQGISNWLAWFQHKPGKAPKLLIYAASSLLSGV
PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPITFGQGTRLEIK

>SEQ ID NO: 17 HC1

QVQLVESGGGVVQPGRSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVAVIWDDG
SYKYYGDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDGITMVRGVMKD
YFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN

SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEP
KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTTPVLDSGDSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGK

>SEQ ID NO: 18 LC1

AIQLTQSPSSLSASVGDRVITTCRASQDISSALVWYQQKPGKAPKLLIYDASSLESQVP
SRFSGSESGTDFTLTISLQPEDFATYYCQQFNSYPLTFGGGKVEIKRTVAAPSVEFIF
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYS
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>SEQ ID NO: 19 HC2

QVQLVQSGAEVKKPGASVKVSCETSGYTFTSYGISWVRQAPGHGLEWMGWISAYN
GYTNYAQKLQGRVTMTDTSTSTAYMELRSLRSDDAVYYCARDLRGTNYFDYWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDK
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSGDSFLYSLRSLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>SEQ ID NO: 20 LC2

DIQMTQSPSSVSASVGDRVITTCRASQGISNWLAWFQHKPGKAPKLLIYAASSLLSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQQANSFPITFGQGRLEIKRTVAAPSVEFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[00126] 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.

[00127] 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.

[00128] In some embodiments, the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

[00129] 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.

[00130] In some embodiments, the bispecific anti-EGFR/c-Met antibody is amivantamab.

[00131] In some embodiments, the bispecific anti-EGFR/c-Met antibody is a biosimilar of amivantamab.

[00132] 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/.

[00133] 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.

[00134] 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.

[00135] 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/.

[00136] 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.

[00137] 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.

[00138] In one embodiment, the bispecific anti-EGFR/c-Met antibody comprises one or more Fc silencing mutations.

[00139] In one embodiment, the one or more Fc silencing mutations decrease affinity to Fc γ receptors.

[00140] In one embodiment, the one or more Fc silencing mutations comprise V234A/G237A/P238S/H268A/V309L/A330S/P331S.

[00141] 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(2):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).

[00142] 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.

[00143] 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.

[00144] 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).

[00145] 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.

[00146] 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).

[00147] 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.

[00148] 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.

[00149] 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.

[00150] 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 non-small cell lung cancer (NSCLC) having one or more epidermal growth factor receptor (EGFR) exon 20 insertion mutations who are treatment-naïve, the 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,
- and
- (ii) chemotherapy,

wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC having one or more EGFR exon 20 insertion mutations who are treatment-naïve, the reference population having been administered chemotherapy only.

2. A method of improving median overall survival (OS) in a population of subjects with non-small cell lung cancer (NSCLC) having one or more epidermal growth factor receptor (EGFR) exon 20 insertion mutations who are treatment-naïve, the 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,
- and
- (ii) chemotherapy,

wherein the improvement in median OS is relative to median OS of a reference population of subjects with NSCLC having one or more EGFR exon 20 insertion mutations who are treatment-naïve, the reference population having been administered chemotherapy only.

3. A method comprising:

- a) administering to a population of subjects with non-small cell lung cancer (NSCLC) having one or more epidermal growth factor receptor (EGFR) exon 20 insertion

mutations who are treatment-naïve, a combination therapy comprising (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody, and (ii) chemotherapy; and;

b) achieving an improvement in median PFS, wherein the improvement in median PFS is greater than subjects having been administered chemotherapy only.

4. A method comprising:

a) administering to a population of subjects with non-small cell lung cancer (NSCLC) having one or more epidermal growth factor receptor (EGFR) exon 20 insertion mutations who are treatment-naïve, a combination therapy comprising (i) a therapeutically effective amount of a bispecific anti-EGFR/c-Met antibody, and (ii) chemotherapy; and;

b) achieving an improvement in median OS, wherein the improvement in median OS is greater than subjects having been administered chemotherapy only

5. The method of any one of embodiments 1-4, wherein the NSCLC is locally advanced or metastatic.

6. The method of any one of embodiments 1-4, wherein the NSCLC is nonsquamous NSCLC.

7. The method of any one of embodiments 1-6, wherein the chemotherapy comprises administration of pemetrexed and carboplatin.

8. The method of embodiment 7, wherein pemetrexed is administered at a dose of 500 mg/m² on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression.

9. The method of embodiment 8, wherein carboplatin is administered at a dose to achieve area under the concentration-time curve 5 mg/mL per minute (AUC 5) on Day 1 of each 21-day cycle, for up to 4 cycles.

10. The method of any one of embodiments 1-9, wherein the method elicits a clinical response in the subject according to RECIST v1.1 criteria.

11. The method of any one of embodiments 1-9, wherein the method achieves a partial response or better in the subject according to RECIST v1.1 criteria.

12. The method of any one of embodiments 1-11, wherein the method achieves a clinical response comprising a median duration of response (DOR) of at least 9 months.

13. The method of any one of embodiments 1-12, wherein the subject is progression-free after at least 11 months.

14. The method of any one of embodiments 1-13, 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.

15. The method of embodiment 14, wherein 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.

16. The method of embodiment 14 or 15, wherein the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

17. The method of any one of embodiments 1-16, wherein 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.

18. The method of any one of embodiments 1-17, wherein the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about between 1% to about 15%.

19. The method of any one of embodiments 1-18, wherein the bispecific anti-EGFR/c-Met antibody is administered intravenously to the subject.

20. The method of embodiment 19, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of between about 350 mg to about 2240 mg.

21. The method of embodiment 20, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 350 mg, 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, 2100 mg, or 2240 mg.

22. The method of embodiment 21, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1400 mg if the subject has a body weight of less than 80 kg.

23. The method of embodiment 21, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1750 mg if the subject has a body weight of less than 80 kg.

24. The method of embodiment 21, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1750 mg if the subject has a body weight of greater than or equal to 80 kg.

25. The method of embodiment 21, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of 2100 mg if the subject has a body weight of greater than or equal to 80 kg.

26. The method of embodiment 21, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1,400 mg (1,750 mg if body weight is ≥ 80 kg) once weekly up to Cycle 2 Day 1, then 1,750 mg (2,100 mg if body weight is ≥ 80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3.

27. The method of any one of embodiments 1-26, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously or intradermally to the subject.

28. The method of embodiment 27, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously or intradermally at a dose sufficient to achieve a therapeutic effect in the subject.

29. The method of any one of embodiments 1-28, wherein 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.

30. The method of any one of embodiments 1-28, wherein the bispecific anti-EGFR/c-Met antibody is administered once per 21 day cycle.

31. The method of any one of embodiments 1-30, wherein the method comprises administering a composition comprising the bispecific anti-EGFR/c-Met antibody at a concentration of 50 mg/mL.

32. The method of any one of embodiments 1-31, wherein method comprises administering a composition comprising the bispecific anti-EGFR/c-Met antibody, EDTA disodium salt dihydrate, L histidine, L histidine hydrochloride monohydrate, L methionine, polysorbate 80, sucrose, and water.

33. The method of any one of embodiments 1-32, wherein the method comprises administering a composition comprising the bispecific anti-EGFR/c-Met antibody at a concentration of 50 mg/mL, EDTA disodium salt dihydrate at a concentration of 0.02 mg/mL, L histidine at a concentration of 0.33 mg/mL, L histidine hydrochloride monohydrate at a concentration of 1.23 mg/mL, L methionine at a concentration of 1 mg/mL, polysorbate 80 at a concentration of 0.6 mg/mL, sucrose at a concentration of 85 mg/mL, and water.

34. The method of any one of embodiments 1-33, wherein the method comprises extracting a composition from a vial comprising 350 mg of the bispecific anti- EGFR/c-Met antibody, 0.14 mg of EDTA disodium salt dihydrate, 2.3 mg of L histidine, 8.6 mg of L histidine hydrochloride monohydrate, 7 mg of L methionine, 4.2 mg of polysorbate 80, 595 mg of sucrose, and water.

35. The method of any one of embodiments 1-34, wherein the dose of the bispecific anti-EGFR/c-Met antibody is decreased upon detection of an adverse reaction in the subject.

36. The method of embodiment 35, wherein the dose is reduced according to Table 11.

37. The method of embodiment 35 wherein the dose is decreased from 1050 mg to 700 mg.

38. The method of embodiment 35, wherein the dose is decreased from 1400 mg to 1050 mg.

39. The method of embodiment 35, wherein the dose is decreased from 1750 mg to 1400 mg.

40. The method of embodiment 35, wherein the dose is decreased from 2100 mg to 1750 mg.

41. The method of any one of embodiments 35-40, wherein the dose is further reduced upon continued detection of an adverse reaction in the subject.

42. The method of embodiment 41, wherein the dose is reduced according to Table 11.

43. The method of embodiment 41, wherein the dose is decreased from 700 mg to 350 mg.

44. The method of embodiment 41, wherein the dose is decreased from 1050 mg to 700 mg.

45. The method of embodiment 41, wherein the dose is decreased from 1400 mg to 1050 mg.

46. The method of embodiment 41, wherein the dose is decreased from 1750 mg to 1400 mg.

47. The method of any one of embodiments 41-46, wherein the administration of the bispecific anti-EGFR/c-Met antibody is discontinued upon further continued detection of an adverse reaction in the subject.

48. The method of any one of embodiments 1-47, wherein the administration of the bispecific anti-EGFR/c-Met antibody is modified according to Table 12 upon detection of an adverse reaction.

49. The method of any one of embodiments 1-48, wherein the administration of the bispecific anti-EGFR/c-Met antibody is interrupted if a grade 1 to 2 infusion-related reaction is detected until reaction symptoms resolve.

50. The method of embodiment 49, wherein the administration of the bispecific anti-EGFR/c-Met antibody is resumed at 50% of the infusion rate at which the reaction occurred.

51. The method of embodiment 50, wherein the infusion rate is escalated according to Table 13 or Table 14 upon detection of no additional symptoms after 30 minutes.

52. The method of any one of embodiments 49-51, wherein corticosteroids are included with pre-medications for the subsequent dose.

53. The method of any one of embodiments 1-48, wherein the administration of the bispecific anti-EGFR/c-Met antibody is interrupted and supportive care medications are administered if a grade 3 infusion-related reaction is detected.

54. The method of embodiment 53, wherein the administration of the bispecific anti-EGFR/c-Met antibody is resumed at 50% of the infusion rate at which the reaction occurred.

55. The method of embodiment 54, wherein the infusion rate is escalated according to Table 13 or Table 14 upon detection of no additional symptoms after 30 minutes.

56. The method of any one of embodiments 53-55, wherein corticosteroids are included with pre-medications for the subsequent dose.

57. The method of any one of embodiments 53-56, wherein administration of the bispecific anti-EGFR/c-Met antibody is discontinued upon recurrent grade 3 infusion related reactions.

58. The method of any one of embodiments 1-48, wherein the administration of the bispecific anti-EGFR/c-Met antibody is discontinued if a grade 4 infusion-related reaction is detected.

59. The method of any one of embodiments 1-58, wherein the administration of the bispecific anti-EGFR/c-Met antibody is withheld if Interstitial Lung Disease (ILD)/pneumonitis is suspected.

60. The method of embodiment 59, wherein the administration of the bispecific anti-EGFR/c-Met antibody is discontinued if ILD/pneumonitis is confirmed.

61. The method of any one of embodiments 1-60, wherein supportive care management is initiated and symptoms are reassessed after 2 weeks upon detection of a grade 1 or grade 2 dermatologic adverse reaction.

62. The method of embodiment 61, wherein the dose of the bispecific anti-EGFR/c-Met antibody is reduced if grade 2 reaction does not improve after 2 weeks.

63. The method of any one of embodiments 1-62, wherein the administration of the bispecific anti-EGFR/c-Met antibody is withheld and supportive care is initiated upon detection of a grade 3 dermatologic adverse reaction.

64. The method of embodiment 63, wherein the administration of the bispecific anti-EGFR/c-Met antibody is resumed at reduced dose upon recovery to less than or equal to a grade 2 dermatologic adverse reaction.

65. The method of embodiment 63 or 64, wherein the administration of the bispecific anti-EGFR/c-Met antibody is discontinued if the reaction does not improve within 2 weeks.

66. The method of any one of embodiments 1-65, wherein the administration of the bispecific anti-EGFR/c-Met antibody is discontinued upon detection of a grade 4 dermatologic adverse reaction or severe bullous, blistering or exfoliating skin conditions (including toxic epidermal necrolysis (TEN)).

67. The method of any one of embodiments 1-66, wherein supportive care management is initiated and symptoms are reassessed after 2 weeks upon detection of a grade 1 or grade 2 ocular toxicity.

68. The method of embodiment 67, wherein the dose of the bispecific anti-EGFR/c-Met antibody is reduced if grade 2 reaction does not improve after 2 weeks.

69. The method of any one of embodiments 1-68, wherein the administration of the bispecific anti-EGFR/c-Met antibody is withheld and supportive care is initiated upon detection of a grade 3 ocular toxicity.

70. The method of embodiment 69, wherein the administration of the bispecific anti-EGFR/c-Met antibody is resumed at reduced dose upon recovery to less than or equal to a grade 2 ocular toxicity.

71. The method of embodiment 69 or 70, wherein the administration of the bispecific anti-EGFR/c-Met antibody is discontinued if the reaction does not improve within 2 weeks.

72. The method of any one of embodiments 1-71, wherein the administration of the bispecific anti-EGFR/c-Met antibody is discontinued upon detection of a grade 4 ocular toxicity.

73. The method of any one of embodiments 67-72, wherein the ocular toxicity is selected from the group consisting of keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, uveitis, blepharitis, and eye pruritus.

74. The method of any one of embodiments 1-73, wherein the administration of the bispecific anti-EGFR/c-Met antibody is withheld upon detection of a grade 3 adverse reaction until recovery to less than or equal to a grade 1 reaction or baseline.

75. The method of embodiment 74, wherein the administration of the bispecific anti-EGFR/c-Met antibody is resumed if recovery occurs within 1 week.

76. The method of embodiment 74, wherein the administration of the bispecific anti-EGFR/c-Met antibody is resumed at a reduced dose if recovery occurs between 1 week and 4 weeks.

77. The method of embodiment 74, wherein the administration of the bispecific anti-EGFR/c-Met antibody is discontinued if recovery does not occur within 4 weeks.

78. The method of any one of embodiments 1-77, wherein the administration of the bispecific anti-EGFR/c-Met antibody is withheld upon detection of a grade 4 adverse reaction until recovery to less than or equal to a grade 1 reaction or baseline.

79. The method of embodiment 78, wherein the administration of the bispecific anti-EGFR/c-Met antibody is resumed at a reduced dose if recovery occurs within 4 weeks.

80. The method of embodiment 78, wherein the administration of the bispecific anti-EGFR/c-Met antibody is discontinued if recovery does not occur within 4 weeks or if grade 4 reactions are recurrent.

81. A composition comprising a bispecific anti-EGFR/c-Met antibody.

82. The composition of embodiment 81, 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.

83. The composition of embodiment 81, wherein 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.

84. The composition of any one of embodiments 81-83, wherein the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

85. The composition of any one of embodiments 81-84, wherein 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.

86. The composition of any one of embodiments 81-85, wherein the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about between 1% to about 15%.

87. The composition of any one of embodiments 81-86, further comprising packaging comprising one or more drug product label elements disclosed in Example 2.

88. The composition of embodiment 87, wherein the packaging includes data from a randomized, double-blind, placebo-controlled, clinical study in subjects with non-small cell lung cancer (NSCLC) having one or more epidermal growth factor receptor (EGFR) exon 20 insertion mutations who are treatment-naïve.

89. The composition of any one of embodiments 81-88, wherein the bispecific anti-EGFR/c-Met antibody is administered at a concentration of 50 mg/mL.

90. The composition of any one of embodiments 81-89, further comprising EDTA disodium salt dihydrate, L histidine, L histidine hydrochloride monohydrate, L methionine, polysorbate 80, sucrose, and water.

91. The composition of any one of embodiments 81-90, further comprising EDTA disodium salt dihydrate at a concentration of 0.02 mg/mL, L histidine at a concentration of 0.33 mg/mL, L histidine hydrochloride monohydrate at a concentration of 1.23 mg/mL, L methionine at a concentration of 1 mg/mL, polysorbate 80 at a concentration of 0.6 mg/mL, sucrose at a concentration of 85 mg/mL, and water.

92. The composition of any one of embodiments 81-91, wherein the composition is in a vial containing 350 mg of the bispecific anti-EGFR/c-Met antibody, 0.14 mg of EDTA disodium salt dihydrate, 2.3 mg of L histidine, 8.6 mg of L histidine hydrochloride monohydrate, 7 mg of L methionine, 4.2 mg of polysorbate 80, 595 mg of sucrose, and water.

93. A method of selling a drug product comprising a bispecific anti-EGFR/c-Met antibody, comprising: manufacturing a bispecific anti-EGFR/c-Met antibody; promoting that a therapy comprising a bispecific anti-EGFR/c-Met antibody is safe and effective for treatment of subjects with non-small cell lung cancer (NSCLC) having one or more epidermal growth factor receptor (EGFR) exon 20 insertion mutations who are treatment-naïve, wherein performing the steps a) and b) results in a health care professional (HCP) to purchase the drug product; thereby selling the drug product.

94. The method of embodiment 93, wherein the therapy further comprises chemotherapy.

EXAMPLES

[00151] 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.

Example 1. PAPILLON Clinical Study

[00152] The purpose of this study (NCT04538664) is to compare the efficacy, as demonstrated by progression-free survival (PFS), in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone in participants with locally advanced or metastatic non-small cell lung cancer (NSCLC) characterized by EGFR Exon 20ins mutations.

[00153] Arms and Interventions

Table 2

Arm	Intervention/treatment
Experimental: Arm A: Amivantamab + Chemotherapy Participants will receive pemetrexed 500 milligram per meter square (mg/m^2) intravenous (IV) infusion (with vitamin supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression. Carboplatin area under the concentration-	Drug: Amivantamab Amivantamab will be administered as an IV infusion at a dose of 1400 mg (1750 mg if body weight is >=80 kilogram [kg]) by once weekly up to Cycle 2 Day 1, then 1750 mg (2100 mg if body weight is >=80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3 and will continue the same treatment in OLE phase then in LTE phase. Other Name: JNJ-61186372

time curve 5 milligram per milliliter (mg/mL) per minute (AUC 5) will be administered as IV infusion on Day 1 of each 21 day cycle, for up to 4 cycles. Participants will receive amivantamab 1400 mg (1750 mg if body weight is ≥ 80 kilogram [kg]) by IV infusion once weekly up to Cycle 2 Day 1, then 1750 mg (2100 mg if body weight is ≥ 80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3. Following the primary analysis for efficacy, the study will transition to an OLE phase and participants will continue to receive the amivantamab plus chemotherapy in OLE phase. Participants who completed OLE period will enter LTE period and continue to receive same treatment.	Drug: Pemetrexed Pemetrexed will be administered as 500 mg/m² IV infusion (with vitamin supplementation) on Day 1 of each 21-day cycle and then as maintenance monotherapy until disease progression in Arm A and will continue the same treatment in OLE phase then in LTE phase. Drug: Carboplatin Carboplatin will be administered as AUC 5 IV infusion for up to 4 cycles on Day 1 of each 21-day cycle.
Experimental: Arm B: Chemotherapy Alone Participants will receive pemetrexed 500 mg/m² IV infusion (with vitamin supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression. Carboplatin AUC 5 IV infusion will be administered on Day 1 of each 21-day cycle for up to 4 cycles. Following the primary analysis for efficacy, the study will transition to an OLE phase and participants will either continue to receive the chemotherapy or cross over to amivantamab in OLE phase. Participants who completed	Drug: Carboplatin Carboplatin will be administered as AUC 5 IV infusion for up to 4 cycles on Day 1 of each 21-day cycle. Drug: Pemetrexed Pemetrexed will be administered as 500 mg/m² IV infusion (with vitamin supplementation) on Day 1 of each 21-day cycle and then as maintenance monotherapy until disease progression in Arm B and will continue the same treatment in OLE phase then in LTE phase.

OLE period will enter LTE period and continue to receive same treatment.	
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[00154] An exemplary study design of this Phase 3 clinical study is shown in **Figure 1**.

[00155] **Outcome Measures**

[00156] **Primary Outcome Measures**

[00157] 1. Progression-Free Survival (PFS) According to RECIST v1.1 as Assessed by Blinded Independent Central Review (BICR) [Time Frame: Up to 18 months]. PFS is defined as the time from randomization until the date of objective disease progression based on blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death (by any cause) in the absence of progression, whichever comes first.

[00158] **Secondary Outcome Measures**

[00159] 1. Objective Response Rate (ORR) [Time Frame: Up to 48 months]. ORR is defined as the percentage of participants who achieve either a complete response (CR) or partial response (PR) as defined by BICR using RECIST v1.1 criteria.

[00160] 2. Duration of Response (DoR) [Time Frame: Up to 48 months]. DoR is defined as the time from the date of first documented response (CR or PR) until the date of documented progression or death, whichever comes first, only for participants who achieve CR or PR as determined by the investigator using RECIST v1.1 criteria.

[00161] 3. Overall Survival (OS) [Time Frame: Up to 48 months]. Overall Survival is defined as the time from the date of randomization to the date of participant's death due to any cause.

[00162] 4. Time to Subsequent Therapy (TST) [Time Frame: Up to 48 months]. TST is defined as the time from the date of randomization to the start date of the subsequent anti-cancer therapy following study treatment discontinuation, or death.

[00163] 5. Progression-Free Survival After First Subsequent Therapy (PFS2) [Time Frame: Up to 48 months]. PFS2 is defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the primary variable PFS or death after starting the next line of treatment.

[00164] 6. Time to Symptomatic Progression (TTSP) [Time Frame: Up to 48 months]. TTSP is defined as the time from randomization to documentation in the electronic case report form (eCRF) of any of the following (whichever occurs earlier): onset of new symptoms or

symptom worsening that is considered by the investigator to be related to lung cancer and requires either a change in anticancer treatment and/or clinical intervention to manage symptoms.

[00165] 7. Incidence and Severity of Adverse Events (AEs) [Time Frame: Up to 48 months]. An AE is any untoward medical occurrence in a participant participating in a clinical study that does not necessarily have a causal relationship with the pharmaceutical/biological agent under study.

[00166] 8. Number of Participants with Clinical Laboratory Abnormalities [Time Frame: Up to 48 months]. Number of participants with clinical laboratory abnormalities (serum chemistry, hematology, blood coagulation, and urine samples) will be reported.

[00167] 9. Number of Participants with Vital Signs Abnormalities [Time Frame: Up to 48 months]. Number of participants with vital signs abnormalities (temperature, heart rate, respiratory rate, oxygen saturation, blood pressure) will be reported.

[00168] 10. Number of Participants with Physical Examination Abnormalities [Time Frame: Up to 48 months]. Number of participants with physical examination abnormalities will be reported.

[00169] 11. Serum Concentration of Amivantamab [Time Frame: Up to 48 months]. Serum samples will be analyzed to determine concentrations of amivantamab.

[00170] 12. Number of Participants with Anti-Amivantamab Antibodies [Time Frame: Up to 48 months]. Number of participants with antibodies to amivantamab will be reported.

[00171] 13. European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) [Time Frame: Up to 48 months]. The EORTC QLQ-C30 includes 30 items in 5 functional scales, 1 global health status scale, 3 symptom scales, and 6 single symptom items. The responses are reported using a verbal rating scale. The item and scale scores are transformed to a 0 to 100 scale. A higher score represents greater HRQoL, better functioning, and more (worse) symptoms.

[00172] 14. Patient Reported Outcomes Measurement Information System-Physical Function (PROMIS-PF) [Time Frame: Up to 48 months]. PROMIS-PF is used to characterize and better understand overall health, level of physical disability, and general well-being. Physical function is a foundation for commonly used general and cancer-specific patient reported outcomes (PRO) measures.

[00173] **Eligibility Criteria.**

[00174] Ages Eligible for Study: 18 Years and older (Adult, Older Adult).

[00175] Sexes Eligible for Study: All.

[00176] Accepts Healthy Volunteers: No.

[00177] Inclusion Criteria:

- Participant must have histologically or cytologically confirmed, locally advanced or metastatic, nonsquamous non-small cell lung cancer (NSCLC) with documented primary epidermal growth factor receptor (EGFR) Exon 20ins activating mutation.
- Participant must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Participant must have Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
- Participant must agree to genetic characterization of tumor status through the required pretreatment tumor biopsy (or submission of equivalent archival material), as well as baseline and periodic blood samples for analysis of tumor mutations in the bloodstream.
- A female participant of childbearing potential must have a negative serum or urine 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.

[00178] Exclusion Criteria:

- Participant has evidence of synchronous NSCLC disease (as suggested by genetic characterization or radiographic appearance).
- Participant has untreated brain metastases (a participant with definitively, locally treated metastases who is clinically stable, asymptomatic, and off corticosteroid treatment for at least 2 weeks prior to randomization is eligible).
- Participant has history of spinal cord compression that has not been treated definitively with surgery or radiation.
- Participant has a medical history of interstitial lung disease (ILD), including drug-induced ILD, or radiation pneumonitis.
- Participant has a contraindication to the use of carboplatin or pemetrexed (refer to local prescribing information for each agent). Participant has a history of hypersensitivity to, or cannot take, vitamin B12 or folic acid.

[00179] Results

[00180] Demographics and Baseline Characteristics are shown in Table 3.

Table 3

Characteristic, n (%)	Amivantamab + Chemotherapy (n=153)	Chemotherapy (n=155)
Median age, years (range)	61 (27–86)	62 (30–92)
Female / male	85 (56) / 68 (44)	93 (60) / 62 (40)
Race ^a		
Asian	97 (64)	89 (59)
White	49 (32)	60 (39)
Other ^b	5 (3)	3 (2)
ECOG PS 0 / 1	54 (35) / 99 (65)	55 (35) / 100 (65)
History of smoking: yes / no	65 (42) / 88 (58)	64 (41) / 91 (59)
History of brain metastases: yes / no	35 (23) / 118 (77)	36 (23) / 119 (77)
Prior EGFR TKI use: yes ^c / no	1 (1) / 152 (99)	3 (2) / 152 (98)
Histology: adenocarcinoma subtype / other ^d	151 (99) / 2 (1)	153 (99) / 2 (1)

^aIn some regions, reporting of race was not required (n for amivantamab + chemotherapy, 151; n for chemotherapy alone, 152).

^bOther includes American Indian or Alaska Native, Black or African-American, multiple, and unknown.

^cTransient monotherapy with common EGFR TKIs was allowed if lack of response was documented.

^dOther includes large cell carcinoma, squamous cell carcinoma, and other.

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor. Note: percentages may not sum to 100 due to rounding.

[00181] Progression-free survival (PFS) is shown in **Figure 2**. The results suggested that amivantamab + chemotherapy combination treatment in first-line EGFR Ex20ins advanced NSCLC provided significantly longer PFS, with 60% reduction in disease progression or death, as compared to chemotherapy only treated patients. The observed PFS was 11.4 months in the amivantamab + chemotherapy combination group, and 6.7 months in chemotherapy only group; HR, **0.395** (95% CI, 0.30–0.53); $P < 0.0001$.

[00182] Consistent PFS benefit across predefined subgroups by BICR is shown in **Figure 3**.

[00183] ORR and Best Response are shown in **Figure 4**. BICR-assessed response is summarized in **Table 4**. The results suggested that amivantamab + chemotherapy combination treatment in first-line EGFR Ex20ins advanced NSCLC provided significantly

higher ORR, as compared to chemotherapy only treated patients. The observed ORR was 73% in the amivantamab + chemotherapy combination group and 47% in chemotherapy only group (P<0.0001, **Figure 4**).

Table 4

BICR-assessed response, n (%) ^b	Amivantamab + Chemotherapy (n=153)	Chemotherapy (n=155)
Median time to response	6.7 weeks (range, 5.1 to 72.5)	11.4 weeks (range, 5.1 to 60.2)
Best response		
Complete response	6 (4)	1 (1)
Partial response	105 (69)	71 (47)
Stable disease	29 (19)	62 (41)
Progressive disease	4 (3)	16 (11)
NE/Unknown	8 (5)	2 (1)

^bNo. of patients with measurable disease at baseline by BICR was 152 in both arms.

BICR, blinded independent central review; CI, confidence interval; OR, odds ratio; ORR, objective response rate; SoD, sum of diameters.

[00184] Duration of Response (DoR) by BICR is shown in **Figure 5**. The results suggested that amivantamab + chemotherapy combination treatment in first-line EGFR Ex20ins advanced NSCLC provided significantly longer DoR, as compared to chemotherapy only treated patients. The observed DoR was 9.7 months in the amivantamab + chemotherapy combination group, and 4.4 months in chemotherapy only group (**Figure 5**).

[00185] PFS After First Subsequent Therapy (PFS2) is shown in **Figure 6**. PFS2 is defined from time of randomization until time of second objective disease progression (based on investigator assessment) or death, whichever comes first, after the initiation of first subsequent anticancer therapy. The results suggested that amivantamab + chemotherapy combination treatment in first-line EGFR Ex20ins advanced NSCLC provided significantly longer PFS2, as compared to chemotherapy only treated patients, reducing the risk of 2nd progression or death by over 50% .

[00186] First Subsequent Therapy results are shown in Table 5.

Table 5

First Subsequent Therapy, n (%)	Amivantamab + Chemotherapy (n=153)	Chemotherapy (n=155)
Started first subsequent therapy	43 (28)	94 (61)
Key treatment classes		
Ex20ins-specific monotherapy		

Amivantamab	1 (1)	71 (46) ^a
Mobocertinib	2 (1)	4 (3)
EGFR TKI monotherapy	7 (5)	3 (2)
EGFR TKI combination therapy	2 (1)	4 (3)
Immunotherapy only	1 (1)	2 (1)
Immunotherapy-chemotherapy	2 (1)	1 (1)
Immunotherapy-VEGF-chemotherapy	1 (1)	5 (3)
Chemotherapy	13 (8)	2 (1)
Chemotherapy-VEGF	6 (4)	1 (1)
Other	8 (5)	1 (1)

^aA total of 71 patients (65 patients as part of the crossover arm plus an additional 6 patients off-protocol) received second-line amivantamab monotherapy out of 107 chemotherapy-randomized patients with disease progression. EGFR, epidermal growth factor receptor; Ex20ins, Exon 20 insertion mutations; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

[00187] Interim Overall Survival (33% maturity; there were 70 deaths in the study at the time of the prespecified interim OS analysis (of the ~210 projected deaths for the final OS analysis)) is shown in **Figure 7**. Amivantamab + chemotherapy treatment arm showed trend in reducing risk of death by over 30%, as compared to the chemotherapy only treatment arm.

[00188] Amivantamab + chemotherapy had longer median treatment duration than chemotherapy (9.7 vs 6.7 months, respectively). Serious AEs and AEs leading to death were comparable between arms. Equal rates of discontinuations of all agents (8% each) were observed. Treatment-related discontinuations of amivantamab were low at 7%.

[00189] Additionally, the safety profile of amivantamab + chemotherapy combination treatment was consistent with the safety profiles of individual agents. Low rates of treatment-related discontinuations were observed in amivantamab-treated group (7%).

[00190] Updated Data: Patient-relevant Endpoints From PAPILLON

[00191] As discussed below, the time to symptomatic progression (TTSP) and patient-reported outcomes (PROs) from PAPILLON were evaluated.

[00192] **Methods:** These analyses included 153 patients (pts) randomized to ami-chemo and 155 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. PROs were measured using the EORTC-QLQ-C30 and PROMIS-PF 8c instruments.

[00193] Results: At a median follow-up of 14.9 mo, median TTSP was significantly longer for ami-chemo vs chemo (NE vs 20.1 mo; HR, 0.67 [95% CI, 0.46–0.98]; $P=0.04$). Median treatment duration was 9.7 mo for ami-chemo and 6.7 mo for chemo. At 6 mo (189 days), the percentage of ITT pts with improved or stable physical functioning relative to baseline was 54% for ami-chemo vs 41% for chemo. There were higher percentages of pts with improved or stable emotional functioning (63% vs 47%), cognitive functioning (47% vs 38%), role functioning (50% vs 41%), and global health status (51% vs 42%) for ami-chemo vs chemo, respectively. At 6 mo, 43% vs 25% pts reported no dyspnea, 36% vs 31% reported no pain, and 18% vs 8% reported no fatigue for ami-chemo vs chemo, respectively. Analyses of longer-term comparisons (eg, 12 mo) were limited due to few chemo-randomized pts remaining on-treatment with available PRO data.

[00194] Per the EORTC-QLQ-C30, more patients in the amivantamab-chemotherapy arm reported improved/stable functioning or absence of symptoms vs chemotherapy. Per the PROMIS-PF 8c, amivantamabchemotherapy prolonged time to sustained deterioration vs chemotherapy (18.1 vs 11.7 mo).

[00195] Conclusions: Ami-chemo significantly 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 and ORR benefit of ami-chemo corresponds with patient-relevant endpoints in first-line *EGFR* Ex20ins advanced NSCLC.

[00196] Updated Data: Analysis of Post-Progression Endpoints From PAPILLON

[00197] Post-progression outcomes from PAPILLON were evaluated, as described below.

[00198] Methods: A total of 308 pts were randomized: 153 to ami-chemo and 155 to chemo. Chemo-randomized pts were allowed crossover upon blinded independent central review (BICR)-confirmed progression. Post-progression endpoints were time to treatment discontinuation (TTD) and time to subsequent (systemic anticancer) therapy (TTST).

[00199] Results: At a median follow-up of 14.9 months (mo), 54% (83/153) and 85% (131/155) pts in the ami-chemo and chemo arms, respectively, discontinued treatment. Median TTD was 13.2 for ami-chemo vs 7.5 mo for chemo (HR, 0.38 [95% CI, 0.28–0.51]; $P<0.0001$). Median TTST was 17.7 for ami-chemo vs 9.9 mo for chemo (HR, 0.35 [95% CI, 0.25–0.49]; $P<0.0001$). These findings are consistent with PFS after first subsequent therapy (HR, 0.49 [95% CI, 0.32–0.76]; $P=0.001$) and interim overall survival (HR, 0.67 [95% CI, 0.42–1.09]; $P=0.11$) favoring ami-chemo vs chemo.

[00200] Among pts who discontinued, 52% (43/83) and 72% (94/131) of pts in the ami-chemo and chemo arms started a subsequent therapy. Most common were pemetrexed for ami-chemo (6 pts) and ami monotherapy for chemo (71 pts). 11 pts in the ami-chemo arm were treated beyond progression for a median (95% CI) duration after progression of 40.4 (8.7–NE) weeks.

[00201] Among 71 chemo-randomized pts who received second-line ami monotherapy, 65 pts were part of the study crossover arm, with 6 receiving ami off protocol. Among the 65 pts in the crossover arm, median treatment duration was 4.9 mo (range, 0–18.2). 46% (30/65) of pts discontinued ami monotherapy, with a median TTD of 9.7 mo (95% CI, 6.7–11.0). Safety and efficacy were consistent with previous ami monotherapy experience.

[00202] **Conclusions:** Ami-chemo significantly prolonged TTD and TTST vs chemo. Ami-chemo is the new first-line standard of care for *EGFR* Ex20ins-mutant advanced NSCLC.

Example 2. RYBREVANT label

[00203] Highlights

[00204] **Indications and usage:** RYBREVANT is a bispecific EGF receptor-directed and MET receptor-directed antibody indicated:

- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test. (1, 2.2)
- as a single agent for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. (1, 2.2)

[00205] Dosage and administration:

- The recommended dosage of RYBREVANT is based on baseline body weight and administered as an intravenous infusion after dilution. (2.3, 2.5, 2.6, 2.7)
- Administer premedications as recommended. (2.4)
- Administer via a peripheral line on Week 1 and Week 2. (2.7)
- Administer RYBREVANT in combination with chemotherapy weekly for 4 weeks, with the initial dose as a split infusion in Week 1 on Day 1 and Day 2, then administer every 3 weeks starting at Week 7. (2.3)

- Administer RYBREVANT as a single agent weekly for 4 weeks, with the initial dose as a split infusion in Week 1 on Day 1 and Day 2, then administer every 2 weeks starting at Week 5. (2.4)
- Administer diluted RYBREVANT intravenously according to the infusion rates in Tables 13 and 14. (2.8)

Table 6: dosage and administration summary

Body Weight (at Baseline)	Dosage	Recommended Dose
RYBREVANT in Combination with Carboplatin and Pemetrexed		
Less than 80 kg	Weeks 1-4	1400 mg
	Week 7 onwards	1750 mg
Greater than or equal to 80 kgs	Weeks 1-4	1750 mg
	Week 7 onwards	2100 mg
RYBREVANT as a Single Agent		
Less than 80 kg	Weeks 1-5	1050 mg
	Week 7 onwards	
Greater than or equal to 80 kg	Weeks 1-5	1400 mg
	Week 7 onwards	

[00206] Dosage forms and strengths: Injection: 350 mg/7 mL (50 mg/mL) solution in a single-dose vial (3)

[00207] Contraindications: None. (4)

[00208] Warnings and Precautions:

- Infusion-Related Reactions (IRR): Interrupt infusion at the first sign of IRRs. Reduce infusion rate or permanently discontinue RYBREVANT based on severity. (2.5, 5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Monitor for new or worsening symptoms indicative of ILD. Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed. (2.5, 5.2)
- Dermatologic Adverse Reactions: May cause rash including acneiform dermatitis and toxic epidermal necrolysis. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity. (2.5, 5.3)
- Ocular Toxicity: Promptly refer patients with worsening eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity. (2.5, 5.4)

- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.5, 8.1, 8.3)

[00209] Adverse reactions:

[00210] RYBREVANT in Combination with Carboplatin and Pemetrexed

- The most common adverse reactions ($\geq 20\%$) were rash, nail toxicity, stomatitis, infusion-related reaction, fatigue, edema, constipation, decreased appetite, nausea, COVID-19, diarrhea, and vomiting. (6.1)
- The most common Grade 3 or 4 laboratory abnormalities ($\geq 2\%$) were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, decreased magnesium, and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes. (6.1)

[00211] RYBREVANT as a Single Agent

- The most common adverse reactions ($\geq 20\%$) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. (6.1)
- The most common Grade 3 or 4 laboratory abnormalities ($\geq 2\%$) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased alkaline phosphatase, increased glucose, increased gamma-glutamyl transferase, and decreased sodium. (6.1)

[00212] Use in specific populations: Lactation: Advise not to breastfeed. (8.2)

[00213] Full Prescribing Information: Contents* (*Sections or subsections omitted from the full prescribing information are not listed.):

1 INDICATIONS AND USAGE

- 1.1 First-Line Treatment of NSCLC with EGFR Exon 20 Insertion Mutations
- 1.2 Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations

2 DOSAGE AND ADMINISTRATION

- 2.1 Important Dosage Information
- 2.2 Patient Selection
- 2.3 Recommended Dosage of RYBREVANT for First-line Treatment of NSCLC

with Exon 20 Insertion Mutations (RYBREVANT in Combination with Carboplatin and Pemetrexed)

2.4 Recommended Dosage of RYBREVANT for Patients with Previously Treated
NSCLC with Exon 20 Insertion Mutations (RYBREVANT as a Single Agent)

2.5 Recommended Premedications

2.6 Dosage Modifications for Adverse Reactions

2.7 Preparation

2.8 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

5.2 Interstitial Lung Disease/Pneumonitis

5.3 Dermatologic Adverse Reactions

5.4 Ocular Toxicity

5.5 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.6 Immunogenicity

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 First Line Treatment of NSCLC with Exon 20 Insertion Mutations-

PAPILLON

14.2 Previously Treated NSCLC with Exon 20 Insertion Mutations-
CHRYSALIS

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

[00214] 1. Indications and Usage

[00215] 1.1 First-Line Treatment of NSCLC with EGFR Exon 20 Insertion Mutations:

RYBREVANT is indicated in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [*see Dosage and Administration (2.2)*].

[00216] 1.2 Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations:

RYBREVANT is indicated as a single agent for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test [*see Dosage and Administration (2.2)*], whose disease has progressed on or after platinum-based chemotherapy.

[00217] 2. Dosage and Administration

[00218] 2.1 Important Dosage Information

- Administer premedications before each RYBREVANT infusion as recommended [*see Dosage and Administration (2.5)*].
- Administer diluted RYBREVANT intravenously according to the infusion rates in Tables 7 and 8, with the initial dose as a split infusion on Week 1 on Day 1 and Day 2 [*see Dosage and Administration (2.8)*].
- Administer RYBREVANT via peripheral line for Week 1 Day 1 and 2 and Week 2 to reduce the risk of infusion-related reactions [*see Dosage and Administration 2.8*].
- When administering RYBREVANT in combination with carboplatin and pemetrexed, infuse pemetrexed first, carboplatin second, and RYBREVANT last [*see Dosage and Administration 2.8*].

[00219] 2.2 Patient Selection: Select patients for treatment with RYBREVANT based on

the presence of EGFR exon 20 insertion mutations in tumor or plasma specimens [*see Clinical Studies (14)*]. If no mutation is detected in a plasma specimen, test tumor tissue.

Information on FDA-approved tests is available at:

<http://www.fda.gov/CompanionDiagnostics>.

[00220] **2.3 Recommended Dosage of RYBREVANT for First-line Treatment of NSCLC with Exon 20 Insertion Mutations (RYBREVANT in Combination with Carboplatin and Pemetrexed):** The recommended dosages of RYBREVANT, administered in combination with carboplatin and pemetrexed, based on baseline body weight are provided in Table 7.

Table 7: Recommended Dosage for RYBREVANT in Combination with Carboplatin and Pemetrexed

Body weight at Baseline ^a	Recommended Dose	Dosing Schedule
Less than 80 kg	1400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1 • Weeks 5 and 6 – no dose
	1750 mg	Every 3 weeks starting at Week 7 onwards
Greater than or equal to 80 kg	1750 mg	Weekly (total of 4 doses) for Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1 • Weeks 5 and 6 – no dose
	2100 mg	Every 3 weeks starting at Week 7 onwards

^a Dose adjustments not required for subsequent body weight changes.

[00221] The recommended order of administration and regimen for RYBREVANT in combination with carboplatin and pemetrexed is provided in Table 8.

Table 8: Order of Administration and Regimen for RYBREVANT in Combination with Pemetrexed and Carboplatin

RYBREVANT in Combination with Carboplatin and Pemetrexed		
<u>Administer the regimen in the following order:</u> pemetrexed first, carboplatin second and RYBREVANT last.		
Drug	Dose	Duration/Timing of Treatment
Pemetrexed	Pemetrexed 500 mg/m ² intravenously Refer to the pemetrexed Full Prescribing Information for complete information.	Every 3 weeks, continue until disease progression or unacceptable toxicity.
Carboplatin	Carboplatin AUC 5 intravenously Refer to the carboplatin Full Prescribing Information for complete information.	Every 3 weeks for up to 12 weeks.
RYBREVANT	RYBREVANT intravenously See Table 7.	Every 3 weeks, continue until disease progression or unacceptable toxicity.

[00222] 2.4 Recommended Dosage of RYBREVANT for Patients with Previously treated NSCLC with Exon 20 Insertion Mutations (RYBREVANT as a Single Agent):

The recommended dosages of RYBREVANT as a single agent, based on baseline body weight, are provided in Table 9.

Table 9: Recommended Dosage Schedule for RYBREVANT as a Single Agent

Body weight at Baseline ^a	Recommended Dose	Dosing Schedule
Less than 80 kg	1050 mg	Weekly (total of 5 doses) from Weeks 1 to 5 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 5 - infusion on Day 1 • Week 6 – no dose Every 2 weeks starting at Week 7 onwards
Greater than or equal to 80 kg	1400 mg	Weekly (total of 5 doses) from Weeks 1 to 5 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 5 - infusion on Day 1 • Week 6 – no dose Every 2 weeks starting at Week 7 onwards

^a Dose adjustments not required for subsequent body weight changes.

[00223] Administer RYBREVANT until disease progression or unacceptable toxicity.

[00224] 2.5 Recommended Premedications:

[00225] Prior to the initial infusion of RYBREVANT (Week 1, Day 1 and 2), administer premedication as described in Table 4 to reduce the risk of infusion related reactions [*see Warnings and Precautions (5.1)*].

[00226] Glucocorticoid administration is required for Week 1, Day 1 and 2 dose only and upon re-initiation after prolonged dose interruptions, then as necessary for subsequent infusions (*see Table 10*). Administer both antihistamine and antipyretic prior to all infusions.

Table 10: Premedications

Medication	Dose	Route of Administration	Dosing Window Prior to RYBREVANT Administration
Antihistamine*	Diphenhydramine (25 to 50 mg) or equivalent	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic*	Acetaminophen (650 to 1,000 mg)	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid [‡]	Dexamethasone (20 mg) or equivalent	Intravenous	45 to 60 minutes
Glucocorticoid ⁺	Dexamethasone (10 mg) or equivalent	Intravenous	45 to 60 minutes

* Required at all doses.

[‡] Required at initial dose (Week 1 Day 1)

⁺ Required at second dose (Week 1 Day 2); optional for subsequent doses.

[00227] 2.6 Dosage Modifications for Adverse Reactions: The recommended dose reductions for adverse reactions for RYBREVANT are listed in Table 11.

Table 11: Dose Reductions for Adverse Reactions for RYBREVANT

Dose*	1 st Dose Reduction	2 nd Dose Reduction	3 rd Dose Reduction
1050 mg	700 mg	350 mg	Discontinue RYBREVANT
1400 mg	1050 mg	700 mg	
1750 mg	1400 mg	1050 mg	
2100 mg	1750 mg	1400 mg	

* Dose at which the adverse reaction occurred

[00228] The recommended dosage modifications and management for adverse reactions for RYBREVANT are provided in Table 12.

Table 12: Recommended Dosage Modifications and Management for Adverse Reactions for RYBREVANT

Adverse Reaction	Severity	Dosage Modifications
Infusion-related reactions (IRR) [see <i>Warnings and Precautions</i> (5.1)]	Grade 1 to 2	- Interrupt RYBREVANT infusion if IRR is suspected and monitor patient until reaction symptoms resolve. - Resume the infusion at 50% of the infusion rate at which the reaction occurred. - If there are no additional symptoms after 30 minutes, the infusion rate may be escalated (see Tables 13 and 14). - Include corticosteroid with premedications for subsequent dose (see Table 10).
	Grade 3	- Interrupt RYBREVANT infusion and administer supportive care medications. Continuously monitor patient until reaction symptoms resolve. - Resume the infusion at 50% of the infusion rate at which the reaction occurred. - If there are no additional symptoms after 30 minutes, the infusion rate may be escalated (see Tables 13 and 14). - Include corticosteroid with premedications for subsequent dose (see Table 10). For recurrent Grade 3, permanently discontinue RYBREVANT.
	Grade 4	Permanently discontinue RYBREVANT.
Interstitial Lung Disease (ILD)/pneumonitis [see <i>Warnings and Precautions</i> (5.2)]	Any Grade	- Withhold RYBREVANT if ILD/pneumonitis is suspected. - Permanently discontinue RYBREVANT if ILD/pneumonitis is confirmed.
Dermatologic Adverse Reactions (including dermatitis acneiform, pruritus, dry skin) [see <i>Warnings and Precautions</i> (5.3)]	Grade 1	- Initiate supportive care management. - Reassess after 2 weeks.
	Grade 2	- Initiate supportive care management. - Reassess after 2 weeks; if rash does not improve, consider dose reduction.
	Grade 3	- Withhold RYBREVANT and initiate supportive care management. - Upon recovery to ≤ Grade 2, resume RYBREVANT at reduced dose. - If no improvement within 2 weeks, permanently discontinue treatment.
	Grade 4	Permanently discontinue RYBREVANT.

	Severe bullous, blistering or exfoliating skin conditions (including toxic epidermal necrolysis (TEN))	• Permanently discontinue RYBREVANT.
Other Adverse Reactions [see <i>Adverse Reactions</i> (6.1)]	Grade 3	• Withhold RYBREVANT until recovery to $\leq$ Grade 1 or baseline. • Resume at the same dose if recovery occurs within 1 week. • Resume at reduced dose if recovery occurs after 1 week but within 4 weeks. • Permanently discontinue if recovery does not occur within 4 weeks.
	Grade 4	• Withhold RYBREVANT until recovery to $\leq$ Grade 1 or baseline. • Resume at reduced dose if recovery occurs within 4 weeks. • Permanently discontinue if recovery does not occur within 4 weeks. • Permanently discontinue for recurrent Grade 4 reactions.

[00229] Recommended Dosage Modifications for Adverse Reactions for RYBREVANT in Combination with Carboplatin and Pemetrexed: When administering RYBREVANT in combination with carboplatin and pemetrexed, modify the dosage of one or more drugs. Withhold or discontinue RYBREVANT as shown in Table 12. Refer to prescribing information for carboplatin and pemetrexed for additional dosage modification information.

[00230] **2.7 Preparation:** Dilute and prepare RYBREVANT for intravenous infusion before administration.

- Check that the RYBREVANT solution is colorless to pale yellow. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if discoloration or visible particles are present.
- Determine the dose required of RYBREVANT needed based on patient's baseline weight [see *Dosage and Administration* (2.3)]. Each vial of RYBREVANT contains 350 mg of amivantamab-vmjw.
- Withdraw and then discard a volume of either 5% dextrose solution or 0.9% sodium chloride solution from the 250 mL infusion bag equal to the volume of RYBREVANT to be added (i.e., discard 7 mL diluent from the infusion bag for each RYBREVANT vial). Only use infusion bags made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).

- Withdraw 7 mL of RYBREVANT from each vial and add it to the infusion bag. The final volume in the infusion bag should be 250 mL. Discard any unused portion left in the vial.
- Gently invert the bag to mix the solution. Do not shake.
- Diluted solutions should be administered within 10 hours (including infusion time) at room temperature 59°F to 77°F (15°C to 25°C).

[00231] 2.8 Administration

- Administer the diluted RYBREVANT solution [*see Dosage and Administration (2.7)*] by intravenous infusion using an infusion set fitted with a flow regulator and with an in line, sterile, non pyrogenic, low protein binding polyethersulfone (PES) filter (pore size 0.2 micrometer).
- Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
- The administration set with filter, **must** be primed with either 5% dextrose solution or 0.9% sodium chloride solution prior to the initiation of each RYBREVANT infusion.
- Do not infuse RYBREVANT concomitantly in the same intravenous line with other agents.

[00232] RYBREVANT in Combination with Carboplatin and Pemetrexed

- Administer RYBREVANT in combination with carboplatin and pemetrexed infusions every 3 weeks intravenously according to the infusion rates in Table 13.
- Administer RYBREVANT via a peripheral line on Week 1 and Week 2 given the high incidence of infusion-related reactions during initial treatment [*see Warnings and Precautions (5.1)*].
- RYBREVANT may be administered via central line for subsequent weeks.
- For the initial infusion, prepare RYBREVANT as close to administration time as possible to allow for the possibility of extended infusion time in the event of an infusion related reaction.
- Administer the pemetrexed infusion first, carboplatin infusion second, and the RYBREVANT infusion last.

Table 13: Infusion Rates of RYBREVANT for First-line Treatment of NSCLC with Exon 20 Insertion Mutations (RYBREVANT in Combination with Carboplatin and Pemetrexed)

Body Weight Less Than 80 kg			
Week	Dose (per 250 mL bag)	Initial Infusion Rate (mL/hr)	Subsequent Infusion Rate [†] (mL/hr)
Week 1 (split dose infusion)			
Week 1 <i>Day 1</i>	350 mg	50	75
Week 1 <i>Day 2</i>	1050 mg	33	50
Week 2	1400 mg		65
Week 3	1400 mg		85
Week 4	1400 mg		125
Weeks 5 and 6	No dose		
Week 7 and every 3 weeks thereafter	1750 mg		125
Body Weight Greater Than or Equal to 80 kg			
Week	Dose (per 250 mL bag)	Initial Infusion Rate (mL/hr)	Subsequent Infusion Rate (mL/hr)
Week 1 (split dose infusion)			
Week 1 <i>Day 1</i>	350 mg	50	75
Week 1 <i>Day 2</i>	1400 mg	25	50
Week 2	1750 mg		65
Week 3	1750 mg		85
Week 4	1750 mg		125
Week 5 and 6	No dose		
Week 7 and every 3 weeks thereafter	2100 mg		125

[†] In the absence of infusion-related reactions, increase the initial infusion rate to the subsequent infusion rate after 2 hours based on patient tolerance. Total infusion time approximately 4-6 hours for day 1 and 6-8 hours for day 2. Subsequent infusion time is approximately 2 hours.

[00233] RYBREVANT as a Single Agent

- Administer RYBREVANT as a single agent infusion every 2 weeks intravenously according to the infusion rates in Table 14.
- Administer RYBREVANT via a peripheral line on Week 1 and Week 2, given the high incidence of infusion-related reactions during initial treatment [*see Warnings and Precautions (5.1)*].
- RYBREVANT may be administered via central line for subsequent weeks.
- For the initial infusion, prepare RYBREVANT as close to administration time as possible to allow for the possibility of extended infusion time in the event of an infusion related reaction.

Table 14: Infusion Rates of RYBREVANT for Patients with Previously Treated NSCLC with Exon 20 Insertion Mutations (RYBREVANT as Single Agent)

Body Weight Less Than 80 kg			
Week	Dose (per 250 mL bag)	Initial Infusion Rate (mL/hr)	Subsequent Infusion Rate [†] (mL/hr)
Week 1 (split dose infusion)			
Week 1 <i>Day 1</i>	350 mg	50	75
Week 1 <i>Day 2</i>	700 mg	50	75
Week 2	1050 mg	85	
Week 3	1050 mg	125	
Week 4	1050 mg	125	
Week 5	1050 mg	125	
Week 6	No dose		
Week 7 and every 2 weeks thereafter	1050 mg	125	
Body Weight Greater Than or Equal to 80 kg			
Week	Dose (per 250 mL bag)	Initial Infusion Rate (mL/hr)	Subsequent Infusion Rate [†] (mL/hr)
Week 1 (split dose infusion)			
Week 1 <i>Day 1</i>	350 mg	50	75
Week 1 <i>Day 2</i>	1050 mg	35	50
Week 2	1400 mg	65	
Week 3	1400 mg	85	
Week 4	1400 mg	125	
Week 5	1400 mg	125	
Week 6	No dose		
Week 7 and every 2 weeks thereafter	1400 mg	125	

[†] In the absence of infusion-related reactions, increase the initial infusion rate to the subsequent infusion rate after 2 hours based on patient tolerance. Total infusion time approximately 4-6 hours for day 1 and 6-8 hours for day 2. Subsequent infusion time is approximately 2 hours.

[00234] **3. Dosage Forms and Strengths:** Injection: 350 mg/7 mL (50 mg/mL) colorless to pale yellow solution in a single-dose vial.

[00235] **4. Contraindications:** None.

[00236] **5. Warnings and Precautions**

[00237] **5.1 Infusion-Related Reactions:** RYBREVANT can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension and vomiting.

[00238] *RYBREVANT with Carboplatin and Pemetrexed:* RYBREVANT in combination with carboplatin and pemetrexed can cause infusion-related reactions. Based on the safety population [see *Adverse Reactions (6.1)*], infusion-related reactions occurred in 42% of patients treated with RYBREVANT in combination with carboplatin and pemetrexed,

including Grade 3 (1.3%) adverse reactions. The incidence of infusion modifications due to IRR was 40%, and 0.7% of patients permanently discontinued RYBREVANT.

[00239] *RYBREVANT as a Single Agent*: Based on the safety population [see *Adverse Reactions* (6.1)], IRR occurred in 66% of patients treated with RYBREVANT as a single agent. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62%, and 1.3% of patients permanently discontinued RYBREVANT due to IRR.

[00240] Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT as recommended [see *Dosage and Administration* (2.4)]. Administer RYBREVANT via a peripheral line on Week 1 and Week 2 [see *Dosage and Administration* (2.7)].

[00241] Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT based on severity [see *Dosage and Administration* (2.5)].

[00242] **5.2 Interstitia Lung Disease/Pneumonitis**: RYBREVANT can cause interstitial lung disease (ILD)/pneumonitis.

[00243] *RYBREVANT with Carboplatin and Pemetrexed*: Based on the safety population [see *Adverse Reactions* (6.1)], Grade 3 ILD/pneumonitis occurred in 2.6% of patients treated with RYBREVANT in combination with carboplatin and pemetrexed, all patients required permanent discontinuation.

[00244] *RYBREVANT as a Single Agent*: Based on the safety population [see *Adverse Reactions* (6.1)], ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT as a single agent, with 0.7 % of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT due to ILD/pneumonitis.

[00245] Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed [see *Dosage and Administration* (2.5)].

[00246] **5.3 Dermatologic Adverse Reactions:** RYBREVANT can cause rash (including dermatitis acneiform), pruritus and dry skin.

[00247] *RYBREVANT with Carboplatin and Pemetrexed:* RYBREVANT in combination with carboplatin and pemetrexed can cause dermatologic adverse reactions. Based on the safety population [see *Adverse Reactions (6.1)*], rash occurred in 89% of patients treated with RYBREVANT in combination with carboplatin and pemetrexed, including Grade 3 (19%) adverse reactions. Rash leading to dose reductions occurred in 19% of patients, and 2% permanently discontinued RYBREVANT and 1.3% discontinued pemetrexed.

[00248] *RYBREVANT as a Single Agent:* Based on the safety population [see *Adverse Reactions (6.1)*], rash occurred in 74% of patients treated with RYBREVANT as a single agent, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT was permanently discontinued due to rash in 0.7% of patients [see *Adverse Reactions (6.1)*]. Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with RYBREVANT as a single agent.

[00249] Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT. Advise patients to wear protective clothing and use broad spectrum UVA/UVB sunscreen. Alcohol free emollient cream is recommended for dry skin.

[00250] If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity [see *Dosage and Administration (2.6)*].

[00251] **5.4 Ocular Toxicity:** RYBREVANT can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis.

[00252] *RYBREVANT with Carboplatin and Pemetrexed:* Based on the safety population [see *Adverse Reactions (6.1)*] RYBREVANT in combination with carboplatin and pemetrexed can cause ocular toxicity including blepharitis, dry eye, conjunctival redness, blurred vision, and eye pruritus. All events were Grade 1-2.

[00253] *RYBREVANT as a Single Agent:* Based on the safety population [see *Adverse Reactions (6.1)*], keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT. All events were Grade 1-2. Promptly refer patients presenting with eye

symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity [see *Dosage and Administration* (2.6)].

[00254] 5.5 Embryo-Fetal Toxicity: Based on its mechanism of action and findings from animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo fetal development, embryo lethality, and abortion. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT. [see *Use in Specific Populations* (8.1, 8.3)].

[00255] 6. Adverse Reactions: The following adverse reactions are discussed elsewhere in the labeling

- Infusion Related Reactions [see *Warnings and Precautions* (5.1)]
- Interstitial Lung Disease/Pneumonitis [see *Warnings and Precautions* (5.2)]
- Dermatologic Adverse Reactions [see *Warnings and Precautions* (5.3)]
- Ocular Toxicity [see *Warnings and Precautions* (5.4)]

[00256] 6.1 Clinical Trials Experience

[00257] Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

[00258] The data described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBREVANT in combination with carboplatin and pemetrexed in the PAPILLON study in 151 patients with locally advanced or metastatic NSCLC. Patients received RYBREVANT intravenously at 1400 mg (for patients < 80 kg) or 1750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1750 mg (for patients < 80 kg) or 2100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity, in combination with carboplatin at area under the curve AUC 5 once every 3 weeks, for up to 12 weeks, and pemetrexed at 500 mg/m² once every 3 weeks until disease progression or unacceptable toxicity. Among 151 patients who received RYBREVANT in combination with carboplatin and pemetrexed, 76% were exposed for 6 months or longer and 38% were exposed for greater than one year. In the safety population, the most common (≥ 20%) adverse reactions were rash, nail toxicity, stomatitis, infusion-related reaction, fatigue, edema, constipation, decreased appetite, nausea, COVID-19, diarrhea, and vomiting. The

most common Grade 3 to 4 laboratory abnormalities ($\geq 2\%$) were increased alanine aminotransferase decreased albumin, decreased potassium and decreased magnesium.

[00259] The data in the WARNINGS AND PRECAUTIONS also reflect exposure to RYBREVANT as a single agent in the CHRYSALIS study in 302 patients with locally advanced or metastatic NSCLC. Patients received RYBREVANT at 1050 mg (for patient baseline body weight < 80 kg) or 1400 mg (for patient baseline body weight ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity. Among 302 patients who received RYBREVANT as a single agent, 36% were exposed for 6 months or longer and 12% were exposed for greater than one year. In the safety population, the most common ($\geq 20\%$) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting and pruritus. The most common Grade 3 to 4 laboratory abnormalities ($\geq 2\%$) were increased gamma glutamyl transference, decreased sodium, decreased potassium and increased alkaline phosphatase.

[00260] First-line Treatment of Non-Small Cell Lung Cancer (NSCLC) with Exon 20 Insertion Mutations

[00261] The data described below reflect exposure to RYBREVANT in combination with carboplatin and pemetrexed at the recommended dosage in the PAPILLON trial [*see Clinical Studies (14.1)*] in 151 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. Among patients who received RYBREVANT in combination with carboplatin and pemetrexed the median exposure was 9.7 months (range: 0.0 to 26.9 months). In patients that received carboplatin and pemetrexed alone, the median exposure was 6.7 months (range 0.0 to 25.3).

[00262] The median age was 61 years (range: 27 to 86 years); 56% were female; 64% were Asian, 32% were White, 1.3% were Black or African American, race was not reported in 1.3% of patients; 89% were not Hispanic or Latino; 86% had baseline body weight <80 kg.

[00263] Serious adverse reactions occurred in 37% of patients who received RYBREVANT in combination with carboplatin and pemetrexed. Serious adverse reactions in $\geq 2\%$ of patients included rash, pneumonia, interstitial lung disease (ILD), pulmonary embolism, vomiting and COVID-19. Fatal adverse reactions occurred in 7 patients (4.6%) due to pneumonia, cerebrovascular accident, cardio-respiratory arrest, COVID-19, sepsis and death not otherwise specified.

[00264] Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in $\geq 1\%$ of patients were rash and ILD.

[00265] Dose interruptions of RYBREVANT due to an adverse reaction occurred in 64% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 38% of patients. Adverse reactions requiring dose interruption in $\geq 5\%$ of patients included rash and nail toxicity.

[00266] Dose reductions of RYBREVANT due to an adverse reaction occurred in 36% of patients. Adverse reactions requiring dose reductions in $\geq 5\%$ of patients included rash, and nail toxicity.

[00267] The most common adverse reactions ($\geq 20\%$) were rash, nail toxicity, stomatitis, infusion-related reaction, fatigue, edema, constipation, decreased appetite, nausea, COVID-19, diarrhea, and vomiting. The most common Grade 3 to 4 laboratory abnormalities ($\geq 2\%$) were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, decreased magnesium, and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes.

[00268] Table 15 summarizes the adverse reactions in PAPILLON.

Table 15: Adverse Reactions ($\geq 10\%$) in Patients with Metastatic NSCLC with Exon 20 Insertion Mutations Who Received RYBREVANT in Combination with Carboplatin and Pemetrexed in PAPILLON

Adverse Reaction ¹	RYBREVANT in Combination with Carboplatin and Pemetrexed (n=151)		Carboplatin and Pemetrexed (n=155)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash ²	90	19	19	0
Nail toxicity ²	62	7	3	0
Dry skin ²	17	0	6	0
Gastrointestinal disorders				
Stomatitis ²	43	4	11	0
Constipation	40	0	30	0.7
Nausea	36	0.7	42	0
Vomiting	21	3.3	19	0.7
Diarrhea	21	3	13	1.3
Hemorrhoids	12	1	1.3	0
Abdominal pain ²	11	0.7	8	0
General disorders and administration site conditions				
Infusion related reaction	42	1.3	1.3	0
Fatigue ²	42	6	45	3.9
Edema ²	40	1.3	19	0
Pyrexia ²	17	0	6	0
Metabolism and nutrition disorders				
Decreased appetite	36	2.6	28	1.3

Infections and Infestations				
COVID-19	24	2	14	0.6
Pneumonia ²	13	5	6	1.9
Vascular Disorders				
Hemorrhage ²	18	0.7	11	1.9
Respiratory, thoracic and mediastinal disorders				
Cough ²	17	0	16	0
Dyspnea ²	11	1.3	16	3.2
Investigations				
Weight decreased	14	0.7	8	0
Nervous System Disorders				
Dizziness ²	11	0	12	0
Psychiatric Disorders				
Insomnia	11	0	13	0

¹ Adverse reactions were graded using CTCAE version 5.0

² Grouped Term

[00269] Clinically relevant adverse reactions in <10% of patients who received RYBREVANT in combination with carboplatin and pemetrexed included pulmonary embolism, deep vein thrombosis, skin ulcer, conjunctivitis and interstitial lung disease (ILD)/pneumonitis.

[00270] Table 16 summarizes the laboratory abnormalities in PAPILLON.

Table 16: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Who Received RYBREVANT in Combination with Carboplatin and Pemetrexed in PAPILLON

Laboratory Abnormality ¹	RYBREVANT in Combination with Carboplatin and Pemetrexed ²		Carboplatin in Combination with Pemetrexed ³	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Decreased white blood cells	89	17	76	10
Decreased hemoglobin	79	11	85	13
Decreased neutrophils	76	36	61	23
Decreased platelets	70	10	54	12
Decreased lymphocytes	61	11	49	13
Chemistry				
Decreased albumin	87	7	34	1
Increased aspartate aminotransferase	60	1	61	1
Increased alanine aminotransferase	57	4	54	1
Decreased sodium	55	7	39	4
Increased alkaline phosphatase	51	1	28	0
Decreased potassium	44	11	17	1
Decreased magnesium	39	2	30	1
Increased gamma-glutamyl transferase	38	4	43	4
Decreased calcium (corrected)	27	1	18	1

¹ Adverse reactions were graded using CTCAE version 5.0

² The denominator used to calculate the rate varied from 113 to 150 based on the number of patients with a baseline value and at least one post-treatment value.

³ The denominator used to calculate the rate varied from 119 to 154 based on the number of patients with a baseline value and at least one post-treatment value.

[00271] Previously Treated NSCLC Exon 20 Insertion Mutations

[00272] The data described below reflect exposure to RYBREVANT at the recommended dosage in 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations in the CHRYSALIS trial [see *Clinical Studies (14.2)*], whose disease had progressed on or after platinum-based chemotherapy. Among patients who received RYBREVANT, 44% were exposed for 6 months or longer and 12% were exposed for greater than one year.

[00273] The median age was 62 years (range: 36 to 84 years); 61% were female; 55% were Asian, 35% were White, and 2.3% were Black; and 82% had baseline body weight <80 kg.

[00274] Serious adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in $\geq 2\%$ of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

[00275] Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in $\geq 1\%$ of patients were pneumonia, IRR, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

[00276] Dose interruptions of RYBREVANT due to an adverse reaction occurred in 78% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 59% of patients. Adverse reactions requiring dose interruption in $\geq 5\%$ of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

[00277] Dose reductions of RYBREVANT due to an adverse reaction occurred in 15% of patients. Adverse reactions requiring dose reductions in $\geq 2\%$ of patients included rash and paronychia.

[00278] The most common adverse reactions ($\geq 20\%$) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities ($\geq 2\%$) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased

glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.

[00279] Table 17 summarizes the adverse reactions in CHRYSALIS.

Table 17: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-based Chemotherapy and Received RYBREVANT in CHRYSALIS

Adverse Reactions	RYBREVANT ¹ (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Skin and subcutaneous tissue disorders		
Rash*	84	3.9
Pruritus	18	0
Dry skin	14	0
General disorders and administration site conditions		
Infusion related reaction	64	3.1
Fatigue*	33	2.3
Edema*	27	0.8
Pyrexia	13	0
Infections and infestations		
Paronychia	50	3.1
Pneumonia*	10	0.8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	47	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea*	37	2.3
Cough*	25	0
Gastrointestinal disorders		
Nausea	36	0
Stomatitis*	26	0.8
Constipation	23	0
Vomiting	22	0
Diarrhea	16	3.1
Abdominal Pain*	11	0.8
Vascular disorders		
Hemorrhage*	19	0
Metabolism and nutrition disorders		
Decreased appetite	15	0
Nervous system disorders		
Peripheral neuropathy*	13	0
Dizziness	12	0.8
Headache*	10	0.8

*Grouped term

¹ Adverse reactions were graded using CTCAE version 4.03

[00280] Clinically relevant adverse reactions in <10% of patients who received RYBREVANT included ocular toxicity, ILD/pneumonitis, and toxic epidermal necrolysis (TEN).

[00281] Table 18 summarizes the laboratory abnormalities in CHRYSALIS.

Table 18: Select Laboratory Abnormalities ($\geq 20\%$) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYBREVANT in CHRYSALIS

Laboratory Abnormality	RYBREVANT ⁺ (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Chemistry		
Decreased albumin	79	8
Increased glucose	56	4
Increased alkaline phosphatase	53	4.8
Increased creatinine	46	0
Increased alanine aminotransferase	38	1.6
Decreased phosphate	33	8
Increased aspartate aminotransferase	33	0
Decreased magnesium	27	0
Increased gamma-glutamyl transferase	27	4
Decreased sodium	27	4
Decreased potassium	26	6
Hematology		
Decreased lymphocytes	36	8

⁺ The denominator used to calculate the rate was 126 based on the number of patients with a baseline value and at least one post-treatment value.

[00282] 8. Use In Specific Populations

[00283] 8.1 Pregnancy

[00284] Risk Summary

[00285] Based on the mechanism of action and findings in animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVANT in pregnant women or animal data to assess the risk of RYBREVANT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryo fetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryo lethality, malformations, and post natal death in animals (see Data). Advise pregnant women of the potential risk to a fetus.

[00286] In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

[00287] Data

[00288] *Animal Data*

[00289] No animal studies have been conducted to evaluate the effects of amivantamab-vmjw on reproduction and fetal development; however, based on its mechanism of action,

RYBREVANT can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab vmjw has the potential to be transmitted from the mother to the developing fetus.

[00290] 8.2 Lactation

[00291] Risk Summary

[00292] There are no data on the presence of amivantamab-vmjw in human milk, the effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed children, advise women not to breast-feed during treatment with RYBREVANT and for 3 months after the last dose.

[00293] 8.3 Females and Males of Reproductive Potential

[00294] RYBREVANT can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

[00295] Pregnancy Testing

[00296] Verify pregnancy status of females of reproductive potential prior to initiating RYBREVANT.

[00297] Contraception

[00298] *Females*

[00299] Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT.

[00300] 8.4 Pediatric Use

[00301] The safety and efficacy of RYBREVANT have not been established in pediatric patients.

[00302] 8.5 Geriatric Use

[00303] Of the 151 patients with locally advanced or metastatic NSCLC treated with RYBREVANT in combination with carboplatin and pemetrexed in the PAPILLON study, 37% were ≥ 65 years of age and 8% were ≥ 75 years of age.

[00304] Of the 302 patients with locally advanced or metastatic NSCLC treated with RYBREVANT as a single agent in the CHRYSALIS study, 39% were ≥ 65 years of age and 11% were ≥ 75 years of age.

[00305] No clinically important differences in safety or efficacy were observed between patients who were ≥ 65 years of age and younger patients.

[00306] **11. Description**

[00307] Amivantamab-vmjw is a low-fucose human immunoglobulin G1-based bispecific antibody directed against the EGF and MET receptors, produced by mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology that has a molecular weight of approximately 148 kDa. RYBREVANT® (amivantamab-vmjw) injection for intravenous infusion is a sterile, preservative-free, colorless to pale yellow solution in single-dose vials. The pH is 5.7.

[00308] Each RYBREVANT vial contains 350 mg (50 mg/mL) amivantamab-vmjw, EDTA disodium salt dihydrate (0.14 mg), L-histidine (2.3 mg), L-histidine hydrochloride monohydrate (8.6 mg), L-methionine (7 mg), polysorbate 80 (4.2 mg), sucrose (595 mg), and water for injection, USP.

[00309] **12. Clinical Pharmacology**

[00310] **12.1 Mechanism of Action**

[00311] Amivantamab vmjw is a bispecific antibody that binds to the extracellular domains of EGFR and MET.

[00312] In in vitro and in vivo studies amivantamab vmjw was able to disrupt EGFR and MET signaling functions through blocking ligand binding and, in exon 20 insertion mutation models, degradation of EGFR and MET. The presence of EGFR and MET on the surface of tumor cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody dependent cellular cytotoxicity (ADCC) and trogocytosis mechanisms, respectively.

[00313] **12.2 Pharmacodynamics**

[00314] The exposure-response relationship and time-course of pharmacodynamic response of amivantamab-vmjw have not been fully characterized in patients with NSCLC with EGFR exon 20 insertion mutations.

[00315] **12.3 Pharmacokinetics**

[00316] Based on RYBREVANT single agent data, amivantamab-vmjw exposures increased proportionally over a dosage range from 350 to 1750 mg. Based on the population pharmacokinetics of RYBREVANT, steady-state concentrations of RYBREVANT were reached by week 13 for both the 3-week and 2-week dosing regimen and the systemic accumulation was 1.9-fold.

[00317] Distribution: The amivantamab-vmjw mean ($\pm$ SD) volume of distribution is 5.34 ($\pm$ 1.81) L.

[00318] Elimination: The geometric mean (% CV) linear clearance (CL) and terminal half-life is 0.266 L/day (30.4%) and 13.7 days (31.9%), respectively.

[00319] Specific Populations: No clinically meaningful differences in the pharmacokinetics of amivantamab vmjw were observed based on age (range: 27-87 years), sex, race, creatinine clearance (CL_{cr} 29 to 301 mL/min), or mild hepatic impairment [(total bilirubin $\leq$ ULN and AST $>$ ULN) or (ULN $<$ total bilirubin $\leq$ 1.5 times ULN)]. The pharmacokinetics of amivantamab vmjw have not been studied in patients with severe renal impairment (CL_{cr} 15 to 29 mL/min) or patients with moderate (total bilirubin 1.5 to 3 times ULN) to severe (total bilirubin $>$ 3 times ULN) hepatic impairment.

[00320] Body Weight: Increases in body weight increased the volume of distribution and clearance of amivantamab vmjw. Amivantamab vmjw exposures are 30-40% lower in patients who weighed $\geq$ 80 kg compared to patients with body weight $<$ 80 kg at the same dose. Exposures of amivantamab vmjw were comparable between patients who weighed $<$ 80 kg and received 1050 mg dose and patients who weighed $\geq$ 80 kg and received 1400 mg dose.

[00321] 12.6 Immunogenicity

[00322] The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies (ADA) in the studies described below with the incidence of anti-drug antibodies in other studies, including those of amivantamab-vmjw or amivantamab products.

[00323] In patients with NSCLC who received RYBREVANT as a single agent or as part of a combination therapy, 3 of the 663 (0.5%) patients who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA) tested positive for treatment-emergent anti-amivantamab-vmjw antibodies. Given the low incidence of detectable antibody-drug antibodies, the effect of ADA on the efficacy of RYBREVANT remains unknown.

[00324] 13. Nonclinical Toxicology

[00325] 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[00326] No studies have been performed to assess the potential of amivantamab vmjw for carcinogenicity or genotoxicity. Fertility studies have not been performed to evaluate the potential effects of amivantamab vmjw. In 6 week and 3 month repeat dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs.

[00327] 14. Clinical Studies**[00328] 14.1 First Line Treatment of NSCLC with Exon 20 Insertion Mutations – PAPILLON**

[00329] The efficacy of RYBREVANT was evaluated in PAPILLON (NCT04538664), in a randomized, open-label, multicenter study. Eligible patients were required to have previously untreated locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutations measurable disease per RECIST v1.1, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1 , and adequate organ and bone marrow function. Patients with brain metastases at screening were eligible for participation once they were definitively treated, clinically stable, asymptomatic, and off corticosteroid treatment for at least 2 weeks prior to randomization. Patients with a medical history of interstitial lung disease or active ILD were excluded from the clinical study.

[00330] A total of 308 patients were randomized 1:1 to receive RYBREVANT in combination with carboplatin and pemetrexed (n=153) or carboplatin and pemetrexed (n=155). Patients received RYBREVANT intravenously at 1400 mg (for patients < 80 kg) or 1750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1750 mg (for patients < 80 kg) or 2100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. Carboplatin was administered intravenously at area under the concentration-time curve 5 mg/mL per minute (AUC 5) once every 3 weeks, for up to 12 weeks. Pemetrexed was administered intravenously at 500 mg/m² on once every 3 weeks until disease progression or unacceptable toxicity. Patients were stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1) and prior brain metastases (yes or no).

[00331] The primary efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR). Additional efficacy outcome measures included overall response rate (ORR), duration of response (DOR) and overall survival (OS). Cross-over to single agent RYBREVANT was permitted for patients who had confirmed disease progression on carboplatin and pemetrexed.

[00332] The median age was 62 (range: 27 to 92) years, with 40% of the patients ≥ 65 years of age; 58% were female; 61% were Asian and 36% were White, 0.7% were Black or African American and race was not reported in 2.3% of patients; 93% were not Hispanic or Latino. Baseline ECOG performance status was 0 (35%) or 1 (65%); 58% were never smokers; 23% had history of brain metastasis and 84% had Stage IV cancer at initial diagnosis.

[00333] PAPILLON demonstrated a statistically significant improvement in progression free survival for patients randomized to RYBREVANT in combination with carboplatin and pemetrexed compared with carboplatin and pemetrexed.

[00334] Efficacy results are summarized in Table 19 and Figure 8.

Table 19: Efficacy Results in PAPILLON

	RYBREVANT+ carboplatin+ pemetrexed (N=153)	carboplatin+ pemetrexed (N=155)
Progression-Free Survival (PFS)		
Number of events (%)	84 (55)	132 (85)
Median, months (95% CI)	11.4 (9.8, 13.7)	6.7 (5.6, 7.3)
HR (95% CI)	0.40 (0.30, 0.53)	
p-value	p<0.0001	
Overall Response Rate (ORR)¹		
ORR, % (95% CI)	67 (59, 75)	36 (29, 44)
Complete response, %	4	1
Partial response, %	63	36
Duration of response (DOR)²		
Median (95% CI), months	10.1 (8.5, 13.9)	5.6 (4.4, 6.9)

CI = confidence interval

¹ Confirmed responses.

² In confirmed responders.

[00335] While OS results were immature at the current analysis, with 44% of pre-specified deaths for the final analysis reported, no trend towards a detriment was observed. Seventy-five (48%) of the treated patients crossed over from the carboplatin and pemetrexed arm after confirmation of disease progression to receive RYBREVANT as a single agent.

[00336] 14.2 Previously Treated NSCLC with Exon 20 Insertion Mutations – CHRYSLIS

[00337] The efficacy of RYBREVANT was evaluated in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations in a multicenter, open label, multi cohort clinical trial (CHRYSLIS, NCT02609776). The study included patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum based chemotherapy. Patients with untreated brain metastases

and patients with a history of ILD requiring treatment with prolonged steroids or other immunosuppressive agents within the last 2 years were not eligible for the study.

[00338] In the efficacy population, EGFR exon 20 insertion mutation status was determined by prospective local testing using tissue (94%) and/or plasma (6%) samples. Of the 81 patients with EGFR exon 20 insertion mutations identified by local testing, plasma samples from 78/81 (96%) patients were tested retrospectively using Guardant360® CDx, identifying 62/78 (79%) samples with an EGFR exon 20 insertion mutation; 16/78 (21%) samples did not have an EGFR exon 20 insertion mutation identified.

[00339] Patients received RYBREVANT at 1050 mg (for patient baseline body weight < 80 kg) or 1400 mg (for patient baseline body weight ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR). An additional efficacy outcome measure was duration of response (DOR) by BICR.

[00340] The efficacy population included 81 patients with NSCLC with EGFR exon 20 insertion mutation with measurable disease who were previously treated with platinum based chemotherapy. The median age was 62 (range: 42 to 84) years, 59% were female; 49% were Asian, 37% were White, 2.5% were Black; 74% had baseline body weight <80 kg; 95% had adenocarcinoma; and 46% had received prior immunotherapy. The median number of prior therapies was 2 (range: 1 to 7). At baseline, 67% had Eastern Cooperative Oncology Group (ECOG) performance status of 1; 53% never smoked; all patients had metastatic disease; and 22% had previously treated brain metastases.

[00341] Efficacy results are summarized in Table 20.

Table 20: Efficacy Results for CHRYSALIS

	Prior Platinum-based Chemotherapy Treated (N=81)
Overall Response Rate (95% CI)	40% (29%, 51%)
Complete response (CR)	3.7%
Partial response (PR)	36%
Duration of Response (DOR)	
Median, months (95% CI), months	11.1 (6.9, NE)
Patients with DOR ≥6 months	63%

Based on Kaplan-Meier estimates.
NE=Not Estimable, CI=confidence interval.

[00342] 16. How Supplied/Storage and Handling

[00343] How Supplied: RYBREVANT® (amivantamab vmjw) injection is a sterile, preservative free, colorless to pale yellow solution for intravenous infusion. Each single dose vial contains 350 mg/7 mL (50 mg/mL) RYBREVANT. Each vial is individually packed in a single carton. (NDC 57894-501-01).

[00344] Storage and Handling: Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze.

[00345] **17. Patient Counseling Information**: Advise the patient to read the FDA-approved patient labeling (Patient Information).

[00346] Infusion-Related Reactions: Advise patients that RYBREVANT can cause infusion related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion related reactions [*see Warnings and Precautions (5.1)*].

[00347] Interstitial Lung Disease/Pneumonitis: Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms [*see Warnings and Precautions (5.2)*].

[00348] Dermatologic Adverse Reactions: Advise patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT [*see Warnings and Precautions (5.3)*]. Advise patients to apply alcohol free emollient cream to dry skin.

[00349] Ocular Toxicity: Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated [*see Warnings and Precautions (5.4)*].

[00350] Paronychia/Nail Toxicity: Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia [*see Adverse Reactions (6.1)*].

[00351] Embryo-Fetal Toxicity: Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT and for 3 months after the last dose, and to inform their healthcare provider of a known or suspected pregnancy. [*see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)*].

[00352] Lactation: Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the last dose [*see Use in Specific Populations (8.2)*].

Table 21: Patient Information

PATIENT INFORMATION RYBREVANT® (RYE–breh–vant) (amivantamab-vmjw) injection, for intravenous use
What is RYBREVANT? RYBREVANT is a prescription medicine used to treat adults: - in combination with carboplatin and pemetrexed as a first-line treatment for non-small cell lung cancer (NSCLC) that: - has spread to other parts of the body (metastatic) or cannot be removed by surgery, and - has a certain abnormal epidermal growth factor receptor “EGFR” gene(s) - alone for the treatment of non-small cell lung cancer (NSCLC) that: - has spread to other parts of the body (metastatic) or cannot be removed by surgery, and - has a certain abnormal EGFR gene(s), whose disease has worsened on or after platinum-based chemotherapy. Your healthcare provider will perform a test to make sure that RYBREVANT is right for you. It is not known if RYBREVANT is safe and effective in children.
Before you receive RYBREVANT, tell your healthcare provider about all of your medical conditions, including if you: - have a history of lung or breathing problems - are pregnant or plan to become pregnant. RYBREVANT can harm your unborn baby. Females who are able to become pregnant: - Your healthcare provider should do a pregnancy test before you start treatment with RYBREVANT. - You should use effective birth control (contraception) during treatment and for 3 months after your last dose of RYBREVANT. - Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with RYBREVANT. - are breastfeeding or plan to breastfeed. It is not known if RYBREVANT passes into your breast milk. Do not breastfeed during treatment and for 3 months after your last dose of RYBREVANT. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
How will I receive RYBREVANT? - RYBREVANT will be given to you by your healthcare provider by intravenous infusion into your vein. - Your healthcare provider will decide the time between doses as well as how many treatments you will receive. - Your healthcare provider will give you medicines before each dose of RYBREVANT to help reduce the risk of infusion-related reactions. - RYBREVANT may be given in combination with the medicines carboplatin and pemetrexed. If you have any questions about these medicines, ask your healthcare provider. - If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.
What should I avoid while receiving RYBREVANT? RYBREVANT can cause skin reactions. You should limit your time in the sun during and for 2 months after your treatment with RYBREVANT. Wear protective clothing and use sunscreen during treatment with RYBREVANT.
What are the possible side effects of RYBREVANT? RYBREVANT may cause serious side effects, including:

- **infusion-related reactions.** Infusion-related reactions are common with RYBREVANT and can be severe or serious. Tell your healthcare provider right away if you get any of the following symptoms during your infusion of RYBREVANT:
 - shortness of breath
 - fever
 - chills
 - nausea
 - flushing
 - chest discomfort
 - lightheadedness
 - vomiting
 - **lung problems.** RYBREVANT may cause lung problems that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you get any new or worsening lung symptoms, including shortness of breath, cough, or fever.
 - **skin problems.** RYBREVANT may cause rash, itching, and dry skin. You may use alcohol-free moisturizing cream for dry skin. Tell your healthcare provider right away if you get any skin reactions. Your healthcare provider may treat you with a medicine(s) or send you to see a skin specialist (dermatologist) if you get skin reactions during treatment with RYBREVANT. See “What should I avoid while receiving RYBREVANT?”
 - **eye problems.** RYBREVANT may cause eye problems. Tell your healthcare provider right away if you get symptoms of eye problems which may include:
 - eye pain
 - dry eyes
 - eye redness
 - blurred vision
 - changes in vision
 - itchy eyes
 - excessive tearing
 - sensitivity to light
- Your healthcare provider may send you to see an eye specialist (ophthalmologist) if you get eye problems during treatment with RYBREVANT. You should not use contact lenses until your eye symptoms are checked by a healthcare provider.

The most common side effects of RYBREVANT in combination with carboplatin and pemetrexed include:

- rash
- infected skin around the nail
- sores in the mouth
- infusion-related reactions
- feeling very tired
- swelling of hands, ankles, feet, face, or all of your body
- constipation
- decreased appetite
- nausea
- COVID-19
- diarrhea
- vomiting
- changes in certain blood tests

The most common side effects of RYBREVANT when given alone:

- rash
- infusion-related reactions
- infected skin around the nail
- muscle and joint pain
- shortness of breath
- nausea
- feeling very tired
- swelling of hands, ankles, feet, face, or all of your body
- sores in the mouth
- cough
- constipation
- vomiting
- changes in certain blood tests

Your healthcare provider may temporarily stop, decrease your dose or completely stop your treatment with RYBREVANT if you have serious side effects. These are not all of the possible side effects of RYBREVANT. Call your doctor for medical advice about side effects.
General information about safe and effective use of RYBREVANT Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about RYBREVANT that is written for health professionals.
What are the ingredients of RYBREVANT? Active ingredient: amivantamab-vmjw Inactive ingredients: EDTA disodium salt dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, sucrose, and water for injection.

* * *

[00353] 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.

[00354] 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 non-small cell lung cancer (NSCLC) having one or more epidermal growth factor receptor (EGFR) exon 20 insertion mutations who are treatment-naïve, the 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, and
 - (ii) chemotherapy,wherein the improvement in median PFS is relative to median PFS of a reference population of subjects with NSCLC having one or more EGFR exon 20 insertion mutations who are treatment-naïve, the reference population having been administered chemotherapy only.
2. A method of improving median overall survival (OS) in a population of subjects with non-small cell lung cancer (NSCLC) having one or more epidermal growth factor receptor (EGFR) exon 20 insertion mutations who are treatment-naïve, the 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, and
 - (ii) chemotherapy,wherein the improvement in median OS is relative to median OS of a reference population of subjects with NSCLC having one or more EGFR exon 20 insertion mutations who are treatment-naïve, the reference population having been administered chemotherapy only.
3. The method of claim 1 or claim 2, wherein the NSCLC is locally advanced or metastatic.
4. The method of claim 1 or claim 2, wherein the NSCLC is nonsquamous NSCLC.
5. The method of any one of claims 1-4, wherein the chemotherapy comprises administration of pemetrexed and carboplatin.

6. The method of claim 5, wherein pemetrexed is administered at a dose of 500 mg/m² on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression.
7. The method of claim 5, wherein carboplatin is administered at a dose to achieve area under the concentration-time curve 5 mg/mL per minute (AUC 5) on Day 1 of each 21-day cycle, for up to 4 cycles.
8. The method of any one of claims 1-7, wherein the method elicits a clinical response in the subject according to RECIST v1.1 criteria.
9. The method of any one of claims 1-7, wherein the method achieves a partial response or better in the subject according to RECIST v1.1 criteria.
10. The method of any one of claims 1-8, wherein the clinical response comprises a median duration of response (DOR) of at least 9 months.
11. The method of any one of claims 1-10, wherein the subject is progression-free after at least 11 months.
12. The method of any one of claims 1-11, 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.
13. The method of claim 12, wherein 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.
14. The method of claim 12 or 13, wherein the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

15. The method of any one of claims 1-14, wherein 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.
16. The method of any one of claims 1-15, wherein the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content of about between 1% to about 15%.
17. The method of any one of claims 1-16, wherein the bispecific anti-EGFR/c-Met antibody is administered intravenously to the subject.
18. The method of claim 17, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of between about 350 mg to about 2100 mg.
19. The method of claim 18, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 350 mg, 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, or 2100 mg.
20. The method of claim 19, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1400 mg if the subject has a body weight of less than 80 kg.
21. The method of claim 19, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1750 mg if the subject has a body weight of less than 80 kg.
22. The method of claim 19, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1750 mg if the subject has a body weight of greater than or equal to 80 kg.
23. The method of claim 19, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of 2100 mg if the subject has a body weight of greater than or equal to 80 kg.
24. The method of claim 19, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of 1,400 mg (1,750 mg if body weight is ≥ 80 kg) once weekly up to Cycle 2 Day 1, then 1,750 mg (2,100 mg if body weight is ≥ 80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3.
25. The method of any one of claims 1-24, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously or intradermally to the subject.

26. The method of claim 25, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously or intradermally at a dose sufficient to achieve a therapeutic effect in the subject.
27. The method of any one of claims 1-26, wherein 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.
28. The method of any one of claims 1-26, wherein the bispecific anti-EGFR/c-Met antibody is administered once per 21 day cycle.