Use of Bispecific anti-EGFR/c-Met Antibodies to Treat Solid Tumors

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/563,567, filed on 11 March 2024 which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing, which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on March 10, 2025, is named JBI6892WOPCT1_SL.xml, and is 37,799 bytes in size.

FIELD OF THE INVENTION

[0003] The present invention relates to methods of treating an epidermal growth factor receptor (EGFR)-expressing or hepatocyte growth factor receptor (c-Met)-expressing cancer in a subject in need thereof. The methods comprise administering to the subject a therapy comprising an isolated bispecific anti-EGFR/c-Met antibody, wherein the administration comprises a dose administered once per a 28-day cycle.

BACKGROUND

[0004] Amivantamab, a low fucose, fully human IgG1-based bispecific antibody directed against the EGF and cMet receptors, shows activity against tumors with either the primary activating or second-site resistance EGFR mutations, overexpressed wild type EGFR, and activation of the cMet pathway. By inhibiting EGFR and cMet signaling functions, amivantamab may disrupt these signaling pathways, thereby preventing tumor growth and progression. Furthermore, the presence of high levels of EGFR and cMet on the surface of tumor cells allows for targeting of these cells for destruction by immune effector cells, through antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) mechanisms.

[0005] Amivantamab administration can cause frequent infusion-related reactions (IRRs) in a proportion of patients (67% of patients, according to Minchom A, et al. Presented at American Society of Clinical Oncology (ASCO) 2023; June 2–6, 2023; Chicago, IL, USA). Signs and symptoms of IRR include but are not limited to dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting. Systemic IRRs, including severe reactions, upon the introduction of a new protein therapeutic infusion are frequently observed but the mechanisms inducing the reactions are varied.

[0006] There is a need for improved treatment regimens that are both efficacious and would reduce the infusion-related reactions (IRRs) in patients treated with EGFR/c-Met bispecific antibodies, such as amivantamab.

SUMMARY

[0007] The disclosure generally relates to methods that are useful for treating an epidermal growth factor receptor (EGFR)-expressing or hepatocyte growth factor receptor (c-Met)-expressing cancer in a subject in need thereof, comprising administering to the subject an isolated bispecific anti-EGFR/c-Met antibody comprising a first domain binding EGFR and a second domain binding 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 a HCDR1 of SEQ ID NO: 7, a HCDR2 of SEQ ID NO: 8, a HCDR3 of SEQ ID NO: 9, a LCDR1 of SEQ ID NO: 10, a LCDR2 of SEQ ID NO: 11, and a LCDR3 of SEQ ID NO: 12, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose from about 3520 mg to about 4640 mg.

[0008] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 3520 mg.

[0009] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 4640 mg.

[0010] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 3520 mg if the subject weighs less than 80 kg, and at a dose of about 4640 mg if the subject weighs 80 kg or more.

[0011] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered once per a 28-day cycle.

[0012] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.

[0013] In some embodiments, the bispecific anti-EGFR/c-Met antibody is co-formulated with hyaluronidase.

[0014] In some embodiments, the method further comprises an initial cycle (Cycle 1) comprising administering the bispecific antibody once a week for four weeks at a dose of about 1600 mg if the subject weighs less than 80 kg, or at a dose of about 2240 mg if the subject weighs 80 kg or more.

[0015] In some embodiments, the first domain that 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 binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.

[0016] In some embodiments, the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

[0017] 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.

[0018] In some embodiments, the bispecific anti-EGFR/c-Met antibody has a biantennary glycan structure with a fucose content of between about 1% to about 15%.

[0019] In some embodiments, the EGFR or c-Met expressing cancer is a solid tumor. In some embodiments, the EGFR or c-Met expressing cancer is non-small cell lung cancer (NSCLC).

[0020] In another aspect, the disclosure generally relates to methods of subcutaneous administration of an isolated bispecific anti-EGFR/c-Met antibody comprising a first domain binding EGFR and a second domain binding c-Met to a subject having EGFR or c-Met expressing cancer, 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 a HCDR1 of SEQ ID NO: 7, a HCDR2 of SEQ ID NO: 8, a HCDR3 of SEQ ID NO: 9, a LCDR1 of SEQ ID NO: 10, a LCDR2 of SEQ ID NO: 11, and a LCDR3 of SEQ ID NO: 12, wherein the bispecific anti-EGFR/c-Met antibody is administered so as to produce a Cycle 2 C_{trough} value of about 325 µg/mL and/or $AUC_{0\text{-}672h}$ value of about 286612 µg•h/mL.

[0021] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 3520 mg.

[0022] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 4640 mg.

[0023] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 3520 mg if the subject weighs less than 80 kg, and at a dose of about 4640 mg if the subject weighs 80 kg or more.

[0024] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered once per a 28-day cycle.

[0025] In some embodiments, the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.

[0026] In some embodiments, the bispecific anti-EGFR/c-Met antibody is co-formulated with hyaluronidase.

[0027] In some embodiments, the method further comprises an initial cycle (Cycle 1) comprising administering the bispecific antibody once a week for four weeks at a dose of about 1600 mg if the subject weighs less than 80 kg, or at a dose of about 2240 mg if the subject weighs 80 kg or more.

[0028] In some embodiments, the first domain that 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 binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.

[0029] In some embodiments, the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

[0030] 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.

[0031] In some embodiments, the bispecific anti-EGFR/c-Met antibody has a biantennary glycan structure with a fucose content of between about 1% to about 15% or less than 20%.

[0032] In some embodiments, the EGFR or c-Met expressing cancer is a solid tumor.

[0033] In some embodiments, the EGFR or c-Met expressing cancer is non-small cell lung-cancer (NSCLC).

[0034] In some embodiments, infusion related reactions (IRRs) occur less frequently in a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

[0035] In some embodiments, infusion related reactions (IRRs) are less severe in a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

[0036] In some embodiments, infusion related reactions (IRRs) occur less frequently in a population of subjects that is subcutaneously administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is intravenously administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

[0037] In some embodiments, infusion related reactions (IRRs) are less severe in a population of subjects that is subcutaneously administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is intravenously administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W)

[0038]

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] **FIG. 1** shows incidence of IRRs and IRR-related symptoms in subjects that received SC Ami Q4W (once every 4 weeks) versus subjects that received IV Ami Q2W (once every 2 weeks). Ami, amivantamab; h, hours; IRR, infusion-related reaction; IV, intravenous; min, minutes; SC, subcutaneous.

DETAILED DESCRIPTION

Definitions

[0040] 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.

[0041] 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.

[0042] 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.

[0043] 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."

[0044] 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.

[0045] 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."

[0046] 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."

[0047] "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.

[0048] The term "antibody" or "antibodies" is meant in a broad sense and includes immunoglobulin molecules including monoclonal antibodies including murine, human, humanized and chimeric monoclonal antibodies, full-length 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.

[0049] "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 $5x10^{-8}$ M or less, for example about $1x10^{-9}$ M or less, about $1x10^{-10}$ M or less, about $1x10^{-11}$ M or less, or about $1x10^{-12}$ 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.

[0050] "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 Bmol 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://www_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.

[0051] "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.

[0052] "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.

[0053] "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.

[0054] "Humanized antibodies" refers to antibodies in which the antigen binding sites are derived from non-human species and the variable region frameworks are derived from human immunoglobulin sequences. Humanized antibodies may include intentionally introduced mutations in the framework regions so that the framework may not be an exact copy of expressed human immunoglobulin or germline gene sequences.

[0055] "Human antibodies" refers to antibodies having heavy and light chain variable regions in which both the framework and the antigen binding site are derived from sequences of human origin. If the antibody contains a constant region or a portion of the constant region, the constant region is also derived from sequences of human origin. Antibodies in which antigen binding sites are derived from a non-human species are not included in the definition of "human antibody."

[0056] A human antibody comprises heavy or light chain variable regions that are derived from sequences of human origin if the variable regions of the antibody are obtained from a system that uses human germline immunoglobulin or rearranged immunoglobulin genes. Non-limiting example systems include human immunoglobulin gene libraries displayed on phage, and transgenic non-human animals such as mice or rats carrying human immunoglobulin loci. A human antibody typically contains amino acid differences when compared to the human germline or rearranged immunoglobulin sequences due to, for example, naturally occurring somatic mutations, intentional substitutions in the framework or antigen binding site, and substitutions introduced during cloning or VDJ recombination in non-human animals. Typically, a human antibody is at least 80% identical in amino acid sequence to an amino acid sequence encoded by a human germline or rearranged immunoglobulin gene. For example, about: 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical. In some cases, a human antibody may contain consensus framework sequences derived from human framework sequence analyses (*see*, *e.g.*, Knappik *et al*., J. Mol. Biol. 296:57-86 (2000)), or synthetic HCDR3 incorporated into human immune-globulin gene libraries displayed on phage (*see*, *e.g.*, Shi *et al*., J. Mol. Biol. 397:385-96 (2010) and Int. Pat. Publ. No. WO2009/085462).

[0057] "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.

[0058] "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.

[0059] "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.

[0060] 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.

[0061] "Low fucose" or "low fucose content" as used in the application refers to antibodies with fucose content of about between 1%-15% or less than 20%.

[0062] "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%.

[0063] "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.

[0064] "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.

[0065] "Dosage" refers to the information of the amount of the therapeutic or the drug to be taken by the subject and the frequency of the number of times the therapeutic is to be taken by the subject. "Dose" refers to the amount or quantity of the therapeutic or the drug to be taken each time.

[0066] "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.

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

[0068] "Fixed combination" refers to a single pharmaceutical composition comprising two or more compounds.

[0069] "Non-fixed combination" refers to separate pharmaceutical compositions, wherein each comprises one or more compounds. The one or more compounds or unit dosage forms can be administered as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the subject.

[0070] "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.

[0071] "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.

[0072] "Prevent", "preventing", "prevention", or "prophylaxis" of a disease or disorder means preventing that a disorder occurs in subject.

[0073] "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.

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

[0075] "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.

[0076] "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, next generation sequencing, fluorescent *in situ* hybridization, immunohistochemistry, flow cytometry or western blotting.

[0077] "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.

[0078] "Hepatocyte growth factor receptor" or "c-Met" or "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.

[0079] "Newly diagnosed" refers to a subject who has been diagnosed with a cancer, such as a solid tumor, but has not yet received treatment for cancer.

[0080] "Metastatic" refers to a cancer wherein cancer cells separate from the original tumor, enter the bloodstream or lymph system and spread to other areas of the body.

[0081] "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.

[0082] "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.

[0083] "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.

[0084] "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.

[0085] "C_{max}" refers to maximum observed serum concentration

[0086] "C_{trough}" refers to observed serum concentration immediately prior to the next drug administration.

[0087] "$AUC_{(0-t)}$" refers to area under the plasma/serum concentration time curve from time zero to time t.

[0088] "Hyaluronidase" refers to a class of enzymes that degrade hyaluronan. Hyaluronidases are endoglycosidases used to increase the dispersion and absorption of other co-administered drugs when

administered subcutaneously (*e.g.*, subcutaneous injections, subcutaneous infusion such as hypodermoclysis). Hyaluronidases include, but are not limited to, bacterial hyaluronidases (EC 4.2.2.1 or EC 4.2.99.1), hyaluronidases from leeches, other parasites and crustaceans (EC 3.2.1.36), and mammalian-type hyaluronidases (EC 3.2.1.35). Hyaluronidase (recombinant human) has a molecular weight of approximately 61 kDa. Hyaluronidases include those of non-human origin including, but not limited to, murine, canine, feline, leporine, avian, bovine, ovine, porcine, equine, piscine, ranine, bacterial, and any from leeches, other parasites, and crustaceans. Exemplary human hyaluronidases include HYAL1, HYAL2, HYAL3, HYAL4, and PH20. Also included amongst hyaluronidases are soluble hyaluronidases, including, ovine and bovine PH20, and soluble forms of PH20. Exemplary hyaluronidases include those set forth in U.S. Pub. No. 2013/0302275, which is incorporated by reference herein, including, for example, hyaluronidases set forth as SEQ ID NOs: 6, 7-31, 69, 70, 71, 72, 856-861, 869-921 from U.S. Pub. No. 2013/0302275 (which are incorporated herein by reference), mature forms thereof (lacking the signal sequence), allelic variants thereof, and truncated forms thereof that exhibit hyaluronidase activity, including C-terminal truncated variants that are soluble.

[0089] As used herein, PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active.

[0090] Soluble PH20 refers to a polypeptide characterized by its solubility under physiological conditions. Generally, a soluble PH20 lacks all or a portion of a glycophosphatidyl anchor (GPI) attachment sequence, or does not otherwise sufficiently anchor to the cell membrane. For example, a soluble PH20 can be a C-terminally truncated variant of a PH20 lacking a contiguous sequence of amino acids that corresponds to all or a portion of a GPI anchor attachment sequence. Hence, upon expression from a cell, a soluble PH20 is secreted into the medium.

[0091] Soluble human PH20 (sHuPH20) includes human PH20 polypeptides that lack a contiguous sequence of amino acids from the C-terminus of human PH20 that includes all or a portion of the GPI anchor sequence (C-terminally truncated PH20 polypeptides) such that upon expression, the polypeptides are soluble under physiological conditions. For example, soluble human PH20 polypeptides are C-terminally truncated polypeptides of human PH20 in its precursor form or in its mature form lacking the signal sequence, or allelic variants thereof as set forth in SEQ ID NOs: 36-42 herein and as disclosed in U.S. Pub. No. 20130302275 as SEQ ID NOs: 6, 7, and 68-72 of that reference which are incorporated herein by reference.

[0092] U.S. Pub. No. 2004/0268425, which is incorporated by reference herein, describes members of the soluble, neutral active Hyaluronidase Glycoprotein family, particularly the human soluble PH-20 Hyaluronidase Glycoproteins (also referred to as sHASEGPs). U.S. Pub. No. 20100143457, which is incorporated herein by reference, describes shorter active soluble PH20 (*i.e.*, 36-469, -470, 471, and longer forms *i.e.*, 36-495 to 36-500) the sequences of which are also incorporated herein by reference.

[0093] Hyaluronidase activity refers to the ability to enzymatically catalyze the cleavage of hyaluronic acid. The United States Pharmacopeia (USP) XXII assay for hyaluronidase determines hyaluronidase activity indirectly by measuring the amount of higher molecular weight hyaluronic acid, or hyaluronan, (HA) substrate remaining after the enzyme is allowed to react with the HA for 30 min at 37 °C (USP XXII-NF XVII (1990) 644-645 United States Pharmacopeia Convention, Inc, Rockville, MD). A Reference Standard solution can be used in an assay to ascertain the relative activity, in units, of any hyaluronidase. In vitro assays to determine the hyaluronidase activity of hyaluronidases, such as PH20, including modified PH20 polypeptides, are known in the art and described herein. Exemplary assays include the microturbidity assay that measures cleavage of hyaluronic acid by hyaluronidase indirectly by detecting the insoluble precipitate formed when the uncleaved hyaluronic acid binds with serum albumin. Reference Standards can be used, for example, to generate a standard curve to determine the activity in Units of the hyaluronidase being tested.

[0094] Specific activity refers to Units of activity per mg protein. The milligrams of hyaluronidase is defined by the absorption of a solution of at 280 nm assuming a molar extinction coefficient of approximately 1.7, in units of M-1 cm-1.

[0095] Neutral active refers to the ability of a PH20 polypeptide to enzymatically catalyze the cleavage of hyaluronic acid at neutral pH, such as at a pH between or about between pH 6.0 to pH 7.8.

[0096] Human recombinant DNA-derived hyaluronidase enzyme PH20 (rHuPH20) is a glycosylated single-chain protein produced by CHO cells containing a DNA plasmid encoding residues 36-482 of SEQ ID NO: 36, resulting in a heterogeneous mixture of soluble forms of human hyaluronidase (PH20) that begin at residue 36 and terminate at residues 478, 479, 480, 481, and 482 of SEQ ID NO: 36, including any one of SEQ ID NOs: 31, 35, 34, 33 and 32.

[0097] "Variant" refers to a polypeptide or a polynucleotide that differs from a reference polypeptide or a reference polynucleotide by one or more modifications for example, substitutions, insertions, or deletions.

Methods of the Disclosure

[0098] It is well-known in the art that drug development is an unpredictable field. The lack of predictability in the art is evidenced, for example, by health authority requirements (such as those of the Food and Drug Administration) to establish a safe and effective dosing regimen for each individual drug candidate in clinical trials. Over the last decade (2011-2020), only 7.9% of all developmental drug candidates achieved FDA approval from a Phase I clinical study. See Clinical Development Success Rates and Contributing Factors 2011-2020. The rate of success is even lower in oncology, such that only 5.3% of oncology drug candidates succeed.

[0099] In the field of oncology, even for a drug that already has an established dose in a particular indication, the Food and Drug Administration (FDA) recommends further clinical studies to

identify an optimal dose for a new indication; otherwise, patients may be exposed to unreasonable and significant risk, among other potential deficiencies. See, e.g., Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases; Draft Guidance for Industry; January 2023).

[0100] Non-small cell lung cancer, and other EGFR or c-Met expressing cancers, remain an unmet medical need with significant morbidity and mortality. The present inventors have developed novel dosing regimens for an EGFR-MET bispecific antibody that provide improved safety profiles over currently approved regimens while achieving comparable exposure.

[0101] Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity that has been FDA-approved as an intravenous (IV) formulation. The EGFR/c-Met bispecific antibody administered parenterally can cause an adverse reaction or adverse event (AE) in a patient or subject, specifically an infusion-related reaction (IRR). As reported in the United States Prescribing Information for RYBREVANT (amivantamab) (www.janssenlabels.com/package-insert/product-monograph/prescribing-information/RYBREVANT-pi.pdf), among 302 patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who received IV amivantamab at recommended Phase 2 dose (RP2D) as a single agent in the CHRYSALIS study, IRRs were among the most commonly occurring adverse reactions with an incidence of 66%.

[0102] An adverse reaction or adverse event (AE) is any untoward medical occurrence in a patient or a subject to whom EGFR/c-Met bispecific antibody is being administered or was administered. In some embodiments, the AE is an IRR. In some embodiments, the IRRs are mild IRR, manifesting as, but not limited to, chills, nausea, dyspnea, flushing, chest discomfort, hypotension, vomiting, tachycardia, fever, or any other symptoms during the time of the infusion or after the infusion. In some embodiments, the IRRs are systemic IRRs, including severe reactions, upon the introduction of a new protein therapeutic infusion, such as EGFR/c-Met bispecific antibody. In some embodiments, the EGFR/c-Met bispecific antibody is amivantamab. In some embodiments, the severity of IRRs is graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Severity scale ranges from Grade 1 (Mild) to Grade 5 (Death). Grade 1= Mild, Grade 2= Moderate, Grade 3= Severe, Grade 4= Life-threatening and Grade 5= Death related to adverse event. In some embodiments, the presence of IRRs in a patient or subject is evaluated at any time starting at Cycle 1 Day 1 and ending 30 days after end of treatment with the EGFR/c-Met bispecific antibody. In some embodiments, the presence of IRRs in a patient or subject is evaluated at Cycle 1 Day 1 of treatment with the EGFR/c-Met bispecific antibody. In some embodiments, the presence of IRRs in a patient or subject is evaluated at a time up to 3 month after the start of treatment with the EGFR/c-Met bispecific antibody. In some embodiments, the presence of IRRs in a patient or subject is evaluated at any time between 1 day to 30 days after end of treatment with the EGFR/c-Met bispecific antibody. In some embodiments, the presence of IRRs in a patient or

subject is evaluated at any time between 1 day to 5 days after end of treatment with the EGFR/c-Met bispecific antibody. In some embodiments, the presence of IRRs in a patient or subject is evaluated at any time between 1 day to 10 days after end of treatment with the EGFR/c-Met bispecific antibody. In some embodiments, the presence of IRRs in a patient or subject is evaluated at any time between 1 day to 15 days after end of treatment with the EGFR/c-Met bispecific antibody. In some embodiments, the presence of IRRs in a patient or subject is evaluated at any time between 1 day to 20 days after end of treatment with the EGFR/c-Met bispecific antibody.

[0103] In one aspect, the disclosure provides a method of treating an epidermal growth factor receptor (EGFR)-expressing or hepatocyte growth factor receptor (c-Met)-expressing cancer (e.g., NSCLC) in a subject in need thereof, comprising administering to the subject an isolated bispecific anti-EGFR/c-Met antibody comprising a first domain binding EGFR and a second domain binding c-Met.

Anti-EGFR/c-Met Antibodies

[0104] In some embodiments, the anti-EGFR/c-Met antibody is a bispecific antibody. In certain embodiments, the antibody is an isolated antibody. In particular embodiments, the antibody is an isolated bispecific antibody.

[0105] In some embodiments, the antibody (*e.g.*, bispecific antibody) comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met.

EGFR Binding Arm

[0106] In some embodiments, the first domain that specifically binds EGFR comprises:

a) heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3 amino acid sequences of SEQ ID NOs:1, 2 and 3, respectively; and/or

b) light chain complementarity determining region 1 (LCDR1), LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs:4, 5 and 6, respectively.

[0107] In some embodiments, the first domain that specifically binds EGFR comprises:

a) HCDR1, HCDR2, HCDR3 amino acid sequences of SEQ ID NOs:1, 2 and 3, respectively; and

b) LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs:4, 5 and 6, respectively.

[0108] HCDR1: TYGMH (SEQ ID NO:1)

[0109] HCDR2: VIWDDGSYKYYGDSVKG (SEQ ID NO:2)

[0110] HCDR3: DGITMVRGVMKDYFDY (SEQ ID NO:3)

[0111] HCDR1: RASQDISSALV (SEQ ID NO:4)

[0112] HCDR2: DASSLES (SEQ ID NO:5)

[0113] HCDR3: QQFNSYPLT (SEQ ID NO:6)

[0114] In some embodiments, the first domain comprises a heavy chain variable region (VH) amino acid sequence that is at least 90% identical to SEQ ID NO:13, *e.g.*, about: 91%, 92%, 93%,

94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% identical to SEQ ID NO:13. In some embodiments, the sequence identity is about: 90-99.9%, 90-99.8%, 92-99.8%, 92-99.6%, 94-99.6%, 94-99.5%, 95-99.5%, 95-99.4%, 96-99.4%, 96-99.2%, 97-99.2% or 97-99%. In particular embodiments, the first domain comprises a VH of SEQ ID NO:13.

[0115] In certain embodiments, the first domain comprises a light chain variable region (VL) amino acid sequence that is at least 90% identical to SEQ ID NO:14, *e.g.*, about: 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% identical to SEQ ID NO:14. In some embodiments, the sequence identity is about: 90-99.9%, 90-99.8%, 92-99.8%, 92-99.6%, 94-99.6%, 94-99.5%, 95-99.5%, 95-99.4%, 96-99.4%, 96-99.2%, 97-99.2% or 97-99%. In particular embodiments, the first domain comprises a VL of SEQ ID NO:14.

[0116] As used herein, the term "identical" or "has sequence identity," refers to the extent to which two amino acid sequences have the same residues at the same positions when the sequences are aligned to achieve a maximal level of identity, expressed as a percentage. For sequence alignment and comparison, typically one sequence is designated as a reference sequence, to which a test sequences are compared. The sequence identity between reference and test sequences is expressed as the percentage of positions across the entire length of the reference sequence where the reference and test sequences share the same amino acid upon alignment of the reference and test sequences to achieve a maximal level of identity. As an example, two sequences are considered to have 70% sequence identity when, upon alignment to achieve a maximal level of identity, the test sequence has the same amino acid residue at 70% of the same positions over the entire length of the reference sequence.

[0117] In some embodiments, the first domain comprises:

a) a VH amino acid sequence that is at least 90% identical to SEQ ID NO:13; and/or

b) a VL amino acid sequence that is at least 90% identical to SEQ ID NO:14.

[0118] In some embodiments, the first domain comprises:

a) a VH amino acid sequence that is at least 90% identical to SEQ ID NO:13; and

b) a VL amino acid sequence that is at least 90% identical to SEQ ID NO:14.

[0119] In some embodiments, the first domain comprises:

a) a VH of SEQ ID NO:13; and/or

b) a VL of SEQ ID NO:14.

[0120] In particular embodiments, the first domain comprises:

a) a VH of SEQ ID NO:13; and

b) a VL of SEQ ID NO:14.

[0121] VH: QVQLVESGGGVVQPGRSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVAV IWDDGSYKYYGDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDGITMVRGVMKD YFDYWGQGTLVTVSS (SEQ ID NO:13)

[0122] VL: AIQLTQSPSSLSASVGDRVTITCRASQDISSALVWYQQKPGKAPKLLIYDASS LESGVPSRFSGSESGTDFTLTISSLQPEDFATYYCQQFNSYPLTFGGGTKVEIK (SEQ ID NO:14)

[0123] In some embodiments, the first domain comprises a first heavy chain (HC1) amino acid sequence that is at least 80% identical to SEQ ID NO:17, *e.g.*, about: 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% identical to SEQ ID NO:17. In certain embodiments, the sequence identity is about: 80-99.9%, 80-99.8%, 85-99.8%, 85-99.6%, 90-99.6%, 90-99.5%, 95-99.5%, 95-99.4%, 96-99.4%, 96-99.2%, 97-99.2% or 97-99%. In particular embodiments, the first domain comprises a HC1 amino acid sequence of SEQ ID NO:17.

[0124] In some embodiments, the first domain comprises a first light chain (LC1) amino acid sequence that is at least 80% identical to SEQ ID NO:18, *e.g.*, about: 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% identical to SEQ ID NO:18. In certain embodiments, the sequence identity is about: 80-99.9%, 80-99.8%, 85-99.8%, 85-99.6%, 90-99.6%, 90-99.5%, 95-99.5%, 95-99.4%, 96-99.4%, 96-99.2%, 97-99.2% or 97-99%. In particular embodiments, the first domain comprises a LC1 amino acid sequence of SEQ ID NO:18.

[0125] In some embodiments, the first domain comprises:

a) a HC1 amino acid sequence that is at least 80% identical to SEQ ID NO:17; and/or

b) a LC1 amino acid sequence that is at least 80% identical to SEQ ID NO:18.

[0126] In some embodiments, the first domain comprises:

a) a HC1 amino acid sequence that is at least 80% identical to SEQ ID NO:17; and

b) a LC1 amino acid sequence that is at least 80% identical to SEQ ID NO:18.

[0127] In some embodiments, the first domain comprises:

a) a HC1 of SEQ ID NO:17; and/or

b) a LC1 of SEQ ID NO:18.

[0128] In some embodiments, the first domain comprises:

a) a HC1 of SEQ ID NO:17; and

b) a LC1 of SEQ ID NO:18.

[0129] HC1: QVQLVESGGGVVQPGRSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVA VIWDDGSYKYYGDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDGITMVRGVMK DYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFLLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:17)

[0130] LC1: AIQLTQSPSSLSASVGDRVTITCRASQDISSALVWYQQKPGKAPKLLIYDASS LESGVPSRFSGSESGTDFTLTISSLQPEDFATYYCQQFNSYPLTFGGGTKVEIKRTVAAPSVFIF

PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 18)

c-Met (MET) binding arm

[0131] In certain embodiments, the second domain that specifically binds c-Met comprises:

a) HCDR1, HCDR2, HCDR3 amino acid sequences of SEQ ID NOs:7, 8 and 9, respectively; and/or

b) LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs:10, 11 and 12, respectively.

[0132] In certain embodiments, the second domain that specifically binds c-Met comprises:

a) HCDR1, HCDR2, HCDR3 amino acid sequences of SEQ ID NOs:7, 8 and 9, respectively; and

b) LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs:10, 11 and 12, respectively.

[0133] HCDR1: SYGIS (SEQ ID NO:7)

[0134] HCDR2: WISAYNGYTNYAQKLQG (SEQ ID NO:8)

[0135] HCDR3: DLRGTNYFDY (SEQ ID NO:9)

[0136] HCDR1: RASQGISNWLA (SEQ ID NO:10)

[0137] HCDR2: AASSLLS (SEQ ID NO:11)

[0138] HCDR3: QQANSFPIT (SEQ ID NO:12)

[0139] In some embodiments, the second domain comprises a VH amino acid sequence that is at least 90% identical to SEQ ID NO:15, *e.g.*, about: 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% identical to SEQ ID NO:15. In some embodiments, the sequence identity is about: 90-99.9%, 90-99.8%, 92-99.8%, 92-99.6%, 94-99.6%, 94-99.5%, 95-99.5%, 95-99.4%, 96-99.4%, 96-99.2%, 97-99.2% or 97-99%. In particular embodiments, the second domain comprises a VH of SEQ ID NO:15

[0140] In certain embodiments, the second domain comprises a VL amino acid sequence that is at least 90% identical to SEQ ID NO:16, *e.g.*, about: 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% identical to SEQ ID NO:16. In some embodiments, the sequence identity is about: 90-99.9%, 90-99.8%, 92-99.8%, 92-99.6%, 94-99.6%, 94-99.5%, 95-99.5%, 95-99.4%, 96-99.4%, 96-99.2%, 97-99.2% or 97-99%. In particular embodiments, the second domain comprises a VL of SEQ ID NO:16.

[0141] In some embodiments, the second domain comprises:

a) a VH amino acid sequence that is at least 90% identical to SEQ ID NO:15; and/or

b) a VL amino acid sequence that is at least 90% identical to SEQ ID NO:16.

[0142] In some embodiments, the second domain comprises:

a) a VH amino acid sequence that is at least 90% identical to SEQ ID NO:15; and

b) a VL amino acid sequence that is at least 90% identical to SEQ ID NO:16.

[0143] In some embodiments, the second domain comprises:

a) a VH of SEQ ID NO:15; and/or

b) a VL of SEQ ID NO:16.

[0144] In particular embodiments, the second domain comprises:

a) a VH of SEQ ID NO:15; and

b) a VL of SEQ ID NO:16.

[0145] VH: QVQLVQSGAEVKKPGASVKVSCETSGYTFTSYGISWVRQAPGHGLEWMGW ISAYNGYTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDLRGTNYFDYWG QGTLVTVSS (SEQ ID NO:15)

[0146] VL: DIQMTQSPSSVSASVGDRVTITCRASQGISNWLAWFQHKPGKAPKLLIYAAS SLLSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPITFGQGTRLEIK (SEQ ID NO:16)

[0147] In some embodiments, the second domain comprises a second heavy chain (HC2) amino acid sequence that is at least 80% identical to SEQ ID NO:19, *e.g.*, about: 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% identical to SEQ ID NO:19. In certain embodiments, the sequence identity is about: 80-99.9%, 80-99.8%, 85-99.8%, 85-99.6%, 90-99.6%, 90-99.5%, 95-99.5%, 95-99.4%, 96-99.4%, 96-99.2%, 97-99.2% or 97-99%. In particular embodiments, the second domain comprises a HC2 amino acid sequence of SEQ ID NO:19.

[0148] In some embodiments, the second domain comprises a second light chain (LC2) amino acid sequence that is at least 80% identical to SEQ ID NO:20, *e.g.*, about: 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% identical to SEQ ID NO:20. In certain embodiments, the sequence identity is about: 80-99.9%, 80-99.8%, 85-99.8%, 85-99.6%, 90-99.6%, 90-99.5%, 95-99.5%, 95-99.4%, 96-99.4%, 96-99.2%, 97-99.2% or 97-99%. In particular embodiments, the second domain comprises a LC2 amino acid sequence of SEQ ID NO:20.

[0149] In some embodiments, the second domain comprises:

a) a HC2 amino acid sequence that is at least 80% identical to SEQ ID NO:19; and/or

b) a LC2 amino acid sequence that is at least 80% identical to SEQ ID NO:20.

[0150] In some embodiments, the second domain comprises:

a) a HC2 amino acid sequence that is at least 80% identical to SEQ ID NO:19; and

b) a LC2 amino acid sequence that is at least 80% identical to SEQ ID NO:20.

[0151] In some embodiments, the second domain comprises:

a) a HC2 of SEQ ID NO:19; and/or

b) a LC2 of SEQ ID NO:20.

[0152] In some embodiments, the second domain comprises:

a) a HC2 of SEQ ID NO:19; and

b) a LC2 of SEQ ID NO:20.

[0153] HC2: QVQLVQSGAEVKKPGASVKVSCETSGYTFTSYGISWVRQAPGHGLEWMG WISAYNGYTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDLRGTNYFDYW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:19)

[0154] LC2: DIQMTQSPSSVSASVGDRVTITCRASQGISNWLAWFQHKPGKAPKLLIYAAS SLLSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPITFGQGTRLEIKRTVAAPSVFIF PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 20)

[0155] In some embodiments, the antibody (*e.g.*, bispecific antibody) comprises:

a) a first domain that specifically binds EGFR, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs:1, 2, 3, 4, 5 and 6, respectively; and/or

b) a second domain that specifically binds c-Met, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs:7, 8, 9, 10, 11 and 12, respectively.

[0156] In certain embodiments, the antibody (*e.g.*, bispecific antibody) comprises:

a) a first domain that specifically binds EGFR, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs:1, 2, 3, 4, 5 and 6, respectively; and

b) a second domain that specifically binds c-Met, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs:7, 8, 9, 10, 11 and 12, respectively.

[0157] In some embodiments, the antibody (*e.g.*, bispecific antibody) comprises:

a) a first domain comprising a VH amino acid sequence that is at least 90% identical to SEQ ID NO:13;

b) a first domain comprising a VL amino acid sequence that is at least 90% identical to SEQ ID NO:14;

c) a second domain comprising a VH amino acid sequence that is at least 90% identical to SEQ ID NO:15; and/or

d) a second domain comprising a VL amino acid sequence that is at least 90% identical to SEQ ID NO:16.

[0158] In certain embodiments, the antibody (*e.g.*, bispecific antibody) comprises:

a) a first domain comprising a VH amino acid sequence that is at least 90% identical to SEQ ID NO:13;

b) a first domain comprising a VL amino acid sequence that is at least 90% identical to SEQ ID NO:14;

c) a second domain comprising a VH amino acid sequence that is at least 90% identical to SEQ ID NO:15; and

d) a second domain comprising a VL amino acid sequence that is at least 90% identical to SEQ ID NO:16.

[0159] In some embodiments, the antibody (*e.g.*, bispecific antibody) comprises:

a) a first domain comprising a VH of SEQ ID NO:13;

b) a first domain comprising a VL of SEQ ID NO:14;

c) a second domain comprising a VH of SEQ ID NO:15; and/or

d) a second domain comprising a VL of SEQ ID NO:16.

[0160] In some embodiments, the antibody (*e.g.*, bispecific antibody) comprises:

a) a first domain comprising a VH of SEQ ID NO:13;

b) a first domain comprising a VL of SEQ ID NO:14;

c) a second domain comprising a VH of SEQ ID NO:15; and

d) a second domain comprising a VL of SEQ ID NO:16.

[0161] In certain embodiments, the antibody (*e.g.*, bispecific antibody) comprises:

a) a HC1 amino acid sequence that is at least 80% identical to SEQ ID NO:17;

b) a LC1 amino acid sequence that is at least 80% identical to SEQ ID NO:18;

c) a HC2 amino acid sequence that is at least 80% identical to SEQ ID NO:19; and/or

d) a LC2 amino acid sequence that is at least 80% identical to SEQ ID NO:20.

[0162] In certain embodiments, the antibody (*e.g.*, bispecific antibody) comprises:

a) a HC1 amino acid sequence that is at least 80% identical to SEQ ID NO:17;

b) a LC1 amino acid sequence that is at least 80% identical to SEQ ID NO:18;

c) a HC2 amino acid sequence that is at least 80% identical to SEQ ID NO:19; and

d) a LC2 amino acid sequence that is at least 80% identical to SEQ ID NO:20.

[0163] In certain embodiments, the antibody (*e.g.*, bispecific antibody) comprises:

a) a HC1 of SEQ ID NO:17;

b) a LC1 of SEQ ID NO:18;

c) a HC2 of SEQ ID NO:19; and/or

d) a LC2 of SEQ ID NO:20.

[0164] In particular embodiments, the antibody (*e.g.*, bispecific antibody) comprises:

a) a HC1 of SEQ ID NO:17;

b) a LC1 of SEQ ID NO:18;

c) a HC2 of SEQ ID NO:19; and

d) a LC2 of SEQ ID NO:20.

[0165] In some embodiments, the antibody (*e.g.*, bispecific antibody) is of the IgG isotype. In certain embodiments, the antibody (*e.g.*, bispecific antibody) is of the IgG1 isotype. Some variation exists within the IgG1 constant domain (*e.g.*, well-known allotypes), for example, with variation at positions 214, 356, 358, 422, 431, 435 and/or 436 (residue numbering according to the EU numbering) (*see e.g.*, IMGT Web resources; IMGT Repertoire (IG and TR); Proteins and alleles; allotypes). The bispecific anti-EGFR/c-Met antibody may be of any IgG1 allotype, such as G1m17, G1m3, G1m1, G1m2, G1m27 or G1m28.

[0166] In some embodiments, the antibody is a human antibody.

[0167] In particular embodiments, the antibody is amivantamab. Amivantamab is an IgG1 anti-EGFR/c-Met bispecific antibody described in U.S. Pat. No. 9,593,164.

[0168] Other anti-EGFR/c-Met antibodies (*e.g.*, bispecific antibodies) may also be used in the methods of the disclosure, for example, by combining publicly available EGFR binding VH/VL domains and c-Met binding VH/VL domains.

[0169] In some embodiments, the antibody (*e.g.*, bispecific antibody) comprises a biantennary glycan structure with a fucose content of between about 1% to about 15% or less than 20%.

[0170] Antibodies with reduced fucose content can be made using different methods reported to lead to the successful expression of relatively high defucosylated antibodies bearing the biantennary complex-type of Fc oligosaccharides such as control of culture osmolality (Konno *et al.*, Cytotechnology 64(:249-65, 2012), application of a variant CHO line Lec13 as the host cell line (Shields *et al.*, J Biol Chem 277:26733-26740, 2002), application of a variant CHO line EB66 as the host cell line (Olivier *et al.*, MAbs ;2(4), 2010; Epub ahead of print; PMID:20562582), application of a rat hybridoma cell line YB2/0 as the host cell line (Shinkawa *et al.*, J Biol Chem 278:3466-3473, 2003), introduction of small interfering RNA specifically against the α 1,6-fucosyltrasferase (*FUT8)* gene (Mori *et al.*, Biotechnol Bioeng88:901-908, 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 Chem281:5032-5036, 2006, Ferrara *et al.*, Biotechnol Bioeng 93:851-861, 2006; Zhou *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).

Generating Anti-EGFR/c-Met Antibodies

[0171] 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, the first monospecific bivalent antibody and the second monospecific bivalent antibody are engineered to have the aforementioned mutation in the Fc region, and 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.

[0172] 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).

[0173] 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.

[0174] CrossMAb technology, in addition to utilizing the "knob-in-hole" strategy to promote 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).

[0175] 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.

[0176] 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 the 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.

[0177] 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.

[0178] Mutations are typically made at the DNA level to a molecule such as the constant domain of the antibody using standard methods.

[0179] In some embodiments, the antibody (*e.g.*, bispecific antibody) comprises a biantennary glycan structure with a fucose content of between about 1% to about 15%. In some embodiments, the antibody comprises a biantennary glycan structure with a fucose content of less than about 20%.

[0180] Antibodies with reduced fucose content can be made using different methods reported to lead to the successful expression of relatively high defucosylated antibodies bearing the biantennary complex-type of Fc oligosaccharides such as control of culture osmolality (Konno *et al.*, Cytotechnology 64(:249-65, 2012), application of a variant CHO line Lec13 as the host cell line (Shields *et al.*, J Biol Chem 277:26733-26740, 2002), application of a variant CHO line EB66 as the host cell line (Olivier *et al.*, MAbs ;2(4), 2010; Epub ahead of print; PMID:20562582), application of

a rat hybridoma cell line YB2/0 as the host cell line (Shinkawa *et al.*, J Biol Chem 278:3466-3473, 2003), introduction of small interfering RNA specifically against the α 1,6-fucosyltrasferase (*FUT8)* gene (Mori *et al.*, Biotechnol Bioeng88:901-908, 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 Chem281:5032-5036, 2006, Ferrara *et al.*, Biotechnol Bioeng 93:851-861, 2006; Zhou *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).

Administration

[0181] The anti-EGFR/c-Met antibody (*e.g.*, bispecific antibody) and/or additional therapeutic (*e.g.*, chemotherapeutic) agent may be administered in a pharmaceutical composition or compositions. In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

[0182] The methods for subcutaneous formulation and administration of the anti-EGFR/c-Met antibody, such as amivantamab, are described in WO2022224187, which are incorporated herein by reference.

[0183] In some embodiments, the pharmaceutical composition comprising the anti-EGFR/c-Met antibody (*e.g.*, bispecific antibody) is administered via a subcutaneous injection.

[0184] In some embodiments, the antibody (*e.g.*, bispecific antibody) is administered at a dose of about 140 mg to about 4,640 mg, for example, about 1,050 mg to about 1,400 mg, about 1,750 mg to about 2,100 mg, about 1,600 mg to about 2240 mg, about 3,200 mg to about 4,320, about 1,600 mg to about 4,320 mg, about 3,520 mg to about 4,640 mg, or about 1,600 mg to about 4,640 mg.

[0185] In some embodiments, the antibody (*e.g.*, bispecific antibody) is administered at a dose of about: 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, 1,000, 1,010, 1,020, 1,030, 1,040, 1,050, 1,060, 1,070, 1,080, 1,090, 1,100, 1,110, 1,120, 1,130, 1,140, 1,150, 1,160, 1,170, 1,180, 1,190, 1,200, 1,210, 1,220, 1,230, 1,240, 1,250, 1,260, 1,270, 1,280, 1,290, 1,300, 1,310, 1,320, 1,330, 1,340, 1,350, 1,360, 1,370, 1,380, 1,390, 1,400, 1,410, 1,420, 1,430, 1,440, 1,450, 1,460, 1,470, 1,480, 1,490, 1,500, 1,510, 1,520, 1,530, 1,540, 1,550, 1,560, 1,570, 1,580, 1,590, 1,600, 1,610, 1,620, 1,630, 1,640, 1,650, 1,660, 1,670, 1,680, 1,690, 1,700, 1,710, 1,720, 1,730, 1,740, 1,750, 1,760, 1,770, 1,780, 1,790, 1,800, 1,810, 1,820, 1,830, 1,840, 1,850, 1,860, 1,870, 1,880, 1,890, 1,900, 1,910, 1,920, 1,930, 1,940, 1,950, 1,960, 1,970, 1,980, 1,990, 2,000, 2,010, 2,020, 2,030, 2,040, 2,050, 2,060, 2,070, 2,080, 2,090, 2,100, 2,110, 2,120, 2,130, 2,140, 2,150, 2,200, 2,230, 2,240, 2,250, 2,300, 2,350, 2,400, 2,450, 2,500, 2,550, 2,600, 2,650, 2,700, 2,750, 2,800, 2,850, 2,900, 3,000, 3,100, 3,200, 3,300, 3,350, 3,360, 3,370, 3,400, 3,450, 3,500, 3,510, 3,515, 3,520, 3,525, 3,530, 3,540,

3,550, 3,560, 3,570, 3,580, 3,590, 3,600, 3,650, 3,700, 3,750, 3,800, 3,850, 3,900, 3,950, 4,000, 4,100, 4,200, 4,300, 4,310, 4,320, 4,330, 4,400, 4,500, 4,600, 4,610, 4,620, 4,630, 4,640, 4,650, or 4,700 mg.

[0186] In some embodiments, the antibody is administered at a dose of about 700 mg, about 1,050 mg, about 1,400 mg, about 1,750 mg, about 2,100 mg, about 1,600 mg, about 2,240 mg, about 2,400 mg, about 3,360 mg, about 3,200 mg, about 4,320 mg, about 3,520 mg, or about 4,640 mg. In some embodiments, the antibody is administered at a dose of about 1,050 mg. In certain embodiments, the antibody is administered at a dose of about 1,400 mg. In particular embodiments, the antibody is administered at a dose of about 700 mg. In some embodiments, the antibody is administered at a dose of about 1,750 mg. In some embodiments, the antibody is administered at a dose of about 1,600 mg. In some embodiments, the antibody is administered at a dose of about 2,100 mg. In some embodiments, the antibody is administered at a dose of about 2,240 mg. In some embodiments, the antibody is administered at a dose of about 2,400 mg. In some embodiments, the antibody is administered at a dose of about 3,360 mg. In some embodiments, the antibody is administered at a dose of about 3,200 mg. In some embodiments, the antibody is administered at a dose of about 4,320 mg. In some embodiments, the antibody is administered at a dose of about 3,520 mg. In some embodiments, the antibody is administered at a dose of about 4,640 mg.

[0187] In some embodiments, the antibody is administered at a dose of about 350 mg.

[0188] In some embodiments, the antibody is administered at a dose of about 750 mg.

[0189] In some embodiments, the antibody is administered at a dose of about 800 mg.

[0190] In some embodiments, the antibody is administered at a dose of about 850 mg.

[0191] In some embodiments, the antibody is administered at a dose of about 900 mg.

[0192] In some embodiments, the antibody is administered at a dose of about 950 mg.

[0193] In some embodiments, the antibody is administered at a dose of about 1,000 mg.

[0194] In some embodiments, the antibody is administered at a dose of about 1,050 mg.

[0195] In some embodiments, the antibody is administered at a dose of about 1,100 mg.

[0196] In some embodiments, the antibody is administered at a dose of about 1,150 mg.

[0197] In some embodiments, the antibody is administered at a dose of about 1,200 mg.

[0198] In some embodiments, the antibody is administered at a dose of about 1,250 mg.

[0199] In some embodiments, the antibody is administered at a dose of about 1,300 mg.

[0200] In some embodiments, the antibody is administered at a dose of about 1,350 mg.

[0201] In some embodiments, the antibody is administered at a dose of about 1,400 mg.

[0202] In some embodiments, the antibody is administered at a dose of about 1,600 mg.

[0203] In some embodiments, the antibody is administered at a dose of about 1,750 mg.

[0204] In some embodiments, the antibody is administered at a dose of about 2,240 mg.

[0205] In some embodiments, the antibody is administered at a dose of about 2,100 mg.

[0206] In some embodiments, the antibody is administered at a dose of about 2,400 mg.

[0207] In some embodiments, the antibody is administered at a dose of about 3,200 mg.

[0208] In some embodiments, the antibody is administered at a dose of about 3,520 mg.

[0209] In some embodiments, the antibody is administered at a dose of about 3,360 mg.

[0210] In some embodiments, the antibody is administered at a dose of about 4,320 mg.

[0211] In some embodiments, the antibody is administered at a dose of about 4,640 mg.

[0212] In certain embodiments, the antibody is administered at a dose of at least about 3,000 mg, or at least about 3,100 mg, or at least about 3,200 mg, or at least about 3,300 mg, or at least about 3,400 mg, or at least about 3,500 mg. In certain embodiments, the antibody is administered at a dose of greater than about 3,000 mg, or greater than about 3,100 mg, or greater than about 3,200 mg.

[0213] In certain embodiments, the antibody is administered to a subject with body weight <80 kg at a dose of at least about 3,000 mg, or at least about 3,100 mg, or at least about 3,200 mg, or at least about 3,300 mg, or at least about 3,400 mg, or at least about 3,500 mg. In certain embodiments, the antibody is administered to a subject with body weight <80 kg at a dose of greater than about 3,000 mg, or greater than about 3,100 mg, or greater than about 3,200 mg.

[0214] In certain embodiments, the antibody is administered to a subject with body weight ≥ 80 kg at a dose of at least about 4,000 mg, or at least about 4,100 mg, or at least about 4,200 mg, or at least about 4,300 mg, or at least about 4,400 mg, or at least about 4,500 mg, or at least about 4,600 mg. In certain embodiments, the antibody is administered to a subject with body weight ≥ 80 kg at a dose of greater than about 4,300 mg, or greater than about 4,400 mg, or greater than about 4,500 mg, or greater than about 4,600 mg.

[0215] In certain embodiments, the antibody is administered at a dose of 1,600 mg for body weight <80 kg and 2,240 mg for body weight ≥ 80 kg.

[0216] In particular embodiments, the antibody is administered at a dose of 3,200 mg for body weigh <80 kg and 4,320 mg for body weight ≥ 80 kg.

[0217] In particular embodiments, the antibody is administered at a dose greater than 3,200 mg for body weight <80 kg and greater than 4,320 mg for body weight ≥ 80 kg.

[0218] In particular embodiments, the antibody is administered at a dose of 3,520 mg for body weigh <80 kg and 4,640 mg for body weight ≥ 80 kg.

[0219] In some embodiments, the antibody is administered twice a week.

[0220] In certain embodiments, the antibody is administered once a week.

[0221] In some embodiments, the antibody is administered once every two weeks.

[0222] In certain embodiments, the antibody is administered once every three weeks.

[0223] In some embodiments, the antibody is administered once every four weeks.

[0224] In certain embodiments, the antibody is administered once a week or once every four weeks. In particular embodiments, the antibody is administered once weekly for the first 4 weeks and then once every 4 weeks.

[0225] In some embodiments, the antibody is administered on a 28-day cycle.

[0226] In some embodiments, the subject has a body weight (BW) of <80 kg, and the antibody (*e.g.*, bispecific antibody such as amivantamab) is administered at a dose of 1600 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose of 3200 mg once every 4 weeks (Q4W) from Cycle 2 onwards. In some embodiments, the antibody is administered subcutaneously.

[0227] In some embodiments, the subject has a body weight (BW) of 80 kg or larger, and the antibody (*e.g.*, bispecific antibody such as amivantamab) is administered at a dose of 2240 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose of 4320 mg once every 4 weeks (Q4W) from Cycle 2 onwards. In some embodiments, the antibody is administered subcutaneously.

[0228] In some embodiments, the subject has a body weight (BW) of <80 kg, and the antibody (*e.g.*, bispecific antibody such as amivantamab) is administered at a dose of 1600 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose of 3520 mg once every 4 weeks (Q4W) from Cycle 2 onwards. In some embodiments, the antibody is administered subcutaneously.

[0229] In some embodiments, the subject has a body weight (BW) of <80 kg, and the antibody (*e.g.*, bispecific antibody such as amivantamab) is administered at a dose of 1600 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose of about 3,500 mg once every 4 weeks (Q4W) from Cycle 2 onwards. In some embodiments, the antibody is administered subcutaneously.

[0230] In some embodiments, the subject has a body weight (BW) of <80 kg, and the antibody (*e.g.*, bispecific antibody such as amivantamab) is administered at a dose of 1600 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose greater than 3200 mg once every 4 weeks (Q4W) from Cycle 2 onwards. In some embodiments, the antibody is administered subcutaneously.

[0231] In some embodiments, the subject has a body weight (BW) of 80 kg or larger, and the antibody (*e.g.*, bispecific antibody such as amivantamab) is administered at a dose of 2240 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose of 4640 mg once every 4 weeks (Q4W) from Cycle 2 onwards. In some embodiments, the antibody is administered subcutaneously.

[0232] In some embodiments, the subject has a body weight (BW) of 80 kg or larger, and the antibody (*e.g.*, bispecific antibody such as amivantamab) is administered at a dose of 2240 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose of about 4600 mg once every 4 weeks (Q4W) from Cycle 2 onwards. In some embodiments, the antibody is administered subcutaneously.

[0233] In some embodiments, the subject has a body weight (BW) of 80 kg or larger, and the antibody (*e.g.*, bispecific antibody such as amivantamab) is administered at a dose of 2240 mg once

every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose greater than 4,320 mg once every 4 weeks (Q4W) from Cycle 2 onwards. In some embodiments, the antibody is administered subcutaneously.

[0234] In some embodiments, the subject has a body weight (BW) of <80 kg, and the antibody (*e.g.*, bispecific antibody such as amivantamab) is administered at a dose of 3520 mg once every 4 weeks (Q4W). In some embodiments, the antibody is administered subcutaneously.

[0235] In some embodiments, the subject has a body weight (BW) of 80 kg or larger, and the antibody (*e.g.*, bispecific antibody such as amivantamab) is administered at a dose of 4640 mg once every 4 weeks (Q4W). In some embodiments, the antibody is administered subcutaneously.

[0236] In some embodiments, the antibody (*e.g.*, bispecific antibody) is administered so as to produce a Cycle 2 C_{trough} value of about 325 µg/mL or $AUC_{0\text{-}672h}$ value of about 286612 µg•h/mL. In some embodiments, the antibody (*e.g.*, bispecific antibody) is administered so as to produce a Cycle 2 C_{trough} value from about 300 to about 350 µg/mL. In some embodiments, the antibody is administered so as to produce a Cycle 2 C_{trough} value from about 310 to about 340 µg/mL. In some embodiments, the antibody is administered so as to produce a Cycle 2 C_{trough} value from about 320 to about 330 µg/mL.

[0237] In some embodiments, the antibody (*e.g.*, bispecific antibody) is administered so as to produce a Cycle 2 $AUC_{0\text{-}672h}$ value of about 286000 to about 287000 µg•h/mL. In some embodiments, the antibody is administered so as to produce a Cycle 2 $AUC_{0\text{-}672h}$ value of about 286100 to about 286900 µg•h/mL. In some embodiments, the antibody is administered so as to produce a Cycle 2 $AUC_{0\text{-}672h}$ value of about 286200 to about 286800 µg•h/mL. In some embodiments, the antibody is administered so as to produce a Cycle 2 $AUC_{0\text{-}672h}$ value of about 286300 to about 286700 µg•h/mL. In some embodiments, the antibody is administered so as to produce a Cycle 2 $AUC_{0\text{-}672h}$ value of about 286400 to about 286700 µg•h/mL. In some embodiments, the antibody is administered so as to produce a Cycle 2 $AUC_{0\text{-}672h}$ value of about 286500 to about 286700 µg•h/mL. In some embodiments, the antibody is administered so as to produce a Cycle 2 $AUC_{0\text{-}672h}$ value of about 286550 to about 286650 µg•h/mL. In some embodiments, the antibody is administered so as to produce a Cycle 2 $AUC_{0\text{-}672h}$ value of about 286600 to about 286650 µg•h/mL.

[0238] In some embodiments, infusion related reactions (IRRs) occur less frequently in a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

[0239] In some embodiments, infusion related reactions (IRRs) are less severe in a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W)

compared to a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

[0240] In some embodiments, infusion related reactions (IRRs) occur less frequently in a population of subjects that is subcutaneously administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is intravenously administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

[0241] In some embodiments, infusion related reactions (IRRs) are less severe in a population of subjects that is subcutaneously administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is intravenously administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

[0242] In some embodiments, the cancer is NSCLC, the bispecific anti-EGFR/c-Met antibody is amivantamab, and the amivantamab is administered subcutaneously, wherein (i) if the subject has a body weight (BW) of <80 kg, the amivantamab is administered at a dose of 1600 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose greater than 3200 mg once every 4 weeks (Q4W) from Cycle 2 onwards; or (ii) if the subject has a body weight (BW) of 80 kg or larger, the amivantamab is administered at a dose of 2240 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose greater than 4,320 mg once every 4 weeks (Q4W) from Cycle 2 onwards.

[0243] In some embodiments, the cancer is NSCLC, the bispecific anti-EGFR/c-Met antibody is amivantamab, and the amivantamab is administered subcutaneously, wherein (i) if the subject has a body weight (BW) of <80 kg, the amivantamab is administered at a dose of 1600 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose of about 3,500 mg once every 4 weeks (Q4W) from Cycle 2 onwards; or (ii) if the subject has a body weight (BW) of 80 kg or larger, the amivantamab is administered at a dose of 2240 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose about 4,600 mg once every 4 weeks (Q4W) from Cycle 2 onwards.

[0244] In some embodiments, the cancer is NSCLC, the bispecific anti-EGFR/c-Met antibody is amivantamab, and the amivantamab is administered subcutaneously, wherein (i) if the subject has a body weight (BW) of <80 kg, the amivantamab is administered at a dose of 1600 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose of about 3,520 mg once every 4 weeks (Q4W) from Cycle 2 onwards; or (ii) if the subject has a body weight (BW) of 80 kg or larger, the amivantamab is administered at a dose of 2240 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose about 4,640 mg once every 4 weeks (Q4W) from Cycle 2 onwards.

[0245] In some embodiments, the subject is further administered one or more anticancer agents.

[0246] In some embodiments, the subject is further administered chemotherapeutic agent.

[0247] Additional information regarding amivantamab can be found, for example, in the prescribing information product insert for RYBREVANT® (amivantamab-vmjw) (www.janssenlabels.com/package-insert/product-monograph/prescribing-information/RYBREVANT-pi.pdf), which is incorporated herein by reference.

[0248] Additional information regarding the use of amivantamab in patients can be found, for example, in Park K. et al., Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol. 2021 Oct 20;39(30):3391-3402; Vyse S, Huang PH. Amivantamab for the treatment of EGFR exon 20 insertion mutant non-small cell lung cancer. Expert Rev Anticancer Ther. 2021 Dec 16; and Cho BC et al., MARIPOSA: phase 3 study of first-line amivantamab + lazertinib versus osimertinib in EGFR-mutant non-small cell lung cancer. Future Oncol. 2021 Dec 16; which are incorporated herein by reference.

[0249] In some embodiments, the antibody is administered as a monotherapy.

[0250] In some embodiments, the method achieves a partial response or complete response in the subject, as defined by investigator assessment using Response Criteria in Solid Tumors (RECIST) version 1.1.

Hyaluronidase

[0251] The composition can comprise an amount of hyaluronidase enzyme that results in an increase in the dispersion of the bispecific antibody during the subcutaneous administration. The hyaluronidase enzyme has no adverse effect on the molecular integrity of the bispecific antibody. Furthermore, the hyaluronidase enzyme merely modifies the delivery of the bispecific antibody to the systemic circulation but does not possess any properties that could provide or contribute to the therapeutic effects of systemically absorbed bispecific antibody. The hyaluronidase enzyme is not systemically bioavailable and does not adversely affect the molecular integrity of the bispecific antibody at the recommended storage conditions of the composition. A number of suitable hyaluronidase enzymes are known. The preferred enzyme is a human hyaluronidase enzyme, such as a soluble human PH20 hyaluronidase, preferably the recombinant human hyaluronidase enzyme product known as rHuPH20. The amino acid sequence of soluble human PH20 hyaluronidases include the soluble human PH20 known as rHuPH20 and available under CAS Registry No. 757971-58-7. Soluble human PH20 hyaluronidases are described in Int'l Pub. No. WO2004/078140 and U.S. Patent No. 7,767,429 incorporated herein by reference, in their entirety. In some embodiments, soluble hyaluronidases include those whose sequence are set forth in any of SEQ ID NOs: 31-35. Soluble PH20 hyaluronidase, when expressed in a cell, include a signal sequence for trafficking in the cell. Thus, in some embodiments, the amino acid sequence of the soluble PH20 hyaluronidase comprises SEQ ID NO: 36. In some embodiments, the amino acid sequence of the soluble PH20 hyaluronidase comprises SEQ ID NO: 32, namely residues 36-482 of wild type human hyaluronidase. In some embodiments, the amino acid sequence of the soluble PH20 hyaluronidase comprises SEQ ID NO: 33.

In some embodiments, the amino acid sequence of the soluble PH20 hyaluronidase comprises SEQ ID NO: 34. In some embodiments, the soluble PH20 hyaluronidase comprises rHuPH20 comprising the amino acid sequence of SEQ ID NO: 35. In some embodiments, the amino acid sequence of the soluble PH20 hyaluronidase comprises SEQ ID NO: 31. In some embodiments, the soluble PH20 hyaluronidases, when expressed in a cell, comprise a mixture of species that can include any one of SEQ ID NOs: 31, 32, 33, 34, and 35 in various abundance. The average molecular weight is 61 kDa.

[0252] rHuPH20 refers to the composition produced upon expression in a cell, such as CHO cell, of nucleic acids that encode residues 36-482 of SEQ ID NO: 36, generally linked to the native or a heterologous signal sequence (residues 1-35 of SEQ ID NO: 36). rHuPH20 is produced by expression of a nucleic acid molecule, such as encoding amino acids 1-482 (set forth in SEQ ID NO: 36) in a mammalian cell. Translational processing removes the 35 amino acid signal sequence. As produced in the culture medium there is heterogeneity at the C-terminus such that the product, designated rHuPH20, includes a mixture of species that can include one or more of the polypeptides 36-480, 36-481, and 36-482 of SEQ ID NO: 36, and some shorter polypeptides, in various abundance. Typically, rHuPH20 is produced in cells, such as CHO cells, for example DG44 CHO cells, that facilitate correct N-glycosylation to retain activity. In some embodiments, the hyaluronidase is a soluble human PH20 (rHuPH20) comprising the amino acid sequence of SEQ ID NO: 35. In some embodiments, the hyaluronidase is a soluble human PH20 (rHuPH20) comprising the amino acid sequence of SEQ ID NO: 31. In some embodiments, the hyaluronidase is a soluble human PH20 (rHuPH20) comprising the amino acid sequence of SEQ ID NO: 32. In some embodiments, the hyaluronidase is a soluble human PH20 (rHuPH20) comprising the amino acid sequence of SEQ ID NO: 33. In some embodiments, the hyaluronidase is a soluble human PH20 (rHuPH20) comprising the amino acid sequence of SEQ ID NO: 34.

SEQ ID NO: 31: rHuPH20	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGS PRINATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQ DHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVY KNRSIELVQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLG KLLRPNHLWGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLS WLWNESTALYPSIYLNTQQSPVAATLYVRNRVREAIRVSKIPD AKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASGI VIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQV LCQEQGVCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAVDVCIADGVCI DAFLKPPMETEEP
SEQ ID NO: 32: rHuPH20 variant 1	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGS PRINATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQ DHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVY KNRSIELVQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLG KLLRPNHLWGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLS WLWNESTALYPSIYLNTQQSPVAATLYVRNRVREAIRVSKIPD AKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASGI VIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQV LCQEQGVCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT

	LEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAVDVCIADGVCI DAFLKPPMETEEPQIFY
SEQ ID NO: 33: rHuPH20 variant 2	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGS PRINATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQ DHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVY KNRSIELVQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLG KLLRPNHLWGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLS WLWNESTALYPSIYLNTQQSPVAATLYVRNRVREAIRVSKIPD AKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASGI VIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQV LCQEQGVCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAVDVCIADGVCI DAFLKPPMETEEPQIF
SEQ ID NO: 34: rHuPH20 variant 3	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGS PRINATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQ DHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVY KNRSIELVQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLG KLLRPNHLWGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLS WLWNESTALYPSIYLNTQQSPVAATLYVRNRVREAIRVSKIPD AKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASGI VIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQV LCQEQGVCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAVDVCIADGVCI DAFLKPPMETEEPQI
SEQ ID NO: 35: rHuPH20 variant 4	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGS PRINATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQ DHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVY KNRSIELVQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLG KLLRPNHLWGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLS WLWNESTALYPSIYLNTQQSPVAATLYVRNRVREAIRVSKIPD AKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASGI VIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQV LCQEQGVCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAVDVCIADGVCI DAFLKPPMETEEPQ
SEQ ID NO: 36	MGVLKFKHIFFRSFVKSSGVSQIVFTFLLIPCCLTLNFRAPPV IPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRINATGQ GVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKK DITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVYKNRSIELV QQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHL WGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTA LYPSIYLNTQQSPVAATLYVRNRVREAIRVSKIPDAKSPLPVF AYTRIVFTDQVLKFLSQDELVYTFGETVALGASGIVIWGTLSI MRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQVLCQEQGVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFS EKFYCSCYSTLSCKEKADVKDTDAVDVCIADGVCIDAFLKPPM ETEEPQIFYNASPSTLSATMFIVSILFLIISSVASL
SEQ ID NO: 37	LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGS PRINATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQ DHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVY KNRSIELVQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLG KLLRPNHLWGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLS WLWNESTALYPSIYLNTQQSPVAATLYVRNRVREAIRVSKIPD AKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASGI VIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQV

	LCQEQGVCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAVDVCIADGVCI DAFLKPPMETEEPQIFYNASPSTLSATMFIVSILFLIISSVAS L
SEQ ID NO: 38	MGVLKFKHIFFRSFVKSSGVSQIVFTFLLIPCCLTLNFRAPPV IPNVAFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRINATGQ GVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKK DITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVYKNRSIELV QQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHL WGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTA LYPSIYLNTQQSPVAATLYVRNRVREAIRVSKIPDAKSPLPVF AYTRIVFTDQVLKFLSQDELVYTFGETVALGASGIVIWGTLSI MRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQVLCQEQGVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFS EKFYCSCYSTLSCKEKADVKDTDAVDVCIADGVCIDAFLKPPM ETEEPQIFYNASPSTLSATMFIVSIWFLIISSVASL
SEQ ID NO: 39	LNFRAPPVIPNVAFLWAWNAPSEFCLGKFDEPLDMSLFSFIGS PRINATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQ DHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVY KNRSIELVQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLG KLLRPNHLWGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLS WLWNESTALYPSIYLNTQQSPVAATLYVRNRVREAIRVSKIPD AKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASGI VIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQV LCQEQGVCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAVDVCIADGVCI DAFLKPPMETEEPQIFYNASPSTLSATMFIVSIWFLIISSVAS L
SEQ ID NO: 40	MGVLQFKHIFFRSFVKSSGVSQIVFTFLLIPCCLTLNFRAPPV IPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRINATGQ GVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKK DITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVYKNRSIELV QQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHL WGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTA LYPSIYLNTQQSPVAATLYVRNRVREAIRVSKIPDAKSPLPVF AYTRIVFTDQVLKFLSQDELVYTFGETVALGASGIVIWGTLSI MRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQVLCQEQGVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFS EKFYCSCYSTLSCKEKADVKDTDAVDVCIADGVCIDAFLKPPM ETEEPQIFYNASPSTLSATMFIVSILFLIISSVASL
SEQ ID NO: 41	MGVLKFKHIFFRSFVKSSGVSQIVFTFLLIPCCLTLNFRAPPV IPNAPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRINATGQ GVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQDHLDKAKK DITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVYKNRSIELV QQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHL WGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLSWLWNESTA LYPSIYLNTQQSPVAATLYVRNRVREAIRVSKIPDAKSPLPVF AYTRIVFTDQVLKFLSQDELVYTFGETVALGASGIVIWGTLSI MRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQVLCQEQGVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFS EKFYCSCYSTLSCKEKADVKDTDAVDVCIADGVCIDAFLKPPM ETEEPQIFYNASPSTLSATMFIVSILFLIISSVASL
SEQ ID NO: 42	LNFRAPPVIPNAPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGS PRINATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQ DHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVY

	KNRSIELVQQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLG KLLRPNHLWGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDDLS WLWNESTALYPSIYLNTQQSPVAATLYVRNRVREAIRVSKIPD AKSPLPVFAYTRIVFTDQVLKFLSQDELVYTFGETVALGASGI VIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTLAAKMCSQV LCQEQGVCIRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAVDVCIADGVCI DAFLKPPMETEEPQIFYNASPSTLSATMFIVSILFLIISSVAS L

[0253]

Additional Therapeutic Agents

[0254] In some embodiments, the subject is further administered one or more anticancer agents. In some embodiments, the anti-EGFR/c-Met antibody (*e.g.*, bispecific antibody) and the one or more additional therapeutic agents (*e.g.*, chemotherapeutic agents) are administered according to each of their respective dosing schedules during the same treatment cycles. In some embodiments, the antibody and the one or more additional therapeutic agents are administered separately (*e.g.*, sequentially). For combination therapies, the one or more anti-cancer agents may be administered using recommended doses and dosages of the anti-cancer agent.

[0255] In some embodiments, the one or more additional therapeutic agents are one or more anti-cancer therapies. In some embodiments, the one or more additional therapeutic agents comprise one or more chemotherapeutic agents.

[0256] In some embodiments, the subject is further administered a tyrosine kinase inhibitor (TKI). In some embodiments, the TKI is lazertinib. In some embodiments, lazertinib is administered at a dose of 240 mg daily.

Subjects

[0257] The terms "subject" and "patient" can be used interchangeably herein. "Patient in need thereof" or "subject in need thereof" refers to a mammalian subject, preferably human, diagnosed with or suspected of having a disease, to whom will be or has been administered a bi-specific anti-EGFR anti-MET antibody according to a method of the invention. "Patient in need thereof" or "subject in need thereof" includes those subjects already with the undesired physiological change or disease as well as those subjects prone to have the physiological change or disease.

[0258] In some embodiments, the subject is 18 years of age or older, *e.g.*, 18 to less than 40 years of age, 18 to less than 45 years of age, 18 to less than 50 years of age, 18 to less than 55 years of age, 18 to less than 60 years of age, 18 to less than 65 years of age, 18 to less than 70 years of age, 18 to less than 75 years of age, 40 to less than 75 years of age, 45 to less than 75 years of age, 50 to less than 75 years of age, 55 to less than 75 years of age, 60 to less than 75 years of age, 65 to less than 75 years of age, 60 to less than 75 years of age, 40 years of age or older, 45 years of age or older, 50 years of age or older, 55 years of age or older, 60 years of age or older, 65 years of age or older, 70 years of age or older or 75 years of age or older.

[0259] In some embodiments, the subject is a child. In some embodiments, the subject is 18 years of age or younger, *e.g.*, 0-18 years of age, 0-12 years of age, 0-16 years of age, 0-17 years of age, 2-12 years of age, 2-16 years of age, 2-17 years of age, 2-18 years of age, 3-12 years of age, 3-16 years of age, 3-17 years of age, 3-18 years of age, 4-12 years of age, 4-16 years of age, 4-17 years of age, 4-18 years of age, 6-12 years of age, 6-16 years of age, 6-17 years of age, 6-18 years of age, 9-12 years of age, 9-16 years of age, 9-17 years of age, 9-18 years of age, 12-16 years of age, 12-17 years of age or 12-18 years of age.

[0260] In some embodiments, the subject has been diagnosed with a cancer for at least about 1 month, *e.g.*, at least about: 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 18 months, 2 years, 30 months, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years or 10 years. In particular embodiments, the subject is newly diagnosed with cancer.

[0261] In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is an advanced cancer. In some embodiments, the cancer is an advanced solid malignancy. In some embodiments, the cancer is recurrent and/or metastatic. In some embodiments, the cancer is recurrent. In some embodiments, the cancer is metastatic. In some embodiments, the cancer is unresectable.

[0262] In some embodiments, the subject has been diagnosed with an advanced solid malignancy and have received all standard treatment options or is no longer eligible for additional standard treatment options.

[0263] In some embodiments, the subject has EGFR or c-Met expressing cancer.

[0264] In some embodiments, the subject has a cancer having an at least one mutation in EGFR. In some embodiments, the at least one mutation in EGFR is a exon 19 deletion (Ex19del) or a L858R substitution.

[0265] In certain embodiments, the subject is treatment naïve.

[0266] In some embodiments, the subject has received one or more prior anti-cancer therapies. In certain embodiments, the one or more prior anti-cancer therapies comprises one or more chemotherapeutic agents, checkpoint inhibitors, targeted anti-cancer therapies or kinase inhibitors, or any combination thereof. In particular embodiments, the subject is relapsed or resistant to treatment with one or more prior anti-cancer therapies.

[0267] In some embodiments, the subject has received prior treatment with platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. In some embodiments, the subject has received prior treatment with platinum-based chemotherapy. In some embodiments, the subject has received prior treatment with a PD-1/PD-L1 inhibitor.

[0268] In some embodiments, the subject has not previously received anti-EGFR therapy. In some embodiments, the subject has not previously received anti-EGFR antibody therapy. In some embodiments, the subject has not previously received anti-EGFR tyrosine kinase inhibitor (TKI) therapy.

Embodiments

[0269] Provided below are enumerated embodiments of the present invention. These embodiments are illustrative only and do not limit the scope of the present disclosure or of the claims attached hereto.

1. A method of treating an epidermal growth factor receptor (EGFR)-expressing or hepatocyte growth factor receptor (c-Met)-expressing cancer in a subject in need thereof, comprising administering to the subject an isolated bispecific anti-EGFR/c-Met antibody comprising a first domain binding EGFR and a second domain binding 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 a HCDR1 of SEQ ID NO: 7, a HCDR2 of SEQ ID NO: 8, a HCDR3 of SEQ ID NO: 9, a LCDR1 of SEQ ID NO: 10, a LCDR2 of SEQ ID NO: 11, and a LCDR3 of SEQ ID NO: 12,
wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose from about 3520 mg to about 4640 mg.

2. The method of embodiment 1, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 3520 mg.

3. The method of embodiment 1, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 4640 mg.

4. The method of embodiment 1, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 3520 mg if the subject weighs less than 80 kg, and at a dose of about 4640 mg if the subject weighs 80 kg or more.

5. The method of any one of embodiments 1-4, wherein the bispecific anti-EGFR/c-Met antibody is administered once per a 28-day cycle.

6. The method of any one of embodiments 1-5, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.

7. The method of any one of embodiments 1-6, wherein the bispecific anti-EGFR/c-Met antibody is co-formulated with hyaluronidase.

8. The method of any one of embodiments 1-7, wherein the method further comprises an initial cycle (Cycle 1) comprising administering the bispecific antibody once a week for four weeks at a dose of about 1600 mg if the subject weighs less than 80 kg, or at a dose of about 2240 mg if the subject weighs 80 kg or more.

9. The method of any one of embodiments 1-8, wherein the first domain that 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 binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.

10. The method of any one of embodiments 1-9, wherein the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

11. The method of any one of embodiments 1-10, 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.

12. The method of any one of embodiments 1-11, wherein the bispecific anti-EGFR/c-Met antibody has a biantennary glycan structure with a fucose content of between about 1% to about 15% or less than 20%.

13. The method of any one of embodiments 1-12, wherein the EGFR or c-Met expressing cancer is a solid tumor.

14. A method of subcutaneous administration of an isolated bispecific anti-EGFR/c-Met antibody comprising a first domain binding EGFR and a second domain binding c-Met to a subject having EGFR or c-Met expressing cancer,

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

wherein the bispecific anti-EGFR/c-Met antibody is administered so as to produce a Cycle 2 C_{trough} value of about 325 µg/mL or $AUC_{0\text{-}672h}$ value of about 286612 µg•h/mL.

15. The method of embodiment 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 3520 mg.

16. The method of embodiment 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 4640 mg.

17. The method of embodiment 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 3520 mg if the subject weighs less than 80 kg, and at a dose of about 4640 mg if the subject weighs 80 kg or more.

18. The method of any one of embodiments 14-17, wherein the bispecific anti-EGFR/c-Met antibody is administered once per a 28-day cycle.

19. The method of any one of embodiments 14-18, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.

20. The method of any one of embodiments 14-19, wherein the bispecific anti-EGFR/c-Met antibody is co-formulated with hyaluronidase.

21. The method of any one of embodiments 14-20, wherein the method further comprises an initial cycle (Cycle 1) comprising administering the bispecific antibody once a week for four weeks at a dose of about 1600 mg if the subject weighs less than 80 kg, or at a dose of about 2240 mg if the subject weighs 80 kg or more.

22. The method of any one of embodiments 14-21, wherein the first domain that 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 binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.

23. The method of any one of embodiments 14-22, wherein the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

24. The method of any one of embodiments 14-23, 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.

25. The method of any one of embodiments 14-24, wherein the bispecific anti-EGFR/c-Met antibody has a biantennary glycan structure with a fucose content of between about 1% to about 15% or less than 20%.

26. The method of any one of embodiments 14-25, wherein the EGFR or c-Met expressing cancer is a solid tumor.

27. The method of any of embodiments 1-26, wherein the EGFR or c-Met expressing cancer is non-small cell lung-cancer (NSCLC).

28. The method of any of embodiments 1-27, wherein infusion related reactions (IRRs) occur less frequently in a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

29. The method of any of embodiments 1-28, wherein infusion related reactions (IRRs) are less severe in a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

30. The method of any of embodiments 1-27, wherein infusion related reactions (IRRs) occur less frequently in a population of subjects that is subcutaneously administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is intravenously administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

31. The method of any of embodiments 1-28, wherein infusion related reactions (IRRs) are less severe in a population of subjects that is subcutaneously administered the bispecific anti-EGFR/c-Met

antibody once every 4 weeks (Q4W) compared to a population of subjects that is intravenously administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

32. The method of any one of embodiments 1-31, wherein the cancer is NSCLC, the bispecific anti-EGFR/c-Met antibody is amivantamab, and the amivantamab is administered subcutaneously, wherein (i) if the subject has a body weight (BW) of <80 kg, the amivantamab is administered at a dose of 1600 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose greater than 3200 mg once every 4 weeks (Q4W) from Cycle 2 onwards; or (ii) if the subject has a body weight (BW) of 80 kg or larger, the amivantamab is administered at a dose of 2240 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose greater than 4,320 mg once every 4 weeks (Q4W) from Cycle 2 onwards.

33. The method of any one of embodiments 1-31, wherein the cancer is NSCLC, the bispecific anti-EGFR/c-Met antibody is amivantamab, and the amivantamab is administered subcutaneously, wherein (i) if the subject has a body weight (BW) of <80 kg, the amivantamab is administered at a dose of 1600 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose of about 3,500 mg once every 4 weeks (Q4W) from Cycle 2 onwards; or (ii) if the subject has a body weight (BW) of 80 kg or larger, the amivantamab is administered at a dose of 2240 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose about 4,600 mg once every 4 weeks (Q4W) from Cycle 2 onwards.

34. The method of any one of embodiments 1-31, wherein the cancer is NSCLC, the bispecific anti-EGFR/c-Met antibody is amivantamab, and the amivantamab is administered subcutaneously, wherein (i) if the subject has a body weight (BW) of <80 kg, the amivantamab is administered at a dose of 1600 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose of about 3,520 mg once every 4 weeks (Q4W) from Cycle 2 onwards; or (ii) if the subject has a body weight (BW) of 80 kg or larger, the amivantamab is administered at a dose of 2240 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose about 4,640 mg once every 4 weeks (Q4W) from Cycle 2 onwards.

35. The method of any one of embodiments 1-34, wherein the cancer is a EGFR or c-Met expressing cancer, wherein EGFR comprises one or more mutations.

36. The method of embodiment 35, wherein the one or more EGFR mutations is a deletion in exon 19 (Ex19del) or L858R substitution.

37. The method of any one of embodiments 1-36, wherein the subject is treatment naïve.

38. The method of any one of embodiments 1-36, wherein the subject has received one or more prior anti-cancer therapies.

39. The method of embodiment 38, wherein the one or more prior anti-cancer therapies comprised at least one standard of care therapy (SOC).

40. The method of any one of embodiments 1-39, wherein the bispecific anti-EGFR/c-Met antibody is co-administered with hyaluronidase.

41. The method of any one of embodiments 1-39, wherein the bispecific anti-EGFR/c-Met antibody is co-formulated with hyaluronidase.

42. The method of embodiments 40 or 41, wherein the hyaluronidase is a PH20.

43. The method of any one of embodiments 40-42, wherein the PH20 is human recombinant PH20 (rHuPH20).

44. The method of any one of embodiments 40-43, wherein the PH20 comprises any one or more of SEQ ID NOs: 31-42.

45. The method of any one of embodiments 40-44, wherein the PH20 comprises any one or more of SEQ ID NOs: 31, 35, 34, 33 or 32.

EXAMPLES

Example 1. Subcutaneous amivantamab administered every 4 weeks (Q4W) in patients with advanced solid malignancies: The phase 1b PALOMA study.

Abstract

[0270] **Background**: Amivantamab (ami) is an EGFR-MET bispecific antibody with immune cell-directing activity that has been approved as an intravenous (IV) formulation. A subcutaneous (SC) formulation of ami using Q2W (1600 mg (2240 mg if ≥80 kg)) and Q3W (2400 mg (3360 mg if ≥80 kg)) regimens substantially reduced IRR rates (16% for SC vs 67% for IV) and administration time (≤7 minutes for SC vs 2-4 hours for IV) compared to historical experience (Minchom ASCO 2023). We sought to identify an ami Q4W SC dose, which would improve patient (pt) convenience.

[0271] **Methods**: Objectives of PALOMA (NCT0406381) were to evaluate administration feasibility, safety, and pharmacokinetics of ami SC in pts with advanced solid tumors who may benefit from EGFR/MET-directed therapy. Ami SC was dosed weekly for the first 4 weeks (1600 mg [≥80 kg: 2240 mg]), and Q4W thereafter (3200 mg [≥80 kg: 4320 mg]). Ami SC was administered by manual push injection in the abdominal area.

[0272] **Results**: Of 127 pts enrolled in PALOMA, 19 pts (median age: 62 years) received ami SC Q4W. Most pts were Asian (68%) and female (53%); 17 (89%) pts had non-small cell lung cancer, and 2 (11%) had other solid tumors. Four pts (21%) experienced IRRs, all of which were grade 1–2. IRR-associated symptoms were pyrexia (2 pts), chills, pruritus, urticaria, and myalgia (1 pt each). Rash was the most common AE (79%), mostly grade 1–2, with 2 cases being grade 3. Eight pts (42%) reported grade ≥3 AEs, with 3 (16%) related to ami SC (rash 2 pts, hypokalemia 1 pt). Two pts discontinued ami SC due to AEs, both unrelated to treatment.

[0273] No anti-drug antibodies were detected among 17 pts with immunogenicity data. The geometric mean values for Cycle 2 C_{trough} and $AUC_{0\text{-}672h}$ for the tested Q4W SC dose were 325 µg/mL and 286612 µg•h/mL, respectively. Based on these data, the SC Q4W RP2D was refined to 3520 mg

(≥80 kg: 4640 mg). Simulated geometric mean ratio for the Q4W RP2D vs reference IV dose was 1.20 (90% CI, 1.12–1.30) for C_{trough} and 1.31 (90% CI, 1.24–1.39) for $AUC_{0\text{-}662h}$.

[0274] **Conclusions**: Ami SC Q4W had lower rates of IRRs and qualitatively fewer symptoms versus historic ami IV rates. The SC Q4W R2PD of 3520 mg (≥80 kg: 4640 mg) achieved comparable exposure to the approved IV dose and is being further evaluated in the phase 2, PALOMA-2 (NCT05498428) study. Monthly SC dosing of ami would improve pt and provider experience.

Results

[0275] Patient demographics and baseline characteristics are shown in **Table 1**.

Table 1. Demographics and Baseline Characteristics

Characteristic, n (%)	**SC Ami Q4W (n=19)**
Median age, years (range)	62 (39–84)
Male / female	9 (47) / 10 (53)
Body weight: <80 kg / ≥80 kg	16 (84) / 3 (16)
Race	
Asian	13 (68)
White	6 (32)
Number of prior systemic therapies	
1–3	10 (53)
≥4	9 (47)
Cancer type	
NSCLC	17 (89)
Adenocarcinoma	16 (94)
Squamous cell carcinoma	1 (6)
Generic solid tumor[a]	2 (11)

[a] - One patient had colorectal cancer and the other had renal cell cancer.

SC Q4W Pharmacokinetics

[0276] As previously reported, amivantamab SC Q2W dose was 1600 mg (≥80 kg: 2240 mg) and SC Q3W dose was 2400 mg (≥80 kg: 3360 mg) (Minchom A, et al. Presented at American Society of Clinical Oncology (ASCO) 2023; June 2–6, 2023; Chicago, IL, USA).

[0277] First, the Q4W amivantamab dose that was evaluated was:

[0278] Cycle 1: weekly (QW) for the first 4 weeks (1600 mg if the subject weighed less than 80 kg [2240 mg, if the subject weighed 80 kg or more]) and

[0279] Cycle 2+: Q4W thereafter (3200 mg if the subject weighed less than 80 kg [4320 mg, if the subject weighed 80 kg or more]); administration was by manual push injection in the abdomen.

[0280] However, this dosing regimen resulted in a lower C_{max}, an equal or higher C_{trough}, and a non-inferior $AUC_{0\text{-}672h}$ when compared with these values for the approved Q2W IV dose of 1050 mg (≥80 kg: 1400 mg).

[0281] Next, the SC Q4W dose was increased to 3520 mg if the subject weighed less than 80 kg (4640 mg, if the subject weighed 80 kg or more) as the RP2D to achieve the steady state C_{trough} of the approved IV Q2W dose with the predicted steady state C_{max} of SC Q4W (not exceeding 125% of the C_{max} of the approved IV dose). Pharmacokinetic parameters for the Q4W SC 3520 mg (≥80 kg: 4640 mg) dosing as compared with Q2W IV dosing are shown in **Table 2**. The administration time of SC amivantamab Q4W was consistent with that of Q2W and Q3W dosing (~7 to 10 min), assuming an injection rate of 3 mL/min. No antidrug antibodies have been observed with SC amivantamab

Table 2. Simulated GMR for 3520 mg (≥80 kg: 4640 mg) Q4W SC dose vs reference 1050 mg (≥80 kg: 1400 mg) Q2W IV dose

PK parameter, GMR (90% CI)	**For <80 kg: 3520 mg SC / 1050 mg IV For ≥80 kg: 4640 mg SC / 1400 mg IV**		
	Q4W SC / Q2W IV		
	Cycle 2	Cycle 5	Steady state
C_{trough} (µg/mL)	1.07 (1.04–1.09)	1.00 (0.96–1.05)	0.92 (0.76–1.11)
$AUC_{0\text{-}672h}$ (µg•h/mL)	1.07 (1.05–1.10)	1.06 (1.03–1.08)	1.27 (1.18–1.36)

Safety Profile

[0282] Most common adverse events (AEs) were EGFR- and MET-related, primarily of grade 1-2. Safety profile with SC amivantamab Q4W was consistent with previous amivantamab monotherapy experience (Minchom A, et al. ASCO 2023). Grade ≥3 AEs with SC amivantamab occurred in 9 (47%) patients, including 3 events reported to be related to treatment (2 dermatitis acneiform, 1 paronychia). Cumulative grouped rash of all grades occurred in 15 (79%) patients. Rash was defined by the following preferred terms: dermatitis, dermatitis acneiform, rash erythematous, and rash

maculopapular. Three patients underwent dose reduction due to treatment-related AEs. Two patients discontinued SC amivantamab, due to AEs unrelated to treatment. Safety profile summary is shown in **Table 3**.

Table 3. Safety Profile

AEs (≥15%) by preferred term, n (%)	SC Ami Q4W (n=19)	
	All grades	Grade ≥3
Associated with EGFR inhibition		
Dermatitis acneiform	14 (74)	2 (11)
Paronychia	11 (58)	1 (5)
Stomatitis	6 (32)	0
Pruritus	4 (21)	0
Associated with MET inhibition		
Peripheral edema	5 (26)	0
Hypoalbuminemia	3 (16)	0
Other		
Myalgia	8 (42)	0
Fatigue	6 (32)	0
Nausea	6 (32)	1 (5)
Back pain	5 (26)	1 (5)
Pyrexia	4 (21)	0
Vomiting	4 (21)	1 (5)
Dyspnea	4 (21)	1 (5)
Headache	4 (21)	0
IRR	3 (16)	0
Constipation	3 (16)	0
Cough	3 (16)	0
Pleural effusion	3 (16)	1 (5)
Hypomagnesemia	3 (16)	0
ALT increased	3 (16)	0

Incidence of IRRs and IRR-related Symptoms

[0283] Three patients (16%) experienced infusion related reactions (IRRs) with SC amivantamab Q4W; all were grade 1-2 and occurred after the first dose. For the 3 IRRs, onset was 3, 11, and >24 hours after the end of SC administration. One patient received diphenhydramine and clotrimazole for pruritus (as IRR treatment). No recurrent IRRs were reported with consecutive administrations. The incidence of IRRs and IRR-related symptoms in SC amivantamab Q4W as compared to the IV amivantamab Q2W, is shown in **Fig. 1**.

Conclusions

[0284] The SC amivantamab Q4W dose was identified to be 3520 mg (≥80 kg: 4640 mg); wherein SC amivantamab Q4W was dosed weekly (QW) for the first 4 weeks (1600 mg [≥80 kg: 2240 mg]) and Q4W thereafter; administration was by manual push injection in the abdomen. The identified SC amivantamab Q4W dose achieved comparable exposure to the approved IV dose. The administration time of SC amivantamab Q4W was consistent with that of Q2W and Q3W dosing (~7 to 10 minutes).

[0285] The safety profile of SC amivantamab demonstrated a reduction of IRRs. The observed rate of IRRs was 16%. IRRs were less severe and occurred less frequently with Q4W dosing of SC amivantamab compared to Q2W IV amivantamab.

Example 2. Subcutaneous (SC) amivantamab administered every 4 weeks (Q4W) plus lazertinib as first-line treatment in EGFR-mutated (EGFRm) advanced NSCLC: Results from the phase 2 PALOMA-2 study

[0286] **Background**: Intravenous (IV) amivantamab (ami) plus lazertinib (laz) is approved for first-line (1L) treatment of *EGFR*m advanced NSCLC based on the MARIPOSA study. In MARIPOSA (median follow-up, 22.0 mo), ami IV administered every 2 weeks (Q2W) + laz significantly prolonged progression-free survival (PFS) vs osimertinib (HR, 0.70; P<0.001). Among all responders, objective response rate (ORR) by blinded independent central review for participants (pts) treated with ami IV + laz was 86%. In Cohorts 1 and 6 of the bridging PALOMA-2 study (NCT05498428), 1L ami SC Q2W + laz showed a response rate similar to historical ami IV Q2W + laz data in *EGFR*m NSCLC, with an improved safety profile that included significantly lower administration-related reactions (ARRs). PALOMA-2 Cohort 5 evaluated the efficacy, PK, and safety of 1L ami SC Q4W + laz in *EGFR*m NSCLC.

[0287] **Methods**: Pts with treatment-naïve *EGFR*m (Ex19del/L858R) advanced NSCLC were enrolled. Ami SC (co-formulated with hyaluronidase; rHuPH20) was administered via abdominal injection, with a Q4W dosing regimen of 1600 mg (2240 mg if ≥80 kg) weekly for the first 4 wks, and 3520 mg (4640 mg if ≥80 kg) Q4W thereafter. Laz 240 mg was given orally daily. Prophylactic anticoagulation was recommended for the first 4 mo of treatment. Primary endpoint was ORR as assessed by the investigator per RECIST v1.1.

[0288] **Results**: As of the data cutoff (24 Oct 2024), cohort 5 is fully enrolled with 77 pts who received ami SC Q4W + laz (median follow-up, 6.5 mo). Median age was 63 y; 68% of pts were female and 62% Asian. Brain metastases were present in 43% of pts at screening. At data cutoff, 67 (87%) pts were ongoing with study treatment.

[0289] ORR was 82% (95% CI, 71–90) by investigator and 87% (95% CI, 77–94) by independent central review (ICR). Confirmed ORR was 79% (95% CI, 69–88) by investigator and 83% (95% CI, 73–91) by ICR. Median time to response was 8.1 wks (range, 7.0–16.5). Median duration of response, PFS, and overall survival were not estimable.

[0290] No new safety signals were observed. Most treatment-emergent adverse events (AEs) were EGFR/MET-related, with paronychia, hypoalbuminemia, and rash being the most common. ARRs were reported in 9 (12%) pts (gr≥3, 1 [1%]). In total, 67 (87%) pts received any prophylactic anticoagulation. Venous thromboembolic events (VTE) were reported in 10 (13%) pts (none gr≥3). Gr≥3 bleeding rates were low (1%).

[0291] Discontinuation of ami due to treatment-related AEs was 8%. Mean (SD) ami concentration on Cycle 2 Day 1 was 366 (112) µg/mL (n=56), consistent with historical ami IV and SC Q2W data

[0292] **Conclusions**: In pts with *EGFR*m advanced NSCLC, 1L treatment with ami SC Q4W + laz showed a response rate similar to historical ami IV Q2W data with fewer ARRs; incidence of VTE was low with prophylactic anticoagulation. The ami SC Q4W regimen is expected to further improve pt convenience and overall treatment experience.

CLAIMS

What is claimed is:

1. A method of treating an epidermal growth factor receptor (EGFR)-expressing or hepatocyte growth factor receptor (c-Met)-expressing cancer in a subject in need thereof, comprising administering to the subject an isolated bispecific anti-EGFR/c-Met antibody comprising a first domain binding EGFR and a second domain binding 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 a HCDR1 of SEQ ID NO: 7, a HCDR2 of SEQ ID NO: 8, a HCDR3 of SEQ ID NO: 9, a LCDR1 of SEQ ID NO: 10, a LCDR2 of SEQ ID NO: 11, and a LCDR3 of SEQ ID NO: 12,
wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose from about 3520 mg to about 4640 mg.

2. The method of claim 1, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 3520 mg.

3. The method of claim 1, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 4640 mg.

4. The method of claim 1, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 3520 mg if the subject weighs less than 80 kg, and at a dose of about 4640 mg if the subject weighs 80 kg or more.

5. The method of any one of claims 1-4, wherein the bispecific anti-EGFR/c-Met antibody is administered once per a 28-day cycle.

6. The method of any one of claims 1-5, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.

7. The method of any one of claims 1-6, wherein the bispecific anti-EGFR/c-Met antibody is co-formulated with hyaluronidase.

8. The method of any one of claims 1-7, wherein the method further comprises an initial cycle (Cycle 1) comprising administering the bispecific antibody once a week for four weeks at a dose of about 1600 mg if the subject weighs less than 80 kg, or at a dose of about 2240 mg if the subject weighs 80 kg or more.

9. The method of any one of claims 1-8, wherein the first domain that 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 binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.

10. The method of any one of claims 1-9, wherein the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

11. The method of any one of claims 1-10, 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.

12. The method of any one of claims 1-11, wherein the bispecific anti-EGFR/c-Met antibody has a biantennary glycan structure with a fucose content of between about 1% to about 15% or about less than 20%.

13. The method of any one of claims 1-12, wherein the EGFR or c-Met expressing cancer is a solid tumor.

14. A method of subcutaneous administration of an isolated bispecific anti-EGFR/c-Met antibody comprising a first domain binding EGFR and a second domain binding c-Met to a subject having EGFR or c-Met expressing cancer,

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

wherein the bispecific anti-EGFR/c-Met antibody is administered so as to produce a Cycle 2 C_{trough} value of about 325 µg/mL or $AUC_{0\text{-}672h}$ value of about 286612 µg•h/mL.

15. The method of claim 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 3520 mg.

16. The method of claim 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 4640 mg.

17. The method of claim 14, wherein the bispecific anti-EGFR/c-Met antibody is administered at a dose of about 3520 mg if the subject weighs less than 80 kg, and at a dose of about 4640 mg if the subject weighs 80 kg or more.

18. The method of any one of claims 14-17, wherein the bispecific anti-EGFR/c-Met antibody is administered once per a 28-day cycle.

19. The method of any one of claims 14-18, wherein the bispecific anti-EGFR/c-Met antibody is administered subcutaneously.

20. The method of any one of claims 14-19, wherein the bispecific anti-EGFR/c-Met antibody is co-formulated with hyaluronidase.

21. The method of any one of claims 14-20, wherein the method further comprises an initial cycle (Cycle 1) comprising administering the bispecific antibody once a week for four weeks at a dose

of about 1600 mg if the subject weighs less than 80 kg, or at a dose of about 2240 mg if the subject weighs 80 kg or more.

22. The method of any one of claims 14-21, wherein the first domain that 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 binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.

23. The method of any one of claims 14-22, wherein the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

24. The method of any one of claims 14-23, 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.

25. The method of any one of claims 14-24, wherein the bispecific anti-EGFR/c-Met antibody has a biantennary glycan structure with a fucose content of between about 1% to about 15% or less than 20%.

26. The method of any one of claims 14-25, wherein the EGFR or c-Met expressing cancer is a solid tumor.

27. The method of any of claims 1-26, wherein the EGFR or c-Met expressing cancer is non-small cell lung-cancer (NSCLC).

28. The method of any of claims 1-27, wherein infusion related reactions (IRRs) occur less frequently in a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

29. The method of any of claims 1-28, wherein infusion related reactions (IRRs) are less severe in a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

30. The method of any of claims 1-27, wherein infusion related reactions (IRRs) occur less frequently in a population of subjects that is subcutaneously administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is intravenously administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

31. The method of any of claims 1-28, wherein infusion related reactions (IRRs) are less severe in a population of subjects that is subcutaneously administered the bispecific anti-EGFR/c-Met antibody once every 4 weeks (Q4W) compared to a population of subjects that is intravenously administered the bispecific anti-EGFR/c-Met antibody once every 2 weeks (Q2W).

32. The method of any one of claims 1-31, wherein the cancer is NSCLC, the bispecific anti-EGFR/c-Met antibody is amivantamab, and the amivantamab is administered subcutaneously, wherein (i) if the subject has a body weight (BW) of <80 kg, the amivantamab is administered at a

dose of 1600 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose of about 3,520 mg once every 4 weeks (Q4W) from Cycle 2 onwards; or (ii) if the subject has a body weight (BW) of 80 kg or larger, the amivantamab is administered at a dose of 2240 mg once every week (Q1W) for the first 4 weeks (Cycle 1 Days 1, 8, 15, and 22), and then at a dose about 4,640 mg once every 4 weeks (Q4W) from Cycle 2 onwards.