

METHODS OF TREATING NON-SMALL CELL LUNG CANCER USING MESENCHYMAL EPITHELIAL TRANSITION FACTOR (MET)-TARGETED AGENTS

FIELD OF THE INVENTION

[0001] The present invention relates to a MET X MET bispecific antibody which specifically binds hepatocyte growth factor receptor (c-Met or MET) and modulates MET signal transduction, for use in treating non-small cell lung cancer (NSCLC).

SEQUENCE LISTING

[0002] An official copy of the sequence listing is submitted concurrently with the specification electronically via EFS-Web as an XML formatted sequence listing named 11305WO01_Sequence Listing ST.26, a creation date of August 31, 2023, and a size of about 32,768 bytes. The sequence listing is part of the specification and is herein incorporated by reference in its entirety.

BACKGROUND

[0003] Hepatocyte growth factor (HGF) (a.k.a. scatter factor [SF]) is a heterodimeric paracrine growth factor that exerts its activity by interacting with the HGF receptor (HGFR). HGFR is the product of the c-Met oncogene and is also known as MET. MET is a receptor tyrosine kinase consisting of a transmembrane beta chain linked via a disulfide bridge to an extracellular alpha chain. The binding of HGF to MET activates the kinase catalytic activity of MET resulting in the phosphorylation of Tyr 1234 and Tyr 1235 of the beta chain and subsequent activation of downstream signaling pathways.

[0004] MET and/or HGF overexpression, activation, or amplification has been shown to be involved in non-small cell lung carcinoma (NSCLC) (Sierra and Tsao, Ther. Adv. Med. Oncol., 3(1 Suppl): S21–S35, 2011). MET amplification is thought to be a key driver of oncogenesis in NSCLCs. In addition, mutations resulting in exon 14 deletion of MET have been described as oncogenic drivers in a subset of NSCLC. Tumor cell lines having MET gene amplification are highly dependent on MET for growth and survival. Preclinical data implicate MET signaling in resistance to targeted therapies in NSCLC.

[0005] Both preclinical and recent clinical results indicate that tumors harboring these genetic alterations respond to MET inhibitors, validating MET as a cancer driver. Various monovalent MET blocking antibodies are in clinical development for the treatment of various

cancers (see U.S. Patents No. 5,686,292; 5,646,036; 6,099,841; 7,476,724; 9,260,531; and 9,328,173; and U.S. Patent Application Publications No. 2014/0349310 and 2005/0233960). Those antibodies include onartuzumab (MetMab) and emibetuzumab, (Xiang *et al.*, Clin. Cancer Res. 19(18): 5068-78, 2013, and Rosen *et al.*, Clin. Cancer Res., Published October 10, 2016, doi: 10.1158/1078-0432.CCR-16-1418). Some of these antibodies block ligand-dependent MET signaling, but are not as effective in blocking ligand-independent MET activation.

[0006] There remains a significant unmet medical need for improved anti-cancer drugs that potently block both ligand-dependent and ligand-independent MET signaling.

BRIEF SUMMARY

[0007] Provided herein are methods of using bispecific antibodies and fragments thereof, that bind human c-Met receptor protein (MET x MET) for targeting non-small cell lung cancer (NSCLC) cells having a MET alteration such as an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping, a MET gene amplification, or MET protein overexpression. Patients having NSCLC can be treated according to the acceptable standard of care but ultimately may have exhausted all approved available therapies appropriate for the patient as the tumors develop resistance to treatment. Resistance to MET therapy can be intrinsic or acquired, e.g., chemotherapy, immune checkpoint inhibitors, or targeted therapies.

[0008] By identifying those patients having a tumor harboring MET alterations and treating those patients with a MET x MET bispecific antibody, surprising effects were achieved as described herein.

[0009] Thus, provided herein are methods of treating NSCLC, reducing NSCLC tumor growth, and or causing regression of NSCLC in a subject suffering from a tumor harboring a MET alteration, the method comprising administering to the subject a 250 to 2000 mg dose of a MET x MET bispecific antibody.

[0010] Further provided herein are methods of treating or inhibiting the growth of a NSCLC comprising: (1) selecting a subject with a tumor harboring a MET alteration; and (2) administering to the subject (a) a dose of about 250 mg, 500 mg, 750 mg, 1000 mg, 1500 mg, or 2000 mg of a MET x MET bispecific antibody. In some aspects, the administering of step (2) occurs once every 3 weeks.

[0011] Still further provided herein are methods for treating a tumor comprising: (a) selecting a subject with NSCLC; (b) determining that the tumor exhibits a MET alteration

selected from the group consisting of an Exon 14 alteration in DNA or a deletion that leads to exon 14 skipping, MET gene amplification, and/or Met protein overexpression, comprising (i) obtaining a tissue sample and/or a liquid sample from the subject; and (ii) assessing the tissue sample for MET gene amplification using fluorescent in situ hybridization in tumor tissues or by Next Gen Sequencing in tumor tissues and or ctDNA and/or assessing the tissue sample for Met protein overexpression using immunohistochemistry, and/or assessing the liquid sample for an Exon14 mutation using ctDNA; and, if the tumor exhibits a MET alteration, (c) administering one or more doses of a MET x MET bispecific antibody to the subject in need thereof.

[0012] Also provided herein are methods for identifying a candidate for Met x Met anti-tumor therapy, the method comprising obtaining a tissue sample and/or a fluid sample from a subject having NSCLC; and assessing the tissue sample and/or fluid sample for a MET alteration selected from the group consisting of an Exon 14 alteration in DNA or a deletion that leads to exon 14 skipping, MET gene amplification, and/or Met protein overexpression, wherein presence of at least one Met alteration in the tissue sample or fluid sample identifies the subject as a candidate for anti-tumor therapy, wherein the MET x MET anti-tumor therapy comprises a MET x MET bispecific antibody.

[0013] MET alterations as provided herein include exon 14 alterations in DNA, MET gene amplification, or MET protein overexpression.

[0014] In some aspects, the MET alteration is an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping. An exon 14 alteration in DNA or a deletion that leads to exon 14 skipping includes missense alterations, deletions, splice site changes, and whole exon deletions which result in the skipping of exon 14 of the MET gene. In some aspects, the MET alteration is an exon 14 mutation. In some embodiments, exon 14 mutations can include, but are not limited to, D1010N, D1010fs*19, D1010Y, D1010H, or R1004P.

[0015] In some aspects, the MET alteration is a MET gene amplification. In some aspects, a MET gene which is highly amplified has a MET gene copy number (GCN) ≥ 5 and/or MET to chromosome 7 centromere (MET/CEP7) ratio ≥ 2 by FISH or MET GCN ≥ 6 by Next generation sequencing (NGS) in tissues or MET fold change ≥ 2 in ctDNA.

[0016] In some aspects, the MET alteration is MET protein overexpression. MET protein overexpression can be assessed by MET immunohistochemistry (IHC) in tumor tissue that is higher than expression in normal tissue. In some aspects, elevated MET protein expression is measured as an IHC $\geq 2+$ or H score of >150 . In some aspects, MET protein highly

overexpressed is measured as IHC 3+ or H score of ≥ 200 .

[0017] In some aspects, the MET alteration is identified using ctDNA from blood sample, i.e., a liquid biopsy, obtained from the patient prior to treatment.

[0018] In some aspects, the MET alteration is identified in a tissue sample, i.e. tumor biopsy, obtained from the patient prior to treatment.

[0019] In some aspects, the NSCLC tumor has an *EGFR* mutation. The mutation can include, but is not limited to L858R, G719S, E709A, E746_A750del, and S752_I759del. In some aspects, the subject is selected as having NSCLC with one or more mutations in the *EGFR* gene.

[0020] In some embodiments, the subject has not received prior anti-MET cancer therapy. In some embodiments, the subject is tyrosine kinase inhibitor (TKI) naïve. In other words, the subject has not received prior treatment with a MET targeted TKI. In some embodiments, the subject has received prior anti-cancer therapy comprising one or more of a MET targeted TKI, a PD-1 inhibitor, an EGFR inhibitor, a PD-L1 inhibitor, surgery, radiation therapy, or chemotherapy. In some aspects, the prior anti-cancer therapy comprises a MET targeted TKI. In some aspects, the prior anti-cancer therapy comprises a PD-1 inhibitor or a PD-L1 inhibitor. In some aspects, the prior anti-cancer therapy comprises an EGFR inhibitor. In some aspects, the subject is resistant or inadequately responsive to, or relapsed after prior therapy.

[0021] A MET TKI naïve patient has not been prior treated with any MET TKI; likewise, a patient who has received treatment with a MET TKI is MET TKI experienced. A patient with PD-(L)1 experience has been treated prior with a PD-1 inhibitor (such as, but not limited to, pembrolizumab, nivolumab, cemiplimab, dostarlimab, and retifanlimab) or PD-L1 inhibitor (such as, but not limited to, atezolizumab, avelumab, and durvalumab), and is considered PD-(L)1 experienced; likewise, one with no PD-(L)1 experience (i.e., PD-(L)1 naïve) has not been prior treated with a PD-1 or PD-L1 inhibitor. A patient can be EGFR inhibitor experienced, i.e., has been treated with an EGFR inhibitor. Exemplary EGFR inhibitors include, but are not limited to erlotinib, afatinib, gefitinib, Osimertinib, dacomitinib, cetuximab, panitumumab, dacomitinib, etc.

[0022] In some embodiments, the subject is further selected according to one or more of the following criteria:

- (i) the subject is *MET* TKI naïve;

- (ii) the subject has a histologically confirmed NSCLC;
- (iii) the NSCLC exhibits a MET-exon14 alteration in DNA or a deletion that leads to exon 14 skipping;
- (iv) the NSCLC exhibits a *MET* gene amplification;
- (v) the NSCLC exhibits an elevated MET protein expression (IHC $\geq 2+$ or H score of >150);
- (vi) the NSCLC exhibits a MET exon 14 alteration in DNA or a deletion that leads to exon 14 skipping and MET TKI experienced;
- (vii) the NSCLC exhibits a MET exon 14 alteration in DNA or a deletion that leads to exon 14 skipping and MET TKI naïve;
- (viii) the NSCLC exhibits a *MET* gene highly amplified (MET GCN ≥ 5 and/or MET/CEP7 ratio ≥ 2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA) and MET TKI naïve;
- (ix) the NSCLC exhibits a MET protein highly overexpressed (IHC 3+ or H score of ≥ 200) and MET TKI naïve; and/or
- (x) the NSCLC exhibits a *MET* gene highly amplified (MET GCN ≥ 5 and/or MET/CEP7 ratio ≥ 2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA), MET protein highly overexpressed (IHC 3+ or H score of ≥ 200), and MET TKI naïve.

[0023] In some embodiments, the cancer is non-squamous NSCLC. In some embodiments, the cancer is a NSCLC squamous carcinoma. In some aspects, the NSCLC is metastatic, for example, the cancer has metastasized to the brain and/or liver. In some aspects, the NSCLC is unresectable.

[0024] Provided herein are methods for monitoring efficacy of treatment with a MET x MET bispecific antibody in a subject having NSCLC with a MET alteration, the method comprising:
(i) obtaining a tissue sample and/or a fluid sample from the subject and assessing the tissue sample and/or fluid sample for somatic mutations in one or more genes selected from the group consisting of:

- a. an on-target MET Receptor gene mutation that confers resistance to MET TKI's found in MET Ex14 Mut patients with prior TKI Exp and MET gene silencing (loss-of-

function);

- b. TK driver receptor activation selected from alternative or parallel TK Receptor and ligand gene amplification and TKR activating mutations; and
- c. an activating gene mutation in a pathway selected from the group consisting of JAK2/STAT3 pathway, RAS/RAF/MEK/MAPK pathway, PI3K/AKT/MTOR pathway, TP53 mutations, and cell cycle gene amplification;

(ii) administering a MET x MET bispecific antibody to the subject; and (iii) repeating steps (i) and (ii) over the course of treatment; wherein the acquiring of a mutation by one or more genes is indicative of resistance to therapy and/or indicative of poor prognosis.

[0025] In some aspects, the on-target MET Receptor gene mutation is selected from the group consisting of *MET* Y1230C, *MET* D1228H, *MET* D1228N; and the *MET* gene silencing (loss-of-function) is selected from somatic mutations in DNMT3A and TET2.

[0026] In some aspects, the TKR activating mutation is selected from the group consisting of *EGFR* L858R, *EGFR* G719S, *EGFR* E709A, *EGFR* E746_A750del, and *EGFR* S752_I759del.

[0027] In some aspects, the JAK2/STAT3 pathway mutation is *JAK2* V617F; the RAS/RAF/MEK/MAPK pathway mutation is selected from the group consisting of *KRAS* G12A/V, *GNAS* R201H, MKRN-BRAF fusion, *BRAF* S602Y, RICTOR Amp, and *MAP2K1* K57N; the PI3K/AKT/MTOR pathway mutation is selected from the group consisting of *PIK3CA* H1047L, *PIK3CA* E545K, *PIK3CA* E542K, *PIK3CA* N345K, *IDH1* R132L, and *MTOR* E2338Q; the PI3K/AKT/MTOR pathway amplification is selected from the group consisting of *AKT2* Amp and *RICTOR* Amp; the TP53 mutation is selected from the group consisting of *TP53* R280T and *TP53* R248Q; and the cell cycle gene amplification is selected from the group consisting of *CDK4* Amp, *CDK6* Amp, *CCND1* Amp, and *CCNE1* Amp.

[0028] In some aspects, the patient has confirmed *MET* amplification and MET overexpression, but develops gene amplification in one or more of *HGF*, *EPH*, *EGFR*, *BRAF*, *BCL2L1*, *PI3KCB*, *KRAS*, *AKT2*, *ATR*, *VEFGA*, *FGF*, *CCND*, *CCNE*, *CDK6*, *RAD21*, and *MYC*. In some aspects, the patient has confirmed *MET* amplification and MET overexpression, but develops gene deletion in one or more of *CDKN2A*, *CDKN2B*, *MTAP*, and *RBM10*. In some aspects, the patient has confirmed *MET* amplification and MET overexpression, but develops one or more of the point mutations provided in Table 15.

[0029] In some aspects, the patient has confirmed *MET* amplification (and not *MET* overexpression) and can be an *EGFR* mutant, but develops gene amplification in one or more of *EGFR*, *BRAF*, *PI3KC2G*, *KRAS*, *HGF*, *EPHA3*, *ERCC4*, *RICTOR*, *RAD21*, *LYN*, *MYC*, *MDM2*, *CDK 4/6*, *FgF3/4/19*, *FGF10*, and *CCND1*. In some aspects, the patient has confirmed *MET* amplification (and not *MET* overexpression) and can be an *EGFR* mutant, but develops gene deletion in one or more of *CDKN2A*, *CDKN2B*, *MTAP*, *TEK*, and *BCOR*. In some aspects, the patient has confirmed *MET* amplification (and not *MET* overexpression) and can be an *EGFR* mutant, but develops one or more of the point mutations provided in Table 16.

[0030] In some aspects, the patient has confirmed *MET* Exon 14 alteration and is TKI naïve, but develops gene amplification in one or more of *MDM2*, *EGFR*, *FGFR1*, *ERBB3*, *CDK4*, *GNA13*, *MYC*, *RPTOR*, *TERC*, *IKZF1*, *EZH2*, *SDHA*, *SOX*, *WHSC1L1*, and *ZNF703*. In some aspects, the patient has confirmed *MET* Exon 14 alteration and is TKI naïve, but develops gene deletion in one or more of *CDKN2A*, *CDKN3A*, and *MTAP*. In some aspects, the patient has confirmed *MET* Exon 14 alteration and is TKI naïve, but develops one or more of the point mutations provided in Table 17.

[0031] In some aspects, the patient has confirmed *MET* Exon 14 alteration and is TKI experienced, but develops gene amplification in one or more of *EGFR*, *RAF1*, *PI3KC2G*, *CDK4*, *CEBPA*, *CDKN1A*, *CARD11*, *MYC*, *RICTOR*, *VEGFA*, *CD22*, *DDR1*, *RAC1*, *NBN*, *FGF19*, *MDM2*, *NFKBIA*, *CCND1*, *INPP4B*, *PPARG*, *PMS2*, *GATA4*, *SDHA*, and *RAD21*. In some aspects, the patient has confirmed *MET* Exon 14 alteration and is TKI experienced, but develops gene deletion in one or more of *CDKN2A*, *CDKN3A*, and *MTAP*. In some aspects, the patient has confirmed *MET* Exon 14 alteration and is TKI experienced, but develops one or more of the point mutations provided in Table 18.

[0032] Also provided herein are methods for treating NSCLC in a subject, the method comprising: (i) obtaining a liquid sample from the subject and determining the *MET* amplification in ctDNA from the liquid sample, and (ii) administering a *MET* x *MET* bispecific antibody to the subject; wherein steps (i) and (ii) are repeated once every three weeks, and wherein a loss of *MET* amplification after step (ii) is repeated is indicative of durable response to treatment.

[0033] Provided herein are methods for determining a therapeutically effective amount of a *MET* x *MET* bispecific antibody, the method comprising: (i) administering a dosage of the bispecific antibody to a patient in need thereof, and (ii) measuring soluble *MET* in a blood sample, wherein a maximal increase in soluble *MET* (s*MET*) indicates saturation of receptor

occupancy and a therapeutically effective amount of the bispecific antibody.

[0034] In some aspects, the subject is administered a MET x MET bispecific antibody in an amount of, i.e., a dose of about 250 mg to about 5000 mg, or a dose of about 250 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, 2100 mg, 2200 mg, 2300 mg, 2400 mg, 2500 mg, 3000 mg, 3500 mg, 4000 mg, 4500 mg, or 5000 mg. In some aspects, the dose is about 250 mg MET x MET bispecific antibody. In some aspects, the dose is about 500 mg MET x MET bispecific antibody. In some aspects, the dose is about 1000 mg MET x MET bispecific antibody. In some aspects, the dose is about 2000 mg MET x MET bispecific antibody. In some aspects, the dose is 250 mg, 500 mg, 1000 mg, or 2000 mg MET x MET bispecific antibody.

[0035] In some aspects, the bispecific antibody is administered intravenously, subcutaneously, or intraperitoneally. The bispecific antibody can be administered once every five days, once a week, once every two weeks, once every three weeks, once every four weeks once a month, once every five weeks, once every six weeks, or once every two months. In some aspects, the bispecific antibody is administered once every three weeks. In some aspects, the bispecific antibody is administered three weeks after the immediately preceding dose.

[0036] In some aspects, the treatment produces a therapeutic effect selected from the group consisting of delay in tumor growth, reduced metastasis, reduction in tumor cell number, tumor regression, increase in survival, partial response, and complete response. In some aspects, tumor growth is delayed by at least 10 days, or at least 20 days, or at least 30 days, or at least 40 days, or at least 50 days as compared to an untreated subject. In some aspects, the tumor growth is inhibited by at least 10%, by at least 20%, by at least 30%, by at least 40%, by at least 50%, or by at least 60% as compared to an untreated subject.

[0037] The MET x MET bispecific antibody comprises a first antigen-binding domain (D1) comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence that is at least 95% identical to the sequence of SEQ ID NO: 1 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence that is at least 95% identical to the sequence of SEQ ID NO: 9; and a second antigen-binding domain (D2) comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence that is at least

95% identical to the sequence of SEQ ID NO: 5 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence that is at least 95% identical to the sequence of SEQ ID NO: 9.

[0038] In some aspects, D1 specifically binds a first epitope of human MET.

[0039] In some embodiments, D1 comprises an HCDR1 amino acid sequence as set forth in SEQ ID NO: 2; an HCDR2 amino acid sequence as set forth in SEQ ID NO: 3; an HCDR3 amino acid sequence as set forth in SEQ ID NO: 4; an LCDR1 amino acid sequence as set forth in SEQ ID NO: 10; an LCDR2 amino acid sequence as set forth in SEQ ID NO: 11; and an LCDR3 amino acid sequence as set forth in SEQ ID NO: 12.

[0040] In some embodiments, D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 1; and an LCVR comprising the amino acid sequence of SEQ ID NO: 9.

[0041] In some aspects, D2 specifically binds a second epitope of human MET.

[0042] In some embodiments, D2 comprises an HCDR1 amino acid sequence as set forth in SEQ ID NO: 6; an HCDR2 amino acid sequence as set forth in SEQ ID NO: 7; an HCDR3 amino acid sequence as set forth in SEQ ID NO: 8; an LCDR1 amino acid sequence as set forth in SEQ ID NO: 10; an LCDR2 amino acid sequence as set forth in SEQ ID NO: 11; and an LCDR3 amino acid sequence as set forth in SEQ ID NO: 12.

[0043] In some embodiments, D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 5; and an LCVR comprising the amino acid sequence of SEQ ID NO: 9.

[0044] In some embodiments, the MET alteration is an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping, a MET gene amplification, or MET protein overexpression. In some aspects, the MET alteration is an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping. In some aspects, the MET alteration is a MET gene amplification. In some aspects, the MET alteration is MET protein overexpression.

[0045] Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0046] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0047] **Figures 1A and 1B** contain a bar charts depicting the relative growth of EBC-1 cells as a function of treatment with control antibody and a MET x MET bispecific antibody at 0.1 and 1 µg/mL.

[0048] **Figure 2** depicts an immunoblot of the expression of MET (and tubulin as a loading control) in Hs746T cells after treatment with a control antibody and a MET x MET bispecific antibody for 2, 6 and 18 hours.

[0049] **Figure 3** depicts an immunoblot of pMET, MET, pErk, and tubulin (for loading control) extracted from EBC-1 cells after treatment with a control antibody and a MET x MET bispecific antibody.

[0050] **Figure 4** is a line graph depicting the change in EBC-1 tumor volume in cubic millimeters as a function of time in days after implantation of EBC-1 cells in animals treated with control antibody (filled square ■), MET monovalent antibody (filled circle ●), or MET x MET bispecific antibody (filled diamond ◆).

[0051] **Figure 5** is a bar chart depicting the relative cell growth of NCI-H596 cells as a function of treatment with a control antibody (C), a MET x MET bispecific antibody (MM), the MET x MET parental monospecific antibody 1 (M1), the MET x MET parental monospecific antibody 2 (M2), a combination of parental antibodies 1 and 2 (M1M2), and the MET-agonist hepatocyte growth factor (HGF).

[0052] **Figure 6** depicts the study flow diagram for the clinical trial using REGN5093.

[0053] **Figure 7** is a diagrammatic depiction of the study design showing the dose escalation cohorts and the expansion cohorts.

[0054] **Figure 8** depicts patient tumor response characterized by centrally confirmed MET alterations.

[0055] **Figures 9A and 9B** depict serum concentrations after the first dose of REGN5093 in the dose escalation cohort, Figure 9A, and the various expansion cohorts, Figure 9B. The elimination half-life estimated by non-compartmental analysis over a 3-week dosing interval

is 15 days.

[0056] Figure 10 depicts the interaction of the MET x MET bispecific antibody with the MET ectodomain. The Figure also illustrates how MET alterations impact increased MET signaling and ligand independent activation.

[0057] Figure 11 depicts the methods used to confirm MET alterations in ctDNA and tissue, and the exemplary commercial products that can be used in these methods. (CEP7, chromosome 7 centromere; ELISA, enzyme-linked immunosorbent assay; FFPE, formalin-fixed paraffin-embedded; FISH, fluorescent in situ hybridization; FMI, Foundation Medicine, Inc.; GCN, gene copy number; HGF, hepatocyte growth factor; IHC, immunohistochemistry; MET, mesenchymal epithelial transition; sMET, soluble MET; TSO, Trusight Oncology.)

[0058] Figure 12 illustrates the number of patients enrolled in the dose escalation studies and the characteristics and numbers of patients enrolled in the expansion cohorts. (aNSCLC, advanced non-small cell lung cancer; GCN, gene copy number; FIH, first-in-human; IHC, immunohistochemistry; IV, intravenous; MET, mesenchymal epithelial transition; PK, pharmacokinetic; Q3W, every 3 weeks; Q6W, every 6 weeks; TKI, tyrosine kinase inhibitor.)

[0059] Figure 13 provides the response data at the 2000 mg dose for the dose escalation study – 2000 mg and the expansion cohorts. Overall response rate was highest for the cohort having patients with an Exon14 skip mutation and where the patients were MET TKI naïve and for the cohort having patients with both MET gene amplification and MET protein overexpression and where the patients were MET TKI naïve.

[0060] Figure 14 shows the tumor response by confirmed MET alteration. MET overexpression – IHC: $\geq 75\%$ tumor cells w/ 3+ membrane staining; *MET* amplification – FISH: GCN ≥ 5 or MET/CEP7 >2 (tissue); or NGS: GCN ≥ 6 (tissue); or ≥ 2.2 fold (ctDNA); *MET* exon 14 mutation – NGS in tissue or ctDNA. Response to REGN5093 was observed in MET TKI naïve (2L+) aNSCLC patients with *MET* exon 14 mutation or *MET* amplification and overexpression regardless of EGFR mutation status. For patients whose tumor tissues were analyzed for *MET* amplification using two platforms, *MET* GCN was significantly higher by NGS than by FISH ($p=0.0015$). (aNSCLC, advanced non-small cell lung cancer; CEP7, chromosome 7 centromere; FISH, fluorescence in situ hybridization; GCN, gene copy number; IHC, immunohistochemistry; MET, mesenchymal epithelial transition; NA, not available or to be determined; NGS, next generation sequencing; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.)

[0061] **Figure 15** provides the response in specific *MET* altered subgroups (regardless of the presence of other *MET* alterations) versus overall population. Results are based on small samples sizes and require prospective validation. (CR, complete response; DCR, disease control rate; *MET*, mesenchymal epithelial transition; ORR, objective response rate; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.)

[0062] **Figure 16** is a chart with the baseline demographics and clinical characteristics of the bypass resistance mutation study population. The study population had a median age of 66 years, 53.8% were male, 70.5% were Asian, and patients had received a median of 2.5 prior lines of therapy. (ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; PS, performance status.)

[0063] **Figure 17** depicts the differences in detection of somatic variants in tissue versus ctDNA. Tumor profiling at baseline of 2L+ aNSCLC identified somatic variants with known functional significance. Venn diagram shows the total number of baseline somatic variants identified by NGS using FMI-Dx (tissue; n=51 patients) and FMI-L (ctDNA; n=38 patients) panels (324 genes); genes are grouped by type of alteration and type of clinical sample (ctDNA, tissue, or both). CNVs, including gene amplifications and deletions, were detected more readily in tissue while more NSVs (single nucleotide variations, splice variants, and gene fusions) were detected in ctDNA. Thus, bypass gene detection of NSVs and CNVs in ctDNA can, in some embodiments, supplement tissue results to provide a more comprehensive tumor profiling of *Met* x *Met* resistance mechanism. (2L, second line; aNSCLC, advanced non-small cell lung cancer; CNV, copy number variation; FMI, Foundation Medicine, Inc.; NGS, next generation sequencing; NSV, non-synonymous variations; SNV, single nucleotide variant.)

[0064] **Figure 18** illustrates unbiased clustering of baseline somatic variants with confirmed *MET* alterations. Several genes with known functional significance were detected, which clustered by cohort assignment, centrally confirmed *MET* alterations and *EGFR* status. (Amp, amplification; *EGFR*, epidermal growth factor receptor; Ex14, exon 14; FMI, Foundation Medicine, Inc.; IHC, immunohistochemistry; *MET*, N, no; NA, not available; mesenchymal epithelial transition; O/E, overexpression; SNV, single nucleotide variant; TKI, tyrosine kinase inhibitor; Y, yes.)

[0065] **Figure 19** illustrates unbiased clustering of baseline somatic variants with *MET* alterations and clinical response. Several genes with known functional significance were detected, which clustered by cohort assignment, confirmed *MET* alterations, *EGFR* status and Clinical Response.

[0066] **Figure 20** depicts classification and examples of baseline somatic mutations identified by tumor profiling. These mutations were identified in non-responders and can lead to MET bypass resistance mechanisms and potentially affect clinical response to REGN5093 even in the presence of MET oncogenic drivers. (Amp, amplification; EGFR, epidermal growth factor receptor; Ex14, exon 14; GOF, gain of function; LOF, loss of function; TKI, tyrosine kinase inhibitor)

[0067] **Figure 21** graphically represents total REGN5093 and sMET concentrations during study treatment and individual concentrations of sMET over time by best overall response. Total concentration of REGN5093 was several fold higher than total sMET concentration in serum, suggesting saturation of receptor occupancy was achieved with the 2000 mg Q3W dose regimen. sMET and cHGF levels increased post-dose suggesting target engagement, but neither baseline nor post-treatment levels of sMET and cHGF was significantly associated with response (data not shown). (cHGF, circulating hepatocyte growth factor; Q3W, every 3 weeks; sMET, soluble mesenchymal epithelial transition)

[0068] **Figure 22** illustrates the lack of significant association between baseline concentrations of sMET or cHGF and clinical response. cHGF, circulating hepatocyte growth factor; PD, progressive disease; PR, partial response; SD, stable disease; sMET, soluble mesenchymal epithelial transition.

DETAILED DESCRIPTION

[0069] Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0070] 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 this invention belongs. As used herein, the term “about,” when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression “about 100” includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, *etc.*, including 100).

[0071] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All patents, applications and non-patent publications

mentioned in this specification are incorporated herein by reference in their entireties.

MET PROTEIN

[0072] The expressions “MET,” “c-Met,” and the like, as used herein, refer to the human membrane spanning receptor tyrosine kinase comprising (1) the amino acid sequence as set forth in SEQ ID NO:13, and/or having the amino acid sequence as set forth in NCBI accession No. NM_001127500.2, representing the unprocessed preproprotein of isoform “a”, (2) the amino acid sequence as set forth in SEQ ID NO:14, and/or having the amino acid sequence as set forth in NCBI accession No. NM_000236.2, representing the unprocessed preproprotein of isoform “b”, (3) the amino acid sequence as set forth in SEQ ID NO:15, and/or having the amino acid sequence as set forth in NCBI accession No. NM_001311330.1, representing the unprocessed preproprotein of isoform “c”, and/or (3) the mature protein comprising the cytoplasmic alpha subunit (SEQ ID NO:16) shared by all three isoforms and the transmembrane beta subunit (SEQ ID NO:17, 18, or 19 of isoform a, b and c, respectively). The expression “MET” includes both monomeric and multimeric MET molecules. As used herein, the expression “monomeric human MET” means a MET protein or portion thereof that does not contain or possess any multimerizing domains and that exists under normal conditions as a single MET molecule without a direct physical connection to another MET molecule. An exemplary monomeric MET molecule is the molecule referred to herein as “hMET.mmh” comprising the amino acid sequence of SEQ ID NO: 20 (SEQ ID NO:152 from U.S. Patent No. 11,142,578 Example 3). As used herein, the expression “dimeric human MET” means a construct comprising two MET molecules connected to one another through a linker, covalent bond, non-covalent bond, or through a multimerizing domain such as an antibody Fc domain. An exemplary dimeric MET molecule is the molecule referred to herein as “hMET.mFc” comprising the amino acid sequence of SEQ ID NO: 21 (SEQ ID NO: 153 from U.S. Patent No. 11,142,578_Example 3).

[0073] All references to proteins, polypeptides and protein fragments herein are intended to refer to the human version of the respective protein, polypeptide or protein fragment unless explicitly specified as being from a non-human species. Thus, the expression “MET” means human MET unless specified as being from a non-human species, *e.g.*, “mouse MET,” “monkey MET,” *etc.*

[0074] As used herein, the expression “cell surface-expressed MET” means one or more MET protein(s), or the extracellular domain thereof, that is/are expressed on the surface of a cell *in vitro* or *in vivo*, such that at least a portion of a MET protein is exposed to the extracellular side of the cell membrane and is accessible to an antigen-binding portion of an

antibody. A “cell surface-expressed MET” can comprise or consist of a MET protein expressed on the surface of a cell which normally expresses MET protein. Alternatively, “cell surface-expressed MET” can comprise or consist of MET protein expressed on the surface of a cell that normally does not express human MET on its surface but has been artificially engineered to express MET on its surface.

[0075] Measures of MET alterations in NSCLC include *MET* exon 14 mutation: oncogenic driver in NSCLC with recent TKI approvals in 1L (first line); *MET* gene amplification: major resistance mechanism to EGFR TKI therapy in 2L (second line) + NSCLC; and MET protein overexpression, reported to enrich but not select for treatment response to MET TKI's in NSCLC.

THERAPEUTIC METHODS OF TREATING NSCLC CANCER

[0076] Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer-related mortality worldwide (Siegel *et al.*, *CA Cancer J Clin*, 66(1):7-30, 2016). Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers and is composed of several histopathological subtypes, the most common of which are adenocarcinoma (40% to 60%) and squamous cell carcinoma (30%) (Dela Cruz *et al.*, *Clin Chest Med*, 32(4):605-44, 2011). The majority of patients with NSCLC are found to have advanced cancer at the time of diagnosis.

[0077] Anti-PD-1 and anti-PD-L1 therapies have changed the standard of care for many patients with NSCLC (Topalian *et al.*, *NEJM*, 366(26):3443-54, 2012). However, data is emerging that suggests MET-driven NSCLC patients may not experience equivalent benefit to agents that target the PD-1/PD-L1 axis, even with tumors that express high PD-L1 or exhibit high tumor mutation burden (TMB) (Sabari *et al.*, *Ann Oncol*, 29(10):2085-91, 2018). This is in keeping with data generated in lung cancers harboring EGFR mutations or ALK rearrangements (Garassino *et al.*, *Lancet Oncol*, 19(4):521-36, 2018) (Lee *et al.*, *JAMA Oncol*, 4(2):210-16 2018) (Peters *et al.*, *J Clin Oncol*, 35(24):2781-9, 2017) and indicates that monotherapy with anti-PD-1 or anti-PD-L1 may not be the preferred treatment for patients with MET-driven disease. Thus, there remains a substantial unmet need for therapies that improve response rates and survival for patients with MET-altered NSCLC.

[0078] The present inventors have surprisingly discovered that certain MET x MET bispecific antibodies are exceptionally suited for treating and/or inhibiting NSCLC or mitigating metastasis of a NSCLC associated with a MET alteration such as an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping, a MET gene amplification, or MET protein

overexpression. REGN5093 is an exemplary human bispecific antibody that binds two epitopes on the MET receptor, resulting in blockade of ligand-dependent and ligand-independent signaling with potential activity in lung cancer. The Examples below illustrate that tumor response to treatment with a MET x MET bispecific antibody is enriched by identifying patients having these MET alterations.

[0079] As such, useful according to the methods described herein are MET x MET bispecific antibodies comprising a first antigen-binding domain (also referred to herein as “D1”) which specifically binds a first epitope of human MET, and a second antigen-binding domain (also referred to herein as “D2”) which specifically binds a second epitope of human MET. The simultaneous binding of the two separate MET epitopes by the bispecific antibody results in effective ligand blocking with minimal activation of MET signaling. Such MET x MET bispecific antibodies are described in U.S. Publication No. 2018/0134794, incorporated by reference herein in its entirety.

[0080] The MET x MET bispecific antibodies are useful, *inter alia*, for the treatment, prevention and/or amelioration of NSCLC associated with or mediated by MET expression, signaling or activity, or treatable by blocking the interaction between MET and HGF, or otherwise inhibiting MET activity and/or signaling, and/or promoting receptor internalization and/or decreasing cell surface receptor number. The MET x MET bispecific antibodies are useful, *inter alia*, for the treatment and/or amelioration of NSCLC in a subject suffering from a tumor harboring a MET alteration such as an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping, a MET gene amplification, or MET protein overexpression. The MET x MET bispecific antibodies are useful, *inter alia*, for the preventing recurrence or metastasis of NSCLC in a subject suffering from a tumor harboring a MET alteration such as an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping, a MET gene amplification, or MET protein overexpression.

[0081] For example, MET x MET bispecific antibodies of the present disclosure are useful for the treatment of tumors that express (or overexpress) MET, e.g., NSCLC having a MET alteration. Illustratively, the MET alteration can be an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping, a MET gene amplification, or MET protein overexpression. In some aspects, the MET alteration is an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping. In some aspects, the MET alteration is a MET gene amplification. In some aspects, the MET alteration is MET protein overexpression.

[0082] In some embodiments, the subject suffers from non-squamous NSCLC. In some embodiments, the subject suffers from a NSCLC squamous carcinoma. In some aspects, the

NSCLC has metastasized. In some aspects, the subject has NSCLC which has metastasized to the brain. In some aspects, the subject has NSCLC which has metastasized to the liver. In some embodiments the NSCLC is unresectable. Treatment includes reducing NSCLC tumor growth and/or causing regression of an NSCLC in a subject.

[0083] Illustrative methods of using the MET x MET bispecific antibodies are provided throughout the present disclosure, and detailed below.

[0084] Methods of treating NSCLC in a subject can comprise administering to a subject in need thereof a therapeutic composition comprising a MET x MET bispecific antibody (*e.g.*, a MET x MET bispecific antibody comprising the D1 and D2 components as set forth in Table 1 herein, or an anti-MET antibody selected from the group consisting of onartuzumab, emibetuzumab, telisotuzumab, SAIT301, ARGX-111, Sym015, HuMax-cMet, and CE-355621).

[0085] Methods of treating NSCLC, reducing growth of a NSCLC tumor, inhibiting or mitigating invasion and/or metastasis, and/or causing regression of an NSCLC in a subject having a tumor that harbors a MET alteration can comprise administering to a subject in need thereof a bispecific antibody comprising a first antigen-binding domain (D1); and a second antigen-binding domain (D2); wherein D1 specifically binds a first epitope of human MET; and wherein D2 specifically binds a second epitope of human MET.

[0086] Methods of treating a subject suffering from a NSCLC tumor harboring a MET alteration can comprise administering to the subject a MET x MET bispecific antibody comprising: a first antigen-binding domain (D1); and a second antigen-binding domain (D2); wherein D1 specifically binds a first epitope of human MET; and wherein D2 specifically binds a second epitope of human MET. In some aspects, the MET alteration is an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping. In some aspects, the subject is MET targeted tyrosine kinase inhibitor (MET-TKI) naïve. In some aspects, the MET alteration is a MET gene amplification. In some aspects, the MET alteration is MET protein expression.

[0087] Methods of treating NSCLC, reducing NSCLC tumor growth, and or causing regression of NSCLC in a subject suffering from a tumor harboring a MET alteration can comprise administering to the subject a 250 to 2000 mg dose of a MET x MET bispecific antibody.

[0088] Methods of treating or inhibiting the growth of a NSCLC can comprise: (1) selecting a subject with a tumor harboring a MET alteration; and (2) administering to the subject (a) a

dose of about 250 mg, 500 mg, 750 mg, 1000 mg, 1500 mg, or 2000 mg of a MET x MET bispecific antibody. In some aspects, the administering of step (2) occurs once every 3 weeks.

[0089] Additional methods for treating a tumor comprise: (a) selecting a subject with NSCLC; (b) determining that the tumor exhibits a MET alteration selected from the group consisting of an Exon 14 alteration in DNA or a deletion that leads to exon 14 skipping, MET gene amplification, and/or Met protein overexpression, comprising (i) obtaining a tissue sample and/or a liquid sample from the subject; and (ii) assessing the tissue sample for MET gene amplification using fluorescent in situ hybridization in tumor tissues or by Next Gen Sequencing in tumor tissues and or ctDNA and/or assessing the tissue sample for Met protein overexpression using immunohistochemistry, and/or assessing the liquid sample for an Exon14 mutation using ctDNA; and, if the tumor exhibits a MET alteration, (c) administering one or more doses of a MET x MET bispecific antibody to the subject in need thereof.

[0090] Identification of a patient or patient population who will likely be successfully treated with the MET x MET antibody is desirable at least from the patient perspective. Thus, the present inventors have conceived of methods for identifying a candidate for MET x MET anti-tumor therapy, the methods comprising obtaining a tissue sample and/or a fluid sample from a subject having NSCLC; and assessing the tissue sample and/or fluid sample for a MET alteration selected from the group consisting of an Exon 14 alteration in DNA or a deletion that leads to exon 14 skipping, MET gene amplification, and/or Met protein overexpression, wherein presence of at least one Met alteration in the tissue sample or fluid sample identifies the subject as a candidate for anti-tumor therapy, wherein the MET x MET anti-tumor therapy comprises a MET x MET bispecific antibody.

[0091] Further methods for treating NSCLC in a subject can comprise: (i) obtaining a liquid sample from the subject and determining the MET amplification in ctDNA from the liquid sample, and (ii) administering a MET x MET bispecific antibody to the subject; wherein steps (i) and (ii) are repeated once every three weeks, and wherein a loss of MET amplification after step (ii) is repeated is indicative of durable response to treatment.

[0092] In some aspects, the subject according to any one of the methods provided herein has one or more of (i) histologically confirmed NSCLC; (ii) MET-exon14 gene mutation; (iii) MET gene amplification; (iv) elevated MET protein expression (IHC $\geq 2+$ or H score of >150); (v) MET exon 14 gene mutation and MET TKI experienced; (vi) MET exon 14 gene mutation and MET TKI naïve; (vii) MET gene highly amplified (MET GCN ≥ 5 and/or MET/CEP7 ratio

≥2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA) and MET TKI naïve; (viii) MET protein highly overexpressed (IHC 3+ or H score of ≥200) and MET TKI naïve; (ix) MET gene highly amplified (MET GCN ≥ 5 and/or MET/CEP7 ratio ≥2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA), MET protein highly overexpressed (IHC 3+ or H score of ≥200), and MET TKI naïve.

[0093] In some aspects, the subject is selected as having one or more of the following: Exon 14 alteration in DNA or a deletion that leads to exon 14 skipping with prior MET TKI experience; Exon 14 alteration in DNA or a deletion that leads to exon 14 skipping (MET TKI naïve) with PD-(L)1 experience; Exon 14 alteration in DNA or a deletion that leads to exon 14 skipping (MET TKI naïve) with prior EGFR inhibitor and no PD-(L)1 experience; MET gene amplification and/or MET protein overexpression (MET TKI naïve) and no PD-(L)1 experience; MET gene amplification and/or MET protein overexpression (MET TKI naïve) with PD-(L)1 experience; or MET gene amplification and/or MET protein overexpression (MET TKI naïve) with prior EGFR inhibitor and no PD-(L)1 experience. The subject can also be selected on the basis of having a tumor with one or more mutations in the EGFR gene.

[0094] In some embodiments, the subject has not received prior anti-cancer therapy. In some embodiments, the subject is MET targeted tyrosine kinase inhibitor (TKI) naïve. In other words, the subject has not received prior treatment with a TKI. In some embodiments, the subject has received prior anti-cancer therapy comprising one or more of a TKI, PD-1 inhibitor, a PD-L1 inhibitor, surgery, radiation therapy, or chemotherapy. In some aspects, the prior anti-cancer therapy comprises a TKI. In some aspects, the subject is resistant or inadequately responsive to, or relapsed after prior therapy.

[0095] In the context of the methods of treatment described herein, the MET x MET bispecific antibodies may be administered as a monotherapy (*i.e.*, as the only therapeutic agent) or in combination with one or more additional therapeutic agents.

[0096] Responsiveness to treatment with a MET x MET bispecific antibody can change over time as tumor cells develop bypass resistance mechanisms. Resistance to MET therapy can be acquired in response to prior therapies in heavily pre-treated NSCLC patients, for example, patients treated with chemotherapy, immune checkpoint inhibitors, and/or EGFR inhibitors. It is desirable to provide alternative treatments as early as possible if a tumor has proven resistant to a current therapeutic. As such, methods for monitoring efficacy of treatment with a MET x MET bispecific antibody in a subject having NSCLC with a MET alteration are provided herein. The methods comprise: (i) obtaining a tissue sample and/or a fluid sample from the subject and assessing the tissue sample and/or fluid sample

for somatic mutations in one or more genes selected from the group consisting of:

- a. an on-target MET Receptor gene mutation that confers resistance to MET TKI's found in MET Ex14 Mut patients with prior TKI Exp and MET gene silencing (loss-of-function);
- b. TK driver receptor activation selected from TK Receptor and ligand gene amplification and TKR activating mutations; and
- c. an activating gene mutation in a pathway selected from the group consisting of JAK2/STAT3 pathway, RAS/RAF/MEK/MAPK pathway, PI3K/AKT/MTOR pathway, TP53 mutations, and cell cycle gene amplification;

(ii) administering a MET x MET bispecific antibody to the subject; and (iii) repeating steps (i) and (ii) over the course of treatment; wherein the acquiring of a mutation by one or more genes is indicative of resistance to therapy and/or indicative of poor prognosis.

[0097] In some aspects, the on-target MET Receptor gene mutation is selected from the group consisting of *MET Y1230C*, *MET D1228H*, *MET D1228N*; and the MET gene silencing (loss-of-function) is selected from somatic mutations in DNMT3A and TET2.

[0098] In some aspects, the TKR activating mutation is selected from the group consisting of *EGFR L858R*, *EGFR G719S*, *EGFR E709A*, *EGFR E746_A750del*, and *EGFR S752_I759del*.

[0099] In some aspects, the *JAK2/STAT3* pathway mutation is *JAK2 V617F*; the RAS/RAF/MEK/MAPK pathway mutation is selected from the group consisting of *KRAS G12A/V*, *GNAS R201H*, *MKRN-BRAF* fusion, *BRAF S602Y*, *RICTOR* Amp, and *MAP2K1 K57N*; the *PI3K/AKT/MTOR* pathway mutation is selected from the group consisting of *PIK3CA H1047L*, *PIK3CA E545K*, *PIK3CA E542K*, *PIK3CA N345K*, *IDH1 R132L*, and *MTOR E2338Q*; the PI3K/AKT/MTOR pathway amplification is selected from the group consisting of *AKT2* Amp and *RICTOR* Amp; the *TP53* mutation is selected from the group consisting of *TP53 R280T* and *TP53 R248Q*; and the cell cycle gene amplification is selected from the group consisting of *CDK4* Amp, *CDK6* Amp, *CCND1* Amp, and *CCNE1* Amp.

[0100] Various aspects of the MET x MET bispecific antibody are provided in the following paragraphs, though described in greater detail elsewhere herein.

[0101] In some aspects, D1 and D2 do not compete with one another for binding to human

MET. In some aspects, the first epitope of human MET comprises amino acids 192-204 of SEQ ID NO:22. In some aspects, the second epitope of human MET comprises amino acids 305-315 and 421-455 of SEQ ID NO:22. In some aspects, the first epitope of human MET comprises amino acids 192-204 of SEQ ID NO:22; and the second epitope of human MET comprises amino acids 305-315 and 421-455 of SEQ ID NO:22.

[0102] In some embodiments, D1 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:9. In some embodiments, D2 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 5 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 9.

[0103] In some embodiments, the bispecific antibody comprises the CDRs within the D1-HCVR amino acid sequence of SEQ ID NO: 1 and the CDRs within the D2-HCVR amino acid sequence of SEQ ID NO: 5.

[0104] In some aspects, the bispecific antibody D1 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO:1 or an amino acid sequence that is at least 95% identical thereto and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:9 or an amino acid sequence that is at least 95% identical thereto.

[0105] In some aspects, the D1 HCDR1 comprises the amino acid sequence of SEQ ID NO:2; HCDR2 comprises the amino acid sequence of SEQ ID NO:3; HCDR3 comprises the amino acid sequence of SEQ ID NO:4; LCDR1 comprises the amino acid sequence of SEQ ID NO:10; LCDR2 comprises the amino acid sequence of SEQ ID NO:11; and LCDR3 comprises the amino acid sequence of SEQ ID NO:12.

[0106] In some aspects, the bispecific antibody D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence that is at least 95% identical thereto; and an LCVR comprising the amino acid sequence of SEQ ID NO: 9 or an

amino acid sequence that is at least 95% identical thereto.

[0107] In some aspects, the bispecific antibody D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 1; and an LCVR comprising the amino acid sequence of SEQ ID NO: 9.

[0108] In some aspects, the bispecific antibody D2 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 5 or an amino acid sequence that is at least 95% identical thereto and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical thereto.

[0109] In some aspects, the bispecific antibody D2 HCDR1 comprises the amino acid sequence of SEQ ID NO: 6; HCDR2 comprises the amino acid sequence of SEQ ID NO: 7; HCDR3 comprises the amino acid sequence of SEQ ID NO: 8; LCDR1 comprises the amino acid sequence of SEQ ID NO: 10; LCDR2 comprises the amino acid sequence of SEQ ID NO: 11; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 12.

[0110] In some aspects, the bispecific antibody D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 5 or an amino acid sequence that is at least 95% identical thereto; and an LCVR comprising the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that is at least 95% identical thereto.

[0111] In some aspects, the bispecific antibody D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 5; and an LCVR comprising the amino acid sequence of SEQ ID NO: 9.

Biological Characteristics of the Antibodies Provided Herein

[0112] Useful according to the methods provided herein are bispecific antibodies and antigen-binding fragments thereof that inhibit proliferation, inhibit invasion, cause apoptosis, and/or decrease viability of an NSCLC cell. The bispecific antibodies and antigen-binding fragments thereof bind MET receptors and prevent interaction with HGF.

[0113] Also useful according to the methods provided herein are bispecific antibodies and antigen-binding fragments thereof that bind monomeric human MET with high affinity. For example, the present disclosure includes anti-MET x MET antibodies that bind monomeric human MET (*e.g.*, hMET.mmh) with a K_D of less than about 230 nM as measured by surface

plasmon resonance at 25°C or 37°C, *e.g.*, using an assay format as defined in U.S. Patent No. 11,142,578 Example 3, or a substantially similar assay. According to certain embodiments, anti-MET antibodies are useful according to the methods provided herein bind monomeric human MET at 37°C with a K_D of less than about 230 nM, less than about 200 nM, less than about 150 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 20 nM, less than about 10 nM, Less than about 8 nM, less than about 6 nM, less than about 5 nM, less than about 4 nM, or less than about 3 nM, as measured by surface plasmon resonance, *e.g.*, using an assay format as defined in U.S. Patent No. 11,142,578, Example 3, or a substantially similar assay.

[0114] Such bispecific antibodies and antigen-binding fragments thereof bind monomeric human MET (*e.g.*, hMET.mmh) with a dissociative half-life ($t_{1/2}$) of greater than about 1 minute as measured by surface plasmon resonance at 25°C or 37°C, *e.g.*, using an assay format as defined in U.S. Patent No. 11,142,578 Example 3, or a substantially similar assay. Such bispecific antibodies are provided that bind monomeric human MET at 37°C with a $t_{1/2}$ of greater than about 1 minute, greater than about 2 minutes, greater than about 4 minutes, greater than about 6 minutes, greater than about 8 minutes, greater than about 10 minutes, greater than about 12 minutes, greater than about 14 minutes, greater than about 16 minutes, greater than about 18 minutes, or greater than about 20 minutes, or longer, as measured by surface plasmon resonance, *e.g.*, using an assay format as defined in U.S. Patent No. 11,142,578, Example 3, or a substantially similar assay.

[0115] Such bispecific antibodies and antigen-binding fragments thereof bind dimeric human MET (*e.g.*, hMET.mFc) with high affinity. For example, the bispecific antibodies bind dimeric human MET with a K_D of less than about 3 nM as measured by surface plasmon resonance at 25°C or 37°C, *e.g.*, using an assay format as defined in U.S. Patent No. 11,142,578 Example 3, or a substantially similar assay. According to certain embodiments, anti-MET antibodies are provided that bind dimeric human MET at 37°C with a K_D of less than about 3 nM, less than about 2 nM, less than about 1 nM, less than about 0.9 nM, less than about 0.8 nM, less than about 0.7 nM, less than about 0.6 nM, less than about 0.5 nM, less than about 0.4 nM, less than about 0.3 nM, or less than about 0.25 nM, as measured by surface plasmon resonance, *e.g.*, using an assay format as defined in U.S. Patent No. 11,142,578, Example 3, or a substantially similar assay.

[0116] Such bispecific antigen binding molecules and antigen-binding fragments thereof may bind dimeric human MET (*e.g.*, hMET.mFc) with a dissociative half-life ($t_{1/2}$) of greater than about 4 minutes as measured by surface plasmon resonance at 25°C or 37°C, *e.g.*, using an assay format as defined in U.S. Patent No. 11,142,578 Example 3, or a substantially similar

assay. According to certain embodiments, anti-MET antibodies are provided that bind dimeric human MET at 37°C with a $t_{1/2}$ of greater than about 4 minutes, greater than about 5 minutes, greater than about 10 minutes, greater than about 20 minutes, greater than about 30 minutes, greater than about 40 minutes, greater than about 50 minutes, greater than about 60 minutes, greater than about 70 minutes, greater than about 80 minutes, greater than about 90 minutes, greater than about 100 minutes, greater than about 105 minutes, or longer, as measured by surface plasmon resonance, *e.g.*, using an assay format as defined in U.S. Patent No. 11,142,578, Example 3, or a substantially similar assay.

[0117] Also useful according to the methods provided herein are MET x MET bispecific antigen-binding proteins that bind dimeric human MET (*e.g.*, hMET.mFc) with a dissociative half-life ($t_{1/2}$) of greater than about 10 minutes as measured by surface plasmon resonance at 25°C or 37°C, *e.g.*, using an assay format as defined in U.S. Patent No. 11,142,578, Example 6, or a substantially similar assay. According to certain embodiments, MET x MET bispecific antigen-binding proteins are provided that bind dimeric human MET at 37°C with a $t_{1/2}$ of greater than about 10 minutes, greater than about 20 minutes, greater than about 30 minutes, greater than about 40 minutes, greater than about 50 minutes, greater than about 60 minutes, greater than about 70 minutes, greater than about 80 minutes, greater than about 90 minutes, greater than about 100 minutes, greater than about 200 minutes, greater than about 300 minutes, greater than about 400 minutes, greater than about 500 minutes, greater than about 600 minutes, greater than about 700 minutes, greater than about 800 minutes, greater than about 900 minutes, greater than about 1000 minutes, greater than about 1100 minutes, or longer, as measured by surface plasmon resonance, *e.g.*, using an assay format as defined in U.S. Patent No. 11,142,578, Example 6, or a substantially similar assay.

[0118] Also useful according to the methods provided herein are MET x MET bispecific antibodies that block the interaction between HGF and MET, *e.g.*, in an *in vitro* ligand-binding assay. According to certain embodiments provided herein, the MET x MET bispecific antigen-binding proteins block HGF binding to cells expressing human MET, and induce minimal or no MET activation in the absence of HGF signaling. For example, the present disclosure provides MET x MET bispecific antigen-binding proteins that exhibit a degree of MET agonist activity in a cell-based MET activity reporter assay that is less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, less than 5%, less than 3%, less than 2% or less than 1% of the MET agonist activity observed in an equivalent activity reporter assay using a monospecific antibody comprising D1 or D2 alone.

[0119] The bispecific antibodies useful according to the present disclosure may possess one

or more of the aforementioned biological characteristics, or any combination thereof. The foregoing list of biological characteristics of the antibodies is not intended to be exhaustive. Other biological characteristics of the antibodies provided herein will be evident to a person of ordinary skill in the art from a review of the present disclosure including the working Examples herein.

Epitope Mapping and Related Technologies

[0120] Useful according to the methods provided herein are MET x MET bispecific antibodies that bind a human MET epitope comprising amino acids 192-204, amino acids 305-315, and/or amino acids 421-455 of SEQ ID NO:22.

Preparation of Human Antibodies

[0121] The MET x MET bispecific antibodies useful according to the methods provided herein can be fully human antibodies. Methods for generating monoclonal antibodies, including fully human monoclonal antibodies are known in the art. Any such known methods can be used in the context of the present disclosure to make human antibodies that specifically bind to human MET.

[0122] Using VELOCIMMUNE™ technology, for example, or any other similar known method for generating fully human monoclonal antibodies, high affinity chimeric antibodies to MET are initially isolated having a human variable region and a mouse constant region. As in the experimental section below, the antibodies are characterized and selected for desirable characteristics, including affinity, ligand blocking activity, selectivity, epitope, *etc.* If necessary, mouse constant regions are replaced with a desired human constant region, for example wild-type or modified IgG1 or IgG4, to generate a fully human anti-MET antibody. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region. In certain instances, fully human anti-MET antibodies are isolated directly from antigen-positive B cells.

Bioequivalents

[0123] The methods described herein can utilize MET x MET bispecific antibodies and antibody fragments thereof that encompass proteins having amino acid sequences that vary from those of the described antibodies but that retain the ability to bind human MET. Such variant molecules and antibody fragments comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence but exhibit biological activity that is essentially equivalent to that of the described molecules. Likewise, the anti-

MET x MET antibody-encoding DNA sequences of the present disclosure encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an anti-MET x MET antibody or antibody fragment that is essentially bioequivalent to an anti-MET antibody or antibody fragment of the disclosure. Examples of such variant amino acid and DNA sequences are discussed above.

[0124] Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single does or multiple doses. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, *e.g.*, chronic use, and are considered medically insignificant for the particular drug product studied.

[0125] In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[0126] In one embodiment, two antigen-binding proteins are bioequivalent if a subject can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[0127] In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

[0128] Bioequivalence may be demonstrated by in vivo and in vitro methods. Bioequivalence measures include, *e.g.*, (a) an in vivo test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an in vitro test that has been correlated with and is reasonably predictive of human in vivo bioavailability data; (c) an in vivo test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled

clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

[0129] Bioequivalent variants of anti-MET antibodies provided herein may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other contexts, bioequivalent antibodies may include anti-MET antibody variants comprising amino acid changes which modify the glycosylation characteristics of the antibodies, *e.g.*, mutations which eliminate or remove glycosylation.

Species Selectivity and Species Cross-Reactivity

[0130] The present disclosure, according to certain embodiments, provides methods of using anti-MET antibodies (and antibodies comprising anti-MET antigen-binding domains) that bind to human MET but not to MET from other species. Also useful are anti-MET antibodies (and antibodies comprising anti-MET antigen-binding domains) that bind to human MET and to MET from one or more non-human species. For example, the anti-MET x MET antibodies and antibodies may bind to human MET and may bind or not bind, as the case may be, to one or more of mouse, rat, guinea pig, hamster, gerbil, pig, cat, dog, rabbit, goat, sheep, cow, horse, camel, cynomolgus, marmoset, rhesus or chimpanzee MET. According to certain exemplary embodiments, anti-MET x MET antibodies and antibodies are provided which specifically bind human MET and cynomolgus monkey (*e.g.*, *Macaca fascicularis*) MET. Other anti-MET x MET antibodies and antibodies bind human MET but do not bind, or bind only weakly, to cynomolgus monkey MET.

Therapeutic Formulation and Administration

[0131] Useful herein are pharmaceutical compositions comprising the MET x MET bispecific antibodies of the present invention. The pharmaceutical compositions may be formulated with suitable carriers, excipients, and other agents that provide improved transfer, delivery, tolerance, and the like.

[0132] In some aspects, the pharmaceutical compositions comprising the MET x MET bispecific antibodies are formulated for administration to a subject for treating lung cancer, and specifically, for treating NSCLC.

[0133] Provided herein are methods in which the MET x MET bispecific antibodies that are

administered to the subject are contained within a pharmaceutical formulation. The pharmaceutical formulation may comprise the MET x MET bispecific antibody along with at least one inactive ingredient such as, e.g., a pharmaceutically acceptable carrier. Other agents may be incorporated into the pharmaceutical composition to provide improved transfer, delivery, tolerance, and the like. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the antibody is administered. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences (15th ed, Mack Publishing Company, Easton, Pa., 1975), particularly Chapter 87 by Blaug, Seymour, therein. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN.TM.), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. Any of the foregoing mixtures may be appropriate in the context of the methods of the present disclosure, provided that the anti-MET antibody or MET x MET bispecific antibody is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration. See also Powell et al. PDA (1998) J Pharm Sci Technol. 52:238-311 and the citations therein for additional information related to excipients and carriers well known to pharmaceutical chemists.

[0134] Pharmaceutical formulations useful for administration by injection in the context of the present disclosure may be prepared by dissolving, suspending or emulsifying an anti-MET antibody or MET x MET bispecific antibody in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there may be employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared can be filled in an appropriate ampoule if desired.

Administration Regimens

[0135] According to certain embodiments, multiple doses of an anti-MET antibody or MET x MET bispecific antibody (or a pharmaceutical composition comprising a combination of an anti-MET antibody or MET x MET bispecific antibody and any of the additional therapeutically active agents mentioned herein) may be administered to a subject over a defined time course. The methods according to this aspect comprise sequentially administering to a subject multiple doses of an anti-MET antibody or MET x MET bispecific antibody provided herein. As used herein, “sequentially administering” means that each dose of antibody is administered to the subject at a different point in time, *e.g.*, on different days separated by a predetermined interval (*e.g.*, hours, days, weeks or months). The present disclosure includes methods which comprise sequentially administering to the subject a single initial dose of an anti-MET antibody or MET x MET bispecific antigen-binding molecule, followed by one or more secondary doses of the anti-MET antibody or MET x MET bispecific antigen-binding molecule, and optionally followed by one or more tertiary doses of the anti-MET antibody or MET x MET bispecific antibody.

[0136] The terms “initial dose,” “secondary doses,” and “tertiary doses,” refer to the temporal sequence of administration of the anti-MET antibody or MET x MET bispecific antibody. Thus, the “initial dose” is the dose which is administered at the beginning of the treatment regimen (also referred to as the “baseline dose”); the “secondary doses” are the doses which are administered after the initial dose; and the “tertiary doses” are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of anti-MET antibody or MET x MET bispecific antigen-binding molecule, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of antibody contained in the initial, secondary and/or tertiary doses varies from one another (*e.g.*, adjusted up or down as appropriate) during the course of treatment. In certain embodiments, two or more (*e.g.*, 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as “loading doses” followed by subsequent doses that are administered on a less frequent basis (*e.g.*, “maintenance doses”).

[0137] The anti-MET antibody or MET x MET bispecific antibody can be administered according to any regimen which provides a therapeutic effect. In some aspects, the bispecific antibody is administered at a dosing frequency of about four times a week, twice a week, once a week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every eight weeks, once every twelve weeks, or less frequently so long as a therapeutic response is achieved. In some aspects,

the bispecific antibody is administered once a week, once every two weeks, once every three weeks, or once a month. In some aspects, the bispecific antibody is administered once every three weeks.

[0138] In some aspects, the bispecific antibody is administered one week, two weeks, three weeks, or four weeks after the immediately preceding dose. In some aspects, the bispecific antibody is administered three weeks after the immediately preceding dose.

[0139] According to certain embodiments of the present disclosure, multiple doses of bispecific antibody may be administered to a subject over a defined time course. The methods according to this aspect of the disclosure comprise sequentially administering to a subject more than one dose of the bispecific antibody. As used herein, "sequentially administering" means that each dose of the antibody is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months). The present disclosure includes methods which comprise sequentially administering to the subject a single initial dose of a bispecific antigen-binding molecule, followed by one or more secondary doses of the bispecific antigen-binding molecule, and optionally followed by one or more tertiary doses of the bispecific antibody.

[0140] According to certain embodiments of the present disclosure, multiple doses of a bispecific antibody can be administered to a subject for several months or years, once every 3 or 6 weeks.

[0141] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of the antibody (anti-MET x MET bispecific antigen-binding molecule). In certain embodiments, however, the amount contained in the initial, secondary and/or tertiary doses varies from one another (e.g., adjusted up or down as appropriate) during the course of treatment. In certain embodiments, one or more (e.g., 1, 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (e.g., "maintenance doses"). For example, a bispecific antibody may be administered to a subject with NSCLC at a loading dose of about 1000-3000 mg followed by one or more maintenance doses of about 500 mg, 1000 mg, or 2000 mg.

[0142] In one exemplary embodiment of the present disclosure, each secondary and/or tertiary dose is administered $\frac{1}{2}$ to 14 (e.g., $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2, $2\frac{1}{2}$, 3, $3\frac{1}{2}$, 4, $4\frac{1}{2}$, 5, $5\frac{1}{2}$, 6, $6\frac{1}{2}$, 7, $7\frac{1}{2}$, 8, $8\frac{1}{2}$, 9, $9\frac{1}{2}$, 10, $10\frac{1}{2}$, 11, $11\frac{1}{2}$, 12, $12\frac{1}{2}$, 13, $13\frac{1}{2}$, 14, $14\frac{1}{2}$, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of the bispecific antibody which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0143] The methods according some aspects may comprise administering to a subject any number of secondary and/or tertiary doses of the bispecific antibody. For example, in certain embodiments, only a single secondary dose is administered to the subject. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the subject. Likewise, in certain embodiments, only a single tertiary dose is administered to the subject. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the subject.

[0144] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the subject 1 to 2 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the subject 2, 3, or 4 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a subject can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual subject following clinical examination.

[0145] In certain embodiments, one or more doses of the bispecific antibody are administered at the beginning of a treatment regimen as "induction doses" on a more frequent basis (twice a week, once a week or once in 2 weeks) followed by subsequent doses ("consolidation doses" or "maintenance doses") that are administered on a less frequent basis (e.g., once in 4-12 weeks).

Dosage

[0146] The amount of the MET x MET bispecific antibody administered to a subject according to the methods of the present disclosure is, generally, a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means an amount of the bispecific antibody that results in, or has the therapeutic effect of, one or more of: (a) a

reduction in the severity or duration of a symptom of cancer; (b) inhibition of tumor growth, or an increase in tumor necrosis, tumor shrinkage and/or tumor disappearance; (c) delay in tumor growth and development; (d) inhibit or retard or stop tumor metastasis; (e) prevention of recurrence of tumor growth; (f) increase in survival of a subject with a cancer; and/or (g) a reduction in the use or need for conventional anti-cancer therapy (e.g., reduced or eliminated use of chemotherapeutic or cytotoxic agents) as compared to an untreated subject.

[0147] In some instances, a therapeutically effective amount can be from about 250 mg to about 8000 mg, e.g., about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2200 mg, about 2500 mg, about 2700 mg, about 2800 mg, about 2900 mg, about 3000 mg, about 3200 mg, about 4000 mg, about 5000 mg, about 6000 mg, about 7000 mg, or about 8000 mg of the MET x MET bispecific antibody.

[0148] In some aspects, the bispecific antibody can be administered at a dose of about 250 mg to about 5000 mg, or a dose of about 250 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 750 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, 2100 mg, 2200 mg, 2300 mg, 2400 mg, 2500 mg, 3000 mg, 3500 mg, 4000 mg, 4500 mg, or 5000 mg. In some aspects, the dose is about 500 mg MET x MET bispecific antibody. In some aspects, the dose is about 1000 mg MET x MET bispecific antibody. In some aspects, the bispecific antibody is administered at a dose of about 2000 mg. In some aspects, the MET X MET bispecific antibody can be administered at a dose of 250 mg, 500 mg, 1000 mg, or 2000 mg.

[0149] The bispecific antibody can be administered intravenously, subcutaneously, or intraperitoneally. In some aspects, the bispecific antibody is administered by intravenous infusion.

EXAMPLES

[0150] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions provided herein and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (*e.g.*, amounts, temperature, *etc.*) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight,

molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Construction of Bispecific Antibodies Having Two Different Antigen-Binding Domains Specific for Different Epitopes of MET

[0151] U.S. Patent No. 11,142,578 (incorporated by reference herein in its entirety), Examples 1 through 3, describes the construction of a bispecific antibody comprising two different antigen-binding domains derived from two bivalent, monospecific anti-MET antibodies (a “D1” arm derived from the exemplary anti-MET antibody H4H13306P2 and a “D2” arm derived from the exemplary anti-MET antibody H4H13312P2) and, consequently, bind to separate epitopes on the MET extracellular domain:

[0152] Binding epitope of Anti-Met antibody H4H13312P2: AA 192-204: VRRLKETKDGFMF (SEQ ID NO: 23) of SEQ ID NO: 22.

[0153] Binding epitope of Anti-Met antibody H4H13306P2: AA 305-315: LARQIGASLND (SEQ ID NO: 24) of SEQ ID NO: 22 and AA 421-455: FIKGDLTIANLGTSEGRFMQVVVSRSGPSTPHVNF (SEQ ID NO: 25) of SEQ ID NO: 22.

[0154] Both antigen-binding domains (D1 and D2) comprise a common light chain variable region. The components of the bispecific antibody useful according to the methods provided herein are summarized in Table 1.

Table 1: MET x MET Bispecific Antibody Components Summary

H4H14639D Bispecific Antibody; aka REGN5093	SEQ ID NOs: (Amino Acid Sequences)							
	First Antigen-Binding Domain (D1) H4H13306P2				Second Antigen-Binding Domain (D2) H4H13312P2			
	D1- HCVR	D1- HCDR1	D1- HCDR2	D1- HCDR3	D2- HCVR	D2- HCDR1	D2- HCDR2	D2- HCDR3
	1	2	3	4	5	6	7	8
	D1- LCVR	D1- LCDR1	D1- LCDR2	D1- LCDR3	D2- LCVR	D2- LCDR1	D2- LCDR2	D2- LCDR3
	9	10	11	12	9	10	11	12

[0155] Binding kinetic parameters for H4H14639D to monomeric Met protein (hMET.mmh) are shown in Table 2.

Table 2: Biacore Binding Affinity of H4H14639D at 37°C

Binding at 37°C / Antibody-Capture Format					
Bispecific Antibody	Analyte	k_a (M ⁻¹ s ⁻¹)	k_d (s ⁻¹)	K_D (Molar)	$T_{1/2}$ (min)
H4H14639D	hMet.mmh	N/A	1.63E-04	N/A	70.8

[0156] H4H14639D exhibits a dissociation rate which is significantly lower than the dissociation rates of each of its parental antibodies, H4H13306P2 and H4H13312P2. See Table 3.

Table 3: Biacore Binding Affinities of Bispecific Anti-MET mAb and Monospecific Parents at 37°C

Binding at 37°C / Antibody-Capture Format			
Antibody	Analyte	k_d (s ⁻¹)	$T_{1/2}$ (min)
H4H13306P2	hMet.mmh	1.66E-02	0.7
H4H13312P2	hMet.mmh	8.40E-03	1.4
H4H14639D	hMet.mmh	1.63E-04	70.8

[0157] As noted in U.S. Patent No. 11,142,578, Example 7, the MET x MET bispecific antibody blocks HGF signaling and exhibits low MET agonist activity.

Example 2. Anti-Met Antibodies Inhibit Growth of Met-Amplified Cells

[0158] The blocking activity of a MET x MET bispecific antibody (*i.e.*, H4H14639D) was assessed in the non-small cell lung cancer (NSCLC) cell line EBC-1, which exhibits amplified Met gene and overexpresses MET (Lutterbach *et al.*, Cancer Res. 67(5): 2081-2088, 2007). Complete growth media for the EBC-1 cells contained MEM Earle's Salts, 10% fetal bovine serum (FBS), penicillin/streptomycin/glutamine, and non-essential amino acids for MEM. H4H14369D exhibited the greatest percent inhibition in MET activity according to the SRE-Luciferase read-out. In the current experiment, 3.0×10^3 EBC-1 cells were seeded in complete growth media in the presence of H4H14639D at concentrations ranging from 15 pM to 100 nM. Cells were incubated for 3 days at 37°C in 5% CO₂. The cells were then fixed in 4% formaldehyde and stained with 3 µg/ml Hoechst 33342 to label the nuclei. Images were acquired on the IMAGEEXPRESS® Micro XL (Molecular Devices, Sunnyvale, CA) and nuclear counts were determined via METAXPRESS® Image Analysis software (Molecular Devices, Sunnyvale, CA). Background nuclear counts from cells treated with 40 nM digitonin were subtracted from all wells and viability was expressed as a percentage of the untreated

controls. IC50 values were determined from a four-parameter logistic equation over a 10-point response curve (GRAPHPAD PRISM®). As summarized in Table 4, below, the MET x MET bispecific antibody H4H14639D inhibited growth of EBC-1 cells by 37, and with an IC50 of 0.82 nM.

Table 4: Anti-Met Bispecific Antibody Blocks EBC-1

mAb	IC ₅₀ (nM)	% Growth Inhibition
	EBC-1	EBC-1
H4H14639D	0.82	37

[0159] The effect of MET x MET bispecific antibody on the growth of EBC-1 cells was assessed. 2,500 EBC-1 cells were seeded in a 96 well plate and cultured in Dulbecco's Media supplemented with 10% FBS. The cells were treated with a control antibody or a MET x MET bispecific antibody at 0.1 µg/mL or 1 µg/mL, and were subsequently incubated with 5% CO₂ at 37°C. After 5 days, relative cell growth was determined by measuring the reduction of the indicator dye ALAMARBLUE® to its highly fluorescent form in a SPECTRAMAX® M3 plate reader (Molecular Devices, LLC, Sunnyvale, CA). The results are shown in Table 5 and Figure 1. The MET x MET bispecific antibody (H4H14639D) significantly reduced the relative cell growth of EBC-1 cells compared to the control antibody (Figure 1).

[0160] Several anti-MET antibodies, both bivalent monospecific and MET x MET bivalent, are potent inhibitors of SRE-Luc activation and inhibit the growth of Met-amplified and MET-overexpressing cell lines.

Table 5: Anti-Met Bispecific Antibody Blocks EBC-1 Cell Growth

	Relative Cell Growth (n=3)	Standard Deviation
Control	1.000	0.045
0.1 µg/mL H4H14639D	0.397	0.032
1 µg/mL H4H14639D	0.462	0.028

Example 3. A MET x MET Bispecific Antibody Induces Modest and Transient MET Pathway Activity in NCI-H596 NSCLC Cells

[0161] The effect of a MET x MET bispecific antibody on the MET pathway in human lung adenosquamous carcinoma cells was assessed *in vitro*.

[0162] 250,000 NCI-H596 cells were seeded in a 12 well plate and cultured in RPMI Media supplemented with 10 % FBS. The cells were treated with hepatocyte growth factor (HGF) at 50 ng/ml or the MET x MET bispecific antibody H4H14639D at 10 µg/ml in duplicate. The cells were subsequently incubated in 5% CO₂ at 37°C. After 0, 2, 6 or 18 hours, cell lysates were prepared, protein content was normalized and immunoblot analysis was performed. MET phosphorylation and ERK phosphorylation were quantified with the ImageJ image processing program (T. Collins, BioTechniques 43: S25-S30, 2007). Phosphorylation levels were normalized to the Tubulin loading control and are expressed as fold change relative to control treatment. The results are summarized in Table 6.

Table 6: Phosphorylation of MET and ERK

Treatment (hours)	Phospho-MET (mean ± SD)	Phospho-ERK (mean ± SD)
Control (hFc) (18)	1.0 ± 0.5	1.0 ± 0.3
HGF (2)	202.3 ± 38.7	16.7 ± 1.6
HGF (6)	38.9 ± 4.9	12.4 ± 3.9
HGF (18)	59.2 ± 24.4	12.4 ± 0.9
H4H14639D (2)	69.7 ± 7.0	2.2 ± 0.9
H4H14639D (6)	9.9 ± 7.4	0.3 ± 0.4
H4H14639D (18)	1.4 ± 0.1	0.1 ± 0.1

[0163] HGF treatment of NCI-H596 cells induced strong activation of MET and ERK that peaked at 2 hours and was sustained after 18 hours. Modest MET and ERK phosphorylation was detected with the H4H14636D bispecific antibody treatment, which returned to baseline levels by 18 or 6 hours, respectively.

Example 4. A MET x MET Bispecific Antibody Induces MET Degradation More Potently Than Monospecific Antibodies in NCI-H596 Lung Cancer Cells

[0164] The effect of a MET x MET bispecific antibody and the parental bivalent monospecific anti-MET antibodies on the expression levels of hepatocyte growth factor receptor (HGFR or

MET) on human lung adenosquamous carcinoma cells was assessed. 250,000 NCI-H596 human lung adenosquamous carcinoma cells were seeded in a 12-well plate and cultured in RPMI Media supplemented with 10% FBS. The cells were treated with (1) 5 µg/ml of the hFc control molecule, (2) 5 µg/ml of the parental bivalent monospecific anti-MET antibody H4H13306P2, (3) 5 µg/ml of the parental bivalent monospecific anti-MET antibody H4H13312P2, (4) the combination of 2.5 µg/mL of H4H13306P2 and 2.5 µg/mL of H4H13312P2, or (5) 5 µg/ml of the MET x MET bispecific antibody H4H14639D. The cells were subsequently incubated with 5% CO₂ at 37°C. After 18 hours, cell lysates were prepared, protein content was normalized and immunoblot analysis was performed. MET expression was quantified with the ImageJ image processing program (T. Collins, BioTechniques 43: S25-S30, 2007). The results are summarized in Table 7.

Table 7: Relative Level of MET Protein

Molecule	Relative MET Level
Control (hFc)	1 ± 0.03
H4H13306P2	0.50 ± 0.01
H4H13312P2	0.35 ± 0.04
H4H13306P2+H4H13312P2	0.61 ± 0.04
H4H14639D	0.24 ± 0.01

[0165] NCI-H596 (MET exon14 skip mutation) lung cancer cells were also treated with control or MET x MET bispecific antibodies at 10 µg/ml for 2, 6 or 18 hrs. MET expression was determined by immunoblotting (Figure 2), which shows the MET x MET bispecific antibody-induced degradation of MET with increasing time of treatment.

[0166] The bispecific antibody, H4H14636D, induces MET degradation more potently than its parental conventional antibodies in NCI-H596 lung cancer cells.

Example 5. A MET x MET Bispecific Antibody Induces MET Degradation, Inhibits Pathway Activity, and Inhibits Tumor Growth More Potently Than Monospecific Antibodies in EBC-1 Cells

[0167] MET-amplified human lung squamous cell carcinoma EBC-1 cells (Lutterbach *et al.*, “Lung cancer cell lines harboring MET gene amplification are dependent on Met for growth and survival,” Cancer Res. 2007 Mar 1;67(5):2081-8) were treated with a control antibody or 10 µg/ml of a MET x MET bispecific antibody for 18 hrs as described above. MET expression and MET pathway activation ascertained by pMET and pErk expression were

determined by immunoblotting with the indicated antibodies. The immunoblots are shown in Figure 3.

[0168] Treatment of EBC-1 cells, which harbor MET gene amplification, with MET x MET bispecific antibodies induced more potent degradation of MET than treatment with the control antibody. Treatment of EBC-1 cells with the MET x MET bispecific antibody inhibited downstream effectors of the MET pathway.

[0169] In another experiment, 5 million EBC-1 cells were implanted subcutaneously into the flank of C.B.-17 SCID mice. Once the tumor volumes reached approximately 150 mm³, mice were randomized into groups of 6 and were treated twice a week with a control antibody at 25 mg/kg or the MET x MET bispecific antibody H4H14639D at 25 mg/kg. Tumor growth was monitored for 30 days post-implantation and tumor volume (mm³) was measured for each experimental group over time. The results are depicted in Table 8 and Figure 4, which shows that the MET x MET bispecific antibody significantly inhibits the growth of EBC-1 tumors.

Table 8: Relative EBC-1 Tumor Growth

Treatment	Tumor Growth (mm ³) form the start of treatment (mean ± SEM)
25 mg/kg Control	1394 ± 226
25 mg/kg H4H14639D	89 ± 47

Example 6. A MET x MET Bispecific Antibody Does Not Induce Growth of NCI-H596 Lung Cancer Cells *in vitro*

[0170] The effect of a MET x MET bispecific antibody on the growth of human non-small cell lung cancer (NSCLC) cells (NCI-H596) was assessed *in vitro*. 10,000 NCI-H596 lung adenosquamous carcinoma cells (Nair *et al.*, J. Nat'l. Cancer Inst. 86(5): 378-383, 1994) were seeded in 96 well plates on a layer of 0.66% agar in media supplemented with 1% fetal bovine serum (FBS). The cells were cultured in RPMI 1640 media supplemented with 1 % FBS with 0.3 % agarose. The cells were treated with (1) individual parental bivalent monospecific anti-MET antibodies (H4H13306P2 or H4H13312P2) at 5 µg/ml, (2) a combination of the two parental bivalent monospecific anti-MET antibodies (H4H13306P2 and H4H13312P2) at 2.5 µg/ml each, (3) a bispecific antibody containing one binding arm from H4H13306P2 and the other binding arm from H4H13312P2 (H4H14639D) at 5 µg/ml, or (4) 100 ng/mL of hepatocyte growth factor (HGF). The cells were subsequently incubated with 5% CO₂ at 37°C. After two weeks, relative cell growth was determined by measuring the reduction of the indicator dye, ALAMAR BLUE® (Thermo Fischer Scientific, Waltham, MA),

to its highly fluorescent form in a SPECTRAMAX® M3 plate reader (Molecular Devices, Sunnyvale, CA). Increasing fluorescence correlates with cell growth. Table 9 and Figure 5 depict the relative NCI-H596 cell growth for each antibody treatment normalized to control (no treatment) NCI-H596 cell growth. Treatment of NCI-H596 lung cancer cells with HGF resulted in potent induction of growth in soft agar. The MET x MET (MM in Figure 5) bispecific antibody H4H14639D did not significantly alter growth relative to control treated cells. Modest induction of cell growth was observed with each parental bivalent monospecific antibody H4H13306P2 (M1) or H4H13312P2 (M2) individually, or combined (H4H13306P2 and H4H13312P2) (M1M2).

Table 9: Normalized NCI-H596 Cell Growth

	Relative Cell Growth (n=3)	Standard Deviation
Control	1	0.030074808
H4H14639D	1.070339237	0.075103746
H4H13306P2	2.9593578	0.337877264
H4H13312P2	1.686580346	0.145670753
H4H13306P2+H4H13312P2	1.693724668	0.168651046
HGF	7.87655937	0.46057617

Example 7. Clinical Trial of Met x Met Bispecific Antibody in Non-Small Cell Lung Cancer

Background:

[0171] Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer-related mortality worldwide (Siegel *et al.*, CA Cancer J Clin, 66(1):7-30, 2016). Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers and is composed of several histopathological subtypes, the most common of which are adenocarcinoma (40% to 60%) and squamous cell carcinoma (30%) (Dela Cruz *et al.*, Clin Chest Med, 32(4):605-44, 2011). The majority of patients with NSCLC are found to have advanced cancer at the time of diagnosis.

[0172] First-line treatment of advanced NSCLC is guided by the presence of molecular alterations. Patients may receive targeted, small molecule tyrosine kinase inhibitors (TKIs) (Besse *et al.*, Ann Oncol, 25(8):1475-84, 2014) (Ettinger *et al.*, J Natl Compr Canc Netw 15(4):504-35, 2017) (Reck *et al.*, Ann Oncol, 25 Suppl 3:27-39, 2014), immune-checkpoint–

inhibitor antibodies that inhibit the PD-1 receptor or PD-1 ligand (PD-L1), or platinum-based doublet chemotherapy regimens, with or without maintenance therapy (Besse *et al.*, *Ann Oncol*, 25(8):1475-84, 2014) (Ettinger *et al.*, *J Natl Compr Canc Netw* 15(4):504-35, 2017) (Reck *et al.*, *Ann Oncol*, 25 Suppl 3:27-39, 2014). Long-term survival remains an unmet need in advanced NSCLC. Overall survival (OS) is approximately 12 months for PD-1/PD-L1 inhibitors, with some studies in TKI-treated patients exceeding 2 years (Camidge *et al.*, *J Clin Oncol*, 32:abstract 8001, 2014).

[0173] Mesenchymal epithelial transition factor (MET) is a single-pass transmembrane tyrosine kinase receptor for the hepatocyte growth factor (HGF). It is expressed in normal tissues such as liver, breast, and adipose and is upregulated in several cancers. High levels of MET expression can occur through increased protein expression or through gene amplification in NSCLC tumors and gastric tumors, and are associated with negative outcomes in patients (Catenacci *et al.*, *Cancer*, 123(6):1061-70, 2017) (Topalian *et al.*, *NEJM*, 366(26):2443-54, 2012) (Zhang *et al.*, *Hum Pathol*, 72:59-65, 2018). Mutations in MET resulting in exon 14 deletions promote prolonged ligand-dependent signaling, resulting in receptor stability and increased tumorigenicity (Kong-Beltran *et al.*, *Cancer Res*, 66(1):283-9, 2006).

[0174] Approximately 3% of NSCLC is reported to contain MET exon 14 alterations (Cancer Genome Atlas Research Network, *Nature*, 511(7511):543-50, 2014) (Schrock *et al.*, *J Thorac Oncol*, 11(9):1493-1502, 2016). Furthermore, genetic amplification of the MET gene has been reported in ~3% and elevated MET protein expression has been reported in 25% of NSCLC (Bubendorf *et al.*, *Lung Cancer*, 111:143-9, 2017) (Cappuzzo *et al.*, *J Clin Oncol*, 27(10):1667-74, 2009) (Fang *et al.*, *Oncotarget*, 9(16):12959-70, 2018) (Reis *et al.*, *Clin Lung Cancer*, 19(4):e441-63, 2018) (Sterlacci *et al.*, *Virchows Arch*, 471(1):49-55, 2017). Increased MET gene amplification and expression is a mechanism of resistance to epidermal growth factor receptor (EGFR)-targeted therapy, and up to 25% of tumors that are resistant to third-generation TKIs may harbor elevated MET by these mechanisms (Bean *et al.*, *PNAS*, 104(52):20932-7, 2007) (Catenacci *et al.*, *Cancer*, 123(6):1061-70, 2017) (Go *et al.*, *J Thorac Oncol*, 5(3):283-9, 2010) (Le *et al.*, *JAMA Oncol*, 4(2):210-6, 2018) (Zhang *et al.*, *Hum Pathol*, 72:59-65, 2018).

[0175] Tumors harboring MET-amplification or exon-14 deletions respond to MET TKIs (Crizotinib® [package insert], Pfizer Pharmaceutical Company, New York, NY, 2017) (Angevin *et al.*, *Eur J Cancer*, 87:131-9, 2017) (Camidge *et al.*, *J Clin Oncol*, 32:abstract 8001, 2014) (Camidge *et al.*, *Nat Rev Clin Oncol*, 16(6):341-55, 2019) (Paik *et al.*, *Cancer Discov*, 5(8):842-9, 2015).

[0176] REGN5093 is a human bispecific antibody (bsAb) that binds 2 distinct epitopes of MET with nanomolar affinity, blocks HGF binding to MET, and induces internalization and degradation of MET without inducing MET-driven biological responses. In preclinical studies, REGN5093 has shown dose-dependent anti-tumor activity in immune-deficient mouse models of MET-driven cancer including both exon 14-altered and MET-amplified models.

Unmet Need in Lung Cancer

[0177] First-line treatment of advanced NSCLC is guided by the presence of molecular alterations. Patients with tumors which exhibit sensitizing mutations in EGFR, anaplastic lymphoma kinase (ALK), or c-ros oncogene 1 receptor tyrosine kinase (ROS1) fusion are often targeted using small molecule TKIs (Besse *et al.*, *Ann Oncol*, 25(8):1475-84, 2014) (Ettinger *et al.*, *J Natl Compr Canc Netw* 15(4):504-35, 2017) (Reck *et al.*, *Ann Oncol*, 25 Suppl 3:27-39, 2014). Patients without any of these activating mutations may receive immune-checkpoint-inhibitor antibodies that inhibit the PD-1 receptor or PD-L1, with or without chemotherapy. Beyond these targeted systemic and immunotherapy approaches, advanced NSCLC is treated with platinum-based doublet chemotherapy regimens, with or without maintenance therapy (Besse *et al.*, *Ann Oncol*, 25(8):1475-84, 2014) (Ettinger *et al.*, *J Natl Compr Canc Netw* 15(4):504-35, 2017) (Reck *et al.*, *Ann Oncol*, 25 Suppl 3:27-39, 2014). Long-term survival remains an unmet need in advanced NSCLC. Overall survival is approximately 12 months for PD-1/PD-L1 inhibitors, with some studies in TKI-treated patients exceeding 2 years (Camidge *et al.*, *Nat Rev Clin Oncol*, 16(6):341-55, 2019).

[0178] Anti-PD-1 and anti-PD-L1 therapies have changed the standard of care for many patients with NSCLC (Topalian *et al.*, *NEJM*, 366(26):2443-54, 2012). However, data is emerging that suggests MET-driven NSCLC patients may not experience equivalent benefit to agents that target the PD-1/PD-L1 axis, even with tumors that express high PD-L1 or exhibit high tumor mutation burden (TMB) (Sabari *et al.*, *Ann Oncol*, 29(10):2085-91, 2018). This is in keeping with data generated in lung cancers harboring EGFR mutations or ALK rearrangements (Garassino *et al.*, *Lancet Oncol*, 19(4):521-36, 2018) (Lee *et al.*, *JAMA Oncol*, 4(2):210-16, 2018) (Peters *et al.*, *J Clin Oncol*, 35(24):2781-89, 2017) and indicates that monotherapy with anti-PD-1 or anti-PD-L1 may not be the preferred treatment for patients with MET-driven disease. Thus, there remains a substantial unmet need for therapies that improve response rates and survival for patients with MET-altered NSCLC.

Objectives

[0179] The primary objective of the dose escalation (phase 1) part of the study is to assess the safety, tolerability, and pharmacokinetics (PK) of REGN5093 for determination of the maximum tolerated dose (MTD) and/or definition of the recommended phase 2 dose (RP2D) of REGN5093 in patients with MET-altered NSCLC. The secondary objective of the dose escalation (phase 1) part of the study is to assess preliminary anti-tumor activity of REGN5093 as measured by the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

[0180] The primary objective of the dose expansion (phase 2) part of the study is to assess preliminary anti-tumor activity of REGN5093 as measured by the ORR per RECIST 1.1. The secondary objectives of the dose expansion (phase 2) part of the study are to assess the safety and tolerability of REGN5093 in each expansion cohort and to assess REGN5093 PK and concentrations in serum.

[0181] The secondary objectives of both parts of the study are to assess immunogenicity as measured by anti-drug antibodies (ADA) to REGN5093 and to evaluate other measures of preliminary anti-tumor activity.

[0182] The exploratory objectives of both parts of the study are to evaluate relationships between efficacy of REGN5093 and baseline MET alteration/mutation or amplification/expression and/or prior MET TKI treatment across cohorts, to assess pharmacodynamic changes in putative serum or plasma biomarkers, and to evaluate the impact on efficacy of tumor mutational spectrum at baseline and post-treatment in tissue and in circulating tumor DNA (ctDNA expansion phase only).

Target Population

[0183] Adult patients ≥ 18 years of age (or the legal age of adults to consent to participate in a clinical study per country-specific regulations).

[0184] Dose Escalation: Patients with advanced NSCLC exhibiting MET-altered disease by previously documented presence of any of the following: exon 14 gene mutation, MET gene amplification, or elevated MET protein expression. In the dose escalation phase of the study, patients will be enrolled based on documentation of any of the MET alterations defined by any of the above criteria and irrespective of prior experience with MET-targeted TKIs.

[0185] Dose Expansion: Patients with advanced NSCLC exhibiting MET-altered disease

will be assigned to cohorts based on previously documented presence of the following: MET exon 14-mutated disease and according to prior MET-targeted TKI experience (cohorts 1A MET TKI experienced and 1B no prior MET TKI), high MET gene amplified (cohort 2A no prior MET TKI), high MET protein overexpression (cohort 2B no prior MET TKI), both high MET gene amplified + high MET protein overexpression (cohort 2C no prior MET TKI).

[0186] Documented MET status based on at least 1 test will be sufficient to qualify a patient for a relevant cohort; more than 1 category of test is not required. Therefore, cohorts 2A and 2B may include patients with unknown overexpression or gene amplification status, respectively.

[0187] The dose expansion phase of the study is designed to further explore the safety and biological activity of REGN5093 at the RP2D. Patients will receive the RP2D of REGN5093 administered IV by a 30-minute infusion.

[0188] Patients will be enrolled into separate cohorts according to previously documented MET-altered disease and according to prior MET-targeted TKI experience. The cohorts are designed to provide a relatively homogeneous population of patients according to different cutoffs of the 3 different types of biomarkers: MET exon 14 altered, MET-amplified, and MET protein overexpressed.

[0189] Expansion cohorts are as follows (see also Table 10):

- **Expansion Cohort 1A** (MET exon 14 altered NSCLC; MET TKI experienced)
- **Expansion Cohort 1B** (MET exon 14 altered NSCLC; no prior MET TKI)
- **Expansion Cohort 2A** (highly amplified NSCLC MET GCN ≥ 5 and/or MET/CEP7 ratio ≥ 2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA; no prior MET TKI)
- **Expansion Cohort 2B** (high MET protein expression by IHC 3+ or H score of ≥ 200 ; no prior MET TKI)
- **Expansion Cohort 2C** (highly amplified NSCLC MET GCN ≥ 5 and/or MET/CEP7 ratio ≥ 2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA and high MET protein overexpressed by IHC 3+ or H score of ≥ 200 ; no prior MET TKI)

*if <40 %tumor content in biopsy is observed then FISH or ctDNA local results must be in the range specified

Table 10: Criteria for Assigning Patients to Expansion Cohorts According to Documented MET-Altered Status

Cohort	MET exon 14 alteration	MET amplified gene	MET protein overexpressed	Prior MET TKI
Expansion Cohort 1A	Yes	Any	Any	experienced
Expansion Cohort 1B	Yes	Any	Any	naïve
Expansion Cohort 2A	No*	High: MET GCN $\geq$ 5 and/or MET/CEP7 ratio $\geq$ 2 by FISH or MET GCN $\geq$ 6 by NGS in tissues or MET fold change $\geq$ 2 in ctDNA	Any	naïve
Expansion Cohort 2B	No*	Any	High: IHC 3+ or H score $\geq$ 200	naïve
Expansion Cohort 2C	No*	High: MET GCN $\geq$ 5 and/or MET/CEP7 ratio $\geq$ 2 by FISH or MET GCN $\geq$ 6 by NGS in tissues or MET fold change $\geq$ 2 in ctDNA	High: IHC 3+ or H score $\geq$ 200	naïve

- CEP7: centromeric portion of chromosome 7
- ctDNA: circulating tumor DNA
- GCN: gene copy number
- IHC: immunohistochemistry
- MET: mesenchymal epithelial transition
- TKI: tyrosine kinase inhibitors

* unless cohort 1B is already filled

**if <40 %tumor content in biopsy is observed then FISH or ctDNA local results must be in the range specified

[0190] Patients will not be required to have previously undertaken testing for all 3 categories of MET-altered disease in order to qualify for a relevant expansion cohort. For dose expansion, in cases where patients are MET-TKI naïve and have data from more than one type of test for MET-altered disease indicating that they could qualify for more than one cohort, they will be assigned to expansion cohorts (if slots available) with the following prioritization:

- First priority cohorts: MET exon 14 alterations = cohorts 1A and 1B
- Second priority (MET TKI-naïve patients without MET exon 14 alterations, or patients with exon 14 alterations only after cohort 1B is filled): MET-gene amplified + protein expression will be considered for assignment to cohorts 2A, 2B, and 2C.

[0191] Expansion cohorts will have a Simon 2-stage design. The enrollment of expansion cohorts will be paused after the number of patients required for stage 1 is enrolled into the cohort. The cohort will either be stopped or expanded pending the number of responders observed in stage 1 and the corresponding stage 1 criteria.

Inclusion Criteria

[0192] A patient must meet the following criteria to be eligible for inclusion in the study:

- Histologically confirmed NSCLC that is at advanced stage and for which there is no standard therapy option likely to convey clinical benefit. Advanced is defined as unresectable or metastatic disease. Patients must have exhausted all approved available therapies appropriate for the patient.
- Has available archival tumor tissue, unless discussed with the medical monitor.
- Previously documented presence of:
 - For dose escalation cohorts: either MET-exon14 gene mutation and/or MET gene amplification (by any local CLIA laboratory MET amplification call), and/or elevated MET protein expression (IHC $\geq 2+$ or H score of >150)
 - For dose expansion cohorts 1 A and 1B: MET exon 14-mutation; MET TKI experienced or no prior MET TKI, respectively
 - For dose expansion cohort 2A: MET gene highly amplified (MET GCN ≥ 5 and/or MET/CEP7 ratio ≥ 2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA); no prior MET TKI
 - For dose expansion cohort 2B: MET protein highly overexpressed (IHC 3+ or H score of ≥ 200); no prior MET TKI
 - For dose expansion cohort 2C: MET gene highly amplified (MET GCN ≥ 5 and/or MET/CEP7 ratio ≥ 2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA) and MET protein highly overexpressed (IHC 3+ or H score of ≥ 200); no prior MET TKI

*if <40 %tumor content in biopsy is observed then FISH or ctDNA local results must be in the range specified

- Willing to provide tumor tissue from newly obtained biopsy. Newly obtained biopsies at screening are required unless medically contra indicated and discussed with the medical monitor. For patients in expansion cohorts, biopsies should be taken from tumor site which has not been irradiated previously and is not the only measurable target lesion.
- For expansion cohorts only: At least 1 lesion that is measurable by RECIST 1.1. Tumor lesions in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions after radiation.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ and bone marrow function documented by:
 - Hemoglobin ≥ 9.0 g/dL
 - Absolute neutrophil count $\geq 1.5 \times 10^9/L$
 - Platelet count $\geq 75 \times 10^9/L$
 - Either serum creatinine $\leq 1.5 \times \text{ULN}$ or estimated glomerula filtration rate (GFR) $\geq 30 \text{ mL/min/1.73m}^2$
- Adequate hepatic function:
 - Total bilirubin $\leq 1.5 \times \text{ULN}$ ($\leq 3 \times \text{ULN}$ if tumor liver involvement)
 - AST $\leq 2.5 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ if tumor liver involvement)
 - ALT $\leq 2.5 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ if tumor liver involvement)
 - Alkaline Phosphatase $\leq 2.5 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ if tumor liver or bone involvement)

NOTES:

(a) Patients with tumor liver involvement if levels of AST $\geq 3 \times \text{ULN}$ or ALT $\geq 3 \times \text{ULN}$, and bilirubin levels $\geq 2 \times \text{ULN}$, will be excluded regardless of the above criteria.

(b) Patients with Gilbert's syndrome do not need to meet total bilirubin requirements provided their total bilirubin is not greater than their historical level. Gilbert's syndrome must be documented appropriately as past medical history.

- Adult patients ≥ 18 years of age (or the legal age of adults to consent to participate in a clinical study per country-specific regulations).
- Willing and able to comply with clinic visits and study-related procedures and requirements
- Must be willing and able to provide informed consent as specified by health authorities and institutional guidelines
- Provide informed consent signed by study patient or legally acceptable representative

Exclusion Criteria

[0193] A patient who meets any of the following criteria will be excluded from the study:

- Has received treatment with an approved systemic therapy or has participated in any study of an investigational agent or investigational device according to the following timeframe:
 - For small molecule cytotoxins or other agents unlikely to interact with study drug: within 2 weeks or 5 half-lives of the prior treatment whichever is shorter with a minimum of 7 days from the first dose of study therapy.
 - Exception: Patients who have received or are enrolled in a study involving treatment with an investigational immunoPET reagent are not excluded.
- Has not yet recovered (i.e., grade ≤ 1 or baseline) from any acute toxicities resulting from prior therapy except for:
 - laboratory changes as described in inclusion criteria, and
 - patients with grade ≤ 2 neuropathy

For immune-related AEs affecting any organ system within 2 months prior to enrollment there must be documentation of a trajectory of improvement of this irAE (to grade ≤ 1 or baseline by the time of enrollment) AND for those toxicities that remain at grade 1, documentation of 2 stable evaluations separated by at least 4 weeks.

NOTE: Endocrine immune-mediated AEs controlled with hormonal or other non-immunosuppressive therapies without resolution prior to enrollment are allowed

- Has received radiation therapy or major surgery within 14 days of first administration of study drug or has not recovered (ie, grade ≤ 1 or baseline) from AEs, except for laboratory changes as described in inclusion criteria and patients with grade ≤ 2 neuropathy
- For expansion cohorts only: prior treatment with MET-targeted biologic therapy (function-blocking antibodies or ADCs). In addition, for expansion cohorts 1B, 2A, 2B, and 2C, prior treatment with any MET-targeted agent including small molecule tyrosine kinase inhibitors e.g., crizotinib, capmatinib, tepotinib
- For expansion cohorts only: Another malignancy, with the following exceptions:
 - Non-melanoma skin cancer that has undergone potentially curative therapy or
 - In situ cervical carcinoma or
 - Any other tumor that has been treated, and the patient is deemed to be in complete remission for at least 2 years prior to enrollment and no additional therapy is required during the study period
- Untreated or active primary brain tumor, CNS metastases, leptomeningeal disease or spinal cord compression
 - Exception: Patients with previously treated central nervous system metastases or spinal cord compression may participate provided:
 - No evidence of progression for at least 2 weeks prior to the first dose of study therapy, and any neurologic symptoms have returned to baseline
- Encephalitis, meningitis, organic brain disease (e.g., Parkinson's disease), or uncontrolled seizures in the year prior to first dose of study therapy
- Uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency

NOTES:

(a) Patients with known HIV infection who have controlled infection (undetectable viral load [HIV RNA PCR] and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted. For patients with controlled HIV infection, monitoring will be performed per local standards.

(b) Patients with known hepatitis B (HepBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of HBV DNA. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug.

(c) Patients who are known hepatitis C virus antibody-positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.

- Any infection requiring hospitalization or treatment with IV anti-infectives within 2 weeks prior to first dose of study therapy.
- Placeholder for deleted exclusion criteria
- Placeholder for deleted exclusion criteria
- Known psychiatric or substance abuse disorders that would interfere with participation with the requirements of the study
- Any medical condition, co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, renders the patient unsuitable for participation in a clinical trial due to high safety risks and/or potential to affect interpretation of results of the study
- Women with a positive serum hCG pregnancy test at the screening/baseline visit. Breastfeeding women are also excluded
- Women of childbearing potential* or men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose. Highly effective contraceptive measures include:
 - Stable use of combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal

contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening

- Intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
- Bilateral tubal ligation
- Vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the study participant and that the partner has obtained medical assessment of surgical success for the procedure)
- And/or sexual abstinence[†], [‡]

*Women of childbearing potential are defined as women who are fertile following menarche until becoming post-menopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a post-menopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance.

Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

[†] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

[‡] Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

Methods – Study Design

[0194] Patients with documentation of at least 1 of 3 main categories of MET alterations will be included in this First in Human (FIH) open-label study: exon 14 skipping mutation, MET gene amplification (MET GCN ≥ 5 and/or MET/CEP7 ratio ≥ 2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA), and MET protein overexpression (immunohistochemistry 3+ or H score ≥ 200). Patients will not be required to have previously undertaken all 3 categories of tests for MET-altered disease.

[0195] Figure 6 depicts the study flow from the initial screening period to the post-treatment follow-up.

Description of Study Cohorts and Dose Escalation

[0196] Patients underwent screening procedures to determine eligibility within 28 days prior to the initial administration of REGN5093 and subsequent to signing the informed consent form (ICF).

Dose Escalation

[0197] In the dose escalation phase, a series of 3 DLs of REGN5093 was investigated: 500, 1000, and 2000 mg administered IV once every three weeks (Q3W) by a 30-minute infusion (see Table 11).

Table 11: Dose Escalation

Dose Level	Dose (mg) Q3W	Initial enrollment numbers
DL-1 ¹	250	3 to 4
DL1	500	3 to 4
DL1a ²	750	3 to 4
DL2	1000	3 to 4
DL2a ²	1500	3 to 4
DL3	2000	3 to 4

¹ DL-1 may be used if DL1 proves intolerable

² DL1a and DL2a are optional dose levels to be explored in the event that the dose immediately higher is not tolerable and the dose immediately lower shows insufficient clinical and PK signal.

A modified 3+3 dose escalation design ("4+3") will be utilized (Le Tourneau *et. al.*, J Natl Cancer Inst, 101(10):708-20, 2009). The dose escalation will proceed until an MTD is attained or a dose is selected for expansion based on safety/tolerability and sufficient

evidence of response (RP2D). Dose de-escalation (DL-1) cohort and intermediate cohorts may be enrolled to explore intermediate doses should the initial or subsequent level, respectively be deemed not tolerated. To further evaluate safety and collect biologic information, up to 6 additional patients may, at the discretion of the sponsor (in consultation with investigators), be enrolled at any DL deemed to be tolerated. A diagram of the study design is shown in Figure 7.

[0198] The dose limiting toxicity (DLT) evaluation period will be 21 days starting with cycle 1 day 1. Although a minimum of 3 patients at each DL will be required to be evaluable for DLT, to maximize the efficiency of the phase 1 dose escalation while maintaining patient safety, 4 patients will be enrolled at each DL in case a patient discontinues prior to being evaluable for DLT. The rules for tolerability are as follows:

[0199] Tolerability of a DL will be considered achieved if all potentially DLT-evaluable patients complete the 21-day DLT period without a DLT (0 in 3 patients or 0 in 4 patients).

[0200] Note: If 3 patients complete the DLT period without experiencing a DLT, but there is a fourth patient in the DLT evaluation period, tolerability of the DL will only be considered achieved when the fourth patient completes the DLT evaluation period or discontinues therapy prior to being evaluable for DLT.

[0201] If there is 1 DLT in either 3 or 4 DLT-evaluable patients, then 4 or 3 more patients, respectively, will be enrolled, for a total of 7 patients. A dose will be considered tolerable if there is 1 DLT in 6 or 7 patients. The MTD is reached if there are 2 or more DLTs in 2 to 7 evaluable patients.

[0202] At the highest DL tolerated, to evaluate further safety, an additional 3 to 4 patients may be enrolled for a total of 6 to 10 DLT-evaluable patients. The dose will be considered acceptable if there is 0 to 1 DLT in 6 to 8 patients, or up to 2 DLTs in 9 to 10 patients.

[0203] Escalation to the next dose cohort will occur once all of the initial 3 or 4 patients enrolled in a cohort have been observed for at least 21 days and completed safety assessments on day 22 (cycle 2 day 1), and the data have been reviewed at a Dose Escalation Review meeting.

[0204] After the required number of patients is enrolled in a given dose cohort, the enrollment will be paused for DLT evaluation (although screening for the next dose cohort may begin prior to confirmation that the current dose is safe). The Dose Escalation Review meeting will be led by a designated member of the sponsor's clinical team (generally either

the medical or study director) and at a minimum will be attended by the sponsor's medical/study director and the Global Patient Safety Lead; other individuals, including the investigators, may be included. The dose cohort will be stopped, expanded, or escalated per dose escalation criteria.

Dose-Limiting Toxicities

[0205] Dose-limiting toxicity (DLT) is any toxicity that could preclude advancing to the higher doses that have been specified in this protocol. The DLT observation period for determination of safety for dose escalation is defined as 21 days starting with cycle 1, day 1, with the intent to monitor the safety and tolerability of the first dose of REGN5093. To be evaluable for a DLT, a patient must have:

- Received at least 1 dose of study drug and be monitored for at least 21 days following the first administration of study drug,
- Or experienced a DLT (defined below) prior to the completion of the DLT period.

[0206] The duration of the DLT observation period may be longer for patients experiencing an AE for which the duration must be assessed in order to determine if the event was a DLT.

[0207] Regardless of whether a patient remains on study treatment and/or continues to participate in study procedures, such an event will count as a DLT for the involved cohort if the event occurs during the DLT observation period.

Dose-Limiting Toxicity Definition

[0208] A DLT in general will be defined as any of the following treatment-emergent toxicities, excluding toxicities clearly related to disease progression or inter-current illness. The grades for these toxicities are defined according to CTCAE version 5.0.

Hematologic Toxicity:

- Grade 4 neutropenia lasting >7 days
- Grade 4 thrombocytopenia
- Grade 4 anemia
- Grade 3 thrombocytopenia with bleeding
- Grade ≥ 3 febrile neutropenia (fever $\geq 38.5^{\circ}\text{C}$ with absolute neutrophil count [ANC]

<1.0 x 10⁹/L) or grade ≥3 neutropenia with documented infection

Non-Hematologic Toxicity:

- Non-hematologic grade ≥3 toxicity except for:
 - a. Alopecia
 - b. Grade 3 nausea, vomiting, or diarrhea unless persistent (>72 hours duration), after initiation of supportive care measures as prescribed by the treating physician
 - c. Clinically insignificant laboratory abnormalities
- Clinically significant grade ≥3 laboratory values which require medical intervention or leads to hospitalization
- Liver dysfunction consistent with Hy's law (Temple, J Allergy Clin Immunol, 117(2):391-97, 2006) or ALT or AST >3 × ULN and bilirubin >2 × ULN

[0209] The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays will be analyzed to determine if a given toxicity should be considered a DLT for dose escalation purposes.

[0210] In general, as there is limited clinical experience for the new biologic molecule REGN5093, any AE will be treated as unexpected.

[0211] Treatment-emergent adverse events that appear to meet the DLT definition will be discussed between the sponsor and the investigator. The final decision of whether or not the TEAE meets the DLT definition will be based on a careful review of all relevant data and consensus between the medical/study director and the designated safety lead from the Global Patient Safety department. The investigator may also be consulted.

[0212] Regardless of whether a patient remains on study treatment and/or continues to participate in the study procedures, an event that meets the DLT criteria will count as a DLT for the involved cohort if the event occurs during the DLT observation period.

Maximum Tolerated Dose

[0213] The MTD is defined as the DL immediately below the level at which dosing is stopped due to the occurrence of 2 or more DLTs out of up to 7 evaluable patients. If the

study is not stopped due to the occurrence of a DLT, it will be considered that the MTD has not been determined.

[0214] If the MTD is not reached, the RP2D for further evaluation may be chosen based upon clinical, PK, and/or biomarker data that indicate a pharmacologically active dose has been reached in conjunction with available safety information.

[0215] REGN5093 will be supplied as a lyophile in sterile, single-use vials. During the trial a new presentation is planned to be introduced, a sterile solution. Each vial will contain REGN5093 at a concentration of 25 mg/ml. Both presentations will include a labeled vial in a labeled carton.

[0216] Instructions on dose preparation are provided in the pharmacy manual.

[0217] No pre-medication is needed prior to administration of REGN5093. REGN5093 will be administered by IV infusion over 30 minutes Q3W.

Prohibited Medications

[0218] While participating in this study, a patient may not receive any standard or investigational agent for treatment of a tumor other than REGN5093, per the study's specified dosing regimens.

[0219] Systemic treatments for cancer are not allowed during the study period.

[0220] Patients must not receive live vaccines during the study.

[0221] Radiotherapy is not allowed during the study period with the exception of the following: after communication with the sponsor, focal palliative treatment (e.g., radiation) would be allowed for local control of a tumor. Palliative radiation therapy for pain management at sites of bone disease or lesion sites in the brain are allowed (as long as the lesions are not followed for treatment response evaluation) after discussion with the sponsor.

[0222] Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

Permitted Medications

[0223] Gonadotropin-releasing hormone agonist therapy may be continued and is not prohibited. Hormone-replacement therapy is allowed. Inhaled, topical, ophthalmologic, or

intranasal steroids are allowed. Treatments for bone metastases (bisphosphonates, denosumab) and systemic corticosteroids are allowed. Use of high doses of steroids over a prolonged period of time require discussion with the medical monitor.

Safety

[0224] The safety and tolerability of REGN5093 will be monitored by clinical assessment of AEs, physical examinations (complete and limited), repeated measurements of vital signs (temperature, blood pressure, pulse, and respiration), 12-lead electrocardiograms (ECGs), and laboratory assessment including standard hematology, chemistry, and urinalysis. Vital signs, including temperature, sitting blood pressure, pulse, and respiration will be collected pre-dose at timepoints.

[0225] An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

[0226] An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (e.g., a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions)
- Is a **congenital anomaly/birth defect**

- Is an **important medical event**. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

[0227] Hospitalization or death due solely to manifestations consistent with typical progression of underlying malignancy will not be considered an SAE.

Efficacy

[0228] Radiographic tumor response will be used to determine overall response for each patient defined by RECIST 1.1 (Eisenhauer *et al.*, Eur J Cancer, 45(2):228-47, 2009). Radiographic disease assessment will inform the calculation of:

- ORR, defined as the percentage of patients with a BOR of complete response (CR) or partial response (PR)
- DOR, defined as time from first response of CR or PR to first radiographic progression or death due to any cause for patients with confirmed CR or PR. In the absence of radiographic progression or death before the analysis cutoff date or the date of initiation of a further anti-cancer treatment, the DOR will be censored at the date of the last valid response assessment not showing progression performed prior to the analysis cutoff date or initiation of a further anti-cancer treatment, whichever is earlier.
- DCR, defined as the percentage of patients with a BOR of CR, PR, or stable disease (SD)
- PFS defined as time from first study treatment administration to first radiographic progression or death due to any cause. The same censoring rule as DOR will be used.
- OS defined as the time from first study treatment administration to death due to any cause. For patients who have not died, OS will be censored at the last date that patient is known to be alive. OS will be assessed based on survival data reported by the investigators.

[0229] Diagnostic quality CT with contrast and contrast-enhanced MRI are the preferred

imaging modalities for assessing radiographic tumor response. In patients in whom contrast is strictly contraindicated, non-contrasted CT scans of the chest and non-contrast MRI scans of the body except chest will suffice. The chest, abdomen, and pelvis must be imaged along with any other known or suspected sites of disease. If more than 1 imaging modality is used at screening, the most accurate imaging modality according to RECIST 1.1 (Appendix 1) should be used when recording data. The same imaging modality and techniques used at screening should be used for all subsequent assessments.

[0230] At screening, MRI or CT of the brain with contrast (unless contraindicated then MRI without contrast) should be performed in patients with a known history of treated brain metastasis.

[0231] Additional sites of known disease should be imaged at screening.

[0232] A diagnostic quality (≤ 5 mm slices) CT scan with contrast of the chest and abdomen as well as any other known sites of disease (e.g., neck), will be performed at screening, on day 1 of treatment cycles 2 and 3, every three months post last visit, and at any time when disease progression is suspected. Scans will include description of tumor locations, and up to 5 of the largest dominant disease masses (no more than 2 per organ) should be chosen as target lesions and measured by longest diameter if non-nodal and short axis for nodal lesions, per RECIST 1.1. All lesions should be assessed and documented. If a CT scan is not feasible, an MRI scan may be performed.

[0233] For each patient, the same method of measurements and the same technique must be used to evaluate each lesion throughout the study. If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment, unless signs of clinical progression are present. If, at any time during the treatment phase, there is suspicion of disease progression based on clinical or laboratory findings (and before the next scheduled assessment), an unscheduled tumor assessment should be performed.

Procedures and Assessments

[0234] Anti-tumor activity will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI). The safety and tolerability of REGN5093 will be monitored by clinical assessment of AEs, physical examinations (complete and limited), repeated measurements of vital signs (temperature, blood pressure, pulse, and respiration), 12-lead electrocardiograms (ECGs), and laboratory assessment including standard hematology, chemistry, and urinalysis.

[0235] Blood will be collected to assess REGN5093 PK and concentrations in serum and immunogenicity (ADA) in serum; and for additional biomarker assessments. Additional biomarkers will be measured in serum or plasma. Exploratory predictive and pharmacodynamic biomarkers related to REGN5093 treatment exposure, clinical activity, or underlying disease will be investigated using samples from collected serum, plasma, archived tumor tissue, and on-study tumor biopsy tissue, tumor DNA (including circulating tumor DNA), and tumor RNA samples.

Study Endpoints

[0236] The primary endpoints of the dose escalation (phase 1) part of the study are:

- Safety, as measured by the incidence and severity of treatment-emergent adverse events (TEAEs)/adverse events of special interest (AESIs)/serious adverse events (SAEs), and grade ≥ 3 laboratory abnormalities during the treatment period and up to 90 days after the last dose
- Tolerability, as measured by the incidence of dose-limiting toxicities (DLTs) from the first dose through the end of the DLT observation period for REGN5093
- REGN5093 concentrations in serum over time

[0237] The primary endpoint of the dose expansion (phase 2) part of the study is ORR per RECIST 1.1, defined as the percentage of patients with a best overall response (BOR) of confirmed CR or PR according to RECIST 1.1 criteria.

[0238] The secondary endpoints of the dose escalation part of the study are: ORR per RECIST 1.1.

[0239] The secondary endpoints of the dose expansion part of the study are:

- Safety, as measured by the incidence and severity of TEAEs, AESIs/SAEs, and grade ≥ 3 laboratory abnormalities
- REGN5093 PK and concentrations in serum over time

[0240] The secondary endpoints for both phases of the study are:

- Duration of response (DOR) per RECIST 1.1.
- Disease control rate (DCR) per RECIST 1.1.

- Progression free survival (PFS) per RECIST 1.1.
- OS
- Immunogenicity as measured by ADA to REGN5093.

[0241] The exploratory endpoints for both parts of the study are:

- The response to REGN5093 by type (and extent) of baseline MET alteration and prior MET-targeted TKI experience
- The response to REGN5093 by baseline tumor mutational status

Example 8. Safety, Tolerability, and Efficacy of REGN5093 in Patients with MET Altered Advanced NSCLC

[0242] REGN5093 has a therapeutic benefit in patients with *MET*-altered NSCLC and showed promising efficacy signals with a tolerable safety profile.

[0243] REGN5093 was investigated as monotherapy and was administered intravenously once every 3 weeks in dose escalation cohorts (phase 1) followed by an expansion phase (phase 2). For each patient, the study consisted of a screening period of up to 28 days, followed by 3-week cycles of REGN5093 monotherapy. REGN5093 at 2000 mg was the recommended Phase 2 dose; prior dose levels were 500 mg and 1000 mg.

[0244] Tumor measurements were performed at baseline and every 6 weeks until disease progression, withdrawal of consent, death, or initiation of another anti-cancer treatment.

[0245] Tumor tissue (archival and on-study tumor biopsies) were obtained and utilized for retrospective analysis of MET alterations (and additional biomarker analyses, tissue permitting). Newly obtained biopsies at screening were also required unless considered unsafe.

[0246] Sixty-nine patients received REGN5093 in both the dose-escalation and dose-expansion phases. Patient characteristics were consistent with a heavily treated population, with a median of 2.5 prior lines of therapy (range: 1–8). Most patients had an ECOG PS of 1 (80%). Most patients had non-squamous histology (93.6%), and EGFR mutation was present in 37.2% of patients (Table 12). The study population had a median age of 66 years, 53.8% were male, 70.5% were Asian.

Table 12: Baseline Demographics and Clinical Characteristics

Characteristic	Total (N=78)
Age	Median (range), years
	≥65 year, n(%)
Sex, n(%)	Male
	Female
	Asian
Race, n(%)	White
	Black
	Not reported/missing
	0
ECOG PS, n (%)	1
	Non-squamous
Histology, n (%)	Squamous
	Liver
	Brain
EFGR status, n (%)	Wild type
	Mutant
	Unknown
Number of prior lines of therapy	Median, (range)
	2.5 (1-8)

Safety data

[0247] No dose-limiting toxicities (DLTs) were observed. REGN5093 demonstrated a similar safety profile in the dose-escalation and dose-expansion phases, notably with grade 1/2 peripheral oedema in only six (9%) patients (**Table 13**). At the time of the data cut-off, nine (13%) patients were still on treatment and 60 (87%) patients had discontinued treatment. The primary reasons for discontinuation of treatment were: Disease progression in 52 (75%) patients; Patient decision in five (7%) patients; Adverse event in only three (4%) patients.

Table 13: Safety Summary		
Total (N=69)		
Duration of exposure, median (range), weeks	9.3 (1–82)	
TEAEs, n (%)	Any grade	Grade 3–5
Overall	59 (86)	18 (26)
Serious	16 (23)	12 (17)
Led to discontinuation	3 (4)	2 (3)
Led to death	1 (1)	1 (1)
TEAEs in ≥5% of patients		
Nausea	9 (13)	0
Fatigue	7 (10)	1 (1)
Oedema peripheral	6 (9)	0
Pruritis	6 (9)	0
ALT increased	5 (7)	2 (3)
AST increased	5 (7)	1 (1)
COVID-19	5 (7)	1 (1)
Constipation	5 (7)	0
Dizziness	5 (7)	0
Headache	5 (7)	0
Insomnia	5 (7)	0
Pneumonia	4 (6)	3 (4)
Back pain	4 (6)	3 (4)
Decreased appetite	4 (6)	0
Dyspnea	4 (6)	2 (3)
Hypoalbuminaemia	4 (6)	0
Musculoskeletal chest pain	4 (6)	0
Pleural effusion	4 (6)	2 (3)
Pulmonary embolism	4 (6)	1 (1)
Vomiting	4 (6)	0
Treatment-related AEs	Any grade	Grade 3–5
Overall	27 (39)	3 (4)
Serious	2 (3)	2 (3)
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.		

Tumor Response

[0248] Partial responses (by investigator assessment) were observed in a subset of patients with exon 14 alteration in DNA or a deletion that leads to exon 14 skipping who were naïve to MET TKI treatment, and in patients with MET gene amplification and/or MET protein overexpression (Table 14 and Figure 8).

Table 14. Best overall response rate (ORR) among patients who received the 2000-mg dose Q3W of REGN5093 [†] (MET alteration based on local records)				
	Total number	Number evaluable	Confirmed responses (all partial responses)	ORR
Exon 14 alteration in DNA or a deletion that leads to exon 14 skipping (MET TKI experienced)	11	11	0	0% (0/11)
Exon 14 alteration in DNA or a deletion that leads to exon 14 skipping (MET TKI naïve)	10	10	3	30% (3/10)
Patients with PD-(L)1 experience		7	2	
Patients with prior EGFR inhibitor and no PD-(L)1 experience		1	1	
MET gene amplification and/or MET protein overexpression (MET TKI naïve)	40	35	5	12.5% (5/40)
Patients with PD-(L)1 experience		19	3	
Patients with prior EGFR inhibitor and no PD-(L)1 experience		13	2	
[†] Including all expansion cohort patients and three patients from dose escalation cohort 3 at the 2000-mg dose level. EGFR, epidermal growth factor receptor; MET, mesenchymal epithelial transition; PD-(L)1, programmed cell death-(ligand) 1; PR, partial response; TKI, tyrosine kinase inhibitor.				

[0249] ORR among patients with centrally confirmed MET alterations: • 33% (3/9): MET exon 14 mutation by NGS in tumor tissues or ctDNA (MET TKI-naïve) • 25% (5/20): MET gene amplification (GCN $\geq$ 5 by FISH or NGS in tumor tissues) • 23% (5/22): MET protein overexpression (IHC 3+ in $\geq$ 50% of tumor cells) • 36% (5/14): MET protein overexpression (IHC 3+ in $\geq$ 75% of tumor cells) • 50% (4/8): MET protein overexpression (IHC 3+ in $\geq$ 90% of tumor cells).

Pharmacokinetics

[0250] REGN5093 exposure in serum appeared linear and dose-proportional over a dose range of 500 mg to 2000 mg Q3W intravenous (IV), and concentrations in serum at 2000 mg Q3W IV was similar in the dose-escalation cohort and across the various expansion cohorts (see Figure 9). The elimination half-life estimated by non-compartmental analysis over a 3-week dosing interval was 15 days.

Conclusions

[0251] Among this population of heavily treated patients with MET-altered advanced NSCLC, REGN5093 monotherapy demonstrated an acceptable safety profile. No DLTs were observed. Eighty-six percent of patients experienced TEAEs of any grade. Twenty-six percent of patients experienced Grade ≥ 3 TEAEs. Three (4%) patients discontinued treatment due to a TEAE. REGN5093 exposure in serum appeared to increase in a dose-dependent manner. REGN5093 monotherapy demonstrated preliminary efficacy signals among patients with MET exon 14 alteration in DNA or a deletion that leads to exon 14 skipplings as well as patients with MET gene amplification and/or MET protein overexpression. Tumor response was enhanced with centrally confirmed biomarker selection.

Example 9: Predictive Biomarkers of Response to REGN5093

[0252] In some instances, when treating MET-altered advanced non-small cell lung cancer (aNSCLC), patient selection can be guided by the use of predictive biomarkers of response to REGN5093. REGN5093 monotherapy was investigated in patients with *MET*-altered aNSCLC. Tumor measurements were performed at baseline and Q6W until progression, consent withdrawal, death, or initiation of another anti-cancer treatment.

[0253] Provided herein are selection criteria that can be used to increase the percentage of responders when treating aNSCLC. In some aspects, identification of MET actionable mutations can be used for patient selection for MET-targeted therapy in advanced (2L+, i.e., patients having received two or more prior therapies) NSCLC. MET Exon 14 Skipping/Deletion is an oncogenic driver in 1L NSCLC, causing loss of c-Cbl binding site, that impairs receptor degradation, and ultimately leads to increased MET signaling. MET gene amplification is a resistance mechanism to EGFR tyrosine kinase inhibitor (TKI) therapy in 2L+ NSCLC. MET protein overexpression enriches but does not select for treatment response to MET TKIs

especially in MET amplified TKI resistance-driven NSCLC populations (Figure 10).

[0254] Both tumor biopsies and liquid biopsies can be used to identify and confirm MET alterations. Exon 14 alterations can be determined via gene sequencing of a tumor biopsy or ctDNA obtained from a blood sample. Similarly, MET gene amplification can be assessed via gene sequencing or fluorescence in situ hybridization [FISH; GCN or MET:Chromosome 7 centromere (CEP7) ratio] of a tumor biopsy, or sequencing of ctDNA obtained from a blood sample. MET protein expression can be assessed in tumor biopsies by immunohistochemistry using, for example, a specific c-MET antibody to stain for total MET protein (Figure 11).

[0255] In some instances, assessing ctDNA complements tissue profiling and overcomes the limitations of biopsy collection and analysis. For example, some tumors are located in areas where a tissue biopsy would be difficult or impossible to obtain. ctDNA assessment captures all active “drivers” from all tumor sources in the body, i.e., both primary and metastatic tumors, and permits identification of mutations not present in a single tissue biopsy to overcome spatial heterogeneity. As tumors evolve over time, either or both intrinsically or in response to therapy, a higher concordance and accurate coverage can be obtained by assessing tissue and ctDNA samples obtained simultaneously to overcome temporal heterogeneity.

[0256] MET Amplification status was assessed by FISH and NGS using tissue and/or ctDNA, for example, using a threshold of Gene Copy Number (GCN) in tissues either by Fluorescent In situ Hybridization (FISH) ($GCN \geq 5$) or NGS ($GCN \geq 6$) and/or in ctDNA $\geq 2.2x$ by NGS assays to assess efficacy for other MET inhibitors.

[0257] MET Exon14 was centrally confirmed (i.e., assayed by one central laboratory to control any variabilities arising from sample collection and assay implementation) using various next generation sequencing (NGS) panels for tissues and ctDNA (FoundationOne® CDx (tissue based 324 gene panel) and FoundationOne® LiquidCDx (blood based 324 gene panel) are exemplary gene panels, though others are contemplated as useful herein). Exemplary Exon 14 alterations include but are not limited to D1010N, D1010fs*19, D1010Y, D1010H, or R1004P mutations and Exon 14 skipping.

[0258] Figure 12 provides the study design. The various cohorts had included patients with confirmed MET alterations as determined by a given patient’s medical records. As shown in Figure 12, patient enrollment during the expansion phase of the trial was based on documented

MET alterations (MET Exon 14 alteration in DNA or a deletion that leads to exon 14 skipping, MET gene amplification and/or MET protein overexpression) and correlated to clinical response. As can be seen in Figure 13, among the 65 patients who received the 2000 mg dose of REGN5093, 9 patients had a partial response. The responder distribution by cohort was as follows: Cohort 1A (MET Ex 14 TKI Experienced): 0; Cohort 1B (MET Ex 14 TKI naïve): 4; Cohort 2A (MET Amplification): 0; Cohort 2B (MET Overexpression): 1; Cohort 2C (MET Amplification and Overexpression): 3; DL3 (Dose Level 3, MET Amp and OE): 1.

[0259] As shown in Figure 14, tumor response was observed in MET TKI naïve patients with centrally confirmed (1) MET Exon14 (4/15) or 27% or (2) MET Amp + OE (5/14) 36% regardless of EGFR mutation status. As shown in Figure 15, overall response rates (%ORR) were higher in specific MET altered subgroups vs overall population, by central analysis.

Example 10: Bypass Resistance Mutations at Baseline and Clinical Response to REGN5093

[0260] Resistance to MET therapy can be intrinsic or acquired in response to prior therapies in pre-treated 2L+ NSCLC patient population. The number of therapies received by patients ranged from one to eight, and the median was 2.5 (Figure 16). Previous therapies received by patients in the study included chemotherapy, immune checkpoint inhibitors (ICI), and EGFR inhibitors. Patients who initially respond to therapy, in some instances, acquired other mutations that promote disease progression upon treatment.

[0261] Bypass gene detection of non-synonymous variations such as single nucleotide variations (SNVs), insertion deletions (Indels), frameshifts, non-sense mutations, splice variants, or gene fusions and copy number variations (CNVs) such as gene amplifications or deletions in ctDNA supplemented tissue results and provided a more comprehensive tumor profiling of MET x MET resistance mechanism. Varying sensitivities of detection by FMI NGS panels was dependent on the variant allele frequencies (VAFs) for each of the 324 genes present in each platform. Figure 17 illustrates the detection of non-synonymous variations and CNVs and the overlap in detection by ctDNA and tissue. NSV detection by ctDNA was 39%; in tissue, 33%; and in both, 28%. CNV detection by ctDNA was 9%; in tissue, 84%; and in both, 6%.

[0262] Figure 18 illustrates unbiased co-clustering of baseline somatic mutations detected in both ctDNA and tumor tissues by cohort assignment, EGFR status, and centrally confirmed

MET alterations. Figure 19 shows another unbiased set of clustering as Figure 18, but with clinical response. Several baseline somatic mutations based on the clustering data set were identified in non-responders that may lead to MET bypass resistance mechanisms and potentially affect clinical response to REGN5093 even in the presence of MET oncogenic drivers.

[0263] Figure 20 provides classifications and examples of bypass alterations detected in the study patients who had centrally confirmed MET oncogenic drivers but did not respond to REGN5093. On-target receptor mutations include *MET* TKI resistance mutations (i.e. *MET* Y1230C, *MET* D1228H, *MET* D1228N), *MET* fusion/rearrangements (*MET:MET* gene rearrangement), and *MET* gene silencing (loss-of-function) (i.e. *DNMT3A*, *TET2*). Resistance mechanisms involving alternative or parallel tyrosine kinase driver receptor activation, include tyrosine kinase receptor (TKR) and TK ligand gene amplification (e.g., *FGFR1-4* Amp, *FGF14* Amp, *NTRK1-3* Amp, *MERTK* Amp, *ERBB2/3* Amp and *VEGFA* Amp), TKR activating mutations (*EGFR* L858R, G719S, E709A, E746_A750del, S752_I759del), and oncogenic fusions and rearrangements (*MKRN-BRAF* fusion). Resistance mechanisms involving downstream proliferation/survival/anti-apoptotic pathway activation including JAK2/STAT3 pathway (e.g., *JAK2* V617F; *SFKs* amp); RAS/RAF/MEK/MAPK pathway (e.g., *KRAS* G12A/V and G12D/V; *GNAS* R201H, *MKRN-BRAF* fusion, *BRAF* S602Y; *RICTOR* Amp; MAP2K1 K57N; *RAS* mut/gain; *RAF* mut; *ERK-MAPK* amp), PI3K/AKT/MTOR pathway (e.g., *PI3KCA* H1047L, E545K, E542K, N345K; *IDH1* R132L, *MTOR* E2338Q, *AKT2* Amp, *RICTOR* Amp; *PI3K* mut; PTEN deletion); *TP53* mutations (e.g., *TP53* R280T, *TP53* R248Q) and cell cycle mutations (e.g., *CDK4* Amp, *CDK6* Amp, *CCND1* Amp, *CCNE1* Amp).

[0264] Gene amplifications identified in patients with confirmed *Met* amplification and overexpression who did not respond to RENG5093 included the following: *HGF*, *EPH*, *EGFR*, *BRAF*, *BCL2L1*, *PI3KCB*, *KRAS*, *AKT2*, *ATR*, *VEFGA*, *FGF*, *CCND*, *CCNE*, *CDK6*, *RAD21*, and *MYC*. Gene deletions were also identified: *CDKN2A*, *CDKN2B*, *MTAP*, and *RBM10*. *MET* bypass resistance mechanisms identified in these patients are provided in Table 15.

Table 15: *MET* Bypass Resistance Mechanisms – *MET* Overexpression and *MET* Amplification

Gene	Point Mutations or Deletions					
<i>MET</i>	MET-MET					
<i>EGFR</i>	L858R	E746_A750del	E746_s752>V			
<i>TP53</i>	C275F	R280T	G266R	R248Q	P278A	R110L

<i>PI3KCA</i>	H345K					
<i>IDH1</i>	R132L					
<i>NTRK2</i>	NTRK2- NTRK2					

[0265] Gene amplifications identified in patients with confirmed *MET* amplification (and not *MET* overexpression) were mostly *EGFR* mutants who did not respond to REGN5093: *EGFR*, *BRAF*, *PI3KC2G*, *KRAS*, *HGF*, *EPHA3*, *ERCC4*, *RICTOR*, *RAD21*, *LYN*, *MYC*, *MDM2*, *CDK 4/6*, *FgF3/4/19*, *FGF10*, and *CCND1*. Gene deletions in these patients included: *CDKN2A*, *CDKN2B*, *MTAP*, *TEK*, and *BCOR*. *MET* bypass resistance mechanisms identified in these patients are provided in Table 16.

Table 16: *MET* Bypass Resistance Mechanisms – *MET* Amplification and *EGFR* Mutations

Gene	Point Mutations or Deletions					
<i>EGFR</i>	L858R	T790M	G719S	E709A	L858R	G719A
	R776H	S678I	E746_A75 0D	L861Q	I744M	
<i>TP53</i>	H193D	H193R	V157F	R196*	R248Q	R273L
<i>PI3KCA</i>	E453K					
<i>JAK2</i>	V617F	V615L				
<i>MTOR</i>	MTOR- MTOR					

[0266] Gene amplifications identified in patients with *MET* Exon 14 alterations which were TKI naïve but non-responders to REGN5093 included: *MDM2*, *EGFR*, *FGFR1*, *ERBB3*, *CDK4*, *GNA13*, *MYC*, *RPTOR*, *TERC*, *IKZF1*, *EZH2*, *SDHA*, *SOX*, *WHSC1L1*, and *ZNF703*. Gene deletions identified in these patients included *CDKN2A*, *CDKN3A*, and *MTAP*. *MET* bypass resistance mechanisms identified in these patients are provided in Table 17.

Table 17: *MET* Bypass Resistance Mechanisms – *MET* Ex 14, TKI Naïve

Gene	Point Mutations or Deletions					
<i>EGFR</i>	V742I					
<i>TP53</i>	R248Q	R248W	P151R	R282W	R175H	
<i>PI3KCA</i>	E542K	H1047L				
<i>MTOR</i>	E2388Q					
<i>BRAF</i>	S602Y					
<i>ATM</i>	Y2019C					

[0267] Gene amplifications identified in patients with *MET* Exon 14 alterations which were TKI experienced but non-responders to REGN5093 included: *EGFR*, *RAF1*, *PI3KC2G*, *CDK4*, *CEBPA*, *CDKN1A*, *CARD11*, *MYC*, *RICTOR*, *VEGFA*, *CD22*, *DDR1*, *RAC1*, *NBN*, *FGF19*, *MDM2*, *NFKBIA*, *CCND1*, *INPP4B*, *PPARG*, *PMS2*, *GATA4*, *SDHA*, and *RAD21*. Gene

deletions identified in these patients included *CDKN2A*, *CDKN3A*, and *MTAP*. *MET* bypass resistance mechanisms identified in these patients are provided in Table 18.

Table 18: *MET* Bypass Resistance Mechanisms – *MET* Ex 14, TKI Experienced

Gene	Point Mutations or Deletions		
<i>MET</i>	Y1230C	D1228H	D1228N
<i>TP53</i>	R282W	C242R	
<i>PI3KCA</i>	E545K		
<i>KRAS</i>	G12A	G12D	

Example 11: Circulating Biomarkers of Target Engagement

[0268] Soluble MET (sMET) are extracellular domain fragments of MET that arises from receptors in tumor tissues that were cleaved by proteases. Total sMET and HGF were measured by ELISA.

[0269] Total concentration of REGN5093 was several fold higher than total sMET concentration in serum, suggesting saturation of receptor occupancy was achieved with the 2000 mg Q3W dose regimen at Dose Expansion (Figure 21).

[0270] HGF is a ligand of the MET receptor that gets displaced and increases in circulation when REGN5093 binds to MET receptor in the tumor. Both circulating HGF (cHGF) and total sMET levels increased post-dose suggesting target engagement, but neither baseline nor post-treatment levels of sMET and cHGF was significantly associated with clinical response (Figure 22).

Conclusions

[0271] Of 36 pts who received the 2000 mg dose, 6 had a partial response (5 had prior anti-PD-(L)1 therapy). These responses occurred in 2/5 in pts with exon 14 skipping mutation who were naïve to MET tyrosine kinase inhibitor (TKI) (Cohort 1B); 0/10 in pts with exon 14 skipping mutation previously treated with TKI (Cohort 1A); and 4/21 in MET TKI-naïve pts with MET gene amplification, protein overexpression, or both (Cohorts 2A-C).

[0272] REGN5093 monotherapy can induce tumor responses in patients with MET-altered aNSCLC. Heterogeneity in response rates was observed between MET-altered subgroups in MET TKI naïve patients, with response rates of 4/15 (27%) in pts with MET Ex14 mutations and 5/16 (36%) in pts with MET Amplification and Overexpression, although based on

small sample sizes.

[0273] Certain baseline somatic mutations co-occurring with MET alterations in clinical non-responders act as potential bypass resistance mechanisms and affect clinical response to REGN5093 monotherapy.

[0274] Total concentrations of REGN5093 were several fold higher than total sMET concentration in serum supporting the selection of the 2000 mg Q3W dose regimen. Total sMET and cHGF levels increased post-dose suggesting target engagement by REGN5093 but neither baseline nor post-treatment changes in total sMET nor cHGF concentrations were associated with response.

Table 19: Informal Sequence Listing

SEQ ID NO:	Sequence	Name
1	EVQLVESGGGLVQPGTSLRLSCAASGFTDDYAMHWVRQAPGKGLEWVSGITWN SYNIDYADSVKGRFTISRDNNAKNSLYLQMNSLRAEDTALYYCAKDDDDYSNYVYFDY WGQGTLVTVSS	D1-HCVR
2	GFTFDDYA	D1-CDR1
3	ITWNSYNI	D1-CDR2
4	AKDDDDYSNYVYFDY	D1-CDR3
5	EVQLVESGGGLVQPGGSLRLSCAASGFIVTTNYMTWLRQAPGKGLEWVSLIYSSGH TYYADSVKGRFTISRHNASKNTLYLQMDSLRAEDTAVYYCASAFADVFDIWGQGTM VTVSS	D2-HCVR
6	GFIVTTNY	D2-CDR1
7	IYSSGHT	D2-CDR2
8	ASAFADVFDI	D3-CDR3
9	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPITFGQGTRLEIK	LCVR
10	QSISSY	LCDR1
11	AAS	LCDR2
12	QQSYSTPPIT	LCDR3
13	MKAPAVLAPGILVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETPIQNVILHE HHIFLGATNYIYVLNEEDLQKVAEYKTGPVLEHPDCFCQDCSSKANLSGGVWVDNIN MALVVDYDDYDQLISCGSVNRGTCQRHVFPNHNTADIQSEVHCIFSPQIEEPSQCPDC VVSALGAKVLSSVKDRFINFFVGNTINSSYFPDHLHSISVRLKETKDGMFLTDQSY IDVLPEFRDSYPIKYVHAFESNNFIYFLTVQRETDAQTFHTRIIRFCSINSGLHSEMEM PLECILTEKRKKRSTKKEVFNIQAAYVSKPGAQLARQIGASLNDILFGVFAQSKPDS AEPMDRSAMCAFPKYVNDFFNKIVNKNVNRCLQHFYGPNEHCNRTLLRNSSGCE ARRDEYRTEFTTALQRVDLFMGQFSEVLLTSISTFIKGLTIANLGTSEGRFMQVVS SGPSTPHVNFLLDHPVSPVIVEHTLNQNGYTLVITGKKITKIPLNGLGCRHFGSCS QCLSAPPFVQCGWCHDKCVRSEECLSGTWTQICLPAIYKVPNSAPLEGGTRLT CGWDFGFRNNKFDLKKTRVLLGNESCTLTLSSESTMTLKCTVGPAMNKHFNMSII SNGHGTQYSTFSYVDPVITSISPKYGPMAAGTLLTLTGNYLNSGNSRHSIGGKTCT LKSVSNSILECYTPAQTISTEFAVKLKIDLANRETSIFSREDPIVYIEHPTKSFISTWW KEPLNIVSFLFCFASGGSTITGVGKNLNSVSVPRMVINVEAGRNFTVACQHRNSE IICCTTPSLQQLNLQLPLKTKAFFMLDGLSKYFDLIYVHNVPVFKPFKEKPMISMGNEN	unprocessed preproprotein of isoform "a", NCBI accession No. NM_ 001127500.2

	VLEIKGNDIDPEAVKGEVLKVGKSCENIHLHSEAVLCTVPNDLLKLNSLNIWQKQ ISSTVLGKVIVQPDQNFGLIAGVVSISTALLLLGFFLWLKKRKQIKDLGSELVRYDAR VHTPHLDRLVSARSVSPTTEMVSNESVDYRATFPEDQFPNSSQNGSCRQVQYPLTD MSPILTSGDSDISSPLLQNTVHIDLSALNPELVQAVQHVIGPSSLIVHFNEVIGRGHFG CVYHGTLDDNDGKKIHCAYKSLNRITDIGEVSQFLTEGIIMKDFSHPNVLSLLGICLRSE GSPLVVLPMKHGDLRNFIRNETHNPTVKDLIGFGLQVAKGMKYLASKKFVHRDLAAR NCMLDEKFTVKVADFLGLARDMYDKEYSVHNKTGAKLPVKWMALESQTQKFTTKSD VWSFGVLLWELMTRGAPPYPDVNTFDITVYLLQGRRLQPEYCPDPLYEVMLKCWHP KAEMRPSFSELVSRISAIFSTFIGEHYVHV NATYVNVKCVAPYPSLLSSEDNADDEVDT RPASFWETS	
14	MKAPAVLAPGILVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETPIQNVLHE HHIFLGATNYIYVLNEEDLQKVAEYKTGPVLEHPDCFCQDCSSKANLSGGVWVDNIN MALVVDYYDDQLISCGSVNRGTCQRHVFPNHTADIQSEVHCIFSPQIEEPSQCPDC VVSALGAKVLSSVKDRFINFFVGNTINSSYFPDHLPHSISVRRLKETKDGMFLTDQSY IDVLPEDRDSYPIKYVHAFESNNFIYFLTVQRETLDAQTFHTRIIRFCSINSGLHSMEMP LECILTEKRKKRSTKKEVFNLQAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSAE PMDRSAMCAFIKYVNDFFNKIVNKNVRCQLQHFYGNHEHCFNRTLLRNSSGCEAR RDEYRTEFTTALQRVDFLMGQFSEVLLTSISTFIKGDLTIANLGTSEGRFMQVVVSRSG PSTPHVNFLLDHPVSPVIVEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQCLS APPFVQCGWCHDKCVRSEECLSGTWTQQICLPAIYKVFNPNSAPLEGGTRLTICGWDF GFRNNKFDLKKTRVLLGNESCTLTLESTMTNLKCTVGPAMNKHFNMSIIISNGHGTT QYSTFSYVDPVITSISPKYGPMAGGTLLTLTGNLYNSGNSRHISIGGKTCTLSVSNIL ECYTPAQITISTEFAVKLKIDLANRETSIFSREDPIVYIEHPTKSFISGGSTITGVGKNLNS VSVPRMVINVHEAGRNFVACQHRNSNEICCTTPSLQQLNLQLPLKTKAFFMLDGILSK YFDLIYVHNPFVKPFKPMISMGNENVLEIKGNDIDPEAVKGEVLKVGKSCENIHLHSE EAVLCTVPNDLLKLNSLNIWQKQISSTVLGKVIVQPDQNFGLIAGVVSISTALLLLGF FLWLKKRKQIKDLGSELVRYDARVHTPHLDRLVSARSVSPTTEMVSNESVDYRATFPED QFPNSSQNGSCRQVQYPLTDMSPILTSGDSDISSPLLQNTVHIDLSALNPELVQAVQHV VIGPSSLIVHFNEVIGRGHFGCVYHGTLDDNDGKKIHCAYKSLNRITDIGEVSQFLTEGIIM KDFSHPNVLSLLGICLRSEGSPLVVLPMKHGDLRNFIRNETHNPTVKDLIGFGLQVAKG MKYLAASKKFVHRDLAARNCMLEKFTVKVADFLGLARDMYDKEYSVHNKTGAKLPVKW MALESQTQKFTTKSDVWSFGVLLWELMTRGAPPYPDVNTFDITVYLLQGRRLQPEYC PDPLYEVMLKCWHPKAEMRPSFSELVSRISAIFSTFIGEHYVHV NATYVNVKCVAPYPSL LSSEDNADDEVDT RPASFWETS	unprocessed preproprotein of isoform "b", NCBI accession No. NM_ 000236.2
15	MKAPAVLAPGILVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETPIQNVLHEH HIFLGATNYIYVLNEEDLQKVAEYKTGPVLEHPDCFCQDCSSKANLSGGVWVDNINMA LVVDYYDDQLISCGSVNRGTCQRHVFPNHTADIQSEVHCIFSPQIEEPSQCPDCVVS ALGAKVLSSVKDRFINFFVGNTINSSYFPDHLPHSISVRRLKETKDGMFLTDQSYIDVLP EFRDSYPIKYVHAFESNNFIYFLTVQRETLDAQTFHTRIIRFCSINSGLHSMEMP EKRKKRSTKKEVFNLQAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSAE PMDRSAMCAFIKYVNDFFNKIVNKNVRCQLQHFYGNHEHCFNRTLLRNSSGCEARRDEYR EFTTALQRVDFLMGQFSEVLLTSISTFIKGDLTIANLGTSEGRFMQVVVSRSGPSTPHV NLLDHPVSPVIVEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQ CGWCHDKCVRSEECLSGTWTQQICLPAIYKVFNPNSAPLEGGTRLTICGWDFGFRNN KFDLKKTRVLLGNESCTLTLESTMTNLKCTVGPAMNKHFNMSIIISNGHGTTQYSTFS YVDPVITSISPKYGPMAGGTLLTLTGNLYNSGNSRHISIGGKTCTLSVSNILECYTPA QTISTEFAVKLKIDLANRETSIFSREDPIVYIEHPTKSFISGGSTITGVGKNLNSVSVPRM VINVHEAGRNFVACQHRNSNEICCTTPSLQQLNLQLPLKTKAFFMLDGILSKYFDLIYV HNPVFKPFKPMISMGNENVLEIKGNDIDPEAVKGEVLKVGKSCENIHLHSEAVLCT VPNDLLKLNSLNIWQKQISSTVLGKVIVQPDQNFGLIAGVVSISTALLLLGF FLWLKKRKQIKDLGSELVRYDARVHTPHLDRLVSARSVSPTTEMVSNESVDYRATFPED QFPNSSQNGSCRQVQYPLTDMSPILTSGDSDISSPLLQNTVHIDLSALNPELVQAVQHV VIGPSSLIVHFNEVIGRGHFGCVYHGTLDDNDGKKIHCAYKSLNRITDIGEVSQFLTEGIIM KDFSHPNVLSLLGICLRSEGSPLVVLPMKHGDLRNFIRNETHNPTVKDLIGFGLQVAKG MKYLAASKKFVHRDLAARNCMLEKFTVKVADFLGLARDMYDKEYSVHNKTGAKLPVKW MALESQTQKFTTKSDVWSFGVLLWELMTRGAPPYPDVNTFDITVYLLQGRRLQPEYC PDPLYEVMLKCWHPKAEMRPSFSELVSRISAIFSTFIGEHYVHV NATYVNVKCVAPYPSL LSSEDNADDEVDT RPASFWETS	unprocessed preproprotein of isoform "c", NCBI accession No. NM_ 001311330.1
16	KEALAKSEMNVNMKYQLPNFTAETPIQNVLHEHHIFLGATNYIYVLNEEDLQKVAEYKT GPVLEHPDCFCQDCSSKANLSGGVWVDNINMALVVDYYDDQLISCGSVNRGTCQR HVFPNHTADIQSEVHCIFSPQIEEPSQCPDCVVSALGAKVLSSVKDRFINFFVGNTINS SYFPDHLPHSISVRRLKETKDGMFLTDQSYIDVLPEDRDSYPIKYVHAFESNNFIYFLT VQRETLDAQTFHTRIIRFCSINSGLHSMEMP LECILTEKRKKR	mature protein comprising the cytoplasmic alpha subunit

17	STKKEVFNIIQAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSAEPMDRSAMCAFPIKYVNDDFFNKIVNKNVRCQLQHFYGNHEHCFNRTLLRNSSGCEARRDEYRTEFTTA LQRVDLFMGQFSEVLLTSISTFIKGLDITIANLGTSEGRFMQVVVSRSGPSTPHVNFLLD SHPVSPVEVIEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCGW CHDKCVRSEECLSGTWTQQICLPAIYKVFNPNSAPLEGGTRLTICGWDFGFRNNKFD LKKTRVLLGNESCTLTSESTMNTLKCTVGPAMNKHFNMSIIISNGHGTQYSTFSYVD PVITSISPKYGPMAAGGTLLLTGNYNLSGNSRHSISIGGKTCTLKSVSNSILECYTPAQTIS TEFAVKLKIDLANRETSIFSRYREDPIVYIEHPTKSFISTWWKEPLNIVSFLFCFASGGSTIT GVGKNLNSVSVPRMVINVHEAGRNFVACQHRNSNEIICCTTPSLQQLNLQLPLKTKA FFMLDGILSKYFDLIYVHNPVFKPFKEKPMISMGNENVLEIKGNDIDPEAVKGEVLKVG N KSCENIHLHSEAVLCTVPNDLLKLNSELNIEWKQAISSSTVLGKVIVQPDQNTGLIAGVV SISTALLLLGFFLWLKKRKQIKDLGSELVRYDARVHTPHLDRLVARSVSPPTTEMVSN E SVDYRATFPEDQFPNSSQNGSCRQVQYPLTDMSPILTSGDSDISSPLLQNTVHIDLSAL NPELVQAVQHVIGPSSLIVHFNEVIGRGHFGCVYHGTLLDNDGKKIHC AVKSLNRITDI GEVSQFLTGEIIMKDFSHPNVLSLLGICLRSEGSPLVPLPYMKHGDRLNFIRNETHNP TV KDLIGFGLQVAKGMKYLASKKFVHRDLAARNCMLDEKFTVKVADFLARDMYDKEYYS VHNTGAKLPVKWMALESLOTQKFTTKSDVWSFGVLLWELMTRGAPPYPDVNTFDITV YLLQGRRLQPEYCPDPLYEVMLKCWHPKAEMRPSFSELVSRISAIFSTFIGEHYVHV N ATYVNVKCVAPYPSLLSSEDNADDEVDRPASFWETS	transmembrane beta subunit, isoform a
18	TKKEVFNIIQAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSAEPMDRSAMCAFPIKYVNDDFFNKIVNKNVRCQLQHFYGNHEHCFNRTLLRNSSGCEARRDEYRTEFTTALQ RVDLFMGQFSEVLLTSISTFIKGLDITIANLGTSEGRFMQVVVSRSGPSTPHVNFLLD SHPVSPVEVIEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCGWCHDK CVRSEECLSGTWTQQICLPAIYKVFNPNSAPLEGGTRLTICGWDFGFRNNKFDLKKTRV LLGNESCTLTSESTMNTLKCTVGPAMNKHFNMSIIISNGHGTQYSTFSYVDPVITSISP KYGPMAGGTLLLTGNYNLSGNSRHSISIGGKTCTLKSVSNSILECYTPAQTISTEFAVKLK IDLANRETSIFSRYREDPIVYIEHPTKSFISGGSTITGVGKNLNSVSVPRMVINVHEAGRNF T VACQHRNSNEIICCTTPSLQQLNLQLPLKTKAFFMLDGILSKYFDLIYVHNPVFKPFKEK P VMISMGNENVLEIKGNDIDPEAVKGEVLKVG NKSCENIHLHSEAVLCTVPNDLLKLNSELN I EWKQAISSSTVLGKVIVQPDQNTGLIAGVVSISTALLLLGFFLWLKKRKQIKDLGSELVRY DARVHTPHLDRLVARSVSPPTTEMVSNESVDYRATFPEDQFPNSSQNGSCRQVQYPLT DMSPILTSGDSDISSPLLQNTVHIDLSALNPELVQAVQHVIGPSSLIVHFNEVIGRGHFG CVYHGTLLDNDGKKIHC AVKSLNRITDIGEVSQFLTGEIIMKDFSHPNVLSLLGICLRSEGS PLVPLPYMKHGDRLNFIRNETHNPVKDLIGFGLQVAKGMKYLASKKFVHRDLAARNCM LDEKFTVKVADFLARDMYDKEYYSVHNTGAKLPVKWMALESLOTQKFTTKSDVWSF G VLLWELMTRGAPPYPDVNTFDITVYLLQGRRLQPEYCPDPLYEVMLKCWHPKAEMR PSFSELVSRISAIFSTFIGEHYVHV NATYVNVKCVAPYPSLLSSEDNADDEVDRPASFW E TS	transmembrane beta subunit, isoform b
19	TKKEVFNIIQAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSAEPMDRSAMCAFPIKYVNDDFFNKIVNKNVRCQLQHFYGNHEHCFNRTLLRNSSGCEARRDEYRTEFTTA LQRVDLFMGQFSEVLLTSISTFIKGLDITIANLGTSEGRFMQVVVSRSGPSTPHVNFLLD SHPVSPVEVIEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCG WCHDKCVRSEECLSGTWTQQICLPAIYKVFNPNSAPLEGGTRLTICGWDFGFRNNK FDLKKTRVLLGNESCTLTSESTMNTLKCTVGPAMNKHFNMSIIISNGHGTQYSTFS YVDPVITSISPKYGPMAAGGTLLLTGNYNLSGNSRHSISIGGKTCTLKSVSNSILECYT PAQTISTEFAVKLKIDLANRETSIFSRYREDPIVYIEHPTKSFISGGSTITGVGKNLNSV S VPRMVINVHEAGRNFVACQHRNSNEIICCTTPSLQQLNLQLPLKTKAFFMLDGILSK YFDLIYVHNPVFKPFKEKPMISMGNENVLEIKGNDIDPEAVKGEVLKVG NKSCENI H LHSEAVLCTVPNDLLKLNSELNIEVGLHSSHVDNKEASVIMLFSGLK	transmembrane beta subunit, isoform c
20	TKKEVFNIIQAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSAEPMDRSAMCAFPIKYVNDDFFNKIVNKNVRCQLQHFYGNHEHCFNRTLLRNSSGCEARRDE YRTEFTTALQRVDLFMGQFSEVLLTSISTFIKGLDITIANLGTSEGRFMQVVVSRSGPSTPHVNFLLD SHPVSPVEVIEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCG CSQCLSAPPFVQCGWCHDKCVRSEECLSGTWTQQICLPAIYKVFNPNSAPLEGG TRLTICGWDFGFRNNKFDLKKTRVLLGNESCTLTSESTMNTLKCTVGPAMN	hMet.mmh

	KHFNMSIIISNGHGTTQYSTFSYVDPVITSISPKYGPMAGGTLLTLTGNYLNSGN SRHISIGGKTCTLKSVSNSILECYTPAQTISTEFAVKLKIDLANRETSIFS YREDPI VYIEHPTKSFISTWWKEPLNIVSFLFCFASGGSTITGVGKNLNSVSVPRMVINVH EAGRNFVACQHRNSNSEIICCTTPSLQQLNLQLPLKTKAFFMLDGILSKYFDLIY VHNPVFKPFKEKPMISMGNENVLEIKGNDIDPEAVKGEVLKVGKNKSCENIHLH SEAVLCTVPNDLLKLNSSELNIEWKQAEQKLISEEDLEQKLISEEDLHHHHHH	
21	TKKEVFNIQAAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSEAPMDRSAM CAFPKIYVNDFFNKIVNKNVRLQHFYGPNEHCNRTLLRNSSGCEARRDEY RTEFTTALQRVDLFMGQFSEVLLTSISTFIKGDLTIANLGTSEGRFMQVVVSRSGP STPHVNFLLDSDHPVSPEVIVEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQ CLSAPPFVQCGWCHDKCVRSEECLSGTWTQQICLPAIYKVPNSAPLEGGTRLT ICGWDFGFRNNKFDLKKTRVLLGNESCTLTLESTMTNLKCTVGPAMNKHFM SIIISNGHGTTQYSTFSYVDPVITSISPKYGPMAGGTLLTLTGNYLNSGNSRHISIG GKTCTLKSVSNSILECYTPAQTISTEFAVKLKIDLANRETSIFS YREDPIVYIEHPTK SFISTWWKEPLNIVSFLFCFASGGSTITGVGKNLNSVSVPRMVINVHEAGRNFV ACQHRNSNSEIICCTTPSLQQLNLQLPLKTKAFFMLDGILSKYFDLIYVHNPVFKPFE KPMISMGNENVLEIKGNDIDPEAVKGEVLKVGKNKSCENIHLHSEAVLCTVPNDLL KLNSSELNIEWKQAMEVSSVFIFPPKPKDVLITLTPKVTCVVVDISKDDPEVQFSW FVDDVEVHTAQTPREEQFNSTFRSVSELPIHQDWLNGKEFKCRVNSAAFPAP IEKTSKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQP AENYKNTQPMIDTDGSYFVYSKLVQKSNWEAGNTFTCSVLHEGLHNNHTEKSL SHSPGKE	hMet.mFc
22	ECKEALAKSEMNVNMKYQLPNFTAETPIQNVLHEHHIFLGATNYIYVLNEEDLQK VAEYKTGPVLEHPDCFCQDCSSKANLSGGVWWDNINMALVVDYDDQLISCG SVNRGTCQRHVFPNHHTADIQSEVHCIFSPQIEEPSQCPDCVVSALGAKVLSSVK DRFINFFVGNTINSSYFPDHLHSISVRRKTKDGMFLTDQSYIDVLPEFRDSY PIKYVHAFESNNFIYFLTVQRETLDAQTFHTRIIRFCSINSLHSYMEMPLECILTE KRKKRSTKKEVFNIQAAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSEAPM DRSAMCAFPKIYVNDFFNKIVNKNVRLQHFYGPNEHCNRTLLRNSSGCEA RRDEYRTEFTTALQRVDLFMGQFSEVLLTSISTFIKGDLTIANLGTSEGRFMQVVV SRSGPSTPHVNFLLDSDHPVSPEVIVEHTLNQNGYTLVITGKKITKIPLNGLGCRHF QSCSQCLSAPPFVQCGWCHDKCVRSEECLSGTWTQQICLPAIYKVPNSAPLE GGTRLTICGWDFGFRNNKFDLKKTRVLLGNESCTLTLESTMTNLKCTVGPAM NKHFNMSIIISNGHGTTQYSTFSYVDPVITSISPKYGPMAGGTLLTLTGNYLNSGN SRHISIGGKTCTLKSVSNSILECYTPAQTISTEFAVKLKIDLANRETSIFS YREDPIV YIEHPTKSFISGGSTITGVGKNLNSVSVPRMVINVHEAGRNFVACQHRNSNSEIIC CTTPSLQQLNLQLPLKTKAFFMLDGILSKYFDLIYVHNPVFKPFEKPMISMGNEN VLEIKGNDIDPEAVKGEVLKVGKNKSCENIHLHSEAVLCTVPNDLLKLNSSELNIEWK QAISSTVLGVVQPDQNFTEQKLISEEDLGGEQKLISEEDLHHHHHH	human Met isoform 1 (Uniprot ID: P08581) expressed with a myc-myc- hexahistidine (.mmh) tag
23	VRRKTKDGMF	AA 192-204 of SEQ ID NO: 22
24	LARQIGASLND	AA 305-315 of SEQ ID NO: 22
25	FIKGDLTIANLGTSEGRFMQVVVSRSGPSTPHVNF	AA 421-455 of SEQ ID NO: 22

We claim:

1. A method of treating non-small cell lung cancer (NSCLC), reducing NSCLC tumor growth, and or causing regression of NSCLC in a subject suffering from a tumor harboring a MET alteration, the method comprising administering to the subject a dose of about 250 to 2000 mg of a bispecific antibody comprising:

a first antigen-binding domain (D1) comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 9; and

a second antigen-binding domain (D2) comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 5 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 9;

wherein D1 specifically binds a first epitope of human MET; and

wherein D2 specifically binds a second epitope of human MET.

2. The method of claim 1, wherein the subject is further selected as having one or more of the following criteria:

(i) MET TKI naïve;

(ii) histologically confirmed NSCLC;

(iii) MET-exon14 alteration in DNA or a deletion that leads to exon 14 skipping;

(iv) MET gene amplification;

(v) elevated MET protein expression (IHC $\geq 2+$ or H score of >150);

(vi) MET exon 14 alteration in DNA or a deletion that leads to exon 14 skipping and MET TKI experienced;

(vii) MET exon 14 alteration in DNA or a deletion that leads to exon 14 skipping and

MET TKI naïve;

(viii) MET gene highly amplified (MET GCN ≥ 5 and/or MET/CEP7 ratio ≥ 2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA) and MET TKI naïve;

(ix) MET protein highly overexpressed (IHC 3+ or H score of ≥ 200) and MET TKI naïve; and/or

(x) MET gene highly amplified (MET GCN ≥ 5 and/or MET/CEP7 ratio ≥ 2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA), MET protein highly overexpressed (IHC 3+ or H score of ≥ 200), and MET TKI naïve.

3. The method of claim 1, wherein the MET alteration is an exon 14 alteration in DNA, a MET gene amplification, or MET protein overexpression.

4. The method of claim 1, wherein the MET alteration is an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping.

5. The method of claim 1, wherein the MET alteration is an exon 14 mutation.

6. The method of claim 5, wherein the exon 14 mutation is D1010N, D1010fs*19, D1010Y, D1010H, or R1004P.

7. The method of claim 1, wherein the MET alteration is a MET gene amplification.

8. The method of claim 1, wherein the MET protein overexpression is MET protein expression in tumor tissue that is higher than expression in normal tissue.

9. The method of claim 1, wherein the MET alteration is identified using ctDNA from blood sample obtained from the patient prior to treatment.

10. The method of claim 1, wherein the MET alteration is identified in a tissue sample obtained from the patient prior to treatment.

11. The method of any one of claims 1 to 10, wherein the subject is MET tyrosine kinase inhibitor (TKI) naïve.

12. The method of any one of claims 1 to 10, wherein the subject has received prior anti-cancer therapy comprising one or more of a PD-1 inhibitor, an EGFR inhibitor, a PD-L1 inhibitor, surgery, radiation therapy, or chemotherapy.

13. The method of claim 11, wherein the prior anti-cancer therapy comprises a PD-1 inhibitor or a PD-L1 inhibitor.

14. The method of claim 11, wherein the prior anti-cancer therapy comprises an EGFR inhibitor.

15. The method of claim 11, wherein the subject is resistant or inadequately responsive to, or relapsed after prior therapy.

16. The method of any one of claims 1 to 10, wherein the subject has not received prior anti-cancer therapy.

17. The method of any one of claims 1 to 16, wherein tumor has an EGFR mutation.

18. The method of claim 17, wherein the EGFR mutation is selected from the group consisting of L858R, G719S, E709A, E746_A750del, and S752_I759del.

19. The method of any one of claims 1 to 18, wherein the tumor is non-squamous NSCLC.

20. The method of any one of claims 1 to 18, wherein the tumor is squamous NSCLC.

21. The method of any one of claims 1 to 18, wherein the NSCLC is metastatic.

22. The method of claim 21, wherein the NSCLC has metastasized to the brain.

23. The method of claim 21, wherein the NSCLC has metastasized to the liver.

24. The method of any one of claims 1 through 23, wherein the NSCLC is unresectable.

25. The method of any one of claims 1 to 24, wherein D1 comprises an HCDR1 amino acid sequence as set forth in SEQ ID NO: 2; an HCDR2 amino acid sequence as set forth in SEQ ID NO: 3; an HCDR3 amino acid sequence as set forth in SEQ ID NO: 4; an LCDR1 amino

acid sequence as set forth in SEQ ID NO: 10; an LCDR2 amino acid sequence as set forth in SEQ ID NO: 11; and an LCDR3 amino acid sequence as set forth in SEQ ID NO: 12.

26. The method of any one of claims 1 to 25, wherein D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 1; and an LCVR comprising the amino acid sequence of SEQ ID NO: 9.

27. The method of any one of claims 1 to 26, wherein D2 comprises an HCDR1 amino acid sequence as set forth in SEQ ID NO: 6; an HCDR2 amino acid sequence as set forth in SEQ ID NO: 7; an HCDR3 amino acid sequence as set forth in SEQ ID NO: 8; an LCDR1 amino acid sequence as set forth in SEQ ID NO: 10; an LCDR2 amino acid sequence as set forth in SEQ ID NO: 11; and an LCDR3 amino acid sequence as set forth in SEQ ID NO: 12.

28. The method of any one of claims 1 to 27, wherein D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 5; and an LCVR comprising the amino acid sequence of SEQ ID NO: 9.

29. The method of any one of claims 1 to 28, wherein the bispecific antibody is administered at a dose of about 250 mg, 500 mg, 750 mg, 1000 mg, 1500 mg, or 2000 mg.

30. The method of any one of claims 1 to 29, wherein the bispecific antibody is administered at a dose of 500 mg.

31. The method of any one of claims 1 to 29, wherein the bispecific antibody is administered at a dose of 1000 mg.

32. The method of any one of claims 1 to 29, wherein the bispecific antibody is administered at a dose of 2000 mg.

33. The method of any one of claims 1 to 32, wherein the bispecific antibody is administered intravenously, subcutaneously, or intraperitoneally.

34. The method of any one of claims 1 to 33, wherein the bispecific antibody is administered once every three weeks.

35. The method of any one of claims 1 to 33, wherein bispecific antibody is administered 3 weeks after the immediately preceding dose.

36. The method of any one of claims 1 to 35, wherein the treatment produces a therapeutic effect selected from the group consisting of delay in tumor growth, reduction in tumor cell number, reduction in metastasis, tumor regression, increase in survival, partial response, and complete response.

37. The method of claim 36, wherein tumor growth is delayed by at least 10 days as compared to an untreated subject.

38. The method of claim 36, wherein the tumor growth is inhibited by at least 50% as compared to an untreated subject.

39. A method of treating or inhibiting the growth of a NSCLC comprising:

(1) selecting a subject with a tumor harboring a MET alteration; and

(2) administering to the subject (a) a dose of about 250 mg, 500 mg, 750 mg, 1000 mg, 1500 mg, or 2000 mg of a bispecific antibody comprising:

a first antigen-binding domain (D1) comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 9; and

a second antigen-binding domain (D2) comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 5 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 9;

wherein D1 specifically binds a first epitope of human MET; and

wherein D2 specifically binds a second epitope of human MET.

40. The method of claim 39, wherein the administering of step (2) occurs once every 3 weeks.

41. The method of claim 39, wherein the subject is further selected as having one or more of the following criteria:

- (i) MET TKI naïve;
- (ii) histologically confirmed NSCLC;
- (iii) MET-exon14 alteration in DNA or a deletion that leads to exon 14 skipping;
- (iv) MET gene amplification;
- (v) elevated MET protein expression (IHC $\geq 2+$ or H score of >150);
- (vi) MET exon 14 alteration in DNA or a deletion that leads to exon 14 skipping and MET TKI experienced;
- (vii) MET exon 14 alteration in DNA or a deletion that leads to exon 14 skipping and MET TKI naïve;
- (viii) MET gene highly amplified (MET GCN ≥ 5 and/or MET/CEP7 ratio ≥ 2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA) and MET TKI naïve;
- (ix) MET protein highly overexpressed (IHC 3+ or H score of ≥ 200) and MET TKI naïve; and/or
- (x) MET gene highly amplified (MET GCN ≥ 5 and/or MET/CEP7 ratio ≥ 2 by FISH or MET GCN ≥ 6 by NGS in tissues or MET fold change ≥ 2 in ctDNA), MET protein highly overexpressed (IHC 3+ or H score of ≥ 200), and MET TKI naïve.

42. The method of claim 39, wherein the MET alteration is an exon 14 alteration in DNA, a MET gene amplification, or MET protein overexpression.

43. The method of claim 39, wherein the MET alteration is an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping.

44. The method of claim 39, wherein the MET alteration is an exon 14 mutation.

45. The method of claim 44, wherein the exon 14 mutation is D1010N, D1010fs*19, D1010Y, D1010H, or R1004P.

46. The method of claim 39, wherein the MET alteration is a MET gene amplification.
47. The method of claim 39, wherein the MET protein overexpression is MET protein expression in tumor tissue that is higher than expression in normal tissue.
48. The method of claim 39, wherein the MET alteration is identified using ctDNA from blood sample obtained from the patient prior to treatment.
49. The method of claim 39, wherein the MET alteration is identified in a tissue sample obtained from the patient prior to treatment.
50. The method of claim 39, wherein the subject is further selected as having NSCLC with an EGFR mutation.
51. The method of claim 39, wherein the subject is further selected as having non-squamous NSCLC.
52. The method of claim 39, wherein the subject is further selected as having squamous NSCLC.
53. The method of any one of claims 39 to 52, wherein the NSCLC is metastatic.
54. The method of claim 53, wherein the NSCLC has metastasized to the brain.
55. The method of claim 53, wherein the NSCLC has metastasized to the liver.
56. The method of any one of claims 39 to 55, wherein the NSCLC is unresectable.
57. A method for treating a tumor comprising:
- (a) selecting a subject with NSCLC;
 - (b) determining that the tumor exhibits a MET alteration selected from the group consisting of an Exon 14 alteration in DNA or a deletion that leads to exon 14 skipping, MET gene amplification, and/or Met protein overexpression, comprising (i) obtaining a tissue sample and/or a liquid sample from the subject; and (ii) assessing the tissue sample for MET gene amplification using fluorescent in situ hybridization in tumor tissues or by Next Gen Sequencing in tumor tissues and or ctDNA and/or assessing the tissue sample for Met protein

overexpression using immunohistochemistry, and/or assessing the liquid sample for an Exon14 mutation using ctDNA; and, if the tumor exhibits a MET alteration,

(c) administering one or more doses of a MET x MET bispecific antibody to the subject in need thereof,

wherein the Met x Met anti-tumor therapy comprises a bispecific antibody comprising:

a first antigen-binding domain (D1) comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 9; and

a second antigen-binding domain (D2) comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 5 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 9;

wherein D1 specifically binds a first epitope of human MET; and

wherein D2 specifically binds a second epitope of human MET.

58. A method for identifying a candidate for Met x Met anti-tumor therapy, the method comprising obtaining a tissue sample and/or a fluid sample from a subject having NSCLC; and assessing the tissue sample and/or fluid sample for a MET alteration selected from the group consisting of an Exon 14 alteration in DNA or a deletion that leads to Exon 14 skipping, MET gene amplification, and/or Met protein overexpression,

wherein presence of at least one Met alteration in the tissue sample or fluid sample identifies the subject as a candidate for anti-tumor therapy; and

wherein the Met x Met anti-tumor therapy comprises a bispecific antibody comprising a first antigen-binding domain (D1) comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and three light chain complementarity determining

regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 9; and

a second antigen-binding domain (D2) comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 5 and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 9;

wherein D1 specifically binds a first epitope of human MET; and

wherein D2 specifically binds a second epitope of human MET.

59. The method of claim 58, wherein the MET alteration is an exon 14 alteration in DNA or a deletion that leads to exon 14 skipping.

60. The method of claim 58, wherein the MET alteration is an exon 14 mutation.

61. The method of claim 60, wherein the exon 14 mutation is D1010N, D1010fs*19, D1010Y, D1010H, or R1004P.

62. The method of claim 58, wherein the MET alteration is a MET gene amplification.

63. The method of claim 58, wherein the MET protein overexpression is MET protein expression in tumor tissue that is higher than expression in normal tissue.

64. The method of claim 58, wherein the MET alteration is identified using ctDNA from blood sample obtained from the patient prior to treatment.

65. The method of claim 58, wherein the MET alteration is identified in a tissue sample obtained from the patient prior to treatment.

66. A method for monitoring efficacy of a MET x MET bispecific antibody in a subject having NSCLC with a MET alteration, the method comprising:

(i) obtaining a tissue sample and/or a fluid sample from the subject and assessing the tissue sample and/or fluid sample for somatic mutations in one or more genes selected from the group consisting of:

a. an on-target MET Receptor gene mutation that confers resistance to MET TKI's found in MET Ex14 Mut patients with prior TKI Exp and MET gene silencing (loss-of-function);

b. TK driver receptor activation selected from TK Receptor and ligand gene amplification and TKR activating mutations; and

c. an activating gene mutation in a pathway selected from the group consisting of JAK2/STAT3 pathway, RAS/RAF/MEK/MAPK pathway, PI3K/AKT/MTOR pathway, TP53 mutations, and cell cycle gene amplification;

(ii) administering a MET x MET bispecific antibody to the subject;

(iii) repeating steps (i) and (ii) over the course of treatment; wherein the acquiring of a mutation by one or more genes is indicative of resistance to therapy and/or indicative of poor prognosis.

67. The method of claim 66, wherein:

a. the on-target MET Receptor gene mutation is selected from the group consisting of MET Y1230C, MET D1228H, MET D1228N; and the MET gene silencing (loss-of-function) is selected from somatic mutations in DNMT3A and TET2;

b. the TKR activating mutation is selected from the group consisting of EGFR L858R, EGFR G719S, EGFR E709A, EGFR E746_A750del, and EGFR S752_I759del; and

c. the JAK2/STAT3 pathway mutation is JAK2 V617F; the RAS/RAF/MEK/MAPK pathway mutation is selected from the group consisting of KRAS G12A/V, GNAS R201H, MKRN-BRAF fusion, BRAF S602Y, RICTOR Amp, and MAP2K1 K57N; the PI3K/AKT/MTOR pathway mutation is selected from the group consisting of PIK3CA H1047L, PIK3CA E545K, PIK3CA E542K, PIK3CA N345K, IDH1 R132L, and MTOR E2338Q; the PI3K/AKT/MTOR pathway amplification is selected from the group consisting of AKT2 Amp and RICTOR Amp; the TP53 mutation is selected from the group consisting of TP53 R280T and TP53 R248Q; and the cell cycle gene amplification is selected from the group consisting of CDK4 Amp, CDK6 Amp, CCND1 Amp, and CCNE1 Amp.

68. A method for treating NSCLC in a subject, the method comprising: (i) obtaining a liquid sample from the subject and determining the MET amplification in ctDNA from the liquid

sample, and (ii) administering a MET x MET bispecific antibody to the subject; wherein steps (i) and (ii) are repeated once every three weeks, and wherein a loss of MET amplification after step (ii) is repeated is indicative of durable response to treatment.

69. The method of claim 68, wherein the bispecific antibody is administered intravenously, subcutaneously, or intraperitoneally.

70. The method of claim 68, wherein the bispecific antibody is administered once every three weeks.

71. The method of claim 68, wherein bispecific antibody is administered 3 weeks after the immediately preceding dose.

72. A method for determining a therapeutically effective amount of a MET x MET bispecific antigen-binding molecule, the method comprising: (i) administering a dosage of the bispecific antibody to a patient in need thereof, and (ii) measuring soluble MET in a blood sample, wherein a maximal increase in soluble MET (sMET) indicates saturation of receptor occupancy and a therapeutically effective amount of the bispecific antibody.