

We claim:

1. Use of a bispecific antibody in the manufacture of a medicament for 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, wherein the bispecific antibody is to be administered to the subject at a dose of about 250 to 2000 mg, wherein the bispecific antibody comprises:

a first antigen-binding domain (D1) comprising three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR), wherein HCDR1, HCDR2, and HCDR3 comprise respective amino acid sequences of SEQ ID NOs: 2, 3, and 4, and LCDR1, LCDR2, and LCDR3 comprise respective amino acid sequences of SEQ ID NOs: 10, 11, and 12; and

a second antigen-binding domain (D2) comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a LCVR, wherein HCDR1, HCDR2, and HCDR3 comprise respective amino acid sequences of SEQ ID NOs: 6, 7, and 8, and LCDR1, LCDR2, and LCDR3 comprise respective amino acid sequences of SEQ ID NOs: 10, 11, and 12;

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

wherein D2 specifically binds a second epitope of human MET.

2. The use according to claim 1, wherein the subject has one or more of the following criteria:

- (i) MET tyrosine kinase inhibitor (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 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) and

MET TKI naïve;

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

(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 use according to claim 1, wherein the MET alteration is an exon 14 alteration in DNA, a MET gene amplification, or MET protein overexpression.

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

5. The use according to claim 1, wherein the MET alteration is an exon 14 mutation.

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

7. The use according to claim 1, wherein the MET alteration is a MET gene amplification.

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

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

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

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

12. The use according to any one of claims 1-10, 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, and chemotherapy.

13. The use according to claim 12, wherein the prior anti-cancer therapy comprises a

PD-1 inhibitor or a PD-L1 inhibitor.

14. The use according to claim 12, wherein the prior anti-cancer therapy comprises an EGFR inhibitor.

15. The use according to claim 12, wherein the subject is resistant or inadequately responsive to, or relapsed after prior therapy.

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

17. The use according to any one of claims 1-16, wherein the tumor has an EGFR mutation.

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

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

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

21. The use according to any one of claims 1-20, wherein the NSCLC is metastatic.

22. The use according to claim 21, wherein the NSCLC has metastasized to the brain.

23. The use according to claim 21, wherein the NSCLC has metastasized to the liver.

24. The use according to any one of claims 1-23, wherein the NSCLC is unresectable.

25. The use according to any one of claims 1-24, wherein D1 comprises a HCVR comprising an amino acid sequence of SEQ ID NO: 1, and a LCVR comprising an amino acid sequence of SEQ ID NO: 9; and D2 comprises a HCVR comprising an amino acid sequence of SEQ ID NO: 5, and a LCVR comprising an amino acid sequence of SEQ ID NO: 9.

26. The use according to any one of claims 1-25, wherein the bispecific antibody is to be administered at a dose of about 250 mg, 500 mg, 750 mg, 1000 mg, 1500 mg, or 2000 mg.

27. The use according to any one of claims 1-26, wherein the bispecific antibody is to be administered at a dose of 2000 mg.

28. The use according to any one of claims 1-27, wherein the bispecific antibody is to be administered intravenously, subcutaneously, or intraperitoneally.

29. The use according to any one of claims 1-28, wherein the bispecific antibody is to be administered once every three weeks.

30. The use according to any one of claims 1-28, wherein the bispecific antibody is to be administered 3 weeks after the immediately preceding dose.

31. The use according to any one of claims 1-30, 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.

32. The use according to claim 31, wherein the tumor growth is delayed by at least 10 days as compared to an untreated subject.

33. The use according to claim 31, wherein the tumor growth is inhibited by at least 50% as compared to an untreated subject.

34. Use of a bispecific antibody in the manufacture of a medicament for treating or inhibiting the growth of a NSCLC

in a subject with a tumor harboring a MET alteration, wherein the bispecific antibody is to be administered to the subject at a dose of about 250 mg, 500 mg, 750 mg, 1000 mg, 1500 mg, or 2000 mg; wherein the bispecific antibody comprises:

a first antigen-binding domain (D1) comprising three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR); wherein HCDR1, HCDR2, and HCDR3 comprise respective amino acid sequences of SEQ ID NOs: 2, 3, and 4, and LCDR1, LCDR2, and LCDR3 comprise respective amino acid sequences of SEQ ID NOs: 10, 11, and 12; and

a second antigen-binding domain (D2) comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a LCVR; wherein HCDR1, HCDR2, and HCDR3 comprise

respective amino acid sequences of SEQ ID NOs: 6, 7, and 8, and LCDR1, LCDR2, and LCDR3 comprise respective amino acid sequences of SEQ ID NOs: 10, 11, and 12;

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

wherein D2 specifically binds a second epitope of human MET.

35. The use according to claim 34, wherein the bispecific antibody is to be administered at a dose of about 2000 mg.

36. The use according to claim 34, wherein the bispecific antibody is to be administered once every 3 weeks.

37. The use according to claim 34, wherein the subject has one or more of the following criteria:

- (i) MET tyrosine kinase inhibitor (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 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) and MET TKI naïve;
- (ix) MET protein highly overexpressed (IHC 3+ or H score of ≥ 200) and MET TKI naïve; and
- (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.

38. The use according to claim 34, wherein the MET alteration is an exon 14 alteration in DNA, a MET gene amplification, or MET protein overexpression.

39. The use according to claim 34, wherein the MET alteration is an exon 14 alteration

in DNA or a deletion that leads to exon 14 skipping.

40. The use according to claim 34, wherein the MET alteration is an exon 14 mutation.

41. The use according to claim 40, wherein the exon 14 mutation is D1010N, D1010fs*19, D1010Y, D1010H, or R1004P.

42. The use according to claim 34, wherein the MET alteration is a MET gene amplification.

43. The use according to claim 38, wherein the MET protein overexpression is MET protein expression in tumor tissue that is higher than expression in normal tissue.

44. The use according to claim 34, wherein the MET alteration is identified using ctDNA from blood sample obtained from the patient prior to treatment.

45. The use according to claim 34, wherein the MET alteration is identified in a tissue sample obtained from the patient prior to treatment.

46. The use according to claim 34, wherein the subject is further selected as having NSCLC with an EGFR mutation.

47. The use according to claim 34, wherein the subject is further selected as having non-squamous NSCLC.

48. The use according to claim 34, wherein the subject is further selected as having squamous NSCLC.

49. The use according to any one of claims 34-48, wherein the NSCLC is metastatic.

50. The use according to claim 49, wherein the NSCLC has metastasized to the brain.

51. The use according to claim 49, wherein the NSCLC has metastasized to the liver.

52. The use according to any one of claims 34-51, wherein the NSCLC is unresectable.

53. A method for identifying a candidate for MET x MET anti-tumor therapy, wherein a tissue sample and/or a fluid sample is to be obtained from a subject having NSCLC; and the

tissue sample and/or fluid sample is to be assessed 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 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 (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR); wherein HCDR1, HCDR2, and HCDR3 comprise respective amino acid sequences of SEQ ID NOs: 2, 3, and 4, and LCDR1, LCDR2, and LCDR3 comprise respective amino acid sequences of SEQ ID NOs: 10, 11, and 12; and

a second antigen-binding domain (D2) comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a LCVR; wherein HCDR1, HCDR2, and HCDR3 comprise respective amino acid sequences of SEQ ID NOs: 6, 7, and 8, and LCDR1, LCDR2, and LCDR3 comprise respective amino acid sequences of SEQ ID NOs: 10, 11, and 12;

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

wherein D2 specifically binds a second epitope of human MET.

54. The use according to claim 53, wherein the bispecific antibody is to be administered at a dose of about 250 mg, 500 mg, 750 mg, 1000 mg, 1500 mg, or 2000 mg.

55. The use according to claim 54, wherein the bispecific antibody is to be administered at a dose of about 2000 mg.

56. Use of a MET x MET bispecific antibody in the manufacture of a medicament for treating a subject having NSCLC with a MET alteration, wherein efficacy of the MET x MET bispecific antibody is to be monitored; and wherein:

(xi) a tissue sample and/or a fluid sample is to be obtained from the subject and the tissue sample and/or fluid sample is to be assessed 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 tyrosine kinase inhibitors (TKIs) 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;
- (xii) a MET x MET bispecific antibody to be administered to the subject; and
- (xiii) steps (i) and (ii) are to be repeated 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;

wherein the MET x MET bispecific antibody comprises:

a first antigen-binding domain (D1) comprising three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR), wherein HCDR1, HCDR2, and HCDR3 comprise respective amino acid sequences of SEQ ID NOs: 2, 3, and 4, and LCDR1, LCDR2, and LCDR3 comprise respective amino acid sequences of SEQ ID NOs: 10, 11, and 12; and

a second antigen-binding domain (D2) comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a LCVR, wherein HCDR1, HCDR2, and HCDR3 comprise respective amino acid sequences of SEQ ID NOs: 6, 7, and 8, and LCDR1, LCDR2, and LCDR3 comprise respective amino acid sequences of SEQ ID NOs: 10, 11, and 12;

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

wherein D2 specifically binds a second epitope of human MET.

57. The use according to claim 56, wherein:

- a. the on-target MET Receptor gene mutation is selected from the group consisting of MET Y1230C, MET D1228H, and 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.

58. Use of a MET x MET bispecific antibody in the manufacture of a medicament for treating NSCLC in a subject, wherein: (i) a liquid sample is to be obtained from the subject and the MET amplification in ctDNA is to be determined from the liquid sample, and (ii) the MET x MET bispecific antibody is to be administered to the subject; wherein steps (i) and (ii) are to be repeated once every three weeks, and wherein a loss of MET amplification after step (ii) is indicative of durable response to treatment;

wherein the MET x MET bispecific antibody comprises:

a first antigen-binding domain (D1) comprising three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR), wherein HCDR1, HCDR2, and HCDR3 comprise respective amino acid sequences of SEQ ID NOs: 2, 3, and 4, and LCDR1, LCDR2, and LCDR3 comprise respective amino acid sequences of SEQ ID NOs: 10, 11, and 12; and

a second antigen-binding domain (D2) comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a LCVR, wherein HCDR1, HCDR2, and HCDR3 comprise respective amino acid sequences of SEQ ID NOs: 6, 7, and 8, and LCDR1, LCDR2, and LCDR3 comprise respective amino acid sequences of SEQ ID NOs: 10, 11, and 12;

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

wherein D2 specifically binds a second epitope of human MET.

59. The use according to claim 58, wherein the bispecific antibody is to be administered intravenously, subcutaneously, or intraperitoneally.

60. The use according to claim 58, wherein the bispecific antibody is to be administered once every three weeks.

61. The use according to claim 58, wherein bispecific antibody is to be administered 3 weeks after the immediately preceding dose.