

Claims

1. Use of a composition comprising an isolated bispecific anti-epidermal growth factor receptor (EGFR)/hepatocyte growth factor receptor (c-Met) antibody for the manufacture of a medicament for the treatment of EGFR, c-Met, or EGFR and c-Met expressing cancer in a subject, wherein the medicament is for use in combination with an agent that enhances macrophage activity in the subject.
2. The use according to claim 1, wherein the bispecific anti-EGFR/c-Met antibody comprises:
 - a) a first domain that binds EGFR, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6; and
 - b) a second domain that binds c-Met, wherein the second domain comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.
3. The use according to claim 2, wherein
 - a) the first domain that binds EGFR comprises a heavy chain variable region (VH) of SEQ ID NO: 13 and a light chain variable region (VL) of SEQ ID NO: 14; and
 - b) the second domain that binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.
4. The use according to any one of claims 1-3, wherein the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.
5. The use according to any one of claims 1-4, wherein the bispecific anti-EGFR/c-Met antibody comprises a first heavy chain (HC1) of SEQ ID NO: 17, a first light chain (LC1) of SEQ ID NO: 18, a second heavy chain (HC2) of SEQ ID NO: 19 and a second light chain (LC2) of SEQ ID NO: 20.

6. The use according to any one of claims 1-5, wherein the agent that enhances macrophage activity is GM-CSF, an anti-CD47 antibody, a HDAC2 inhibitor, a PD-(L)1 axis inhibitor or a CD11b agonist.
7. The use according to any one of claims 1-6, wherein the EGFR or c-Met expressing cancer is associated with a wild-type EGFR, an EGFR activating mutation, an EGFR gene amplification, increased levels of circulating HGF, a wild-type c-Met, a c-Met activating mutation, a c-Met gene amplification or a mutant KRAS.
8. The use according to claim 7, wherein the EGFR activating mutation comprises L718Q, G719A, G719X (X being any amino acid), L861X (X being any amino acid), L858R, E746K, L747S, E749Q, A750P, A755V, V765M, C797S, L858P or T790M substitution, deletion of E746-A750, deletion of R748-P753, insertion of Ala (A) between M766 and A767, insertion of Ser, Val and Ala (SVA) between S768 and V769, insertion of Asn and Ser (NS) between P772 and H773, insertion of one or more amino acids between D761 and E762, A763 and Y764, Y764 and Y765, M766 and A767, A767 and V768, S768 and V769, V769 and D770, D770 and N771, N771 and P772, P772 and H773, H773 and V774, V774 and C775, one or more deletions in EGFR exon 20, or one or more insertions in EGFR exon 20, or any combination thereof.
9. The use according to claim 7, wherein the mutant KRAS comprises a G12V, G12C, G12A or G12D substitution, or any combination thereof.
10. The use according to any one of claims 1-9, wherein the subject has a newly diagnosed EGFR, c-Met or EGFR and c-Met expressing cancer.
11. The use according to any one of claims 1-9, wherein the subject is resistant or has acquired resistance to treatment with a prior anti-cancer therapy.
12. The use according to claim 11, wherein the prior anti-cancer therapy is chemotherapy, a targeted anti-cancer therapy or a kinase inhibitor.
13. The use according to claim 12, wherein the kinase inhibitor is an inhibitor of EGFR, c-Met, HER2, HER3, HER4, VEGFR or AXL.
14. The use according to claim 13, wherein the kinase inhibitor is erlotinib, gefitinib, lapatinib, vandetanib, afatinib, osimertinib, lazertinib, poziotinib, criotinib, cabozantinib, capmatinib, axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib or sunitinib.

15. The use according to any one of claims 1-14, wherein the EGFR, c-Met or EGFR and c-Met expressing cancer is an epithelial cell cancer, breast cancer, ovarian cancer, lung cancer, non-small cell lung cancer (NSCLC), lung adenocarcinoma, small cell lung cancer, colorectal cancer, anal cancer, prostate cancer, kidney cancer, bladder cancer, head and neck cancer, pharynx cancer, cancer of the nose, pancreatic cancer, skin cancer, oral cancer, cancer of the tongue, esophageal cancer, vaginal cancer, cervical cancer, cancer of the spleen, testicular cancer, gastric cancer, cancer of the thymus, colon cancer, thyroid cancer, liver cancer, hepatocellular carcinoma (HCC) or sporadic or hereditary papillary renal cell carcinoma (PRCC).

16. The use according to any one of claims 1-15, comprising further administering one or more anti-cancer therapies to the subject.

17. The use according to claim 16, wherein the one or more anti-cancer therapies comprises chemotherapy, a targeted anti-cancer therapy or a kinase inhibitor.

18. The use according to claim 17, wherein the kinase inhibitor is an inhibitor of EGFR, c-Met, HER2, HER3, HER4, VEGFR or AXL.

19. The use according to claim 18, wherein the kinase inhibitor is erlotinib, gefitinib, lapatinib, vandetanib, afatinib, osimertinib, lazertinib, poziotinib, crotinib, cabozantinib, capmatinib, axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib or sunitinib.

20. Use of a composition comprising a bispecific anti-EGFR/c-Met antibody for the manufacture of a medicament for the diagnosis and treatment of a subject having EGFR, c-Met or EGFR and c-Met expressing cancer that is responsive to treatment with a bispecific anti-EGFR/c-Met antibody, comprising:

- a) providing a biological sample from the subject;
- b) measuring macrophage or monocyte levels from the biological sample;
- c) diagnosing the subject having the EGFR, c-Met or EGFR and c-Met expressing cancer that is responsive to treatment with the bispecific anti-EGFR/c-Met antibody when the macrophage or monocyte levels from the biological sample are higher than a threshold value; and
- d) administering or providing for administration of the medicament to the subject diagnosed as responsive to treatment with the anti-EGFR/c-Met antibody.

21. Use of a composition comprising a bispecific anti-EGFR/c-Met antibody for the manufacture of a medicament for the treatment of EGFR, c-Met or EGFR and c-Met expressing cancer, comprising:
- a) determining that the subject has macrophage or monocyte levels higher than a threshold value; and
 - b) administering or providing for administration of the medicament to the subject determined to have macrophage or monocyte levels higher than the threshold value.
22. A method of predicting response of a subject having EGFR, c-Met or EGFR and c-Met expressing cancer to treatment with a bispecific anti-EGFR/c-Met antibody, comprising
- a) providing a biological sample from the subject;
 - b) measuring macrophage or monocyte levels from the biological sample;
 - c) predicting the subject as a responder when the macrophage or monocyte levels from the biological sample are higher than a threshold value.
23. Use of a composition comprising a bispecific anti-EGFR/c-Met antibody for the manufacture of a medicament for the treatment of a subject having EGFR, c-Met or EGFR and c-Met expressing cancer that is responsive to treatment with a bispecific anti-EGFR/c-Met antibody, comprising:
- a) providing a biological sample from the subject;
 - b) measuring macrophage or monocyte levels from the biological sample;
 - c) treating the subject with the medicament when the macrophage or monocyte levels from the biological sample are higher than a threshold value.
24. Use of a composition comprising a bispecific anti-EGFR/c-Met antibody for the manufacture of a medicament in a method of determining whether a subject having an EGFR, c-Met or EGFR and c-Met expressing cancer is responsive to treatment with a bispecific anti-EGFR/c-Met antibody and deciding whether to treat the subject, wherein the method comprises:
- a) providing a biological sample from the subject;
 - b) measuring macrophage or monocyte levels from the biological sample;
 - c) diagnosing the subject with EGFR, c-Met or EGFR and c-Met expressing cancer as responsive to treatment with the bispecific anti-EGFR/c-Met antibody when macrophage or monocyte levels from the biological sample are higher than a threshold value or diagnosing

the subject with EGFR, c-Met or EGFR and c-Met expressing cancer as non-responsive to treatment with the bispecific anti-EGFR/c-Met antibody when macrophage or monocyte levels from the biological sample are below the threshold value; and

d) administering the medicament to the subject diagnosed as responsive to treatment with the bispecific anti-EGFR/c-Met antibody or refraining from administering the medicament to the subject diagnosed as non-responsive to treatment with the bispecific anti-EGFR/c-Met antibody.

25. The method or use according to any one of claims 20-24, wherein the bispecific anti-EGFR/c-Met antibody comprises

a) a first domain that binds EGFR, wherein the first domain comprises a HCDR1 of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a LCDR1 of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6; and

b) a second domain that binds c-Met, wherein the second domain comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.

26. The method or use according to claim 25, wherein

a) the first domain that binds EGFR comprises a VH of SEQ ID NO: 13 and a VL of SEQ ID NO: 14; and

b) the second domain that binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.

27. The method or use according to any one of claims 20-26, wherein the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

28. The method or use according to any one of claims 20-27, wherein the bispecific anti-EGFR/c-Met antibody comprises a HC1 of SEQ ID NO: 17, a LC1 of SEQ ID NO: 18, a HC2 of SEQ ID NO: 19 and a LC2 of SEQ ID NO: 20.

29. The method or use according to any one of claims 20-28, wherein the threshold value is the 30th percentile value or above of macrophages or monocytes observed in the biological sample from a population of subjects having the EGFR, c-Met or EGFR and c-Met positive cancer.

30. The method or use according to any one of claims 20-29, wherein the biological sample is a blood sample.
31. The method or use according to any one of claims 20-29, wherein the biological sample is a tumor tissue biopsy.
32. The method or use according to any one of claims 20-31, wherein EGFR, c-Met or EGFR and c-Met expressing cancer is associated with a wild-type EGFR, an EGFR activating mutation, an EGFR gene amplification, increased levels of circulating HGF, a wild-type c-Met, a c-Met activating mutation, a c-Met gene amplification or a mutant KRAS, or any combination thereof.
33. The method or use according to claim 32, wherein the EGFR activating mutation comprises L718Q, G719A, G719X (X being any amino acid), L861X (X being any amino acid), L858R, E746K, L747S, E749Q, A750P, A755V, V765M, C797S, L858P or T790M substitution, deletion of E746-A750, deletion of R748-P753, insertion of Ala (A) between M766 and A767, insertion of Ser, Val and Ala (SVA) between S768 and V769, insertion of Asn and Ser (NS) between P772 and H773, insertion of one or more amino acids between D761 and E762, A763 and Y764, Y764 and Y765, M766 and A767, A767 and V768, S768 and V769, V769 and D770, D770 and N771, N771 and P772, P772 and H773, H773 and V774, V774 and C775, one or more deletions oin EGFR exon 20, or one or more insertions in EGFR exon 20, or any combination thereof.
34. The method or use according to claim 33, wherein the mutant KRAS comprises a G12V, G12C or G12A substitution.
35. The method or use according to any one of claims 20-34, wherein the subject is suspected to have or has a newly diagnosed EGFR, c-Met or EGFR and c-Met expressing cancer.
36. The method or use according to any one of claims 20-34, wherein the subject is resistant or has acquired resistance to treatment with a prior anti-cancer therapy.
37. The method or use according to claim 36, wherein the prior anti-cancer therapy is chemotherapy, a targeted anti-cancer therapy or a kinase inhibitor.
38. The method or use according to claim 37, wherein the kinase inhibitor is an inhibitor of EGFR, c-Met, HER2, HER3, HER4, VEGFR or AXL.
39. The method or use according to claim 38, wherein the kinase inhibitor is with erlotinib, gefitinib, lapatinib, vandetanib, afatinib, osimertinib, lazertinib, poziotinib, criotinib,

cabozantinib, capmatinib, axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib or sunitinib.

40. The method or use according to any one of claims 20-39, wherein EGFR, c-Met or EGFR and c-Met expressing cancer is an epithelial cell cancer, breast cancer, ovarian cancer, lung cancer, non-small cell lung cancer (NSCLC), lung adenocarcinoma, small cell lung cancer, colorectal cancer, anal cancer, prostate cancer, kidney cancer, bladder cancer, head and neck cancer, pharynx cancer, cancer of the nose, pancreatic cancer, skin cancer, oral cancer, cancer of the tongue, esophageal cancer, vaginal cancer, cervical cancer, cancer of the spleen, testicular cancer, gastric cancer, cancer of the thymus, colon cancer, thyroid cancer, liver cancer, hepatocellular carcinoma (HCC) or sporadic or hereditary papillary renal cell carcinoma (PRCC).

41. The method or use according to any one of claims 20-40, wherein the bispecific anti-EGFR/c-Met antibody is administered in combination with an agent that enhances macrophage activity in the subject.

42. The method or use according to claim 41, wherein the agent that enhances macrophage activity in the subject is GM-CSF, a CD47 antagonist, an anti-CD47 antibody, a HDAC2 inhibitor, a PD-(L)1 axis inhibitor or a CD11b agonist.

43. The method or use according to any one of claims 20-42, further comprising administering one or more anti-cancer therapies to the subject.

44. The method or use according to claim 43, wherein the one or more anti-cancer therapies comprise chemotherapy, a targeted anti-cancer therapy or a kinase inhibitor.

45. The method or use according to claim 44, wherein the kinase inhibitor is an inhibitor of EGFR, c-Met, HER2, HER3, HER4, VEGFR or AXL.

46. The method or use according to claim 45, wherein the kinase inhibitor is erlotinib, gefitinib, lapatinib, vandetanib, afatinib, osimertinib, lazertinib, poziotinib, criotinib, cabozantinib, capmatinib, axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib or sunitinib.

47. The method or use according to any one of claims 1-46, wherein the bispecific anti-EGFR/c-Met antibody has a fucose content of about 15% or less.

48. Use of a composition comprising a bispecific anti-EGFR/c-Met antibody for the manufacture of a medicament for inducing trogocytosis of EGFR or c-Met, or EGFR and c-Met from a donor cell to an acceptor cell, comprising contacting the donor cell with the bispecific anti-EGFR/c-Met antibody for a time sufficient to induce trogocytosis from the donor cell to the acceptor cell.
49. The use according to claim 48, wherein the donor cell is a cancer cell expressing EGFR, c-Met or EGFR and c-Met.
50. The use according to claim 48 or 49, wherein the acceptor cell is a macrophage or a monocyte.
51. The use according to any one of claims 48-50, wherein the bispecific anti-EGFR/c-Met antibody comprises
- a) a first domain that binds EGFR, wherein the first domain comprises a HCDR1 of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6; and
 - b) a second domain that binds c-Met, wherein the second domain comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.
52. The use according to claim 51, wherein
- a) the first domain that binds EGFR comprises a VH of SEQ ID NO: 13 and a VL of SEQ ID NO: 14; and
 - b) the second domain that binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.
53. The use according to any one of claims 48-52, wherein the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.
54. The use according to any one of claims 48-53, wherein the bispecific anti-EGFR/c-Met antibody comprises a HC1 of SEQ ID NO: 17, a LC1 of SEQ ID NO: 18, a HC2 of SEQ ID NO: 19 and a LC2 of SEQ ID NO: 20.
55. The use according to any one of claims 49-54, wherein the cancer cell expressing EGFR, c-Met or EGFR and c-Met is associated with a wild-type EGFR, an EGFR activating mutation,

an EGFR gene amplification, increased levels of circulating HGF, a wild-type c-Met, a c-Met activating mutation, a c-Met gene amplification or a mutant KRAS.

56. The use according to claim 55, wherein the EGFR activating mutation comprises L718Q, G719A, G719X (X being any amino acid), L861X (X being any amino acid), L858R, E746K, L747S, E749Q, A750P, A755V, V765M, C797S, L858P or T790M substitution, deletion of E746-A750, deletion of R748-P753, insertion of Ala (A) between M766 and A767, insertion of Ser, Val and Ala (SVA) between S768 and V769, insertion of Asn and Ser (NS) between P772 and H773, insertion of one or more amino acids between D761 and E762, A763 and Y764, Y764 and Y765, M766 and A767, A767 and V768, S768 and V769, V769 and D770, D770 and N771, N771 and P772, P772 and H773, H773 and V774, V774 and C775, one or more deletions in EGFR exon 20 or one or more insertions in EGFR exon 20, or any combination thereof.

57. The use according to claim 55, wherein the mutant KRAS comprises a G12V, G12C or G12A substitution.

58. The use according to any one of claims 48-56, wherein in the contacting step is done *in vitro*.

59. The use according to any one of claims 48-56, wherein the contacting step comprises administering the medicament to a subject.

60. The use according to claim 59, wherein the subject has a EGFR, c-Met, or EGFR and c-Met expressing cancer.

61. The use according to claim 59 or 60, wherein the subject has a newly diagnosed EGFR, c-Met or EGFR and c-Met expressing cancer.

62. The use according to claim 59 or 60, wherein the subject is resistant or has acquired resistance to treatment with a prior anti-cancer therapy.

63. The use according to claim 62, wherein the prior anti-cancer therapy is chemotherapy, a targeted anti-cancer therapy or a kinase inhibitor.

64. The use according to claim 63, wherein the kinase inhibitor is an inhibitor of EGFR, c-Met, HER2, HER3, HER4, VEGFR or AXL.

65. The use according to claim 63, wherein the kinase inhibitor is erlotinib, gefitinib, lapatinib, vandetanib, afatinib, osimertinib, lazertinib, poziotinib, criotinib, cabozantinib, capmatinib, axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib or sunitinib.

66. The use according to any one of claims 49-65, wherein the cancer cell expressing EGFR, c-Met or EGFR and c-Met is derived from epithelial cell cancer, breast cancer, ovarian cancer, lung cancer, NSCLC, lung adenocarcinoma, small cell lung cancer, colorectal cancer, anal cancer, prostate cancer, kidney cancer, bladder cancer, head and neck cancer, pharynx cancer, cancer of the nose, pancreatic cancer, skin cancer, oral cancer, cancer of the tongue, esophageal cancer, vaginal cancer, cervical cancer, cancer of the spleen, testicular cancer, gastric cancer, cancer of the thymus, colon cancer, thyroid cancer, liver cancer, HCC or sporadic or hereditary papillary renal cell carcinoma PRCC.

67. The use according to any one of claims 59-66, comprising further administering one or more anti-cancer therapies to the subject.

68. The use according to claim 67, wherein the one or more anti-cancer therapies comprises chemotherapy, a targeted anti-cancer therapy or a kinase inhibitor.

69. The use according to claim 68, wherein the kinase inhibitor is an inhibitor of EGFR, c-Met, HER2, HER3, HER4, VEGFR or AXL.

70. The use according to claim 69, wherein the kinase inhibitor is erlotinib, gefitinib, lapatinib, vandetanib, afatinib, osimertinib, lazertinib, poziotinib, criotinib, cabozantinib, capmatinib, axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib or sunitinib.