

Claims

- 1) Use of an isolated bispecific anti-epidermal growth factor receptor (EGFR)/hepatocyte growth factor receptor (c-Met) antibody in the manufacture of a medicament for the treatment of a cancer that is positive for EGFR and lacks an at least one EGFR-activating mutation, wherein a therapeutically effective amount of the antibody is to be administered to a subject having cancer that is positive for EGFR and lacks an at least one EGFR-activating mutation.
- 2) Use of a bispecific anti-EGFR/c-Met antibody in the manufacture of a medicament for the treatment of cancer, wherein the treatment comprises:
 - a) providing a biological sample from a subject having cancer;
 - b) determining presence or absence of an EGFR-activating mutation in the sample;
 - c) providing for administration the bispecific anti-EGFR/c-Met antibody to the subject determined to lack an EGFR-activating mutation.
- 3) The use of claim 1 or 2, wherein the at least one activating mutation is a mutation which increases at least one biological activity of EGFR.
- 4) The use of claim 3, wherein the at least one biological activity of EGFR is selected from the group consisting of tyrosine kinase activity, ligand-independent signaling, increased cell proliferation, signaling to MAPK/ERK pathways, gene transcription, dimerization (EGFR:EGFR), and heterodimerization (EGFR:HER2 or EGFR:HER3).
- 5) The use of claim 3, wherein the at least one activating mutation which increases at least one biological activity of EGFR comprise at least one mutation selected from the group consisting of 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, C775, one or more deletions in EGFR exon 20, one or more insertions in EGFR exon 20, S768I, L861Q and G719X (X being any amino acid).
- 6) The use of any one of claims 1-5, wherein the method further comprises determining presence or absence of at least one mutation in any one gene selected from the group consisting of KRAS, PIK3CA, and PTEN, and providing for administration the bispecific anti-EGFR/c-Met antibody to the subject determined to have the EGFR lacking activating

mutations and determined to lack at least one mutation in any one gene selected from the group consisting of KRAS, PIK3CA, and PTEN.

- 7) The use of claim 6 wherein the at least one mutation in KRAS is selected from the group consisting of G12V, G12C, G12A and G12D.
- 8) The use of claim 7 wherein the at least one mutation in KRAS is G12C.
- 9) The use of claim 8 wherein the at least one mutation in PI3K is selected from the group consisting of E545K, H1047L, and PI3K amplification.
- 10) The use of claim 6 wherein the at least one mutation in PTEN is PTEN deletion.
- 11) The use of claims 1-10, wherein the bispecific anti-EGFR/c-Met antibody comprises a first domain that specifically binds EGFR and a second domain that specifically binds c-Met, wherein the first domain comprises a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, a HCDR2 of SEQ ID NO: 2, a HCDR3 of SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, a LCDR2 of SEQ ID NO: 5 and a LCDR3 of SEQ ID NO: 6, and wherein the second domain that binds c-Met comprises the HCDR1 of SEQ ID NO: 7, the HCDR2 of SEQ ID NO: 8, the HCDR3 of SEQ ID NO: 9, the LCDR1 of SEQ ID NO: 10, the LCDR2 of SEQ ID NO: 11 and the LCDR3 of SEQ ID NO: 12.
- 12) The use of any one of claims 1-11, wherein the first domain that specifically binds EGFR comprises a heavy chain variable region (VH) of SEQ ID NO: 13 and a light chain variable region (VL) of SEQ ID NO: 14, and the second domain that specifically binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.
- 13) The use of any one of claims 1-12, wherein the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.
- 14) The use of any one of claims 1-13, 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.
- 15) The use of any one of claims 1-14, wherein the bispecific anti-EGFR/c-Met antibody comprises one or more Fc silencing mutations.
- 16) The use of claim 14 wherein the one or more Fc silencing mutations decrease affinity to Fc γ receptors.
- 17) The use of claim 15 or 16 wherein the one or more Fc silencing mutations comprise V234A/G237A/P238S/H268A/V309L/A330S/P331S.

- 18) The use of any one of claims 1-17, wherein the bispecific anti-EGFR/c-Met antibody comprises a biantennary glycan structure with a fucose content between about 1% to about 15%.
- 19) The use of any one of claims 1-18, wherein the subject is relapsed or resistant to treatment with one or more prior anti-cancer therapies.
- 20) The use of claim 19, wherein the one or more prior anti-cancer therapies comprises one or more chemotherapeutic agents, checkpoint inhibitors, targeted anti-cancer therapies or kinase inhibitors, or any combination thereof.
- 21) The use of claim 20, wherein the one or more prior anti-cancer therapies comprises carboplatin, paclitaxel, gemcitabine, cisplatin, vinorelbine, docetaxel, palbociclib, crizotinib, PD-(L)1 axis inhibitor, an inhibitor of EGFR, an inhibitor of c-Met, an inhibitor of HER2, an inhibitor of HER3, an inhibitor of HER4, an inhibitor of VEGFR, an inhibitor of AXL, erlotinib, gefitinib, lapatinib, vandetanib, afatinib, osimertinib, lazertinib, poziotinib, criotinib, cabozantinib, capmatinib, axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib or sunitinib, or any combination thereof.
- 22) The use of any one of claims 1-18, wherein the subject is treatment naïve.
- 23) The use of any one of claims 1-22, wherein cancer that is positive for the EGFR lacking activating mutations is positive for at least one mutation in a gene selected from the group consisting of ALK, APC, BRAF, BRCA1, BRCA2, CDKN2A, CDKN2B, CTNNB1, ERBB2, ERBB3, FGFR3, KIT, LRP1B, MET, MLH1, MSH3, NOTCH1, NTRK1, RET, ROS1, STK11, TP53, and VEGFA.
- 24) The use of any one of claims 1-23, wherein the cancer is lung cancer, gastric cancer, colorectal cancer, brain cancer, cancer derived from epithelial cells, breast cancer, ovarian 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), or any combination thereof.
- 25) The use of claim 24, wherein lung cancer is non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) or lung adenocarcinoma, pulmonary sarcomatoid carcinoma or any combination thereof.
- 26) The use of any one of claims 1-25, comprising one or more anti-cancer therapies to be further administered to the subject.

- 27) The use of claim 26, wherein the one or more anti-cancer therapies comprises chemotherapy, radiation therapy, surgery, a targeted anti-cancer therapy, a kinase inhibitor, or any combination thereof.
- 28) The use of claim 20, wherein the kinase inhibitor is an inhibitor of EGFR, an inhibitor of c-Met, an inhibitor of HER2, an inhibitor of HER3, an inhibitor of HER4, an inhibitor of VEGFR or an inhibitor of AXL.
- 29) The use of claim 28, wherein the kinase inhibitor is erlotinib, gefitinib, lapatinib, vandetanib, afatinib, osimertinib, lazertinib, poziotinib, criotinib, cabozantinib, capmatinib, axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib or sunitinib.
- 30) The use of any one of claims 1-29, wherein the bispecific anti-EGFR/c-Met antibody is to be administered at a dose of between about 140 mg to about 2240 mg.
- 31) The use of any one of claims 1-30, wherein the bispecific anti-EGFR/c-Met antibody is to be administered at a dose of about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2150 mg, about 2200, or about 2240 mg.
- 32) The use of any one of claims 1-31, wherein the bispecific anti-EGFR/c-Met antibody is to be administered at a dose of 1050 mg.
- 33) The use of any one of claims 1-31, wherein the bispecific anti-EGFR/c-Met antibody is to be administered at a dose of 1400 mg.
- 34) The use of any one of claims 1-31, wherein the bispecific anti-EGFR/c-Met antibody is to be administered at a dose of 1575 mg.
- 35) The use of any one of claims 1-31, wherein the bispecific anti-EGFR/c-Met antibody is to be administered at a dose of 1600 mg.
- 36) The use of any one of claims 1-31, wherein the bispecific anti-EGFR/c-Met antibody is to be administered at a dose of 2100 mg.
- 37) The use of any one of claims 1-31, wherein the bispecific anti-EGFR/c-Met antibody is to be administered at a dose of 2240 mg.
- 38) The use of any one of claims 1-37, wherein the bispecific anti-EGFR/c-Met antibody is to be administered twice a week, once a week, once in two weeks, once in three weeks or once in four weeks.

- 39) The use of any one of claims 1-38 wherein the bispecific anti-EGFR/c-Met antibody is to be administered intravenously.
- 40) The use of any one of claims 1-38 wherein the bispecific anti-EGFR/c-Met antibody is to be administered subcutaneously.
- 41) An isolated bispecific anti-epidermal growth factor receptor (EGFR)/hepatocyte growth factor receptor (c-Met) antibody or a bispecific anti-EGFR/c-Met antibody for use in therapy.