

Claims

1. Use of a composition comprising 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 EGFR, c-Met, or EGFR and c-Met expressing cancer in a subject, wherein the medicament is to be administered in combination with an agent that enhances macrophage activity in the subject selected from GM-CSF, an anti-CD47 antibody, a HDAC2 inhibitor, a PD-(L)1 axis inhibitor, or a CD11b agonist.
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) comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a light chain complementarity determining region 1 (LCDR1) comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 5, and a LCDR3 comprising SEQ ID NO: 6; and
 - b) a second domain that binds c-Met, wherein the second domain comprises a HCDR1 comprising SEQ ID NO: 7, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 9, a LCDR1 comprising SEQ ID NO: 10, a LCDR2 comprising SEQ ID NO: 11, and a LCDR3 comprising 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) comprising SEQ ID NO: 13 and a light chain variable region (VL) comprising SEQ ID NO: 14; and
 - b) the second domain that binds c-Met comprises a VH comprising SEQ ID NO: 15 and a VL comprising 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) comprising SEQ ID NO: 17, a first light chain (LC1) comprising SEQ ID NO: 18, a second heavy chain (HC2) comprising SEQ ID NO: 19, and a second light chain (LC2) comprising SEQ ID NO: 20.

6. The use according to any one of claims 1-5, 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.

7. The use according to claim 6, 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.

8. The use according to claim 6, wherein the mutant KRAS comprises a G12V, G12C, G12A, or G12D substitution, or any combination thereof.

9. The use according to any one of claims 1-8, wherein the subject has a newly diagnosed EGFR, c-Met, or EGFR and c-Met expressing cancer.

10. The use according to any one of claims 1- 8, wherein the subject is resistant or has acquired resistance to treatment with a prior anti-cancer therapy.

11. The use according to claim 10, wherein the prior anti-cancer therapy is a chemotherapy, a targeted anti-cancer therapy, or a kinase inhibitor.
12. The use according to claim 11, wherein the kinase inhibitor is an inhibitor of EGFR, c-Met, HER2, HER3, HER4, VEGFR, or AXL.
13. The use according to claim 12, wherein the kinase inhibitor is erlotinib, gefitinib, lapatinib, vandetanib, afatinib, osimertinib, lazertinib, poziotinib, criotinib, cabozantinib, capmatinib, axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib, or sunitinib.
14. The use according to any one of claims 1-13, 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).
15. The use according to any one of claims 1-14, comprising further administering one or more anti-cancer therapies to the subject.
16. The use according to claim 15, wherein the one or more anti-cancer therapies comprises a chemotherapy, a targeted anti-cancer therapy, or a kinase inhibitor.
17. The use according to claim 16, wherein the kinase inhibitor is an inhibitor of EGFR, c-Met, HER2, HER3, HER4, VEGFR, or AXL.

18. The use according to claim 17, wherein the kinase inhibitor is erlotinib, gefitinib, lapatinib, vandetanib, afatinib, osimertinib, lazertinib, poziotinib, criotinib, cabozantinib, capmatinib, axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib, or sunitinib.

19. The use according to any one of claims 1-18, wherein the bispecific anti-EGFR/c-Met antibody has a fucose content of about 15% or less.