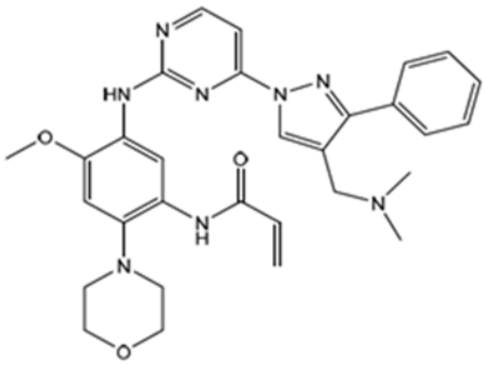
Claims

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 treatment of an EGFR or c-Met expressing cancer in a subject, wherein the medicament is for use in combination with a compound of formula (I)



(I),

or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof.

2. The use of claim 1, wherein the bispecific anti-EGFR/c-Met antibody comprises a first domain that binds EGFR comprising 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 a second domain that binds c-Met comprising 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.

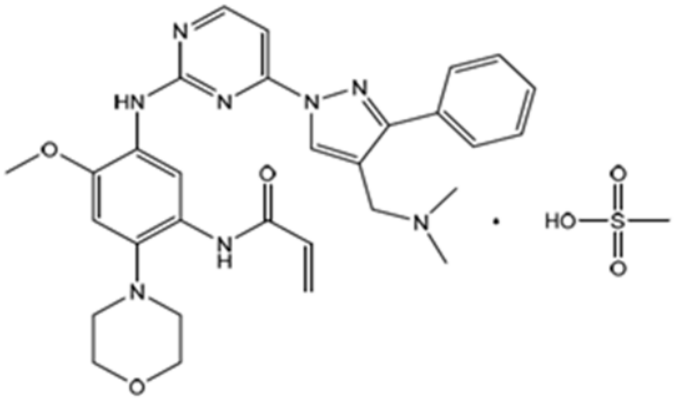
3. The use of claim 2, wherein the first domain that binds EGFR comprises a heavy chain variable region (VH) of SEQ ID NO: 13 and a light chain variable region (VL) of SEQ ID NO: 14 and the second domain that binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.

4. The use of any one of claims 1 to 4, wherein the bispecific anti-EGFR/c-Met antibody is an IgG1 isotype.

5. The use of any one of claims 1 to 5, 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 of any one of claims 1 to 5, wherein the bispecific anti-EGFR/c-Met antibody has a biantennary glycan structure with a fucose content of between about 1% to about 15%.

7. The use of any one of claims 1 to 6, wherein the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is represented by a compound of formula (II)



(II).

8. The use of any one of claims 1 to 6, wherein the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is N-(5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide.

9. The use of any one of claims 1 to 8, wherein the EGFR or c-Met expressing cancer is associated with a wild-type EGFR, an EGFR mutation, an EGFR gene amplification, increased levels of circulating HGF, a wild-type c-Met, a c-Met mutation, a c-Met gene amplification or a mutant KRAS.

10. The use of claim 9, wherein the EGFR mutation is E709K, L718Q, L718V, G719A, G719X, G724X, G724S, I744T, E746K, L747S, E749Q, A750P, A755V, V765M, C775Y, T790M, L792H, L792V, G796S, G796R, G796C, C797S, T854I, L858P, L858R, L861X, delE746-A750, delE746_T751InsKV, delE746_A750InsHS, delE746_T751InsFPT, delE746_T751InsL, delE746_S752InsIP, delE746_P753InsMS, delE746_T751InsA, delE746_T751InsAPT, delE746_T751InsVA, delE746_S752InsV, delE746_P753InsVS, delE746_K754InsGG, delE746_E749, delE746_E749InsP, delL747_E749, delL747_A750InsP, delL747_T751InsP, delL747_T751InsN, delL747_S752InsPT, delL747_P753InsNS, delL747_S752InsPI, delL747_S752, delL747_P753InsS, delL747_K754, dekL747_T751InsS, dekL747_T751, delL747_P753InsS, delA750_I759InsPT, delT751_I759InsT, delS752_I759, delT751_I759InsN, delT751_D761InsNLY, delS752_I759, delR748-P753, delL747-P753insS, delL747-T751,

M766_A767InsA, S768_V769InsSVA, P772_H773InsNS, D761_E762InsX_{1-7}, A763_Y764InsX_{1-7}, Y764_Y765 InsX_{1-7}, M766_A767InsX_{1-7}, A767_V768 InsX_{1-7}, S768_V769 InsX_{1-7}, V769_D770 InsX_{1-7}, D770_N771 InsX_{1-7}, N771_P772 InsX_{1-7}, P772_H773 InsX_{1-7}, H773_V774 InsX_{1-7}, V774_C775 InsX_{1-7}, one or more deletions in EGFR exon 20, or one or more insertions in EGFR exon 20, one or more deletions in EGRF exon 19, or one or more insertions in EGFR exon 19, or any combination thereof, wherein X is any amino acids.

11. The use of claim 10, wherein the EGFR mutation is the one or more deletions in exon 19 or L858R, or any combination thereof.
12. The use of claim 9, wherein the c-Met mutation is c-Met exon 14 skipping mutation.
13. The use of claim 9, wherein the mutant KRAS has a G12V, G12C or G12A substitution.
14. The use of any one of claims 1 to 13, wherein the subject has been diagnosed with the EGFR mutation prior to the treatment.
15. The use of any one of claims 1 to 14, wherein the subject has a newly diagnosed EGFR or c-Met expressing cancer.
16. The use of any one of claims 1 to 15, wherein the subject is EGFR tyrosine kinase inhibitor (TKI) treatment naïve.
17. The use of any one of claims 1 to 15, wherein the subject is resistant or relapsed to treatment with a first generation EGFR TKI.
18. The use of claim 17, wherein the first generation EGFR TKI is erlotinib or gefitinib.
19. The use of any one of claims 1 to 14, wherein the subject is resistant or relapsed to treatment with a second generation EGFR TKI.
20. The use of claim 19, wherein the second generation EGFR TKI is afatinib.
21. The use of any one of claims 1 to 14, wherein the subject is resistant or relapsed to treatment with a third generation EGFR TKI.
22. The use of claim 21, wherein the third generation EGFR TKI is osimertinib.
23. The use of any one of claims 1 to 22, wherein the EGFR or c-Met expressing cancer is a non-small cell lung cancer (NSCLC), an epithelial cell cancer, a breast cancer, an ovarian cancer, a lung cancer, a squamous cell lung cancer, a lung adenocarcinoma, a small cell lung cancer, a colorectal cancer, an anal cancer, a prostate cancer, a kidney cancer, a bladder cancer, a head and neck cancer, a pharynx cancer, a cancer of the nose, a pancreatic cancer, a skin cancer, an oral cancer, a cancer of the tongue, an esophageal cancer, a vaginal cancer, a cervical cancer, a cancer of the spleen, a testicular cancer, a gastric cancer, a cancer of the thymus, a colon cancer, a thyroid cancer, a liver cancer, a hepatocellular carcinoma (HCC) or sporadic or hereditary papillary renal cell carcinoma (PRCC).

24. The use of claim 23, wherein the cancer is the NSCLC.
25. The use of any one of claims 1 to 23, wherein the bispecific anti-EGFR/c-Met antibody is for administration at a dose of between about 200 mg and about 2000 mg.
26. The use of claim 25, wherein the bispecific anti-EGFR/c-Met antibody is for administration at a dose of between about 350 mg and about 1400 mg.
27. The use of claim 26, wherein the bispecific anti-EGFR/c-Met antibody is for administration at a dose of about 350 mg, about 700 mg, about 1050 mg or about 1400 mg.
28. The use of any one of claims 1 to 27, wherein the bispecific anti-EGFR/c-Met antibody is for administration once a week.
29. The use of any one of claims 1 to 27, wherein the bispecific anti-EGFR/c-Met antibody is for administration once in two weeks.
30. The use of any one of claims 1 to 29, wherein the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is for administration at a dose of between about 20 mg and about 320 mg.
31. The use of claim 30, wherein the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is for administration at a dose of about 160 mg or about 240 mg.
32. The use of any one of claims 1 to 31, wherein the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is for administration once a day.
33. The use of any one of claims 1 to 24, wherein the bispecific anti-EGFR/c-Met antibody is for administration at a dose of between about 350 mg and about 1400 mg weekly for four weeks and once in two weeks thereafter, and the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is for administration at a dose of between about 160 mg and about 240 mg daily.
34. The use of claim 33, wherein the bispecific anti-EGFR/c-Met antibody is for administration at a dose of about 700 mg weekly for four weeks and once in two weeks thereafter, and the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is for administration at a dose of about 160 mg daily.
35. The use of claim 33, wherein the bispecific anti-EGFR/c-Met antibody is for administration at a dose of about 1050 mg weekly for four weeks and once in two weeks thereafter, and the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is for administration at a dose of about 160 mg daily.
36. The use of claim 33, wherein the bispecific anti-EGFR/c-Met antibody is for administration at a dose of about 1400 mg weekly for four weeks and once in two weeks thereafter, and the

compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is for administration at a dose of about 160 mg daily.

37. The use of claim 33, wherein the bispecific anti-EGFR/c-Met antibody is for administration at a dose of about 700 mg weekly for four weeks and once in two weeks thereafter, and the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is for administration at a dose of about 240 mg daily.

38. The use of claim 33, wherein the bispecific anti-EGFR/c-Met antibody is for administration at a dose of about 1050 mg weekly for four weeks and once in two weeks thereafter, and the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is for administration at a dose of about 240 mg daily.

39. The use of claim 33, wherein the bispecific anti-EGFR/c-Met antibody is for administration at a dose of about 1400 mg weekly for four weeks and once in two weeks thereafter, and the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is for administration at a dose of about 240 mg daily.

40. The use of any one of claims 1 to 39, wherein the bispecific anti-EGFR/c-Met antibody is for administration after administration of the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof.

41. The use of claim 40, wherein the bispecific anti-EGFR/c-Met antibody is for administration one or more times after administration of the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof.

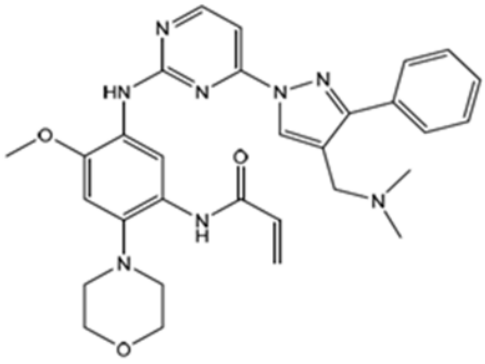
42. The use of claim 41, wherein the bispecific anti-EGFR/c-Met antibody is for administration two, three, four, five, six, seven, eight, nine, ten or more times after administration of the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof.

43. The use of any one of claims 1 to 42, wherein the subject is homozygous for phenylalanine at position 158 of CD16 or heterozygous for valine and phenylalanine at position 158 of CD16.

44. The use of any one of claims 1 to 43, wherein the medicament is for use further in combination with a third anti-cancer therapy to the subject.

45. The use of claim 44, wherein the third anti-cancer therapy is chemotherapy, a targeted anti-cancer therapy or a kinase inhibitor.

46. A pharmaceutical combination of a therapeutically effective amount of an isolated bispecific anti-epidermal growth factor receptor (EGFR)/hepatocyte growth factor receptor (c-Met) antibody and a therapeutically effective amount of a compound of formula (I)

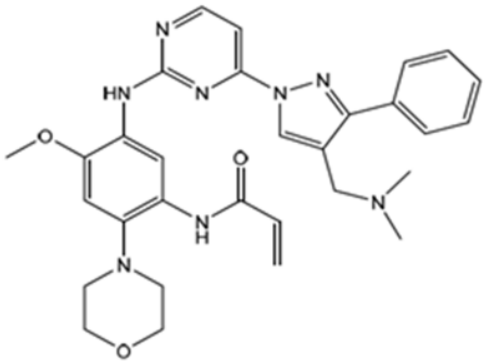


(I),

or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof.

47. The pharmaceutical combination of claim 46 wherein the isolated bispecific anti-epidermal growth factor receptor (EGFR)/hepatocyte growth factor receptor (c-Met) antibody is a bispecific anti-EGFR/c-Met antibody comprising a first domain that binds EGFR comprising the HCDR1 of SEQ ID NO: 1, the HCDR2 of SEQ ID NO: 2, the HCDR3 of SEQ ID NO: 3, the LCDR1 of SEQ ID NO: 4, the LCDR2 of SEQ ID NO: 5 and the LCDR3 of SEQ ID NO: 6 and a second domain that binds c-Met comprising 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.

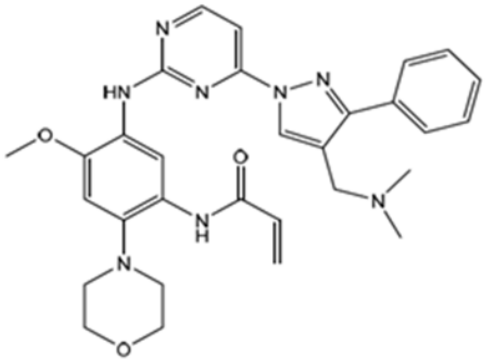
48. The pharmaceutical combination of claim 46 or 47, wherein the compound of formula (I)



(I),

or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is lazertinib.

49. The pharmaceutical combination of claim 46 or 47, wherein the compound of formula (I)



(I),

or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is lazertinib mesylate.

50. The pharmaceutical combination of any one of claims 46 to 49, comprising between about 350 mg and about 1400 mg of the bispecific EGFR/c-Met antibody and between about 160 mg and about 240 mg the compound of formula (I) or solvate, hydrate, tautomer or or a pharmaceutically acceptable salt thereof.

51. The pharmaceutical combination of any one of claims 46 to 50, wherein the compound of formula (I) or solvate, hydrate, tautomer, or a pharmaceutically acceptable salt thereof is N-(5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide.

52. The pharmaceutical combination of any one of claims 46 to 51, wherein the pharmaceutical combination is a non-fixed combination.

53. The pharmaceutical combination of any one of claims 46 to 52, wherein the first domain that binds EGFR of the bispecific anti-EGFR/c-Met antibody comprises the VH of SEQ ID NO: 13 and the VL of SEQ ID NO: 14; and the second domain that binds c-Met comprises the VH of SEQ ID NO: 15 and the VL of SEQ ID NO: 16.

54. The pharmaceutical combination of any one of claim 46 to 53, wherein the bispecific anti-EGFR/c-Met antibody comprises the HC1 of SEQ ID NO: 17, the LC1 of SEQ ID NO: 18, the HC2 of SEQ ID NO: 19 and the LC2 of SEQ ID NO: 20.