

CLAIMS

1. An EGFR TKI for use in the treatment of cancer in a human patient, wherein the EGFR TKI is to be administered in combination with an inhibitor of c-MET and wherein said cancer has a high or very high level of MET amplification and/or overexpression.

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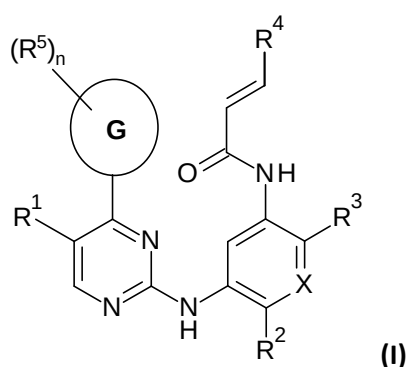
2. An EGFR TKI for use as claimed in claim 1, wherein said cancer has been found to have a high or very high level of MET amplification and/or overexpression prior to the administration of the EGFR TKI in combination with the inhibitor of c-MET.

- 10 3. An EGFR TKI for use as claimed in claim 1 or claim 2, wherein said cancer has a high or very high level of MET amplification and/or overexpression defined by FISH6+, FISH7+, FISH8+, FISH9+ or FISH10+ and/or IHC60+, IHC70+, IHC80+ or IHC90+.

- 15 4. An EGFR TKI for use as claimed in any one of claims 1 to 3, wherein the administration of the EGFR TKI and the inhibitor of c-MET is separate, sequential, or simultaneous.

5. An EGFR TKI for use as claimed in any one of claims 1 to 4, wherein the high or very high level of MET amplification and/or overexpression is defined by FISH10+ and/or IHC90+.

- 20 6. An EGFR TKI for use as claimed in any one of claims 1 to 5, wherein the EGFR TKI is a compound of Formula (I):



wherein:

25 **G** is selected from 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridin-3-yl, indol-3-yl, indazol-1-yl, 3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-10-yl, 6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl, 5,6-dihydro-4H-pyrrolo[3,2,1-*ij*]quinolin-1-yl, pyrrolo[3,2-*b*]pyridin-3-yl and pyrazolo[1,5-*a*]pyridin-3-yl;

R¹ is selected from hydrogen, fluoro, chloro, methyl and cyano;

R² is selected from methoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy and methyl;

R³ is selected from (3*R*)-3-(dimethylamino)pyrrolidin-1-yl, (3*S*)-3-(dimethyl-amino)pyrrolidin-1-yl, 3-(dimethylamino)azetidin-1-yl, [2-(dimethylamino)ethyl]-(methyl)amino, [2-(methylamino)ethyl](methyl)amino, 2-(dimethylamino)ethoxy, 2-(methylamino)ethoxy, 5-methyl-2,5-diazaspiro[3.4]oct-2-yl, (3*aR*,6*aR*)-5-methylhexa-hydro-pyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl, 1-methyl-1,2,3,6-tetrahydropyridin-4-yl, 4-methylpiperizin-1-yl, 4-[2-(dimethylamino)-2-oxoethyl]piperazin-1-yl, methyl[2-(4-methylpiperazin-1-yl)ethyl]amino, methyl[2-(morpholin-4-yl)ethyl]amino, 1-amino-1,2,3,6-tetrahydropyridin-4-yl and 4-[(2*S*)-2-aminopropanoyl]piperazin-1-yl;

R⁴ is selected from hydrogen, 1-piperidinomethyl and N,N-dimethylaminomethyl;

R⁵ is independently selected from methyl, ethyl, propyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, fluoro, chloro and cyclopropyl;

X is CH or N; and

n is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

7. An EGFR TKI for use as claimed in claim 6, wherein **G** is selected from indol-3-yl and indazol-1-yl; **R¹** is selected from hydrogen, fluoro, chloro, methyl and cyano; **R²** is selected from methoxy and 2,2,2-trifluoroethoxy; **R³** is selected from [2-(dimethylamino)ethyl]-(methyl)amino, [2-(methylamino)ethyl](methyl)amino, 2-(dimethylamino)ethoxy and 2-(methylamino)ethoxy; **R⁴** is hydrogen; **R⁵** is selected from methyl, 2,2,2-trifluoroethyl and cyclopropyl; **X** is CH or N; and **n** is 0 or 1; or a pharmaceutically acceptable salt thereof.

8. An EGFR TKI for use as claimed in any one of claims 1 to 5, wherein the EGFR TKI is selected from the group consisting of osimertinib or a pharmaceutically acceptable salt thereof, AZD3759 or a pharmaceutically acceptable salt thereof, alflutinib or a pharmaceutically acceptable salt thereof, HS-10296 or a pharmaceutically acceptable salt thereof, and lazertinib or a pharmaceutically acceptable salt thereof.

9. An EGFR TKI for use as claimed in claim 8, wherein the EGFR TKI is osimertinib or a pharmaceutically acceptable salt thereof.

10. An EGFR TKI for use as claimed in any one of the previous claims, wherein the inhibitor of c-MET is selected from the group consisting of savolitinib (Orpathys[®]; AZD6094; HMPL-504; volitinib)

or a pharmaceutically acceptable salt thereof, capmatinib (Tabrecta®) or a pharmaceutically acceptable salt thereof, and tepotinib (Tepmetko®) or a pharmaceutically acceptable salt thereof.

- 5 11. An EGFR TKI for use as claimed in claim 10, wherein the inhibitor of c-MET is savolitinib (Orpathys®; AZD6094; HMPL-504; volitinib) or a pharmaceutically acceptable salt thereof.
12. An EGFR TKI for use as claimed in claim 11, wherein the savolitinib (Orpathys®; AZD6094; HMPL-504; volitinib), or a pharmaceutically acceptable salt thereof, is to be administered at a dosage
10 of about 600 mg once daily or about 300 mg twice daily or about 300 mg once daily.
13. An EGFR TKI for use as claimed in any one of the previous claims, wherein the cancer is EGFR mutation-positive non-small cell lung cancer.
- 15 14. An EGFR TKI for use as claimed in claim 13, wherein the EGFR mutation-positive non-small cell lung cancer comprises an activating mutation in EGFR selected from exon 19 deletions and L858R substitution mutations.
15. An EGFR TKI for use as claimed in any one of claims 1 to 14, wherein the human patient's cancer
20 has progressed during or after previous treatment with osimertinib.
16. Use of an EGFR TKI in the manufacture of a medicament for the treatment of cancer in a human patient, wherein the EGFR TKI is to be administered in combination with an inhibitor of c-MET and wherein said cancer has a high or very high level of MET amplification and/or overexpression
25 defined by FISH6+, FISH7+, FISH8+, FISH9+ or FISH10+ and/or IHC60+, IHC70+, IHC80+ or IHC90+.
17. An inhibitor of c-MET for use in the treatment of cancer in a human patient, wherein the inhibitor of c-MET is to be administered in combination with an EGFR TKI and wherein said cancer has a high or very high level of MET amplification and/or overexpression defined by FISH6+, FISH7+,
30 FISH8+, FISH9+ or FISH10+ and/or IHC60+, IHC70+, IHC80+ or IHC90+.
18. An inhibitor of c-MET for use in the treatment of cancer as claimed in claim 17, wherein the cancer is non-small cell lung cancer, and wherein the EGFR TKI is osimertinib or a pharmaceutically acceptable salt thereof.

19. An inhibitor of c-MET for use in the treatment of non-small cell lung cancer as claimed in claim 17 or claim 18, wherein the cancer is non-small cell lung cancer, and wherein the inhibitor of c-MET is savolitinib (Orpathys[®]; AZD6094; HMPL-504; volitinib) or a pharmaceutically acceptable salt thereof.

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