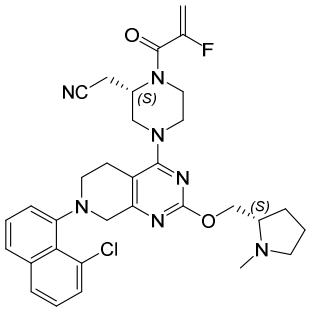
CLAIMS

WE CLAIM:

1. Use of a therapeutically effective amount of a combination of a pan ErbB family inhibitor and a KRAS G12C inhibitor of formula:



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a subject.

2. The use according to claim 1, wherein the pan ErbB family inhibitor is an irreversible pan ErbB inhibitor.

3. The use according to claim 2, wherein the irreversible pan ErbB family inhibitor is: Afatinib ((E)-N-(4-((3-chloro-4-fluorophenyl)amino)-7-((tetrahydrofuran-3-yl)oxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide); dacomitinib ((2*E*)-*N*-{4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl}-4-(1-piperidinyl)-2-butenamide); canertinib (N-(4-((3-chloro-4-fluorophenyl)amino)-7-(3-morpholinopropoxy)quinazolin-6-yl)acrylamide); poziotinib (1-(4-((4-((3,4-dichloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl)prop-2-en-1-one); AV 412 (*N*-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butyn-1-yl]-6-quinazolinyl]-2-propenamide); PF 6274484 (*N*-[4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl]-2-propenamide) or HKI 357 ((2*E*)-*N*-[[4-[[(3-Chloro-4-[(3-fluorophenyl)methoxy]phenyl]amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-2-butenamide).

4. The use according to claim 3, wherein the irreversible pan ErbB family inhibitor is afatinib ((E)-N-(4-((3-chloro-4-fluorophenyl)amino)-7-((tetrahydrofuran-3-yl)oxy)quinazolin-6-yl)-4-(dimethylamino)but-2-enamide).

5. The use according to claim 3, wherein the irreversible pan ErbB family inhibitor is dacomitinib ((2*E*)-*N*-{4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl}-4-(1-piperidinyl)-2-butenamide).

6. The use according to claim 1, wherein the pan ErbB family inhibitor is a reversible pan ErbB family inhibitor.

7. The use according to claim 6, wherein the reversible pan ErbB family inhibitor is: Erlotinib ([6,7-Bis-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine)), Gefitinib (4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, sapitinib (2-(4-((4-((3-chloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl)-N-methylacetamide); varlitinib ((R)-N4-(3-chloro-4-(thiazol-2-ylmethoxy)phenyl)-N6-(4-methyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine); TAK-285 (N-(2-(4-((3-chloro-4-(3-(trifluoromethyl)phenoxy)phenyl)amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl)-3-hydroxy-3-methylbutanamide); AEE788 ((S)-6-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-N-(1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine); tarloxotinib ([(*E*)-4-[[4-(3-bromo-4-chloroanilino)pyrido[3,4-d]pyrimidin-6-yl]amino]-4-oxobut-2-enyl]-dimethyl-[(3-methyl-5-nitroimidazol-4-yl)methyl]azanium); BMS 599626 ((3*S*)-3-Morpholinylmethyl-[4-[[1-[(3-fluorophenyl)methyl]-1*H*-indazol-5-yl]amino]-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl]-carbamate dihydrochloride); and GW 583340 HCl (*N*-[3-Chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[2-[[[2-(methylsulfonyl)ethyl]amino]methyl]-4-thiazolyl]-4-quinazolinamine dihydrochloride).

8. The use according to claim 7, wherein the reversible pan ErbB family inhibitor is sapitinib (2-(4-((4-((3-chloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl)-N-methylacetamide) or tarloxotinib ([(*E*)-4-[[4-(3-bromo-4-chloroanilino)pyrido[3,4-d]pyrimidin-6-yl]amino]-4-oxobut-2-enyl]-dimethyl-[(3-methyl-5-nitroimidazol-4-yl)methyl]azanium).

9. The use according to claim 1, wherein the pan ErbB family inhibitor is an anti-EGFR antibody, an anti-HER2 antibody or a combination of anti-EGFR antibody and an anti-HER2 antibody.

10. The use according to claim 9, wherein the anti-EGFR antibody is necitumumab, panitumumab or cetuximab.

11. The use according to claim 9, wherein the anti-HER2 antibody is trastuzumab, trastuzumab emtansine, or pertuzumab.

12. The use according to any one of claims 1-11, wherein the pan ErbB family inhibitor and the KRAS G12C inhibitor are to be administered on the same day.

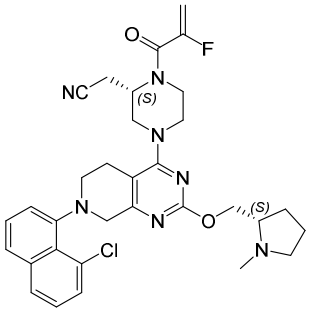
13. The use according to any one of claims 1-11, wherein the pan ErbB family inhibitor and the KRAS G12C inhibitor are to be administered on different days.

14. The use according to any one of claims 1-11, wherein the KRas G12C inhibitor is to be administered at a maximum tolerated dose.

15. The use according to any one of claims 1-11, wherein the pan ErbB family inhibitor and the KRAS G12C inhibitor are each to be administered at a maximum tolerated dose.

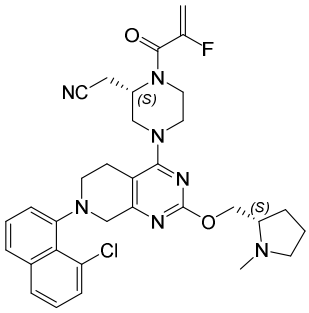
16. The use according to any one of claims 1-15, wherein the therapeutically effective amount of the combination of the pan ErbB family inhibitor and the KRAS G12C inhibitor results in an increased duration of overall survival, an increased duration of progression free survival, an increase in tumor growth regression, an increase in tumor growth inhibition or an increased duration of stable disease in the subjects relative to treatment with only the KRas G12C inhibitor.

17. A pharmaceutical composition, comprising a therapeutically effective amount of a combination of a pan ErbB family inhibitor and a KRas G12C inhibitor of Formula



or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

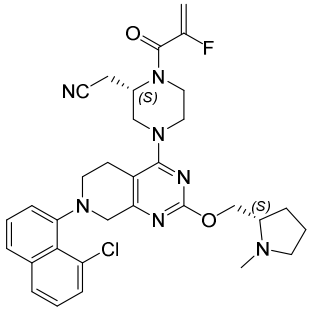
18. A method for inhibiting KRas G12C activity in a cell in vitro or ex vivo, comprising contacting the cell in which inhibition of KRas G12C activity is desired with an effective amount of a pan ErbB family inhibitor and a KRas G12C inhibitor compound of a Formula



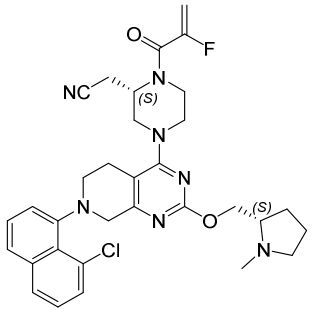
, pharmaceutical compositions or pharmaceutically acceptable salts thereof, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12C inhibitor.

19. The use according to any one of claims 1-16 or the method according to claim 18, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12C inhibitor.

20. A method for increasing the sensitivity of a cancer cell in vitro or ex vivo to a KRas G12C inhibitor compound of Formula



,comprising administering to a subject

undergoing KRas G12C treatment with a compound of Formula  or a pharmaceutically acceptable salt thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, a therapeutically effective amount of a pan ErbB family inhibitor, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the cancer cell to the KRas G12C inhibitor.

21. The use according to any one of claims 1-16 and the method according to any one of claims 18-20, wherein the therapeutically effective amount of the KRas G12C inhibitor is between 0.01 to 100 mg/kg per day.

22. The use or method according to claim 21, wherein the therapeutically effective amount of the KRas G12C inhibitor is between 0.1 to 50 mg/kg per day.

23. The use according to any one of claims 1-16 and the method according to any one of claims 18-20, wherein the therapeutically effective amount of the pan ErbB family inhibitor is between 0.01 to 100 mg/kg per day.

24. The use or method according to claim 23, wherein the therapeutically effective amount of the pan ErbB family inhibitor is between 0.1 to 50 mg/kg per day.

25. The use according to any one of claims 1-16 and the method according to any one of claims 18-20, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma,

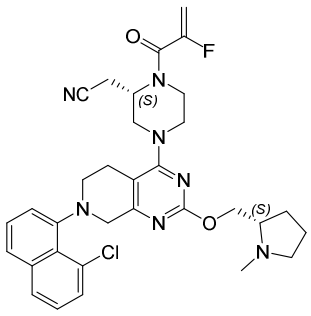
lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial `carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma.

26. The use according to any one of claims 1-16 and the method according to any one of claims 18-20, wherein the cancer wherein the cancer is a KRas G12C-associated cancer.

27. The use or method according to claim 26, wherein the KRas G12C-associated cancer is non-small cell lung cancer.

28. A kit comprising the pharmaceutical composition of claim 27 for treating cancer in a subject.

29. A kit comprising: a) a pharmaceutical composition comprising a pan ErbB family inhibitor and b) a pharmaceutical composition comprising a KRas G12C inhibitor of formula:



or a pharmaceutically acceptable salt thereof for treating cancer in a subject.

30. The kit according to claim 28 or 29, further comprising an insert with instructions for administration of the pharmaceutical composition(s).