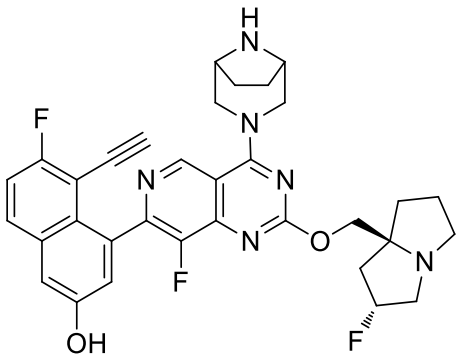
\WHAT IS CLAIMED IS:

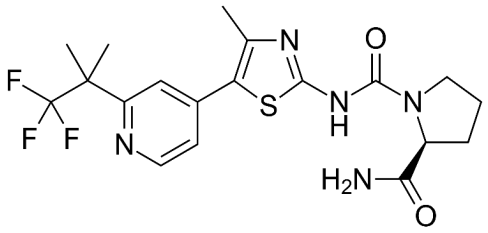
1. Use of a combination a KRas G12D inhibitor or a pharmaceutically acceptable salt thereof, and a PI3Ka inhibitor or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a subject in need thereof.

2. The use of claim 1, wherein the KRas G12D inhibitor or salt is selected from: MRTX1133, 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethynylnaphthalen-2-ol; 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol; 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-chloronaphthalen-2-ol; 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol; 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethylnaphthalen-2-ol; and 4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-fluoronaphthalen-2-ol; and pharmaceutically acceptable salts thereof.

3. The use of claim 1, wherein the KRas G12D inhibitor is MRTX1133:



or a pharmaceutically acceptable salt thereof, and the PI3Ka inhibitor is BYL719:



or a pharmaceutically acceptable salt thereof.

4. The use of according to any one of claims 1-3, wherein the KRas G12D inhibitor or salt, and the PI3Ka inhibitor or salt, are to be administered on the same day, or wherein the KRas G12D inhibitor or salt, and the the PI3Ka inhibitor or salt, are to be administered on different days.

5. The use according to any one of claims 1-4, wherein the KRas G12D inhibitor or salt is to be administered at a maximum tolerated dose and/or wherein the the PI3Ka inhibitor or salt is to be administered at a maximum tolerated dose.

6. The use according to any one of claims 1-4, wherein the KRas G12D inhibitor or salt is to be administered at below maximum tolerated dose, and/or wherein the the PI3Ka inhibitor or salt is to be administered at below maximum tolerated dose.

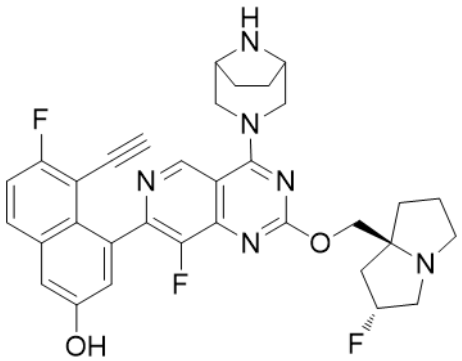
7. The use according to any one of claims 1-6, wherein the therapeutically effective amount of the combination of the KRas G12D inhibitor or salt and the PI3Ka inhibitor or salt results in an increased duration of overall survival, an increased duration of progression free survival, an increase in tumor 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 G12D inhibitor or salt.

8. The use according to any one of claims 1-6, wherein the therapeutically effective amount of the combination of the KRas G12D inhibitor or salt, and the the PI3Ka inhibitor or salt, 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 cytotoxic compound.

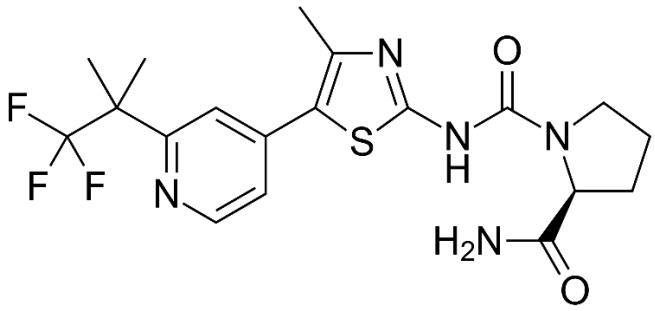
9. A pharmaceutical composition comprising a therapeutically effective amount of a combination of a KRas G12D inhibitor or pharmaceutically acceptable salt thereof, and a PI3Ka inhibitor or salt, and a pharmaceutically acceptable excipient.

10. The composition of claim 9, comprising MRTX1133:



or a pharmaceutically acceptable salt thereof, and

BYL719:



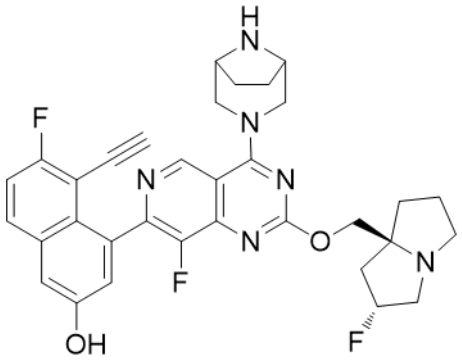
or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

11. Use of a combination a KRas G12D inhibitor or a pharmaceutically acceptable salt thereof, and a PI3Ka inhibitor or a pharmaceutically acceptable salt thereof in the manufacture of

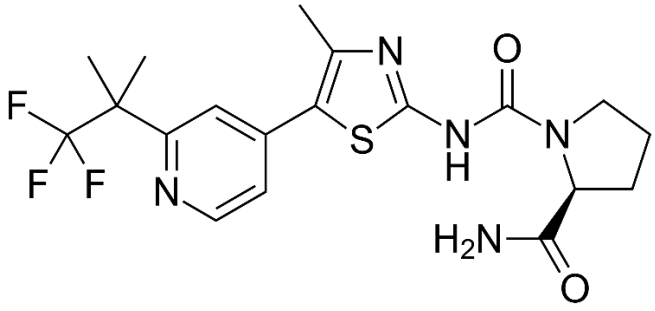
a medicament for inhibiting KRas G12D activity in a cell, wherein the cell is to be contacted with an effective amount of the combination of a KRas G12D inhibitor or a pharmaceutically acceptable salt thereof, and a PI3Ka inhibitor or a pharmaceutically acceptable salt thereof.

12. An *in vitro* method for inhibiting KRas G12D activity in a cell, comprising contacting the cell in which inhibition of KRas G12D activity is desired with an effective amount of a combination of a KRas G12D inhibitor or a pharmaceutically acceptable salt thereof, and a PI3Ka inhibitor or a pharmaceutically acceptable salt thereof.

13. The use of claim 11 or the in vitro method of claim 12, wherein the KRas G12D inhibitor is MRTX1133:



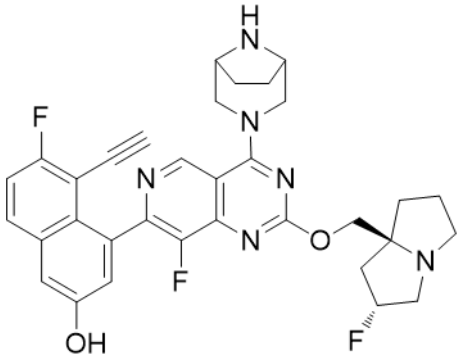
and pharmaceutically acceptable salts thereof, and the PI3Ka inhibitor is BYL719:



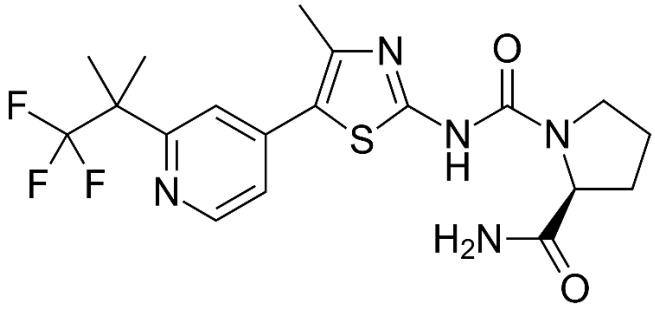
or a pharmaceutically acceptable salt thereof

14. The use according to any one of claims 1-8, 11 and 13 or the *in vitro* method according to claim 12, wherein the PI3Ka inhibitor increases the sensitivity of cancer cells to the KRas G12D inhibitor.

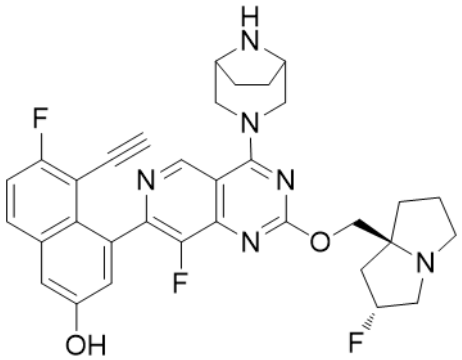
15. Use of a combination of the KRas G12C inhibitor MRTX1133:



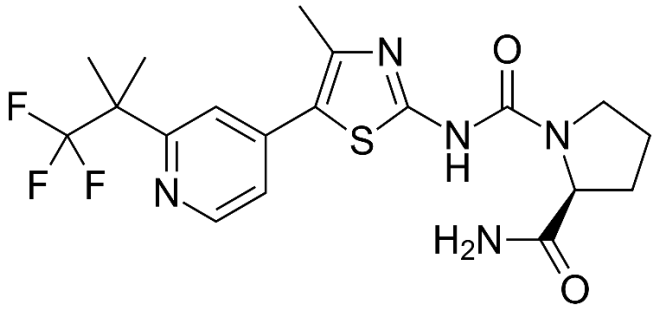
or a pharmaceutically acceptable salt thereof, and BYL719:



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for increasing the sensitivity of a cancer cell to the KRas G12D inhibitor, wherein an effective amount of the combination of the KRas G12C inhibitor MRTX1133:



or a pharmaceutically acceptable salt thereof, and BYL719:



or a pharmaceutically acceptable salt thereof, is to be administered to a subject undergoing KRas G12D treatment,
wherein the BYL719 increases the sensitivity of the cancer cell to the KRas G12D inhibitor.

16. The use according to any one of claims 1-8, 11 and 13-15 or the *in vitro* method according to any one of claims 12- 14, wherein the therapeutically effective amount of the KRas G12D inhibitor in the combination is between about 0.01 to 100 mg/kg per day, preferably wherein the therapeutically effective amount of the KRas G12D inhibitor in the combination is between about 0.1 to 50 mg/kg per day.

17. The use according to any of claims 1-8, 11 and 13-16 or the *in vitro* method according to any one of claims 12-14 and 16, wherein the therapeutically effective amount of PI3Ka inhibitor or salt in the combination is between about 0.01 to 100 mg/kg per day, preferably wherein the therapeutically effective amount of PI3Ka inhibitor or salt in the combination is between about 0.1 to 50 mg/kg per day, preferably wherein the PI3Ka inhibitor or salt os BYL719.

18. The use according to any one of claims 1-8, 11 and 13-17 or the *in vitro* method according to any one of claims 12- 14 and 16-17, 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, preferably wherein the cancer wherein the cancer is a KRas G12D-associated cancer, preferably wherein the cancer is pancreatic, colon, endometrial, or non-small cell lung cancer.

19. A kit comprising the pharmaceutical composition of any of claims 9 and 10 for use in treating KRas G12D cancer in a subject.

20. The kit according to claim 19, further comprising an insert with instructions for administration of the pharmaceutical composition(s).