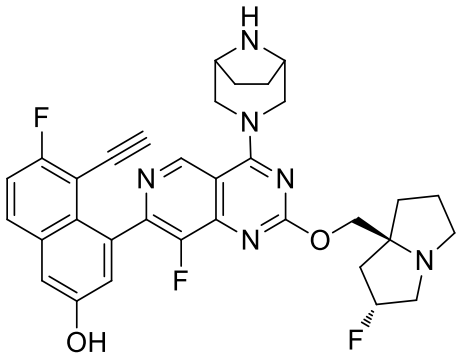
WHAT IS CLAIMED IS:

1. Use of a combination of a KRas G12D inhibitor or a pharmaceutically acceptable salt thereof, and a cytotoxic compound selected from irinotecan, topotecan, belotecan, trastuzumab, deruxtecan and camptothecin, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein a therapeutically effective amount of the combination of a KRas G12D inhibitor or a pharmaceutically acceptable salt thereof, and a cytotoxic compound selected from irinotecan, topotecan, belotecan, trastuzumab, deruxtecan and camptothecin, or a pharmaceutically acceptable salt thereof is to be administered to the subject.

2. The use according to 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-ethynyl-6-fluoronaphthalen-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-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 a pharmaceutically acceptable salt thereof, and where the cytotoxic compound is irinotecan.

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



or a pharmaceutically acceptable salt thereof, and the cytotoxic compond is irinotecan.

4. The use according to any one of claims 1-3, wherein the KRas G12D inhibitor or salt, and the cytotoxic compound, are to be administered on the same day, or wherein the KRas G12D inhibitor or salt, and the cytotoxic compound, 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 cytotoxic compound is to be administered at a maximum tolerated dose.

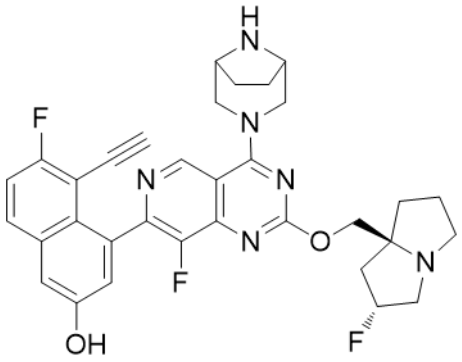
6. The use according to any one of claims 1-4, wherein the KRas G12D inhibitor or salt is to be administered at below maximum tolerated dose and/or wherein the cytotoxic compound is to be administered at below maximum tolerated dose.

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 cytotoxic compound 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 diseasein 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 cytotoxic compound, 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 diseasein 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 cytotoxic compound selected from irinotecan, topotecan, belotecan, trastuzumab deruxtecan and camptothecin or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

10. The composition of claim 9, comprising MRTX1133:



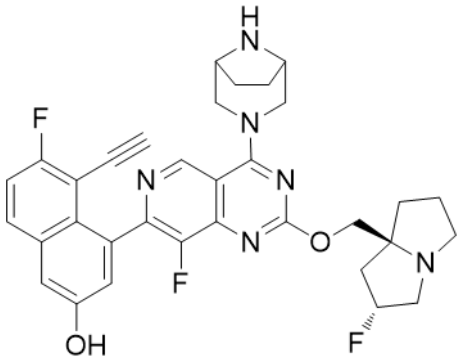
or a pharmaceutically acceptable salt thereof, irinotecan, and a pharmaceutically acceptable excipient.

11. Use of a combination a KRas G12D inhibitor or a pharmaceutically acceptable salt thereof, and a cytotoxic compound selected from irinotecan, topotecan, belotecan, trastuzumab, deruxtecan and camptothecin or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inhibiting KRas G12D activity in a cell, wherein the cell in which inhibition of KRas G12D activity is desired is to be contacted with an effective amount of the combination of a KRas G12D inhibitor or a pharmaceutically acceptable salt thereof, and a cytotoxic compound

selected from irinotecan, topotecan, belotecan, trastuzumab deruxtecan and camptothecin 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 cytotoxic compound selected from irinotecan, topotecan, belotecan, trastuzumab deruxtecan and camptothecin or a pharmaceutically acceptable salt thereof.

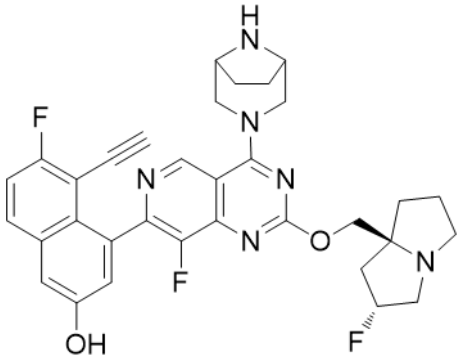
13. The use of claim 11 or the *in vitro* method of claim 12, wherein the KRas G12D inhibitor is MRTX1133:



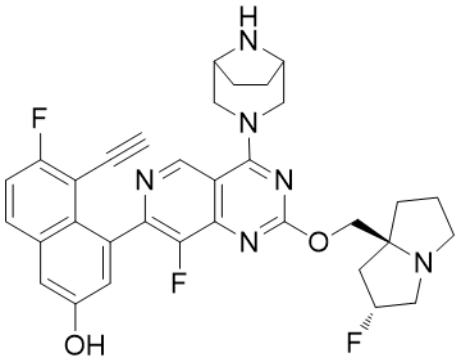
and pharmaceutically acceptable salts thereof, and the cytotoxic compound is irinotecan.

14. The use according to any one of claims 1-18, 11 and 13 or the *in vitro* method of claim 12, wherein irinotecan increases the sensitivity of cancer cells to the KRas G12D inhibitor.

15. A combination of the KRas G12D inhibitor MRTX1133:



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



or a pharmaceutically acceptable salt thereof, and irinotecan, is to be adminstered to a subject undergoing KRas G12D,

wherein the irinotecan increases the sensitivity of the cancer cell to the KRas G12D inhibitor.

16. The use according to any of claims 1-8, 11, and 13-15 or the *in vitro* method of 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 of any one of claims 12-14, and 16, wherein the therapeutically effective amount of irinotecan in the

combination is between about 0.01 to 100 mg/kg per day, preferably wherein the therapeutically effective amount of irinotecan in the combination is between about 0.1 to 50 mg/kg per day.

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

19. A kit comprising the pharmaceutical composition of any of claims 9 and 10 for 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).