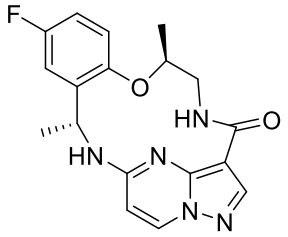
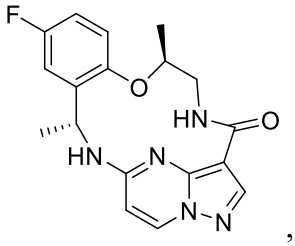
[009a] In an aspect, there is provided the use of a therapeutically effective amound of a compound that inhibits FAK, SRC, and JAK2, in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C, wherein the compound is



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

[009b] In another aspect, there is provided the use of a therapeutically effective amount of a compound that inhibits FAK, SRC, and JAK2, in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C, wherein the compound is



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in the manufacture of a medicament for the treatment of cancer in a patient.

[010] In one example, the disclosure provides a method for treating cancer in a host animal, the method comprising the step of administering to the host animal a therapeutically effective amount of one or more compounds that inhibit FAK, SRC and/or JAK2, in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C. In some examples, the host animal is a human patient. In some examples, the host animal is a laboratory animal such as a rodent.

[011] In another example, the disclosure provides a method for treating cancer in a host animal, the method comprising the step of administering to the host animal a therapeutically effective amount of a compound that inhibits FAK, SRC, and JAK2, in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C. In some examples, the host animal is a human patient. In some examples, the host animal is a laboratory animal such as a rodent.

[012] In another example, the disclosure provides one of more compounds that inhibit FAK, SRC and/or JAK2, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C.

[013] In another example, the disclosure provides a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C.

[014] In another example, the disclosure provides use of one or more compounds that inhibit FAK, SRC and/or JAK2, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament comprising a therapeutically effective amount of the compound, for treating cancer in a patient in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C.

[015] In another example, the disclosure provides use of a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament comprising a therapeutically effective amount of the compound, for treating cancer in a patient in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C.

[016] In another example, the disclosure provides a composition comprising one or more compounds that inhibit FAK, SRC and/or JAK2, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C.

[017] In another example, the disclosure provides a composition comprising a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount, for use in the treatment of cancer in a patient, in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C.

[018] In another example, the disclosure provides a medicament comprising one or more compounds that inhibit FAK, SRC and/or JAK2, or a pharmaceutically acceptable salt thereof, combined with an agent that inhibits KRAS G12C, or a pharmaceutically acceptable salt thereof, in fixed or free combination.

[019] In another example, the disclosure provides a medicament comprising a compound that inhibits FAK, SRC and JAK2, or a pharmaceutically acceptable salt thereof, combined with an agent that inhibits KRAS G12C, or a pharmaceutically acceptable salt thereof, in fixed or free combination.

[020] In another example, the disclosure provides a synergistic composition of one or more compounds that inhibit FAK, SRC and/or JAK2 and an agent that inhibits KRAS G12C, where the two components come into contact with each other at a locus.

[021] In another example, the disclosure provides a synergistic composition of a compound that inhibits FAK, SRC and JAK2 and an agent that inhibits KRAS G12C, where the two components come into contact with each other at a locus.

[022] In another example, the disclosure provides a synergistic composition of one or more compounds that inhibit FAK, SRC and/or JAK2, and an agent that inhibits KRAS G12C, where the two components come into contact with each other only in the human body.

[023] In another example, the disclosure provides a synergistic composition of a compound that inhibits FAK, SRC and JAK2, and an agent that inhibits KRAS G12C, where the two components come into contact with each other only in the human body.

[024] In some examples the compound that inhibits FAK, SRC and JAK2 is of the formula I

-NHS(O)NH(C_1-C_6 alkyl), -NHS(O)$_2$NH(C_1-C_6 alkyl), -NHS(O)N(C_1-C_6 alkyl)$_2$, -NHS(O)$_2$N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 alkyl)S(O)NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)S(O)$_2$NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)S(O)N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 alkyl)S(O)$_2$N(C_1-C_6 alkyl)$_2$, -CO_2H, -C(O)OC_1-C_6 alkyl, -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -SC_1-C_6 alkyl, -S(O)C_1-C_6 alkyl, -S(O)$_2C_1$-C_6 alkyl, -S(O)NH(C_1-C_6 alkyl), -S(O)$_2$NH(C_1-C_6 alkyl), -S(O)N(C_1-C_6 alkyl)$_2$, -S(O)$_2$N(C_1-C_6 alkyl)$_2$, -P(C_1-C_6 alkyl)$_2$, -P(O)(C_1-C_6 alkyl)$_2$, C_3-C_6 cycloalkyl, or 3-to 7-membered heterocycloalkyl;

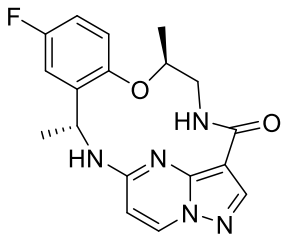
[033] each R^9 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 7-membered heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl or -OR^7;

[034] each Z^1, Z^2, Z^3, Z^4, Z^5, Z^6 or Z^7 is independently N, NH, or C(R^{10}), wherein each R^{10} is independently H, deuterium, halogen, C_1-C_6 alkyl, -O- C_1-C_6 alkyl, -OH, -NH_2, -NH(C_1-C_6 alkyl), -NH(phenyl), -NH(heteroaryl), -CN, or –CF_3, and

[035] provided that at least one of Z^1, Z^2, Z^3, Z^4, Z^5, Z^6 or Z^7 is N or NH;

[036] or a pharmaceutically acceptable salt thereof.

[037] In some examples of the above aspects, the compound that inhibits FAK, SRC and JAK2 is of the formula (referred to herein as Compound 1)



[038] or a pharmaceutically acceptable salt thereof.

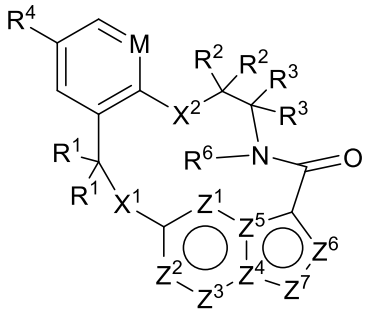
[039] In some examples of the above aspects, the at least one agent that inhibits KRAS G12C is a biological agent that inhibits KRAS G12C or a small molecule that inhibits KRAS G12C. In some examples of the above aspects, the at least one agent that inhibits KRAS G12C is a biological agent that inhibits KRAS G12C. In some examples of the above aspects, the at least one agent that inhibits KRAS G12C is a biological agent that inhibits KRAS G12C is an antibody, an antibody fragment, a peptide, an oligonucleotide, a ribonucleic acid, or

an siRNA. In some examples of the above aspects, the at least one agent that inhibits KRAS G12C is a small molecule inhibitor.

[040] Additional examples, features, and advantages of the disclosure will be apparent from the following detailed description and through practice of the disclosure. The compounds of the present disclosure can be described as examples in any of the following enumerated clauses. It will be understood that any of the examples described herein can be used in connection with any other examples described herein to the extent that the examples do not contradict one another.

[041] 1. A method for treating cancer in a host animal, such as a human patient in need of such treatment, the method comprising the step of administering to the host animal a therapeutically effective amount of a compound that inhibits FAK, SRC, and JAK2, in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C.

[042] 2. The method of clause 1, wherein the compound that inhibits FAK, SRC and JAK2 is of the formula I



I

[043] wherein

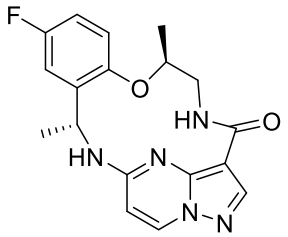
[044] M is CR^5 or N;

[045] X^1 and X^2 are independently $-C(R^7)(R^8)-$, -S-, -S(O)-, $-S(O)_2-$, -O- or $-N(R^9)-$;

[046] each R^1 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, $-C(O)OR^7$ or $-C(O)NR^7R^8$; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_6-C_{10} aryl is independently optionally substituted by deuterium, halogen, -OH, -CN, $-OC_1$-C_6 alkyl, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, $-NHC(O)C_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)C_1$-C_6 alkyl, $-NHC(O)NH_2$, $-NHC(O)NHC_1$-C_6 alkyl, $-N(C_1$-C_6 alkyl)$C(O)NH_2$, $-N(C_1$-C_6 alkyl)$C(O)NHC_1$-C_6 alkyl, $-NHC(O)N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$C(O)N(C_1$-C_6 alkyl)$_2$, $-NHC(O)OC_1$-C_6 alkyl,

What is claimed:

1. Use of a therapeutically effective amound of a compound that inhibits FAK, SRC, and JAK2, in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C, wherein the compound is



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

2. The use of claim 1, wherein the cancer is selected from the group consisting of ALCL, non-small cell lung cancer, neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, triple negative breast, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, pediatric glioma CML, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer, stomach cancer, and lung cancer.

3. The use of claim 1, wherein the cancer is non-small cell lung cancer, metastatic non-small cell lung cancer, colorectal cancer, metastatic colorectal cancer, pancreatic cancer, metastatic pancreatic cancer, uterine cancer, or metastatic uterine cancer.

4. The use of claim 1, wherein the cancer is non-small cell lung cancer.

5. The use of claim 1, wherein the cancer is colorectal cancer.

6. The use of claim 1, wherein the compound that inhibits FAK, SRC, and JAK2 is to be administered at the same time as, before, or after the at least one agent that inhibits KRAS G12C.

7. The use of claim 1, wherein IL-6 secretion from the cancer is decreased.

8. The use of claim 1, wherein the at least one agent that inhibits KRAS G12C is a biological agent that inhibits KRAS G12C or a small molecule inhibitor of KRAS G12C.

9. The use of claim 1, wherein the at least one agent that inhibits KRAS G12C is a biological agent that inhibits KRAS G12C.

10. The use of claim 9, wherein the biological agent that inhibits KRAS G12C is an antibody, an antibody fragment, a peptide, an oligonucleotide, a ribonucleic acid, or an siRNA.

11. The use of claim 1, wherein the at least one agent that inhibits KRAS G12C is a small molecule inhibitor of KRAS G12C.

12. The use of any one of claims 1 to 8, wherein the at least one agent that inhibits KRAS G12C is AMG-510, MRTX849, JNJ-74699157, ARS-1620, MRTX1257, RM-007, or ADT-007.

13. The use of claim 1, wherein the at least one agent that inhibits KRAS G12C is AMG-510, or a pharmaceutically acceptable salt thereof.

14. The use of claim 1, wherein the at least one agent that inhibits KRAS G12C is MRTX849, or a pharmaceutically acceptable salt thereof.

15. The use of claim 1, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered at a dose of about 0.1 mg to about 3 g, or about 1 mg to about 50 mg, or about 50 to about 250 mg, or about 150 to about 500 mg, or about 150 to about 250 mg, or about 250 mg to about 1 g, or about 100 mg to about 2 g, or about 500 mg to about 2 g, or about 500 mg to about 1 g, or about 100 mg to about 300 mg, or about 160 mg; and the at least one agent that inhibits KRAS G12C is to be administered at a dose of about 0.1 mg to about 3 g, or about 1 mg to about 50 mg, or about 50 to about 250 mg, or about 150 to about 500 mg, or about 150 to about 250 mg, or about 250 mg to about 1 g, or about 100 mg to about 2 g, or about 500 mg to about 2 g, or about 500 mg to about 1 g, or about 800 mg to about 1.5 g, or at least 800 mg, or at least 600 mg, or about 960 mg, or about 600 mg.

16. The use of claim 1, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered at a dose of about 0.1 mg/kg to about 1 g/kg, or about 0.5 mg/kg to about 50 mg/kg,

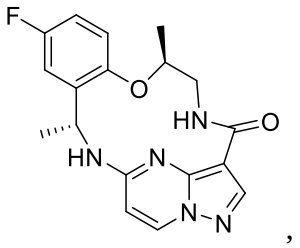
or about 0.5 mg/kg to about 25 mg/kg, or about 1.0 mg/kg to about 10 mg/kg, or about 1.0 mg/kg to about 5 mg/kg, or about 0.1 mg/kg to about 5 mg/kg, or about 0.1 mg/kg to about 1 mg/kg, or about 0.1 mg/kg to about 0.6 mg/kg, or about 1.25 mg/kg to about 3.75 mg/kg, or about 1.0 mg/kg, about 2.0 mg/kg, or about 3.0 mg/kg, or about 4.0 mg/kg and the at least one agent that inhibits KRAS G12C is to be administered at a dose of about 0.1 mg/kg to about 1 g/kg, or about 0.5 mg/kg to about 50 mg/kg, or about 0.5 mg/kg to about 25 mg/kg, or about 1.0 mg/kg to about 10 mg/kg, or about 1.0 mg/kg to about 5 mg/kg, or about 0.1 mg/kg to about 5 mg/kg, or about 0.1 mg/kg to about 1 mg/kg, or about 0.1 mg/kg to about 0.6 mg/kg, or about 1.25 mg/kg to about 3.75 mg/kg, or about 1.0 mg/kg, about 2.0 mg/kg, or about 3.0 mg/kg, or about 4.0 mg/kg.

17. The use according to claim 1, wherein the patient is a human patient in need of such treatment who has not received a prior treatment.

18. The use according to claim 1, wherein the patient is a human patient in need of such treatment who has received at least one prior treatment of one or more chemotherapeutic agents or immunotherapies.

19. The use according to claim 1, wherein the patient is a human patient in need of such treatment who has received at least one prior treatment of one or more chemotherapeutic agents or immunotherapies, and developed an acquired resistance to the treatment, and/or developed bypass resistance to the treatment, and/or developed bypass resistance to the treatment regulated by FAK, SRC or JAK2.

20. Use of a therapeutically effective amount of a compound that inhibits FAK, SRC, and JAK2, in combination with a therapeutically effective amount of at least one agent that inhibits KRAS G12C, wherein the compound is



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in the manufacture of a medicament for the treatment of cancer in a patient.

21. The use of claim 20, wherein the cancer is selected from the group consisting of ALCL, non-small cell lung cancer, neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, triple negative breast, colonic

adenocarcinoma, glioblastoma, glioblastoma multiforme, anaplastic thyroid cancer, cholangiocarcinoma, ovarian cancer, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, head and neck squamous cell carcinoma, pediatric glioma CML, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, castrate-resistant prostate cancer, Hodgkin lymphoma, serous and clear cell endometrial cancer, oral cancer, endometrial cancer, endocrine cancer, skin cancer, gastric cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, colon cancer, bladder cancer, bone cancer, cervical cancer, uterine cancer, testicular cancer, rectal cancer, kidney cancer, liver cancer, stomach cancer, and lung cancer.

22. The use of claim 20, wherein the cancer is non-small cell lung cancer, metastatic non-small cell lung cancer, colorectal cancer, metastatic colorectal cancer, pancreatic cancer, metastatic pancreatic cancer, uterine cancer, or metastatic uterine cancer.

23. The use of claim 20, wherein the cancer is non-small cell lung cancer.

24. The use of claim 20, wherein the cancer is colorectal cancer.

25. The use of claim 20, wherein the compound that inhibits FAK, SRC, and JAK2 is to be administered at the same time as, before, or after the at least one agent that inhibits KRAS G12C.

26. The use of claim 20, wherein IL-6 secretion from the cancer is decreased.

27. The use of claim 20, wherein the at least one agent that inhibits KRAS G12C is a biological agent that inhibits KRAS G12C or a small molecule inhibitor of KRAS G12C.

28. The use of claim 20, wherein the at least one agent that inhibits KRAS G12C is a biological agent that inhibits KRAS G12C.

29. The use of claim 20, wherein the biological agent that inhibits KRAS G12C is an antibody, an antibody fragment, a peptide, an oligonucleotide, a ribonucleic acid, or an siRNA.

30. The use of claim 20, wherein the at least one agent that inhibits KRAS G12C is a small molecule inhibitor of KRAS G12C.

31. The use of any one of claims 20 to 27, wherein the at least one agent that inhibits KRAS G12C is AMG-510, MRTX849, JNJ-74699157, ARS-1620, MRTX1257, RM-007, or ADT-007.

32. The use of claim 20, wherein the at least one agent that inhibits KRAS G12C is AMG-510, or a pharmaceutically acceptable salt thereof.

33. The use of claim 20, wherein the at least one agent that inhibits KRAS G12C is MRTX849, or a pharmaceutically acceptable salt thereof.

34. The use of claim 20, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered at a dose of about 0.1 mg to about 3 g, or about 1 mg to about 50 mg, or about 50 to about 250 mg, or about 150 to about 500 mg, or about 150 to about 250 mg, or about 250 mg to about 1 g, or about 100 mg to about 2 g, or about 500 mg to about 2 g, or about 500 mg to about 1 g, or about 100 mg to about 300 mg, or about 160 mg; and the at least one agent that inhibits KRAS G12C is to be administered at a dose of about 0.1 mg to about 3 g, or about 1 mg to about 50 mg, or about 50 to about 250 mg, or about 150 to about 500 mg, or about 150 to about 250 mg, or about 250 mg to about 1 g, or about 100 mg to about 2 g, or about 500 mg to about 2 g, or about 500 mg to about 1 g, or about 800 mg to about 1.5 g, or at least 800 mg, or at least 600 mg, or about 960 mg, or about 600 mg.

35. The use of claim 20, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered at a dose of about 0.1 mg/kg to about 1 g/kg, or about 0.5 mg/kg to about 50 mg/kg, or about 0.5 mg/kg to about 25 mg/kg, or about 1.0 mg/kg to about 10 mg/kg, or about 1.0 mg/kg to about 5 mg/kg, or about 0.1 mg/kg to about 5 mg/kg, or about 0.1 mg/kg to about 1 mg/kg, or about 0.1 mg/kg to about 0.6 mg/kg, or about 1.25 mg/kg to about 3.75 mg/kg, or about 1.0 mg/kg, about 2.0 mg/kg, or about 3.0 mg/kg, or about 4.0 mg/kg and the at least one agent that inhibits KRAS G12C is to be administered at a dose of about 0.1 mg/kg to about 1 g/kg, or about 0.5 mg/kg to about 50 mg/kg, or about 0.5 mg/kg to about 25 mg/kg, or about 1.0 mg/kg to abo"ut 10 mg/kg, or about 1.0 mg/kg to about 5 mg/kg, or about 0.1 mg/kg to about 5 mg/kg, or about 0.1 mg/kg to about 1 mg/kg, or about 0.1 mg/kg to about 0.6 mg/kg, or about 1.25 mg/kg to about 3.75 mg/kg, or about 1.0 mg/kg, about 2.0 mg/kg, or about 3.0 mg/kg, or about 4.0 mg/kg.

36. The use of claim 20, wherein the patient is a human patient in need of such treatment who has not received a prior treatment.

37. The use of claim 20, wherein the patient is a human patient in need of such treatment who has received at least one prior treatment of one or more chemotherapeutic agents or immunotherapies.

38. The use of claim 20, wherein the patient is a human patient in need of such treatment who has received at least one prior treatment of one or more chemotherapeutic agents or immunotherapies, and developed an acquired resistance to the treatment, and/or developed bypass resistance to the treatment, and/or developed bypass resistance to the treatment regulated by FAK, SRC or JAK2.