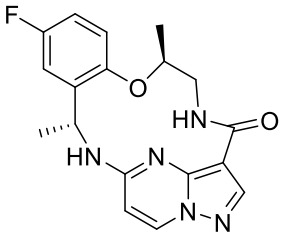
SUMMARY

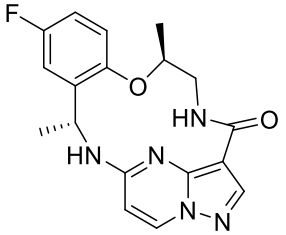
[008] It has been discovered that the combination of a MEK inhibitor, such as trametinib, and one or more compounds that inhibit FAK, SRC and/or JAK2 provides a robust response in cancers driven by KRAS, in particular, cancers harboring one or more KRAS mutations.

[008a] In an aspect, there is provided the use of a therapeutically effective amount of a compound that inhibits FAK, SRC, and JAK2 having structure



or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of a MEK inhibitor, in the manufacture of a medicament for the treatment of cancer in a patient.

[008b] In another aspect, there is provided the use of a therapeutically effective amount of a compound that inhibits FAK, SRC, and JAK2 having structure



in combination with a therapeutically effective amount of a MEK inhibitor in the manufacture of a medicament for the treatment of cancer in a patient.

[009] 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 a MEK inhibitor, such as trametinib. In some examples, the host animal is a human patient. In some examples, the host animal is a laboratory animal such as a rodent.

[010] 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 a MEK inhibitor, such as trametinib. 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 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 a MEK inhibitor, such as trametinib.

[012] 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 a MEK inhibitor, such as trametinib.

[013] 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 a MEK inhibitor, such as trametinib.

[014] 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 a MEK inhibitor, such as trametinib.

[015] 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 a MEK inhibitor, such as trametinib.

[016] 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 a MEK inhibitor, such as trametinib.

[017] 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 a MEK inhibitor, such as trametinib, or a pharmaceutically acceptable salt thereof, in fixed or free combination.

[018] 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 a MEK inhibitor, such as trametinib, or a pharmaceutically acceptable salt thereof, in fixed or free combination.

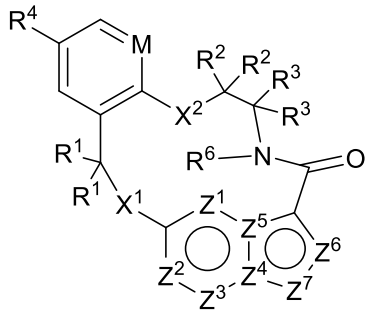
[019] In another example, the disclosure provides a synergistic composition of one or more compounds that inhibit FAK, SRC and/or JAK2 and a MEK inhibitor, such as trametinib, where the two components come into contact with each other at a locus.

[020] In another example, the disclosure provides a synergistic composition of a compound that inhibits FAK, SRC and JAK2 and a MEK inhibitor, such as trametinib, where the two components come into contact with each other at a locus.

[021] In another example, the disclosure provides a synergistic composition of one or more compounds that inhibit FAK, SRC and/or JAK2, and a MEK inhibitor, such as trametinib, where the two components come into contact with each other only in the human body.

[022] In another example, the disclosure provides a synergistic composition of a compound that inhibits FAK, SRC and JAK2, and a MEK inhibitor, such as trametinib, where the two components come into contact with each other only in the human body

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



I

[024] wherein

[025] M is CR^5 or N;

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

[027] 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, $-N(C_1$-C_6 alkyl)$C(O)OC_1$-C_6 alkyl, $-NHS(O)(C_1$-C_6 alkyl), $-NHS(O)_2(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)_2(C_1$-C_6 alkyl), $-NHS(O)NH_2$, $NHS(O)_2NH_2$, $-N(C_1$-C_6 alkyl)$S(O)NH_2$, $-N(C_1$-C_6 alkyl)$S(O)_2NH_2$, $-NHS(O)NH(C_1$-C_6 alkyl), $-NHS(O)_2NH(C_1$-C_6 alkyl), $-NHS(O)N(C_1$-C_6 alkyl)$_2$, $-NHS(O)_2N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$S(O)NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)_2NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$S(O)N(C_1$-C_6 alkyl)$_2$, $-N(C_1$-C_6 alkyl)$S(O)_2N(C_1$-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), $-S(O)_2NH(C_1$-C_6 alkyl), $-S(O)N(C_1$-C_6 alkyl)$_2$, $-S(O)_2N(C_1$-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;

[028] each R^2 and R^3 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

-NHS(O)$_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)S(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 alkyl), -NHS(O)NH_2, NHS(O)$_2NH_2$, -N(C_1-C_6 alkyl)S(O)NH_2, -N(C_1-C_6 alkyl)S(O)$_2NH_2$, -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;

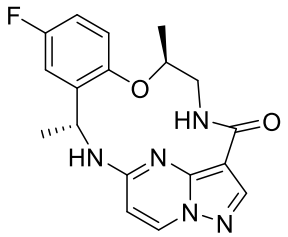
[032] each R^9 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to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

[033] 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

[034] 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;

[035] or a pharmaceutically acceptable salt thereof.

[036] 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)



[037] or a pharmaceutically acceptable salt thereof.

[038] In some examples of the various aspects described herein, and in particular those aspects described above, the cancer is non-small cell lung cancer mediated by a genetically altered KRAS comprising at least one mutation selected from the group consisting of G12C, G12V, G12D, G12A, G13C, G12S, D12R, D12F, G13D, G13V, G13R, G13E, Q61H, Q61E,

Q61L, and Q61R; or selected from the group consisting of G12D, G13D, and Q61H; or the KRAS comprises at least one mutation that is not G12A, G12C, G12S, G12V, and Q61K.

[039] In some examples of the various aspects described herein, and in particular those aspects described above, the cancer is colorectal cancer mediated by a genetically altered KRAS comprising at least one mutation selected from the group consisting of G12D, G12V, G13D, A146T, G12C, G12A, G12S, K117N, Q61K, G12R, M72V, S17G, K5R, D69G, G13C, G13R, Q61H, K117E, Q61L, Q61R, K117R, A146V, A146P, K147N, and R97I.

[040] In some examples of the various aspects described herein, and in particular those aspects described above, the cancer is pancreatic cancer mediated by a genetically altered KRAS comprising at least one mutation selected from the group consisting of G12D, G12V, G12R, Q61H, G12C, and G12S .

[041] 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.

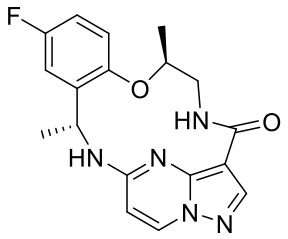
[042] 1. A method of treating cancer in a patient in need of such treatment, the method comprising the step of administering to the patient a therapeutically effective amount of a compound that inhibits FAK, SRC, and JAK2, in combination with a therapeutically effective amount of trametinib.

[043] 2. A method of treating cancer in patient in need of such treatment, the method comprising the step of administering to the patient having cancer a therapeutically effective amount of a compound that inhibits FAK, SRC, and JAK2, in combination with a therapeutically effective amount of trametinib, wherein at least one genetically altered oncogenic gene has been previously identified in the patient.

[044] 3. A method of treating a cancer mediated by at least one genetically altered oncogenic gene, in patient in need of such treatment, the method comprising the step of administering to the patient having cancer a therapeutically effective amount of a compound that inhibits FAK, SRC, and JAK2, in combination with a therapeutically effective amount of trametinib.

We Claim:

1. Use of a therapeutically effective amount of a compound that inhibits FAK, SRC, and JAK2 having structure



or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of a MEK inhibitor, in the manufacture of a medicament for the treatment of cancer in a patient.

2. The use of claim 1, wherein at least one genetically altered oncogenic gene has been previously identified in the patient, wherein the at least one genetically altered oncogenic gene is a genetically altered KRAS, a genetically altered NRAS, a genetically altered HRAS, a genetically altered BRAF, a genetically altered MEK, and/or a genetically altered PI3K.

3. The use of claim 2, wherein the genetically altered KRAS comprises at least one mutation selected from the group consisting of G12C, G12V, G12D, G12A, G13C, G12S, D12R, D12F, G13D, G13V, G13R, G13E, Q61H, Q61E, Q61L, and Q61R; or selected from the group consisting of G12D, G13D, and Q61H; or KRAS comprises at least one mutation that is not G12A, G12C, G12S, G12V, and Q61K.

4. The use of claim 1, wherein the cancer is colorectal cancer or pancreatic cancer.

5. The use of claim 1, wherein the compound that inhibits FAK, SRC, and JAK2 is to be administered in an amount of from about 40 mg to about 200 mg.

6. The use of claim 1, wherein the MEK inhibitor is to be administered in an amount of from about 0.5 mg to about 2.5 mg.

7. The use according to any one of the preceding claims, wherein the MEK inhibitor is trametinib, selumetinib, LY3214996, RO5126766, TNO155 (SHP099), or mirdametinib, or a pharmaceutically acceptable salt thereof.

8. The use of claim 7, wherein the MEK inhibitor is trametinib, or a pharmaceutically acceptable salt thereof.

9. The use of claim 1, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered in an amount of about 40mg, about 80 mg, about 120 mg, or about 160 mg by once a day or twice a day.

10. The use of claim 1, wherein the MEK inhibitor is to be administered in an amount of about 1 mg or about 2 mg.

11. The use of claim 1, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered on a schedule of at least one dose of about 40 mg, about 80 mg QD, about 120 mg QD, or about 160 mg QD, followed by at least one dose of about 40 mg BID, about 80 mg BID, about 120 mg BID, or about 160 mg BID.

12. The use of claim 1, wherein the MEK inhibitor is to be administered in at least one dose of about 1 mg QD, or about 2 mg QD.

13. The use of claim 1, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered at the same time as the MEK inhibitor.

14. The use of claim 1, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered prior to the MEK inhibitor.

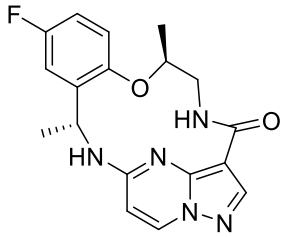
15. The use of claim 1, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered after the MEK inhibitor.

16. The use of claim 1, wherein the patient has not received a prior treatment.

17. The use of claim 1, wherein the patient has received at least one prior treatment of one or more chemotherapeutic agents or immunotherapies.

18. The use of claim 1, wherein the patient has received at least one prior treatment of one or more chemotherapeutic agents or immunotherapies, and has developed an acquired resistance to the treatment, and/or developed bypass resistance to the treatment.

19. Use of a therapeutically effective amount of a compound that inhibits FAK, SRC, and JAK2 having structure



in combination with a therapeutically effective amount of a MEK inhibitor in the manufacture of

a medicament for the treatment of cancer in a patient.

20. The use of claim 19, wherein at least one genetically altered oncogenic gene has been previously identified in the patient, wherein the at least one genetically altered oncogenic gene is a genetically altered KRAS, a genetically altered NRAS, a genetically altered HRAS, a genetically altered BRAF, a genetically altered MEK, and/or a genetically altered PI3K.

21. The use of claim 20, wherein the genetically altered KRAS comprises at least one mutation selected from the group consisting of G12C, G12V, G12D, G12A, G13C, G12S, D12R, D12F, G13D, G13V, G13R, G13E, Q61H, Q61E, Q61L, and Q61R; or selected from the group consisting of G12D, G13D, and Q61H; or KRAS comprises at least one mutation that is not G12A, G12C, G12S, G12V, and Q61K.

22. The use of claim 19, wherein the cancer is colorectal cancer or pancreatic cancer.

23. The use of claim 19, wherein the compound that inhibits FAK, SRC, and JAK2 is to be administered in an amount of from about 40 mg to about 200 mg.

24. The use of claim 19, wherein the MEK inhibitor is to be administered in an amount of from about 0.5 mg to about 2.5 mg.

25. The use according to any one of claims 19 to 24, wherein the MEK inhibitor is trametinib, selumetinib, LY3214996, RO5126766, TNO155 (SHP099), or mirdametinib, or a pharmaceutically acceptable salt thereof.

26. The use of claim 25, wherein the MEK inhibitor is trametinib,
or a pharmaceutically acceptable salt thereof.

27. The use of claim 19, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered in an amount of about 40mg, about 80 mg, about 120 mg, or about 160 mg by once a day or twice a day.

28. The use of claim 19, wherein the MEK inhibitor is to be administered in an amount of about 1 mg or about 2 mg.

29. The use of claim 19, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered on a schedule of at least one dose of about 40 mg, about 80 mg QD, about 120 mg QD, or about 160 mg QD, followed by at least one dose of about 40 mg BID, about 80 mg BID, about 120 mg BID, or about 160 mg BID.

30. The use of claim 19, wherein the MEK inhibitor is to be administered in at least one dose of about 1 mg QD, or about 2 mg QD.

31. The use of claim 19, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered at the same time as the MEK inhibitor.

32. The use of claim 19, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered prior to the MEK inhibitor.

33. The use of claim 19, wherein the compound that inhibits FAK, SRC and JAK2 is to be administered after the MEK inhibitor.

34. The use of claim 19, wherein the patient has not received a prior treatment.

35. The use of claim 19, wherein the patient has received at least one prior treatment of one or more chemotherapeutic agents or immunotherapies.

36. The use of claim 19, wherein the patient has received at least one prior treatment of one or more chemotherapeutic agents or immunotherapies, and has developed an acquired resistance to the treatment, and/or developed bypass resistance to the treatment.