$-CO_2C_1$-C_6 alkyl, $-CONH_2$, $-CONH(C_1$-C_6 alkyl), $-CON(C_1$-C_6 alkyl$)_2$, cycloalkyl, or monocyclic heterocycloalkyl;

[024] each R^7 and R^8 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 heteroaryl;

[025] 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 mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl or $-OR^7$;

[026] 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, $-OC_1$-C_6 alkyl, -OH, $-NH_2$, $-NH(C_1$-C_6 alkyl), -NH(phenyl), -NH(heteroaryl), -CN, or $-CF_3$, and

[027] 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;

[028] or a pharmaceutically acceptable salt thereof.

[028a] In one aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer or pain in a patient, wherein the cancer is mediated by a tyrosine kinase selected from the group consisting of ROS1, TRKB, TRKC, SRC, FYN, LYN, YES, FGR, FAK, ARK5, and combinations thereof, or pain mediated by TRKA, TRKB, or TRKC.

[028b] In another aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by an EML4-ALK fusion protein comprising at least one resistance mutation.

[028c] In another aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by a fusion protein comprising a fragment of a protein encoded by an ALK gene and a fragment of a protein encoded by a TPR gene.

[028d] In another aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by ALK having one or more point mutations

selected from the group consisting of F1174C/I/L/S/V, F1245C/I/L/V, R1275L/Q, T1151M, L1152R, C1156Y, G1202R, S1206Y, G1269A, G1269S, R1275Q, I1170N, I1170S and L1196M.

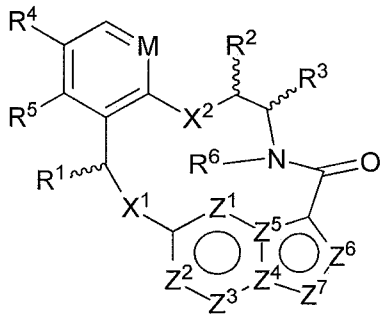
[028e] In another aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by a fusion protein comprising a fragment of a protein encoded by a TRKA gene and a fragment of a protein encoded by a LMNA gene.

[028f] In another aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by a TPM3-TRKA or LMNA-TRKA fusion protein comprising at least one resistance mutation.

[028g] In another aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by JAK1 or JAK3.

[028h] In another aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by a genetically altered TRK that is a fusion protein comprising a fragment of a protein encoded by a TRKA gene and a fragment of a protein encoded by a LMNA gene.

[029] The present disclosure provides a method of treating cancer in a patient previously shown to express a genetically altered tyrosine or serine/threonine kinase comprising, administering to the patient a therapeutically effective amount of a compound of the formula I



I

[030] wherein

[031] M is CR^{4a} or N;

[032] X^1 and X^2 are independently S, S(O), $S(O)_2$, O or $N(R^9)$;

[033] R^1 is 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

[037] each R^7 and R^8 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 heteroaryl;

[038] 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 mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl or $-OR^7$;

[039] 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, $-OC_1$-C_6 alkyl, -OH, $-NH_2$, -NH(C_1-C_6 alkyl), -NH(phenyl), -NH(heteroaryl), -CN, or $-CF_3$, and

[040] 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;

[041] or a pharmaceutically acceptable salt thereof.

[041a] In another aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient previously shown to express a genetically altered tyrosine or serine/threonine kinase, wherein the cancer is mediated by a tyrosine kinase selected from the group consisting of ROS1, TRKB, TRKC, SRC, FYN, LYN, YES, FGR, FAK, ARK5, and combinations thereof.

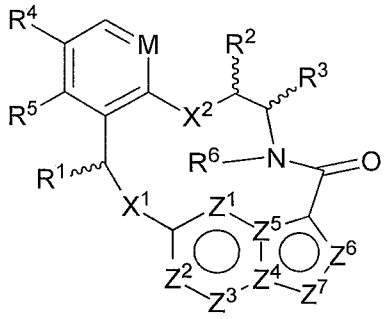
[041b] In another aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient previously shown to express a protein encoded by an ALK gene and a fragment of a protein encoded by a TPR gene.

[041c] In another aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient previously shown to express an EML4-ALK fusion protein comprising at least one resistance mutation.

[042] The present disclosure provides a method of treating cancer in a patient comprising;

[043] i. identifying a genetically altered tyrosine or serine threonine kinase in the patient, and

[044] ii. administering to the patient a therapeutically effective amount of a compound of the formula I



I

[045] wherein

[046] M is CR^{4a} or N;

[047] X^1 and X^2 are independently S, S(O), $S(O)_2$, O or $N(R^9)$;

[048] R^1 is 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)$_2$,

[052] each R^7 and R^8 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 heteroaryl;

[053] 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 mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl or -OR^7;

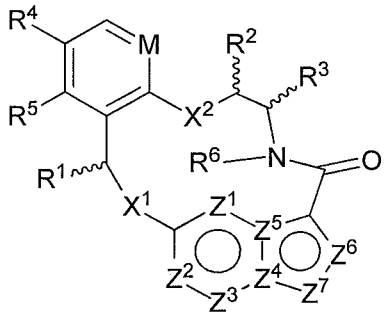
[054] each Z^1, Z^2, Z^3, Z^4, Z^5, Z^6 or Z^7 is independently N, NH, or C(R^{10}), wherein each R^{10} is independently H, deuterium, halogen, C_1-C_6 alkyl, -OC_1-C_6 alkyl, -OH, -NH_2, -NH(C_1-C_6 alkyl), -NH(phenyl), -NH(heteroaryl), -CN, or –CF_3, and

[055] 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;

[056] or a pharmaceutically acceptable salt thereof.

[056a] In another aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriaza-cyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein a genetically altered tyrosine or serine/threonine kinase in the patient is to be identified, and a therapeutically effective amount of the medicament is to be administered if the genetically altered tyrosine or serine/threonine kinase in the patient is identified by subjecting a patient sample to a test selected from the group consisting of FISH, IHC, PCR and gene sequencing.

[057] The present disclosure provides a method of identifying a patient for treatment with a compound of the formula I



I

[058] wherein

[059] M is CR^{4a} or N;

[060] X^1 and X^2 are independently S, S(O), $S(O)_2$, O or N(R^9);

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 mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl or -OR^7;

[067] 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, -OC_1-C_6 alkyl, -OH, -NH_2, -NH(C_1-C_6 alkyl), -NH(phenyl), -NH(heteroaryl), -CN, or –CF_3, and

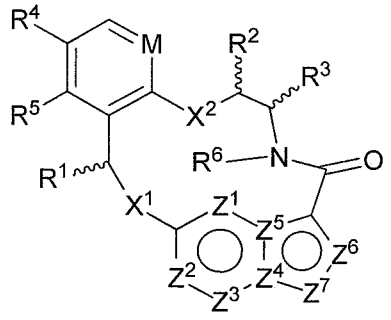
[068] provided that at least one of Z^1, Z^2, Z^3, Z^4, Z^5, Z^6 or Z^7 is N or NH;

[069] or a pharmaceutically acceptable salt thereof,

[070] comprising diagnosing the patient with a cancer mediated by a genetically altered tyrosine or serine/threonine kinase.

[070a] In another aspect, there is provided a method of identifying a patient for treatment with (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriaza-cyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof, comprising subjecting a patient sample to a test selected from the group consisting of FISH, IHC, PCR and gene sequencing to identify the patient as having a cancer mediated by a genetically altered tyrosine or serine/threonine kinase.

[071] The present disclosure provides a use of compound of the formula I



I

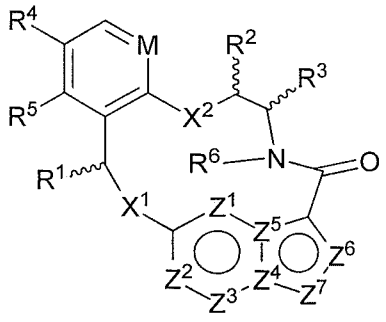
[072] wherein

[073] M is CR^{4a} or N;

[074] X^1 and X^2 are independently S, S(O), $S(O)_2$, O or N(R^9);

[096] or a pharmaceutically acceptable salt thereof, for treating cancer in a patient.

[097] The present disclosure provides the use of compound of the formula I



I

[098] wherein

[099] M is CR^{4a} or N;

[0100] X^1 and X^2 are independently S, S(O), $S(O)_2$, O or $N(R^9)$;

[0101] R^1 is 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;

[0110] The present disclosure provides use of a compound of the formula I

[0136] The present disclosure provides the use of a compound of the formula I

[0149] In some embodiments, the compound of formula (I) is (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriaza-cyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof.

WHAT IS CLAIMED IS:

1. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer or pain in a patient, wherein the cancer is mediated by a tyrosine kinase selected from the group consisting of ROS1, TRKB, TRKC, SRC, FYN, LYN, YES, FGR, FAK, ARK5, and combinations thereof, or pain mediated by TRKA, TRKB, or TRKC.

2. The use of claim 1, wherein the cancer or pain is mediated by a receptor tyrosine kinase.

3. The use of claim 2, wherein the receptor tyrosine kinase is selected from the group consisting of ROS1, TRKA, TRKB and TRKC.

4. The use of claim 1, wherein the cancer is mediated by a non-receptor kinase.

5. The use of claim 4, wherein the non-receptor kinase is FYN, LYN, YES, FGR, SRC, FAK or ARK5.

6. The use of any one of claims 1 to 3, wherein the disease is a cancer mediated by a fusion protein comprising a fragment of a protein encoded by an ALK gene and a fragment of a

protein encoded by a TPR gene.

7. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by an EML4-ALK fusion protein comprising at least one resistance mutation.

8. The use of claim 7, wherein the EML4-ALK fusion protein comprises at least one mutation selected from the group consisting of L1196M, G1202R, D1203R, L1152P/R, F1174C/L/V, C1156Y, I1171N, G1123S, S1206Y, G1269S/A, and a 1151T insertion.

9. The use of claim 8, wherein the mutation is L1196M.

10. The use of claim 8, wherein the mutation is G1202R.

11. The use of claim 8, wherein the mutation is L1152P.

12. The use of claim 8, wherein the mutation is F1174C.

13. The use of claim 8, wherein the mutation is C1156Y.

14. The use of claim 8, wherein the mutation is I1171N.

15. The use of claim 8, wherein the mutation is G1269S.

16. The use of claim 8, wherein the mutation is 1151T insertion.

17. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by a fusion protein comprising a fragment of a protein encoded by an ALK gene and a fragment of a protein encoded by a TPR gene.

18. The use of claim 17, wherein the genetically altered ALK is a TPR-ALK fusion protein.

19. The use of claim 18, wherein the TPR-ALK fusion protein is a wild-type protein.

20. The use of claim 18, wherein the TPR-ALK fusion protein comprises at least one resistance mutation.

21. The use of claim 18, wherein the TPR-ALK fusion protein comprises a L1196M point mutation.

22. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by ALK having one or more point mutations selected from the group consisting of F1174C/I/L/S/V, F1245C/I/L/V, R1275L/Q, T1151M, L1152R, C1156Y, G1202R, S1206Y, G1269A, G1269S, R1275Q, I1170N, I1170S and L1196M.

23. The use of claim 22, wherein the point mutation is a mutation of ALK at F1174.

24. The use of claim 22, wherein the point mutation is a mutation of ALK at F1245.

25. The use of claim 22, wherein the point mutation is a mutation of ALK at R1275.

26. The use of any one of claims 6 to 25, wherein the cancer is selected from the group consisting of ALCL, NSCLC, neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme and anaplastic thyroid cancer.

27. The use of any one of claims 6 to 26, wherein the cancer is NSCLC.

28. The use of any one of claims 1 to 3, wherein the cancer is mediated by ROS1.

29. The use of any one of claims 1 to 3, wherein the cancer is mediated by a genetically altered ROS1.

30. The use of any one of claims 1 to 3, wherein the cancer is mediated by a fusion protein comprising a fragment of a protein encoded by an ROS1 gene and a fragment of a protein encoded by a gene selected from the group consisting of TPM3, SDC4, SLC34A2 and CD74.

31. The use of claim 30, wherein the fusion protein comprises a fragment of a protein encoded by an ROS1 gene and a fragment of a protein encoded by a CD74 gene.

32. The use of claim 29, wherein the genetically altered ROS1 is a CD74-ROS1 fusion protein.

33. The use of claim 32, wherein the CD74-ROS1 fusion protein is a wild-type protein.

34. The use of claim 32, wherein the CD74-ROS1 fusion protein comprises at least one resistance mutation.

35. The use of claim 32, wherein the CD74-ROS1 fusion protein comprises a G2032R, L2026M or D2033N point mutation.

36. The use of claim 29, wherein the genetically altered ROS1 is a SDC4-ROS1 fusion protein.

37. The use of claim 36, wherein the SDC4-ROS1 fusion protein is a wild-type protein.

38. The use of claim 36, wherein the SDC4-ROS1 fusion protein comprises at least one resistance mutation.

39. The use of claim 36, wherein the SDC4-ROS1 fusion protein comprises a G2032R point mutation.

40. The use of claim 29, wherein the genetically altered ROS1 is a SLC34A2-ROS1 fusion protein.

41. The use of claim 40, wherein the SLC34A2-ROS1 fusion protein is a wild-type protein.

42. The use of claim 40, wherein the SLC34A2-ROS1 fusion protein comprises at least one resistance mutation.

43. The use of claim40, wherein the SLC34A2-ROS1 fusion protein comprises a G2032R point mutation.

44. The use of any one of claims 28 to 43, wherein the cancer is selected from the group consisting of glioblastoma, glioblastoma multiforme, NSCLC, cholangiocarcinoma, ovarian cancer, gastric adenocarcinoma, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, and epithelioid hemangioendothelioma.

45. The use of any one of claims28 to 43, wherein the cancer is NSCLC.

46. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by a fusion protein comprising a fragment of a protein encoded by a TRKA gene and a fragment of a protein encoded by a LMNA gene.

47. The use of claim 46, wherein the fusion protein is a LMNA-TRKA fusion protein.

48. The use of claim 47, wherein the LMNA-TRKA fusion protein is a wild-type protein.

49. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by a TPM3-TRKA or LMNA-TRKA fusion protein comprising at least one resistance mutation.

50. The use of any one of claims 1 to 3, wherein the cancer is mediated by TRKB.

51. The use of any one of claims 1 to 3, wherein the cancer is mediated by a genetically altered TRKB.

52. The use of any one of claims 1 to 3, wherein the cancer is mediated by TRKC.

53. The use of any one of claims 1 to 3, wherein the cancer is mediated by a genetically altered TRKC.

54. The use of any one of claims 46 to 53, wherein the cancer is selected from the group consisting of glioblastoma, glioblastoma multiforme, NSCLC, cholangiocarcinoma, intrahepatic cholangiocarcinoma, colorectal cancer, thyroid papillary cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, breast cancer, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, colon adenocarcinoma, thyroid carcinoma, skin cutaneous melanoma, head and neck squamous cell carcinoma and pediatric glioma.

55. The use of any one of claims 46 to 54, wherein the cancer is NSCLC.

56. The use of any one of claims 46 to 54, wherein the cancer is colorectal cancer.

57. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by JAK1 or JAK3.

58. The use of any one of claims 1 to 3, wherein the cancer is mediated by SRC.

59. The use of claim 58, wherein the cancer is selected from the group consisting of glioblastoma, glioblastoma multiforme, NSCLC, cholangiocarcinoma, intrahepatic cholangiocarcinoma, colorectal cancer, thyroid papillary cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, breast cancer, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, colon adenocarcinoma, thyroid carcinoma, skin cutaneous melanoma, head and neck squamous cell carcinoma and pediatric glioma.

60. The use of any one of claims 1 to 3, wherein the medicament is for treating pain.

61. The use of any one of claims 1 to 3, wherein the medicament is for treating pain mediated by TRKA, TRKB or TRKC.

62. The use of claim 61, wherein the pain is mediated by TRKA.

63. The use of claim 61, wherein the pain is mediated by TRKB.

64. The use of claim 61, wherein the pain is mediated by TRKC.

65. The use of any one of claims 1, 4 or 5, wherein the cancer is a cancer exhibiting bypass resistance.

66. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient previously shown to express a genetically altered tyrosine or serine/threonine kinase, wherein the cancer is mediated by a tyrosine kinase selected from the group consisting of ROS1, TRKB, TRKC, SRC, FYN, LYN, YES, FGR, FAK, ARK5, and combinations thereof.

67. The use of claim 66, wherein the genetically altered tyrosine kinase is genetically altered ROS1.

68. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient previously shown to express a protein encoded by an ALK gene and a fragment of a protein encoded by a TPR gene.

69. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient previously shown to express an EML4-ALK fusion protein comprising at least one resistance mutation.

70. The use of claim 69, wherein the EML4-ALK fusion protein comprises at least one mutation selected from the group consisting of L1196M, G1202R, D1203R, L1152P/R, F1174C/L/V, C1156Y, I1171N, G1123S, S1206Y, G1269S/A, and a 1151T insertion.

71. The use of claim 68, wherein the protein is a TPR-ALK fusion protein.

72. The use of claim 71, wherein the TPR-ALK fusion protein is a wild-type protein.

73. The use of claim 71, wherein the TPR-ALK fusion protein comprises at least one resistance mutation.

74. The use of claim 73, wherein the TPR-ALK fusion protein comprises a L1196M point mutation.

75. The use of any one of claims 66 to 74, wherein the cancer exhibits a bypass resistance mechanism.

76. The use of claim 75, wherein the bypass resistance mechanism is mediated by SRC.

77. The use of any one of claims 66 to 76, wherein the cancer is selected from the group consisting of ALCL, NSCLC, neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme and anaplastic thyroid cancer.

78. The use of any one of claims 66 to 77, wherein the cancer is NSCLC.

79. The use of claim 67, wherein the genetically altered ROS1 is a fusion protein comprising a fragment of a protein encoded by an ROS1 gene and a fragment of a protein encoded by a gene selected from the group consisting of TPM3, SDC4, SLC34A2 and CD74.

80. The use of claim 79, wherein the fusion protein comprises a fragment of a protein encoded by an ROS1 gene and a fragment of a protein encoded by a CD74 gene.

81. The use of claim 79, wherein the genetically altered ROS1 is a CD74-ROS1 fusion protein.

82. The use of claim 81, wherein the CD74-ROS1 fusion protein is a wild-type protein.

83. The use of claim 81, wherein the CD74-ROS1 fusion protein comprises at least one resistance mutation.

84. The use of claim 81, wherein the CD74-ROS1 fusion protein comprises a G2032R, L2026M or D2033N point mutation.

85. The use of claim 80, wherein the genetically altered ROS1 is a SDC4-ROS1 fusion protein.

86. The use of claim 85, wherein the SDC4-ROS1 fusion protein is a wild-type protein.

87. The use of claim 85, wherein the SDC4-ROS1 fusion protein comprises at least one resistance mutation.

88. The use of claim 85, wherein the SDC4-ROS1 fusion protein comprises a G2032R point mutation.

89. The use of claim 79, wherein the genetically altered ROS1 is a SLC34A2-ROS1 fusion protein.

90. The use of claim 89, wherein the SLC34A2-ROS1 fusion protein is a wild-type protein.

91. The use of claim 89, wherein the SLC34A2-ROS1 fusion protein comprises at least one resistance mutation.

92. The use of claim 89, wherein the SLC34A2-ROS1 fusion protein comprises a G2032R point mutation.

93. The use of any one of claims 66, 67 or 79 to 92, wherein the cancer is selected from the group consisting of glioblastoma, glioblastoma multiforme, NSCLC, cholangiocarcinoma, ovarian cancer, gastric adenocarcinoma, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, and epithelioid hemangioendothelioma.

94. The use of any one of claims 66, 67 or 79 to 93, wherein the cancer is NSCLC.

95. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by a genetically altered TRK that is a fusion protein comprising a fragment of a protein encoded by a TRKA gene and a fragment of a protein encoded by a LMNA gene.

96. The use of claim 95, wherein the genetically altered TRK is a LMNA-TRKA fusion protein.

97. The use of claim 96, wherein the LMNA-TRKA fusion protein is a wild-type protein.

98. The use of claim 96, wherein the LMNA-TRKA fusion protein comprises at least one resistance mutation.

99. The use of any one of claims 95 to 98, wherein the cancer is selected from the group consisting of glioblastoma, glioblastoma multiforme, NSCLC, cholangiocarcinoma, intrahepatic cholangiocarcinoma, colorectal cancer, thyroid papillary cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, breast cancer, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, colon

adenocarcinoma, thyroid carcinoma, skin cutaneous melanoma, head and neck squamous cell carcinoma and pediatric glioma.

100. The use of any one of claims 95 to 98, wherein the cancer is NSCLC.

101. The use of any one of claims 95 to 98, wherein the cancer is colorectal cancer.

102. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriaza-cyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein a genetically altered tyrosine or serine/threonine kinase in the patient is to be identified, and a therapeutically effective amount of the medicament is to be administered if the genetically altered tyrosine or serine/threonine kinase in the patient is identified by subjecting a patient sample to a test selected from the group consisting of FISH, IHC, PCR and gene sequencing.

103. A method of identifying a patient for treatment with (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriaza-cyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof, comprising subjecting a patient sample to a test selected from the group consisting of FISH, IHC, PCR and gene sequencing to identify the patient as having a cancer mediated by a genetically altered tyrosine or serine/threonine kinase.