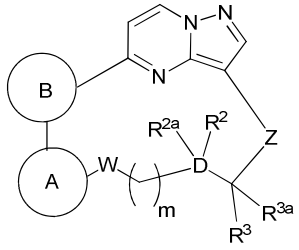
WHAT IS CLAIMED IS:

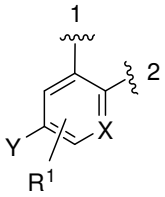
1. Use of a compound in the manufacture of a medicament for treating a subject having a cancer, said subject having been previously administered a first ROS1 inhibitor, a first ALK inhibitor, or a first TRK inhibitor, and wherein the cancer has been determined to have one or more ROS1 inhibitor resistance mutations following the administration of the first ROS1 inhibitor, the first ALK inhibitor, or the first TRK inhibitor, wherein the compound has a chemical structure of Formula I:



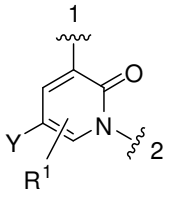
I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

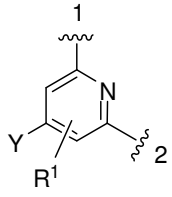
ring A is selected from rings A-1, A-2 and A-3 having the structures:



A-1



A-2



A-3

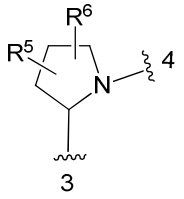
wherein the wavy line labeled 1 indicates the point of attachment of ring A to ring B and the wavy line labeled 2 indicates the point of attachment of ring A to W;

X is N or CH;

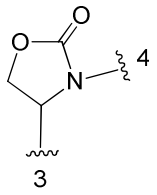
Y is H or F;

R^1 is H, (1-3C)alkoxy or halogen;

ring B is selected from rings B-1 and B-2 having the structures:



B-1



B-2

wherein the wavy line labeled 3 indicates the point of attachment to ring A and the wavy line labeled 4 indicates the point of attachment to the pyrazolo[1,5-a]pyrimidine ring of Formula **I**;

W is O, NH or CH_2, wherein when ring A is A-2, then W is CH_2;

m is 0, 1 or 2;

D is carbon, R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH (provided that R^2 and R^{2a} are not both OH), and R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl, or

D is carbon or nitrogen, R^2 and R^3 are absent, and R^{2a} and R^{3a} together with the atoms to which they are attached form a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms;

Z is *-$NR^{4a}C(=O)$-, *-$ONHC(=O)$-, *-$NR^{4b}CH_2$- or *-$OC(=O)$-, wherein the asterisk indicates the point of attachment of Z to the carbon bearing R^3;

R^{4a} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl);

R^{4b} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl), dihydroxy(2-6C alkyl), (1-6C alkyl)C(O)-, (3-6C cycloalkyl)C(O)-, $Ar^1C(O)$-, $HOCH_2C(O)$-, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, $Ar^2(SO_2)$-, HO_2CCH_2- or (1-6C alkyl)NH(CO)-;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy;

Ar^2 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy; and

R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

2. The use of claim 1, wherein the subject has been previously administered a first ROS1 inhibitor.

3. The use of claim 1, wherein the subject has been previously administered a first ALK inhibitor.

4. The use of claim 1, wherein the subject has been previously administered a first TRK inhibitor.

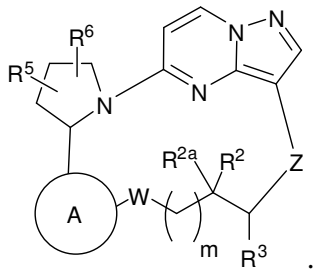
5. The use of any one of claims 1-4, wherein the one or more ROS1 inhibitor resistance mutations result in the production of a ROS1 kinase that has one or more amino acid substitutions at an amino acid position selected from the group consisting of: 1186, 1935, 1945, 1946, 1947, 1948, 1951, 1958, 1959, 1961, 1962, 1971, 1974, 1981, 1982, 1986, 1990, 1993, 1994, 2000, 2002, 2004, 2008, 2009, 2010, 2011, 2016, 2019, 2020, 2022, 2026, 2028, 2029, 2030, 2032, 2033, 2035, 2036, 2039, 2040, 2052, 2059, 2060, 2075, 2077, 2078, 2087, 2091, 2092, 2094, 2098, 2099, 2100, 2101, 2106, 2107, 2112, 2113, 2116, 2125, 2127, 2128, 2131, 2134, 2139, 2141, 2142, 2148, 2151, 2154, 2155, 2160, 2165, 2181, 2184, 2201, 2205, 2207, 2209, 2212, 2223, and 2224.

6. The use of any one of claims 1-5, wherein the one or more ROS1 inhibitor resistance mutations result in the production of a ROS1 kinase that has one or more amino acid substitutions selected from the group consisting of: S1186F, E1935G, L1945Q, T1946S, L1947R, L1947M, R1948S, L1951R, L1951V, E1958V, V1959E, E1961K, G1962E, G1971E, E1974K, T1981M, L1982F, L1982R, S1986Y, S1986F, E1990G, E1990L, E1993K, F1994L, L2000V, S2002N, F2004L, F2004I, F2004V, F2004C, N2008H, I2009L, L2010M, K2011N, C2016G, N2019D, N2019Y, E2020K, Q2022H, L2026M, L2028M, M2029K, E2030K, G2032R, D2033G, D2033N, L2035I, T2036I, T2036N, R2039G, R2039H, R2039M, R2039N, R2039S, K2040E, K2040Q, T2052S, L2059P, C2060G, F2075C, F2075I, F2075V, H2077P, R2078W, V2087I, D2091N, Y2092N, S2094N, V2098I, K2099N, I2100V, G2101A, A2106P, R2107T, N2112K, D2113N, D2113G, R2116T, R2116K, V2125G, V2125L, W2127G, M2128T, E2131D, E2131K, M2134I, T2139I, T2139S, Q2141H, S2142Y, G2148E, I2151N, I2154M,

L2155S, Q2160H, H2165D, E2181D, R2184T, E2201D, R2205I, T2207I, H2209P, Q2212H, Q2212P, and N2224K.

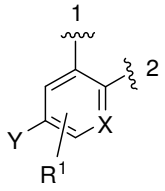
7. The use of any one of claims 1-6, wherein the one or more ROS1 inhibitor resistance mutations result in the production of a ROS1 kinase that has one or more amino acid substitutions selected from the group consisting of L2026M, G2032R, and D2033N.

8. The use of any one of claims 1-7, wherein the compound of Formula I is of the formula



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9. The use of any one of claims 1-8, wherein ring A is selected from ring A-1 having the structure:

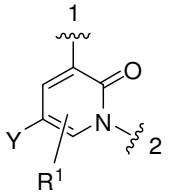


A-1 .

10. The use of any one of claims 1-9, wherein X is CH.

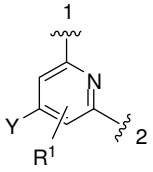
11. The use of any one of claims 1-9, wherein X is N.

12. The use of any one of claims 1-8, wherein ring A is selected from ring A-2 having the structure:



A-2 .

13. The use of any one of claims 1-8, wherein ring A is selected from ring A-3 having the structure:



A-3 .

14. The use of any one of claims 1-13, wherein Y is F.

15. The use of any one of claims 1-13, wherein Y is H.

16. The use of any one of claims 1-15, wherein R^1 is H.

17. The use of any one of claims 1-16, wherein W is O.

18. The use of any one of claims 1-16, wherein W is CH_2.

19. The use of any one of claims 1-18, wherein Z is *-$NR^{4a}C(=O)$-.

20. The use of claim 19, wherein R^{4a} is hydrogen.

21. The use of any one of claims 1-18, wherein Z is *-OC(=O)-.

22. The use of any one of claims 1-18, wherein Z is *-$NR^{4b}CH_2$-.

23. The use of claim 22, wherein R^{4b} is selected from (1-6C alkyl)C(O)-, (3-6C cycloalkyl)C(O)-, $Ar^1C(O)$-, and $HOCH_2C(O)$-.

24. The use of claim 23, wherein R^{4b} is (1-6C alkyl)C(O)-.

25. The use of any one of claims 1-24, wherein R^2 and R^{2a} are each hydrogen.

26. The use of any one of claims 1-24, wherein R^2 and R^{2a} are each fluoro.

27. The use of any one of claims 1-24, wherein R^2 is hydrogen and R^{2a} is OH.

28. The use of any one of claims 1-24, wherein R^2 is hydrogen and R^{2a} is methyl, or R^2 and R^{2a} are each methyl.

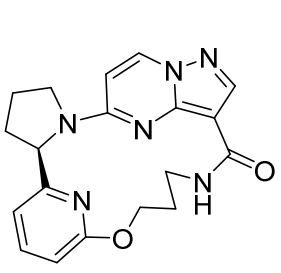
29. The use of any one of claims 1-28, wherein R^5 is hydrogen and R^6 is H, F, OH, methyl, ethyl, $HOCH_2$- or $HOCH_2CH_2$-.

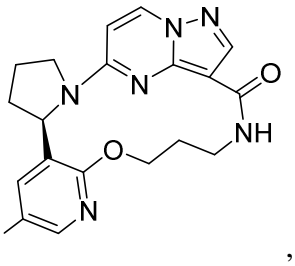
30. The use of any one of claims 1-29, wherein R^6 is H.

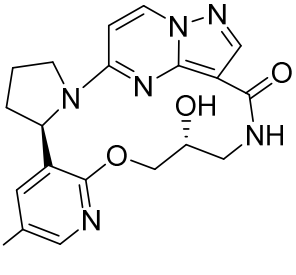
31. The use of any one of claims 1-30, wherein m is 0.

32. The use of any one of claims 1-30, wherein m is 1.

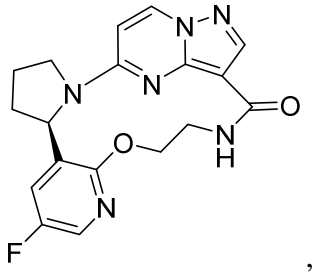
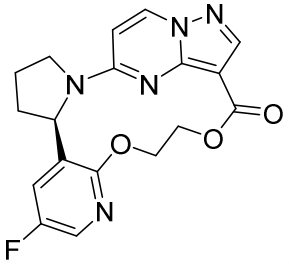
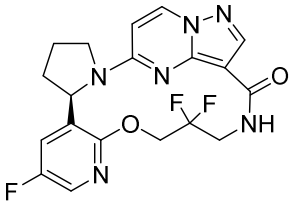
33. The use of any one of claims 1-8 selected from the group consisting of:

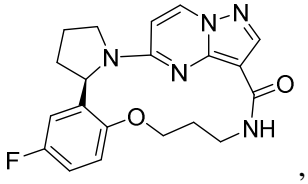
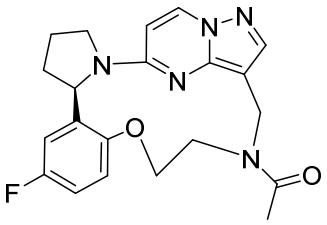
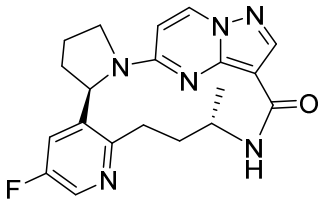


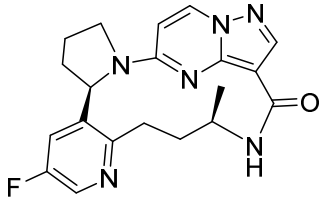
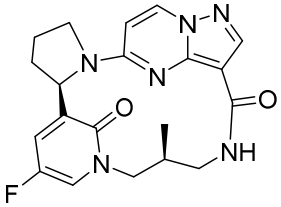
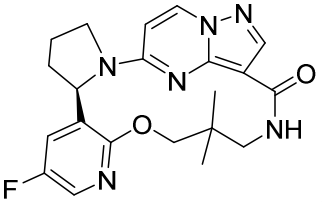
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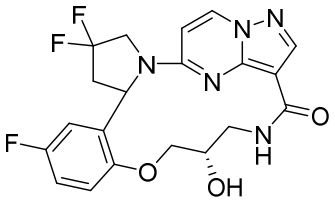
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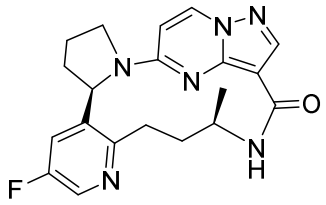

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and ;

or a pharmaceutically acceptable salt or solvate thereof.

34. Use of a compound in the manufacture of a medicament for treating a subject having a cancer, said subject having been previously administered entrectinib, and wherein the cancer has been determined to have one or more ROS1 inhibitor resistance mutations following the administration of entrectinib, wherein the compound has the chemical structure:


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