in the Flt3 kinase are observed in approximately one third of AML subjects (Lee HJ, *et al*., *Oncotarget 2018*; 9: 924-936).

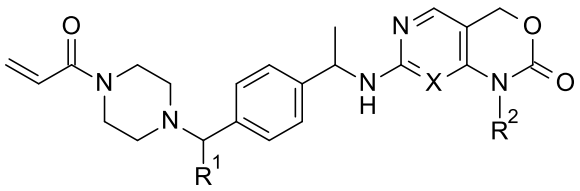
So called "secondary" IDH1 mutations, as defined herein, may contribute to relapse after treatment with a mutant IDH1 inhibitor. For example, to date, six post-ivosidenib treatment secondary IDH1 mutations have been reported: R119P, G131A, D279N, S280F, G289D or H315D (Choe S, *et al*., "Molecular mechanisms mediating relates following ivosidenib monotherapy in subjects with *IDH1*-mutant relapsed or refractory acute myeloid leukemia," *61st Am. Soc. Hematol. (ASH) Annual Meeting poster*, Dec. 7-10, 2019, Orlando, FL, USA; Choe, S., *et al*., Blood Adv. 2020; 4(9): 1894-1905).

Thus, there remains a need for alternative mutant IDH1-related cancer therapies, particularly for subjects in whom secondary IDH1 mutations occur after initial mutant IDH1 inhibitor therapy.

Certain mutant IDH1 inhibitors are disclosed in WO 2018/111707 A1, including a compound defined herein as "Compound A," which is a covalent inhibitor of mutant IDH1 that modifies a single cysteine (Cys269) in an allosteric binding pocket, rapidly inactivates the enzyme, and selectively inhibits 2-HG production, without affecting α-KG levels (WO 2018/111707 A1).

Summary

In one aspect of the present disclosure, there is provided a use of a compound of the Formula:



,

wherein:

R^1 is $-CH_2CH(CH_3)_2$, $-CH_2CH_3$, $-CH_2CH_2OCH_3$, or $-CH_2$-cyclopropyl;

R^2 is $-CH_3$ or $-CH_2CH_3$; and

X is N or CH,

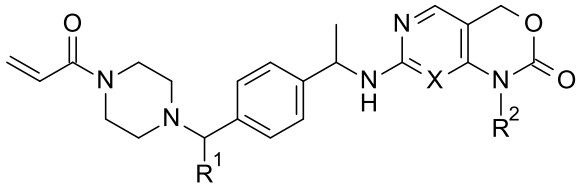
or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for treating cancer in a human subject having an IDH1 R132 mutation and one or more secondary IDH1 mutations.

Description

The present invention provides a method for treating cancer, comprising administering to a human cancer subject having an IDH1 R132 mutation and one or more secondary IDH1 mutations a therapeutically effective amount of a compound of the Formula I:

I



wherein:

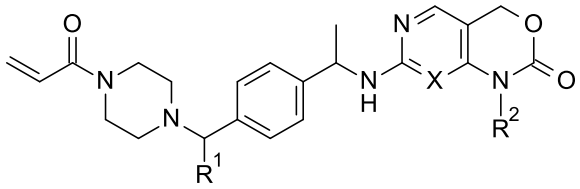
R^1 is $-CH_2CH(CH_3)_2$, $-CH_2CH_3$, $-CH_2CH_2OCH_3$, or $-CH_2$-cyclopropyl;

R^2 is $-CH_3$ or $-CH_2CH_3$; and

X is N or CH;

WE CLAIM:

1. Use of~~A method of treating cancer, comprising administering to a human cancer subject having an IDH1 R132 mutation and one or more secondary IDH1 mutations a therapeutically effective amount of~~ a compound of the ~~f~~Formula:



wherein:

R^1 is $-CH_2CH(CH_3)_2$, $-CH_2CH_3$, $-CH_2CH_2OCH_3$, or $-CH_2$-cyclopropyl;

R^2 is $-CH_3$ or $-CH_2CH_3$; and

X is N or CH,

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for treating cancer in a human subject having an IDH1 R132 mutation and one or more secondary IDH1 mutations.

2. The use according to~~method of~~ claim 1, wherein X is N, or a pharmaceutically acceptable salt thereof.

3. The use according to~~method of~~ claim 1 or 2, wherein ~~X is N,~~ R^1 is $-CH_2$-cyclopropyl, or a pharmaceutically acceptable salt thereof.

4. The use according to any one of claims 1-3, wherein~~and~~ R^2 is $-CH_2CH_3$, or a pharmaceutically acceptable salt thereof.

~~4~~5. The use according to~~method of~~ claim 1, wherein the compound is:

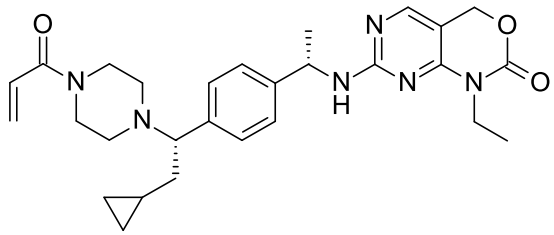
7-[[(1S)-1-[4-[(1R)-2-Cyclopropyl-1-(4-prop-2-enoylpiperazin-1-yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-one;

7-[[(1S)-1-[4-[(1S)-2-cyclopropyl-1-(4-prop-2-enoylpiperazin-1-yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-one; or

1-Ethyl-7-[[(1S)-1-[4-[1-(4-prop-2-enoylpiperazin-1-yl)propyl]phenyl]ethyl]amino]-4H-pyrimido[4,5-d][1,3]oxazin-2-one;

or a pharmaceutically acceptable salt thereof.

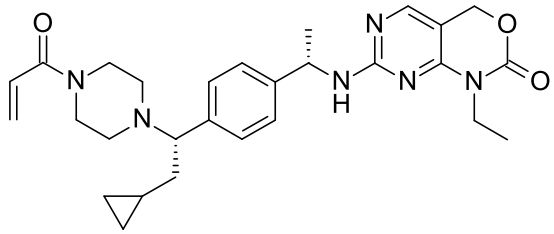
~~5~~6. The use according to~~method of~~ claim 1, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

~~6~~7. The use according to~~method of~~ claim ~~6~~5, wherein the compound is:



.

~~7~~8. The use according to any one~~method~~ of claims 1-7, wherein the one or more secondary IDH1 mutations is one or more of R119P, G131A, D279N, S280F, G289D or H315D.

9. The use according to any one of claims 1-8, wherein the cancer is a solid tumor cancer.

~~8~~10. The use according to~~method of~~ claim ~~9~~7, wherein the solid tumor cancer is cholangiocarcinoma, head and neck cancer, chondrosarcoma, hepatocellular carcinoma, melanoma, pancreatic cancer, astrocytoma, oligodendroglioma, glioma, glioblastoma, bladder carcinoma, colorectal cancer, lung cancer, or sinonasal undifferentiated carcinoma.

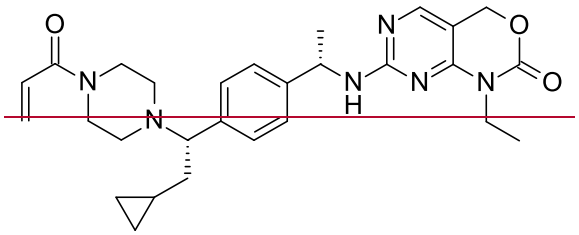
~~9~~11. The use according to~~method of~~ claim 10~~8~~, wherein the solid tumor cancer is cholangiocarcinoma.

~~10~~12. The use according to any one~~method~~ of claims 1-8, wherein the cancer is a hematologic malignancy.

~~11~~13. The use according to~~method of~~ claim 12~~10~~, wherein the hematologic malignancy is acute myeloid leukemia, myelodysplastic syndrome myeloproliferative neoplasm, angioimmunoblastic T-cell lymphoma, T-cell acute lymphoblastic leukemia, polycythemia vera, essential thrombocythemia, primary myelofibrosis, or chronic myelogenous leukemia.

~~12~~14. The use according to~~method of~~ claim 13~~11~~, wherein the hematologic malignancy is acute myeloid leukemia.

~~13. The method of claim 1, wherein the compound is~~



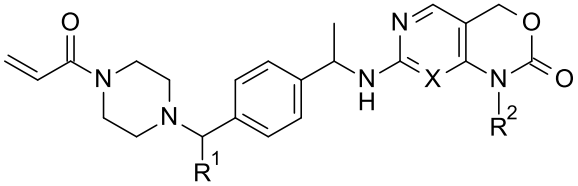
~~;~~

~~and the cancer is acute myeloid leukemia.~~

~~14. The method of claim 1, wherein the one or more secondary IDH1 mutations is one or more of R119P, G131A, D279N, S280F, G289D or H315D.~~

~~15. The method of claim 13, wherein the one or more secondary IDH1 mutations is one or more of R119P, G131A, D279N, S280F, G289D or H315D.~~

~~16~~15. The use according to~~method of~~ any one of claim~~s~~ 1-14, wherein the ~~human~~ subject had been treated with a mutant~~an~~ IDH1 inhibitor other than a compound of the formula:



~~;~~

wherein:

R^1 is $-CH_2CH(CH_3)_2$, $-CH_2CH_3$, $-CH_2CH_2OCH_3$, or $-CH_2$-cyclopropyl;

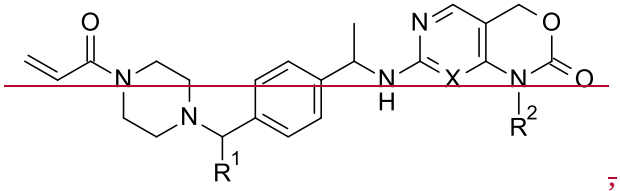
R^2 is $-CH_3$ or $-CH_2CH_3$; and

X is N or CH,

or a pharmaceutically acceptable salt thereof.

~~17~~16. The use according to~~method of~~ claim 15~~16~~, wherein the ~~human~~ subject had been treated with ivosidenib.

~~18. A compound of the Formula:~~



~~,~~

~~wherein:~~

~~R^1 is $-CH_2CH(CH_3)_2$, $-CH_2CH_3$, $-CH_2CH_2OCH_3$, or $-CH_2$-cyclopropyl;~~

~~R^2 is $-CH_3$ or $-CH_2CH_3$; and~~

~~X is N or CH,~~

~~or a pharmaceutically acceptable salt thereof;~~

~~for use in treating cancer in a human subject having an IDH1 R132 mutation and one or more secondary IDH1 mutations.~~

~~19. The compound for use according to claim 18, wherein X is N, or a pharmaceutically acceptable salt thereof.~~

~~20. The compound for use according to claim 18 or 19, wherein R^1 is $-CH_2$-cyclopropyl, or a pharmaceutically acceptable salt thereof.~~

~~21. The compound for use according to any one of claim 18-20, wherein R^2 is $-CH_2CH_3$, or a pharmaceutically acceptable salt thereof.~~

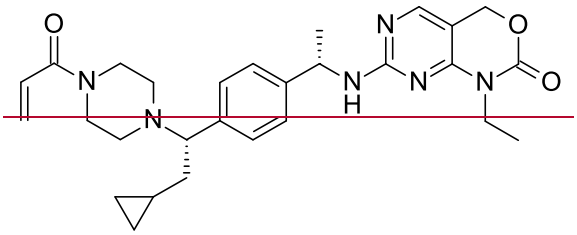
~~22. The compound for use according to claim 18, wherein the compound is:~~

~~7-[[(1S)-1-[4-[(1R)-2-Cyclopropyl-1-(4-prop-2-enoylpiperazin-1-yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-one;~~

7-[[(1S)-1-[4-[(1S)-2-cyclopropyl-1-(4-prop-2-enoylpiperazin-1-yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-one; or

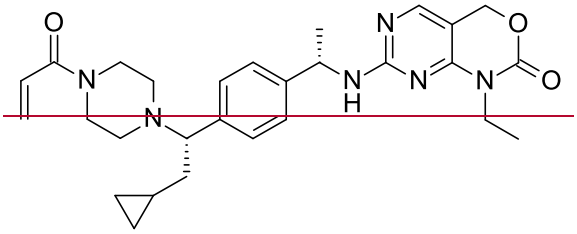
1-Ethyl-7-[[(1S)-1-[4-[1-(4-prop-2-enoylpiperazin-1-yl)propyl]phenyl]ethyl]amino]-4H-pyrimido[4,5-d][1,3]oxazin-2-one; or a pharmaceutically acceptable salt thereof.

23. The compound for use according to claim 18, wherein the compound is:



, or a pharmaceutically acceptable salt thereof.

24. The compound for use according to claim 23, wherein the compound is:



.

25. The compound for use according to any one of claim 18-24, wherein the one or more secondary IDH1 mutations is one or more of R119P, G131A, D279N, S280F, G289D or H315D.

26. The compound for use according to any one of claims 18-25, wherein the cancer is a solid tumor cancer.

27. The compound for use according to claim 26, wherein the solid tumor cancer is cholangiocarcinoma, head and neck cancer, chondrosarcoma, hepatocellular carcinoma, melanoma, pancreatic cancer, astrocytoma, oligodendroglioma, glioma, glioblastoma, bladder carcinoma, colorectal cancer, lung cancer, or sinonasal undifferentiated carcinoma.

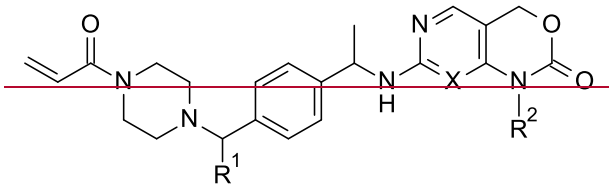
28. The compound for use according to claim 27, wherein the solid tumor cancer is cholangiocarcinoma.

29. The compound for use according to any one of claims 18-25, wherein the cancer is a hematologic malignancy.

30. The compound for use according to claim 29, wherein the hematologic malignancy is acute myeloid leukemia, myelodysplastic syndrome myeloproliferative neoplasm, angioimmunoblastic T-cell lymphoma, T-cell acute lymphoblastic leukemia, polycythemia vera, essential thrombocythemia, primary myelofibrosis, or chronic myelogenous leukemia.

31. The compound for use according to claim 30, wherein the hematologic malignancy is acute myeloid leukemia.

32. The compound for use according to any one of claims 18-31, wherein the subject had been treated with a mutant IDH1 inhibitor other than a compound of the formula:



wherein:

R^1 is $-CH_2CH(CH_3)_2$, $-CH_2CH_3$, $-CH_2CH_2OCH_3$, or $-CH_2$-cyclopropyl;

R^2 is $-CH_3$ or $-CH_2CH_3$; and

X is N or CH, or a pharmaceutically acceptable salt thereof.

33. The compound for use according to claim 32, wherein the subject had been treated with ivosidenib.