25% of adults with AML (about 45% of those who attain CR) can be expected to survive 3 or more years and may be cured.

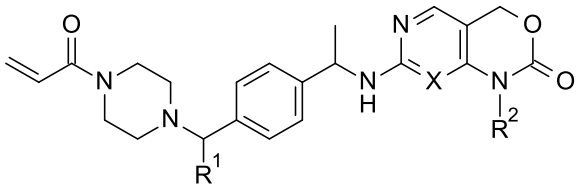
However, IDH1 resistance mutations are observed in 7–14% of AML subjects, and the associated high 2-HG level can result in an epigenetic hyper-methylation phenotype and a block in differentiation, resulting in leukemogenesis (Megias-Vericat J, *et al*., *Blood Lymph. Cancer: Targets and Therapy 2019*; 9: 19-3). In addition, mutations in the Flt3 kinase are observed in approximately one third of AML subjects (Lee HJ, *et al*., *Oncotarget 2018*; 9: 924-936).

Thus, there remains a need for alternative mutant IDH-related cancer therapies.

Certain mutant IDH1 and IDH2 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 the treatment of cancer, in a human subject having an IDH mutation, in combination with one or more of an antimetabolite agent, or a pharmaceutically acceptable salt thereof; a hypomethylating agent, or a pharmaceutically

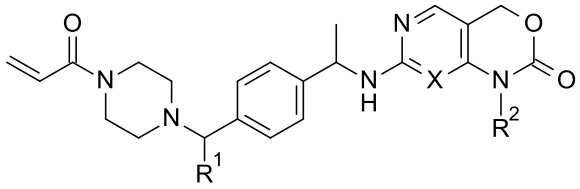
acceptable salt thereof; or a mutant Flt3 inhibitor, or a pharmaceutically acceptable salt thereof.

Description

The present invention provides a method of treating cancer, comprising administering to a human cancer subject having an IDH mutation a therapeutically effective amount of

(a) a first compound of 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;

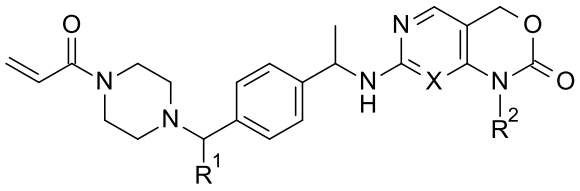
or a pharmaceutically acceptable salt thereof; and

(b) one or more of a second compound that is an antimetabolite agent, or a pharmaceutically acceptable salt thereof; a hypomethylating agent, or a pharmaceutically acceptable salt of thereof; and a mutant Flt3 inhibitor, or a pharmaceutically acceptable salt thereof.

WE CLAIM:

1. Use~~A method~~ of ~~treating cancer, comprising administering to a human cancer subject having an IDH mutation a therapeutically effective amount of~~

~~(a)~~ a ~~first~~ 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,~~; and~~

in the manufacture of a medicament for the treatment of cancer, in a human subject having an IDH mutation, in combination with

~~(b)~~ one or more of ~~a second compound that is~~ an antimetabolite agent, or a pharmaceutically acceptable salt thereof; a hypomethylating agent, or a pharmaceutically acceptable salt ~~of~~ thereof; or a mutant Flt3 inhibitor, or a pharmaceutically acceptable salt thereof.

2. The use~~method~~ of claim 1, wherein the IDH mutation is an IDH1 mutation.

3. The use~~method~~ of claim 2, wherein the IDH1 mutation is an IDH1 R132 mutation.

4. The use~~method~~ of claim 1, wherein the IDH mutation is an IDH2 mutation.

5. The use~~method~~ of claim 4, wherein the IDH2 mutation is an IDH2 R140 or IDH2 R172 mutation.

6. The use according to~~method of~~ claim 1, wherein ~~in the first compound,~~ X is N, or a pharmaceutically acceptable salt thereof.

7. The use according to~~method of~~ claim 1 or 6, wherein ~~X is N,~~ R^1 is $–CH_2$-cyclopropyl, or a pharmaceutically acceptable salt thereof.

8. The use according to any one of claims 1, 6 or 7, wherein~~and~~ R^2 is $-CH_2CH_3$, or a pharmaceutically acceptable salt thereof.

~~8~~9. The use according to~~method of~~ claim 1, wherein the ~~first~~ compound is:

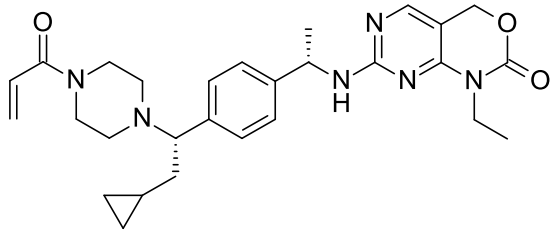
7-[[(1S)-1-[4-[(1R)-2-Cyclopropyl-1-(4-prop-2-enoylpiperazin-1-yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-one;

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 (Compound A); 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.

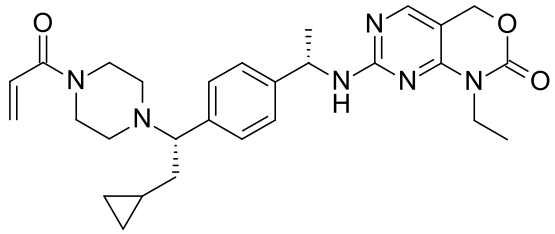
~~9~~10. The use according to~~method of~~ claim 1, wherein the ~~first~~ compound is ~~of the Formula~~:



,

or a pharmaceutically acceptable salt thereof.

~~10~~11. The use according to~~method of~~ claim 10~~9~~, wherein the ~~first~~ compound is:



.

~~11~~12. The use according to any one~~method~~ of claims~~claim~~ 1-11, wherein the cancer is a solid tumor cancer.

~~12~~13. The use according to~~method of~~ claim 12~~11~~, 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.

~~13~~14. The use according to~~method of~~ claim 13~~12~~, wherein the solid tumor cancer is cholangiocarcinoma.

~~14~~15. The use according to any one~~method~~ of claims~~claim~~ 1-11, wherein the cancer is a hematologic malignancy.

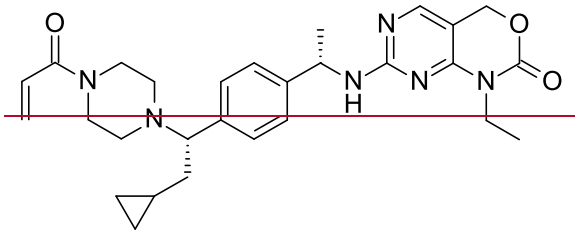
~~15~~16. The use according to~~method of~~ claim 15~~14~~, wherein the hematologic malignancy is acute myeloid leukemia, myelodysplastic syndrome myeloproliferative neoplasm, angioimmunoblastic T-cell lymphoma, T-cell acute lymphoblastic leukemia, ~~chronic myelogenous leukemia,~~ polycythemia vera, essential thrombocythemia, primary myelofibrosis, or chronic myelogenous leukemia.

~~16~~17. The use according to~~method of~~ claim 16~~15~~, wherein the hematologic malignancy is acute myeloid leukemia.

~~17~~18. The use according to any one~~method~~ of claims~~claim~~ 1-17, wherein the medicament is to be used in combination with~~second compound is~~ an antimetabolite agent~~, or a pharmaceutically acceptable salt thereof~~.

~~18~~19. The use according to~~method of~~ claim 18~~17~~, wherein the antimetabolite agent is cytarabine, or a pharmaceutically acceptable salt thereof.

~~19. The method of claim 1, wherein the first compound is~~



~~the cancer is acute myeloid leukemia, and the second compound agent is cytarabine.~~

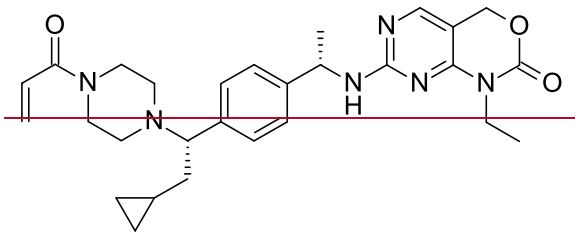
20. The use according to any one~~method~~ of claims 1-17, wherein the medicament is to be used in combination with~~second compound is~~ a hypomethylating agent~~, or a pharmaceutically acceptable salt thereof~~.

21. The use according to~~method of~~ claim 20, wherein the medicament is to be used in further combination with~~comprising administering to the human cancer subject a therapeutically effective amount of~~ a Bcl-2 inhibitor, or a pharmaceutically acceptable salt thereof.

22. The use according to~~method of~~ claim 20, wherein the hypomethylating agent is azacitidine, or a pharmaceutically acceptable salt thereof.

23. The use~~method~~ of claim 21, wherein the medicament is to be used in combination with ~~22, further comprising administering to the human cancer subject a therapeutically effective amount of~~ venetoclax, or a pharmaceutically acceptable salt thereof.

~~24. The method of claim 1, wherein the first compound is~~

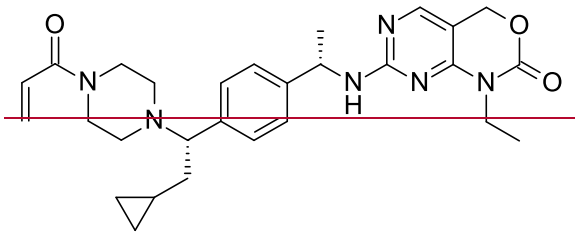


~~the cancer is acute myeloid leukemia, and the second compound is azacitidine.~~

~~25~~24. The use according to~~method of~~ claim ~~24~~22, wherein the medicament is to be used in combination with ~~further comprising administering to the human cancer subject a therapeutically effective amount of~~ venetoclax.

~~26~~25. The use according to~~method of~~ claim ~~24~~1, wherein the mutant Flt3 inhibitor is midostaurin, or a pharmaceutically acceptable salt thereof.

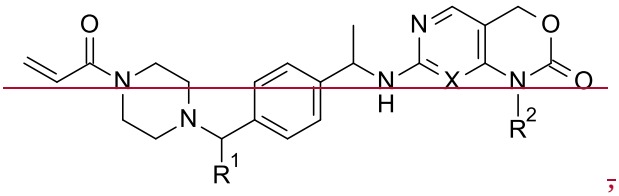
~~27. The method of claim 1, wherein the first compound is~~



~~,~~

~~the cancer is acute myeloid leukemia, and the mutant Flt3 inhibitor is midostaurin.~~

~~28. 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 combination with one or more of an antimetabolite agent, or a pharmaceutically acceptable salt thereof; a hypomethylating agent, or a pharmaceutically acceptable salt thereof; or a mutant Flt3 inhibitor, or a pharmaceutically acceptable salt thereof,~~

~~in the treatment of cancer in a human subject having an IDH mutation.~~

29. The compound for use of claim 28, wherein the IDH mutation is an IDH1 mutation.

30. The compound for use of claim 29, wherein the IDH1 mutation is an IDH1 R132 mutation.

31. The compound for use of claim 28, wherein the IDH mutation is an IDH2 mutation.

32. The compound for use of claim 31, wherein the IDH2 mutation is an IDH2 R140 or IDH2 R172 mutation.

33. The compound for use according to claim 28, wherein X is N, or a pharmaceutically acceptable salt thereof.

34. The compound for use according to claim 28 or 33, wherein R^1 is $-CH_2$-cyclopropyl, or a pharmaceutically acceptable salt thereof.

35. The compound for use according to any one of claims 28, 33 or34, wherein R^2 is $-CH_2CH_3$, or a pharmaceutically acceptable salt thereof.

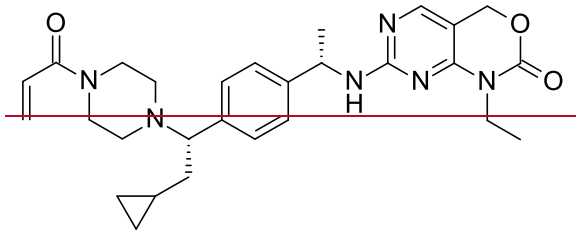
36. The compound for use according to claim 28, wherein the compound is:

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 (Compound A); or

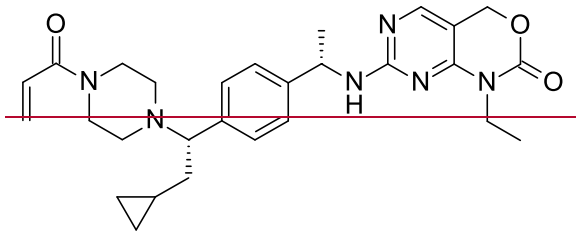
1-Ethyl-7-[[(1S)-1-[4-[1-(4-prop-2-enoylpiperazin-1-yl)propyl]phenyl]ethyl]amino]-4H-pyrimido[4,5-d][1,3]oxazin-2-one; or a pharmaceutically acceptable salt thereof.

37. The compound for use according to claim 28, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

38. The compound for use according to claim 37, wherein the compound is:



39. The compound for use according to any one of claims 28-38, wherein the cancer is a solid tumor cancer.

40. The compound for use according to claim 39, 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.

41. The compound for use according to claim 40, wherein the solid tumor cancer is cholangiocarcinoma.

42. The compound for use according to any one of claims 28-38, wherein the cancer is a hematologic malignancy.

43. The compound for use according to claim 42, 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.

~~44. The compound for use according to claim 43, wherein the hematologic malignancy is acute myeloid leukemia.~~

~~45. The compound for use according to any one of claims 28-44, for use in combination with an antimetabolite agent.~~

~~46. The compound for use according to claim 45, wherein the antimetabolite agent is cytarabine, or a pharmaceutically acceptable salt thereof.~~

~~47. The compound for use according to any one of claims 28-44, for use in combination with a hypomethylating agent.~~

~~48. The compound for use according to clam 47, in further combination with a Bcl-2 inhibitor, or a pharmaceutically acceptable salt thereof.~~

~~49. The compound for use according to claim 47, wherein the hypomethylating agent is azacitidine, or a pharmaceutically acceptable salt thereof.~~

~~50. The compound of use of claim 48, in combination with venetoclax, or a pharmaceutically acceptable salt thereof.~~

~~51. The compound for use according to claim 49, in combination with venetoclax.~~

~~52. The compound for use according to claim 28, wherein the mutant Flt3 inhibitor is midostaurin, or a pharmaceutically acceptable salt thereof.~~