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

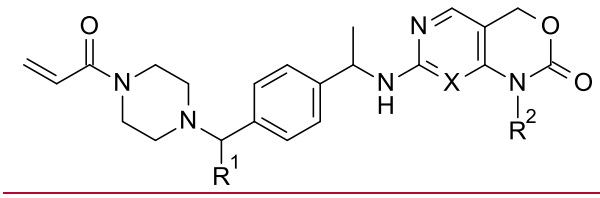
However, IDH1 resistance mutations are observed in 7–14% of AML subjects, and the associated high 2-HG level can result in an epigenetic hyper-methylation phenotype and a block in differentiation, resulting in leukemogenesis (Megias-Vericat J, *et al., Blood Lymph. Cancer: Targets and Therapy 2019*; 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;

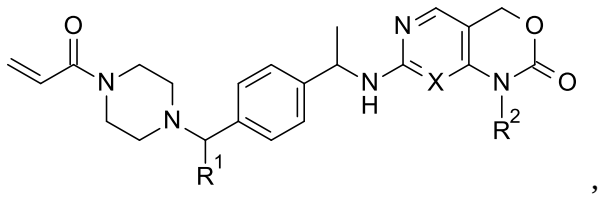
in the manufacture of a medicament for the treatment of cancer, in a human subject having an IDH mutation, in combination with a Bcl-2 inhibitor, or a pharmaceutically acceptable salt thereof.

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,

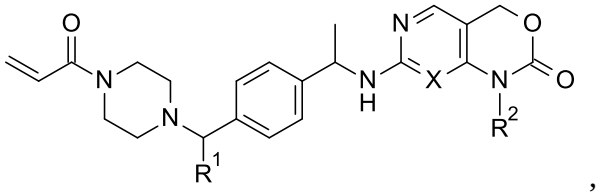
or a pharmaceutically acceptable salt thereof; and

(b) a second compound that is a Bcl-2 inhibitor, or a pharmaceutically acceptable salt thereof.

WE CLAIM:

1. Use of a~~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~~

~~(b) a~~ in the manufacture of a medicament for the treatment of cancer, in a human subject having an IDH mutation, in combination with~~second compound that is~~ a Bcl-2 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 ~~in the first compound X is N,~~ R^1 is –CH_2-cyclopropyl, or a pharmaceutically acceptable salt thereof.

8. The use according to any one of claims 1-7, 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:

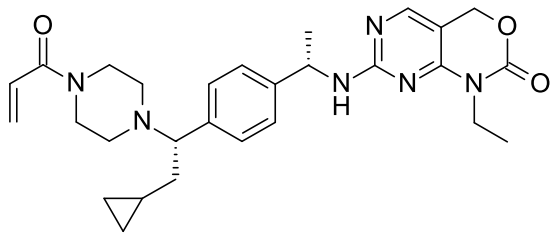
7-[[(1S)-1-[4-[(1R)-2-cyclopropyl-1-(4-prop-2-enoylpiperazin-1-yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-one;

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; 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.

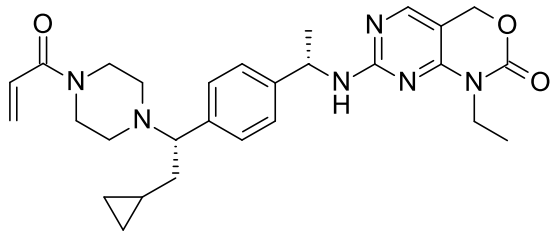
~~9.~~10. The use according to ~~method of~~ claim 1, wherein the ~~first~~ compound is ~~of the Formula~~:



,

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 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, ~~sinonasal undifferentiated carcinoma,~~ or lung cancer.

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

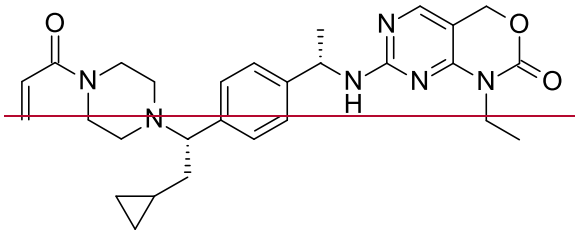
~~14.~~15. The use according to any one~~method~~ of claims 1-11, wherein the cancer is a hematologic malignancy.

~~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, polycythemia vera, essential thrombocythemia, ~~chronic myelogenous leukemia,~~ or primary myelofibrosis.

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

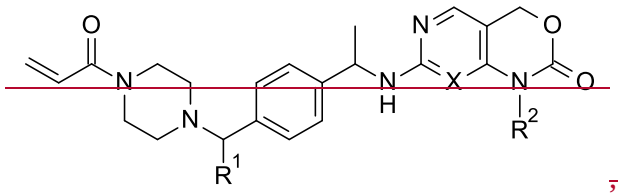
~~17. The method of claim 1, wherein the second compound is venetoclax, obatoclax, or navitoclax, or a pharmaceutically acceptable salt of any one of them.~~

~~18. The method of claim 1, wherein the first compound is~~



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

~~19. 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 a Bcl-2 inhibitor, or a pharmaceutically acceptable salt thereof, in the treatment of cancer in a human subject having an IDH mutation.

20. The compound for use of claim 20, wherein the IDH mutation is an IDH1 mutation.

21. The compound for use of claim 20, wherein the IDH1 mutation is an IDH1 R132 mutation.

22. The compound for use of claim 19, wherein the IDH mutation is an IDH2 mutation.

23. The compound for use of claim 22, wherein the IDH2 mutation is an IDH2 R140 or IDH2 R172 mutation.

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

25. The compound for use according to claim 19 or 24, wherein R^1 is $-CH_2$-cyclopropyl, or a pharmaceutically acceptable salt thereof.

26. The compound for use according to any one of claims 19-25, wherein R^2 is $-CH_2CH_3$, or a pharmaceutically acceptable salt thereof.

27. The compound for use according to claim 19, wherein the compound is:

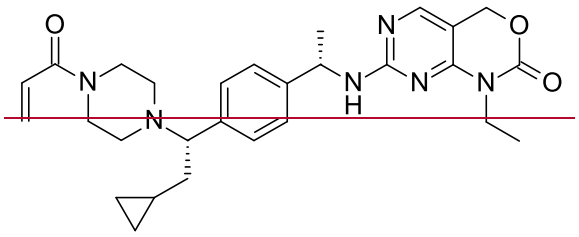
7-[[(1S)-1-[4-[(1R)-2-cyclopropyl-1-(4-prop-2-enoylpiperazin-1-yl)ethyl]phenyl]ethyl]amino]-1-ethyl-4H-pyrimido[4,5-d][1,3]oxazin-2-one;

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.

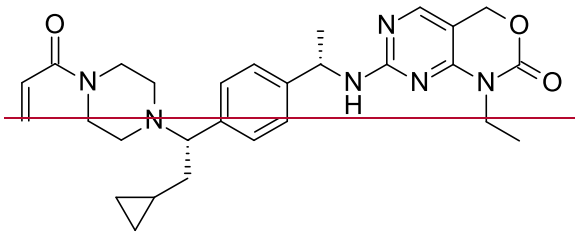
28. The compound for use according to claim 19, wherein the compound is:



;

or a pharmaceutically acceptable salt thereof.

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



;

30. The compound for use according to any one of claims 19-29, wherein the cancer is a solid tumor cancer.

31. The compound for use according to claim 30, 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, or lung cancer.

32. The compound for use according to claim 31, wherein the solid tumor cancer is cholangiocarcinoma.

33. The compound for use according to any one of claims 19-29, wherein the cancer is a hematologic malignancy.

~~34. The compound for use according to claim 33, 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, or primary myelofibrosis.~~

~~35. The compound for use according to claim 34, wherein the hematologic malignancy is acute myeloid leukemia.~~

~~36.~~18. The ~~compound for~~ use according to any one of claims 1-17~~19-35~~, wherein the Bcl-2 inhibitor is selected from the group consisting of venetoclax, obatoclax, navitoclax, or a pharmaceutically acceptable salt thereof.