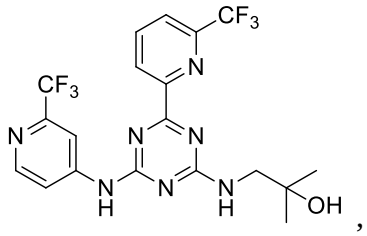
Claims

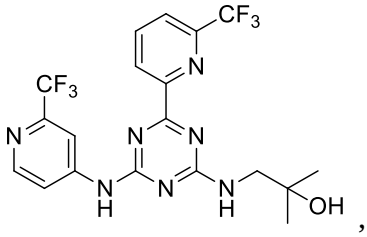
1. ~~A method of treating acute myelogenous leukemia (AML), comprising administering to a subject~~ Use of a therapeutically effective amount of ~~amutant of~~ a mutant isocitrate dehydrogenase 2 (IDH2) inhibitor in the manufacture of a medicament for treating acute myelogenous leukemia (AML) in the subject, wherein the mutant IDH2 inhibitor is to be administered to the subject with~~and~~ a combination of Cytarabine and Daunorubicin as an induction therapy, ~~further comprising administering~~ and further with Cytarabine as a consolidation therapy, wherein the mutant IDH2 inhibitor is 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol, having the following formula:



,

or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, isotopologue, prodrug, metabolite, or a polymorph thereof (COMPOUND 1), and wherein the AML is characterized by the presence of a mutant allele of IDH2.

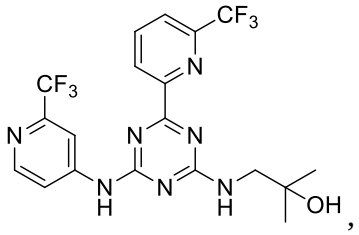
2. ~~A method of treating AML, comprising administering to a subject~~ Use of a therapeutically effective amount of a mutant IDH2 inhibitor in the manufacture of a medicament for treating AML, comprising administering to a subject, wherein the mutant IDH2 inhibitor is to be administered to the subject with ~~and~~ a combination of Cytarabine and Idarubicin as an induction therapy~~, further comprising administering~~ and further with Cytarabine as a consolidation therapy, wherein the mutant IDH2 inhibitor is 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol having the following formula:



,

or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, isotopologue, prodrug, metabolite, or a polymorph thereof (COMPOUND 1), and wherein the AML is characterized by the presence of a mutant allele of IDH2.

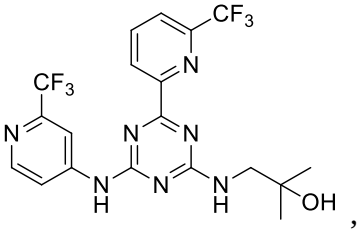
3. ~~A method of treating AML, comprising administering to a subject~~ Use of a therapeutically effective amount of a mutant IDH2 inhibitor in the manufacture of a medicament for treating AML in a subject, wherein the mutant IDH2 inhibitor is to be administered to the subject with~~and~~ a combination of Cytarabine and Daunorubicin as an induction therapy, and further ~~comprising administering~~ with a combination of Mitoxantrone and Etoposide as a consolidation therapy, wherein the mutant IDH2 inhibitor is 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol having the following formula:



or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, isotopologue, prodrug, metabolite, or a polymorph thereof (COMPOUND 1), and wherein the AML is characterized by the presence of a mutant allele of IDH2.

4. ~~A method of treating AML, comprising administering to a subject~~ Use of a therapeutically effective amount of a mutant IDH2 inhibitor in the manufacture of a medicament for treating AML in a subject, wherein the mutant IDH2 inhibitor is to be administered to the subject with ~~and~~ a combination of Cytarabine and Idarubicin as an induction therapy, and further ~~further comprising administering~~with a combination of Mitoxantrone and Etoposide as a consolidation therapy, wherein the mutant IDH2 inhibitor is

2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol having the following formula:



or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, isotopologue, prodrug, metabolite, or a polymorph thereof (COMPOUND 1), and wherein the AML is characterized by the presence of a mutant allele of IDH2.

5. The ~~method~~use of any one of claim 1 to 4, wherein the dose of Cytarabine used as an induction therapy is between ~~about~~ 100 mg/m^2 and ~~about~~ 500 mg/m^2.

6. The ~~method~~use of claim 5, wherein the dose of Cytarabine is between ~~about~~ 150 mg/m^2 and ~~about~~ 300 mg/m^2.

7. The ~~method~~use of claim 6, wherein the dose of Cytarabine is about 200 mg/m^2.

8. The ~~method~~use of claim 1 or 2, therein the dose of Cytarabine used as a consolidation therapy is between ~~about~~ 1 g/m^2 and ~~about~~ 10 g/m^2.

9. The ~~method~~use of claim 8, wherein the dose of Cytarabine is between ~~about~~ 1 g/m^2 and ~~about~~ 5 g/m^2.

10. The ~~metod~~use of claim 9, wherein the dose of Cytarabine is 1 g/m^2, or 1,5 g/m^2, or 2 g/m^2, or 3 g/m^2.

11. The ~~method~~use of claim 1 or 3, wherein the dose of Daunorubicin is between ~~about~~ 10 mg/m^2 and ~~about~~ 300 mg/m^2.

12. The ~~method~~use of claim 11, wherein the dose of Daunorubicin is between ~~about~~ 30 mg/m^2 and ~~about~~ 150 mg/m^2.

13. The ~~method~~use of claim 12, wherein the dose of Daunorubicin is ~~about~~ 60 mg/m^2.

14. The ~~method~~use of claim 2 or 4, wherein the dose of Idarubicin is between ~~about~~ 1 mg/m^2 and ~~about~~ 25 mg/m^2.

15. The ~~method~~use of claim 14, wherein the dose of Idarubicin is between ~~about~~ 3 mg/m^2 and ~~about~~ 15 mg/m^2.

16. The ~~method~~use of claim 15, wherein the dose of Idarubicin is about 12 mg/m^2.

17. The ~~method~~use of claim 3 or 4, wherein the dose of Mitoxantrone is between ~~about~~ 1 mg/m^2 and ~~about~~ 25 mg/m^2.

18. The ~~method~~use of claim 17, wherein the dose of Mitoxantrone is between ~~about~~ 5 mg/m^2 and ~~about~~ 20 mg/m^2.

19. The ~~method~~use of claim 18, wherein the dose of Mitoxantrone is about 10 mg/m^2.

20. The ~~method~~use of claim 3 or 4, wherein the dose of Etoposide is between ~~about~~ 50 mg/m^2 and ~~about~~ 500 mg/m^2.

21. The ~~method~~use of claim 20, wherein the dose of Etoposide is between ~~about~~ 75 mg/m^2 and ~~about~~ 250 mg/m^2.

22. The ~~method~~use of claim 21, wherein the dose of Etoposide is about 100 mg/m^2.

23. ~~A method of treating AML characterized by the presence of a mutant allele of IDH2, comprising administering to a subject~~ Use of a therapeutically effective amount of 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (COMPOUND 1) in the manufacture of a medicament for treating AML characterized by the presence of a mutant allele of IDH2 in a subject, wherein the medicament is to be administered ~~and~~with a combination of Cytarabine and Daunorubicin, wherein Cytarabine is to be administered for 7 days and Daunorubicin is to be administered for 3 days.

24. ~~A method of treating AML characterized by the presence of a mutant allele of IDH2, comprising administering to a subject~~ Use of a therapeutically effective amount of 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (COMPOUND 1) in the manufacture of a medicament for treating AML characterized by the presence of a mutant allele of IDH2 in a subject, ~~and~~ wherein the medicament is to be administered with a combination of Cytarabine and Idarubicin, wherein Cytarabine is to be administered for 7 days and Idarubicin is to be administered for 3 days.

25. ~~A method~~The use of any one of claims 1-24, wherein the dose of COMPOUND 1 is between ~~about~~ 50 mg/m^2 and ~~about~~ 1000 mg/m^2.

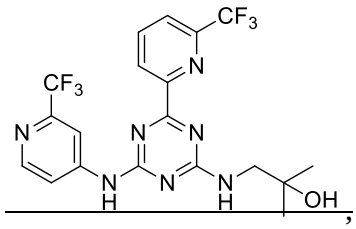
26. The ~~method~~use of claim 25, wherein the dose of COMPOUND 1 is between ~~about~~ 150 mg/m^2 and ~~about~~ 300 mg/m^2.

27. The ~~method~~use of claim 26, wherein the dose of COMPOUND 1 is about 200 mg/m^2.

28. The ~~method~~use of any one of claims 1 to 22, wherein AML is selected from newly diagnosed AML, untreated AML, AML arising from myelodysplastic syndrome, AML arising from antecedent hematologic disorder and AML arising after exposure to genotoxic injury.

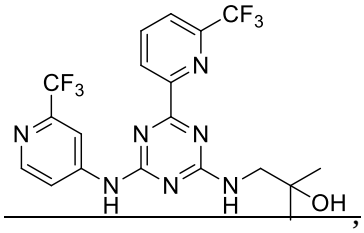
~~29. A mutant isocitrate dehydrogenase 2 (IDH2) inhibitor for use in a method for treating acute myelogenous leukemia (AML), comprising administering to a subject a therapeutically effective amount of said mutant IDH2 inhibitor and a combination of Cytarabine and Daunorubicin or a comnination of Cytarabine and Idarubicin as an induction therapy, further comprising administering Cytarabine as a consolidation therapy, wherein the mutant IDH2 inhibitor is 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-~~

~~(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol, having the following formula:~~



~~or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, isotopologue, prodrug, metabolite, or a polymorph thereof (COMPOUND 1), and wherein the AML is characterized by the presence of a mutant allele of IDH2.~~

~~30. A mutant IDH2 inhibitor for use in a method for treating AML, comprising administering to a subject a therapeutically effective amount of said mutant IDH2 inhibitor and a combination of Cytarabine and Daunorubicin or a combination of Cytarabine and Idarubicin as an induction therapy, further comprising administering a combination of Mitoxantrone and Etoposide as a consolidation therapy, wherein the mutant IDH2 inhibitor is 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol having the following formula:~~



~~or a pharmaceutically acceptable salt, solvate, tautomer, stereoisomer, isotopologue, prodrug, metabolite, or a polymorph thereof (COMPOUND 1), and wherein the AML is characterized by the presence of a mutant allele of IDH2.~~

~~31. The mutant IDH2 inhibitor for use claim 29 or 30, wherein the dose of Cytarabine used as an induction therapy is between about 100 mg/m^2 and about 500 mg/m^2; preferably between about 150 mg/m^2 and about 300 mg/m^2; more preferably about 200 mg/m^2.~~

~~32. The mutant IDH2 inhibitor for use claim 29, wherein the dose of Cytarabine used as a consolidation therapy is between about 1 g/m^2 and about 10 g/m^2; preferably between about 1 g/m^2 and about 5 g/m^2; more preferably 1 g/m^2, or 1.5 g/m^2, or 2 g/m^2, or 3 g/m^2.~~

33. The mutant IDH2 inhibitor for use claim 29 or 30, wherein the dose of Daunorubicin is between about 10 mg/m^2 and about 300 mg/m^2; preferably between about 30 mg/m^2 and about 150 mg/m^2; more preferably about 60 mg/m^2.

34. The mutant IDH2 inhibitor for use claim 29 or 30, wherein the dose of Idarubicin is between about 1 mg/m^2 and about 25 mg/m^2; preferably between about 3 mg/m^2 and about 15 mg/m^2; more preferably about 12 mg/m^2.

35. The mutant IDH2 inhibitor for use claim 29 or 30, wherein the dose of Mitoxantrone is between about 1 mg/m^2 and about 25 mg/m^2; preferably between about 5 mg/m^2 and about 20 mg/m^2; more preferably about 10 mg/m^2.

36. The mutant IDH2 inhibitor for use claim 29 or 30, wherein the dose of Etoposide is between about 50 mg/m2 and about 500 mg/m^2; preferably between about 75 mg/m^2 and about 250 mg/m^2; more preferably about 100 mg/m^2.

37. A compound for use in method for treating AML characterized by the presence of a mutant allele of IDH2, wherein the compound is 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (COMPOUND 1), and wherein the method comprises administering to a subject a therapeutically effective amount of COMPOUND 1 and a combination of Cytarabine and Daunorubicin, or a combination of Cytarabine and Idarubicin, wherein Cytarabine is administered for 7 days and Daunorubicin or Idarubicin is administered for 3 days.

39. The mutant IDH2 inhibitor for use of any one of claims 29 to 36, or the compound for use of claim 37, dose of COMPOUND 1 is between about 50 mg/m2 and about 1000 mg/m^2, preferably between about 150 mg/m^2 and about 300 mg/m^2; more preferably about 200 mg/m^2.

40. The mutant IDH2 inhibitor for use of any one of claims 29 to 36, wherein AML is selected from newly diagnosed AML, untreated AML, AML arising from myelodysplastic syndrome, AML arising from antecedent hematologic disorder and AML arising after exposure to genotoxic injury.