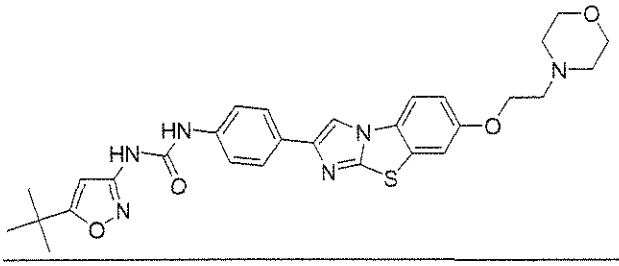
[0006] There is a continuing need for developing therapy for proliferative diseases, including cancer.

SUMMARY ~~OF THE DISCLOSURE~~

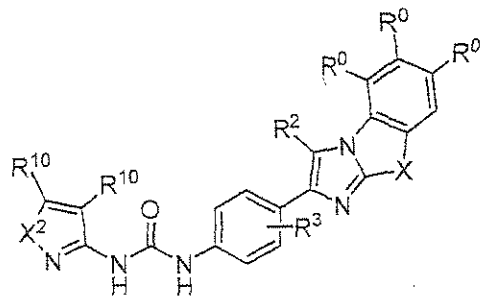
[0007] In one embodiment, ~~provided~~the present invention refers to the use of a compound of formula A



A

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of leukemia in a mammal, wherein said medicament is to be administered to the mammal having or suspected to have leukemia to deliver the compound of formula A or a pharmaceutically acceptable salt thereof in a dose of about 27 to 1000 mg per day, in combination with a second agent selected from azacitidine, cytarabine, etoposide, daunorubicin, cladribine, wherein azacitidine is administered in a dose of 50-100 mg/m^2/day, cytarabine is administered intravenously or subcutaneously in a dose of 5 mg/m^2/day-3 g/m^2/day, etoposide is administered in a dose of 10-150 mg/m^2/day, and daunorubicin is administered in a dose of 10-60 mg/m^2/day. Also disclosed herein is a method of treating a proliferative disease comprising co-administering to a patient in need thereof a therapeutically effective amount of (a) a nucleoside analog, an anthracycline, a topoisomerase inhibitor, or a combination thereof; and (b) a compound of structural formula (I) or a salt, solvate, hydrate, ester and/or prodrug thereof. In one ~~embodiment~~example, the nucleoside analog is a neoplastic cell antimetabolite. In one ~~embodiment~~example, provided herein is a method of treating a hematological neoplastic disease comprising co-administering to a patient in need thereof a therapeutically effective amount of (a) a nucleoside analog, wherein the nucleoside analog is a neoplastic cell antimetabolite; an anthracycline; a topoisomerase inhibitor; or a combination thereof; and (b) a compound of structural formula (I) or a salt, solvate, hydrate, ester and/or prodrug thereof.

[0008] The compound of formula (I) is:

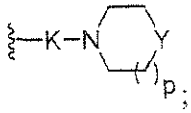


(I);

wherein

X^2 is -O- or -S-;

X is -S-, -N(R^5)- or -O-;

two of the three R^0 are hydrogen; and the other R^0 is halo, hydroxy, optionally substituted alkyl, optionally substituted alkoxy, or ;

Y is -O-, -S-, -N(R^{14})- or -C(H)R^{15}-;

K is -O$(CH_2)_q$-, -C(O), -C(O)NH$(CH_2)_q$-, -$(CH_2)_q$O-, or -$(CH_2)_q$O$(CH_2)_q$-;

p is an integer from 0 to 2;

each q is independently an integer from 1 to 4;

R^2 is hydrogen, halo, nitro, cyano, optionally substituted alkyl, -OR^{12}, -SR^{12}, -N$(R^{12})_2$, -S(O)$_t$$R^{13}$, -C(O)$R^{12}$, -C(O)O$R^{12}$, -C(O)N$(R^{12})_2$, -C(O)S$R^{12}$, or -N($R^{12}$)S(O)$_t$$R^{13}$;

R^3 is hydrogen, halo, nitro, cyano, optionally substituted alkyl, -OR^{12}, - SR^{12}, -N$(R^{12})_2$,

$-S(O)_tR^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-C(O)N(R^{12})_2$, $-C(O)SR^{12}$, or $-N(R^{12})S(O)_tR^{13}$;

R^5 is hydrogen or optionally substituted alkyl;

each R^{10} is independently selected from hydrogen, halo, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted aryl;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

R^{13} is optionally substituted alkyl;

R^{14} is hydrogen, optionally substituted alkyl, $-C(O)OR^{12}$, $-C(O)SR^{12}$, $-C(O)NR^{12}$ or $-S(O)_tR^{13}$;

R^{15} is hydrogen or optionally substituted alkyl; and

t is 1 or 2.

[0009] In another ~~embodiment~~example, provided herein is a combination package comprising (a) at least one individual dose of a nucleoside analog, an anthracycline, a topoisomerase inhibitor, or a combination thereof; and (b) at least one individual dose of a compound of structural formula (I) as described above, or a salt, solvate, ester and/or prodrug thereof.

[0010] In another ~~embodiment~~example, provided herein is a combination package comprising (a) at least one individual dose of a nucleoside analog, wherein the nucleoside analog is a neoplastic cell antimetabolite; and (b) at least one individual dose of a compound of structural formula (I) as described above, or a salt, solvate, ester and/or prodrug thereof.

[0011] In another ~~embodiment~~example, provided herein is a combination package comprising (a) at least one individual dose of an anthracycline, a topoisomerase inhibitor or a combination thereof; and (b) at least one individual dose of a compound of structural formula (I) as described above, or a salt, solvate, ester and/or prodrug thereof.

[0012] In another ~~embodiment~~example, provided herein is a pharmaceutical composition comprising a therapeutically effective amount of (a) a nucleoside analog, an anthracycline, a topoisomerase inhibitor, or a combination thereof; and (b) a compound of structural formula (I) as described above, or a salt, solvate, ester and/or prodrug thereof.

[0013] In another ~~embodiment~~example, provided herein is a pharmaceutical composition comprising a therapeutically effective amount of (a) a nucleoside analog, wherein the nucleoside analog is a neoplastic cell antimetabolite; and (b) a compound of structural

formula (I) as described above, or a salt, solvate, ester and/or prodrug thereof.

[0014] In another ~~embodiment~~example, provided herein is a pharmaceutical composition comprising a therapeutically effective amount of (a) an anthracycline, a topoisomerase inhibitor, or a combination thereof; and (b) a compound of structural formula (I) as described above, or a salt, solvate, ester and/or prodrug thereof.

[0015] In certain ~~embodiments~~examples, provided herein are methods of treating, preventing or managing a proliferative disease. In certain ~~embodiments~~examples, the methods comprise administering to a subject a therapeutically or prophylactically effective amount of AC220, or a pharmaceutically acceptable prodrug, salt, solvate or hydrate thereof in combination with a second anticancer agent. In one ~~embodiment~~example, the second agent is a nucleoside analog, an anthracycline, a topoisomerase inhibitor, or combinations thereof. In one ~~embodiment~~example, the second agent is a nucleoside analog, wherein the nucleoside analog is a neoplastic cell antimetabolite. In one ~~embodiment~~example, the second agent is an anthracycline, a topoisomerase inhibitor or a combination thereof. In one ~~embodiment~~example, the topoisomerase inhibitor is selected from amsacrine, etoposide, etoposide phosphate, and teniposide. In one ~~embodiment~~example, the topoisomerase inhibitor is etoposide. In one ~~embodiment~~example, the anthracycline is selected from daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, amrubicin and valrubicin. In one ~~embodiment~~example, the anthracycline is daunorubicin. In one embodiment, the second agent is cytarabine, daunorubicin, etoposide or a combination thereof.

[0016] In one ~~embodiment~~example, the methods provided include the administration of AC220, or a pharmaceutically acceptable salt, prodrug, solvate or hydrate thereof in combination with cytarabine administered intrathecally at a dose from about 5 mg/m^2 to about 75 mg/m^2 once per day or once every four days, or about 30 mg/m^2 every four days, in another embodiment, intravenously cytarabine administered from about 5 mg/m^2/day to about 3 g/m^2/day or about 100 mg/m^2/day to about 200 mg/m^2/day. In one ~~embodiment~~example, the administration of AC220 occurs once a day for one week, two weeks, three weeks, four weeks or five weeks. The administration of cytarabine can be made by intravenous infusion, intravenous push, bolus injection or subcutaneous injection. In one ~~embodiment~~example, the administration of cytarabine occurs for 5 days. In one ~~embodiment~~example, the administration of cytarabine occurs for 7 days. In one ~~embodiment~~example, the administration of cytarabine occurs on days 1 to 5. In one ~~embodiment~~example, the administration of cytarabine occurs on days 1 to 7.

[0017] In one ~~embodiment~~example, the methods provided include the administration of AC220, or a pharmaceutically acceptable salt, prodrug, solvate or hydrate thereof in

combination with about 10 mg/m^2 to about 150 mg/m^2 etoposide. For example, one embodiment includes administration of etoposide at a dose of about 30 to about 120 mg/m^2. One ~~embodiment~~example includes administration of etoposide at a dose of about 35, 50, or 100 mg/m^2. The administration of etoposide can be made by intravenous infusion, intravenous push, bolus injection or subcutaneous injection. In one ~~embodiment~~example, the administration of etoposide is once a day for 5 days, while the administration of AC220 occurs once a day for one week, two weeks, three weeks, four weeks or five weeks. In one ~~embodiment~~example, the administration of etoposide is once a day on days 1, 3 and 5, while the administration of AC220 occurs once a day for one week, two weeks, three weeks, four weeks or five weeks.

[0018] In one ~~embodiment~~example, the methods provided include the administration of AC220, or a pharmaceutically acceptable salt, prodrug, solvate or hydrate thereof in combination with about 10 mg/m^2 to about 50 mg/m^2 daunorubicin. For example, one embodiment includes administration of daunorubicin at a dose of about 20 to about 50 mg/m^2. One ~~embodiment~~example includes administration of daunorubicin at a dose of about 25, 30, or 45 mg/m^2. The administration of daunorubicin can be made by intravenous infusion, intravenous push, bolus injection or subcutaneous injection. In one ~~embodiment~~example, the administration of daunorubicin is once a day on days 1, 2 and 3, while the administration of AC220 occurs once a day for one week, two weeks, three weeks, four weeks or five weeks. In one ~~embodiment~~example, the administration of daunorubicin is once a day on days 1, and 2, while the administration of AC220 occurs once a day for one week, two weeks, three weeks, four weeks or five weeks. In one ~~embodiment~~example, the administration of daunorubicin is once a day on day 1, while the administration of AC220 occurs once a day for one week, two weeks, three weeks, four weeks or five weeks.

[0019] In one ~~embodiment~~example, the methods provided include the administration of AC220, or a pharmaceutically acceptable salt, prodrug, solvate or hydrate thereof in combination with cytarabine and daunorubicin.

[0020] In certain ~~embodiments~~examples, the administration of AC220 and the second agents selected from a nucleoside analog, an anthracycline, a topoisomerase inhibitor and combinations thereof as set forth above in a week is considered a weekly cycle. The methods contemplate performing one weekly cycle, optionally waiting a period of one day to several days or one week to weeks where neither the second agent nor AC220 is given, then repeating a weekly cycle. The methods also contemplate repeating the weekly cycles continuously, for example, for 2 to 5 weeks. In addition, the methods contemplate repeating

the cycle for several cycles, waiting a period of a day to several days or one week to several weeks where neither AC220 nor the second agent is given then repeating one or more cycles. Finally, the methods provide administration of a AC220/second agent weekly cycle followed by a cycle of only the second agent or AC220.

[0021] Also ~~provided~~described herein is a method of inhibiting the growth of a cell, comprising contacting the cell with an effective amount of AC220, or a pharmaceutically acceptable prodrug, salt, solvate or hydrate thereof in combination with a second anticancer agent selected from an anthracycline, a topoisomerase inhibitor and combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] FIG. 1 is a graph showing the efficacy of AC220 plus cytarabine (overlapping administration) in controlling tumor growth as compared to control, AC220 alone, and cytarabine alone.

[0023] FIG. 2 is a graph showing the efficacy of AC220 plus cytarabine (sequential administration) in controlling tumor growth as compared to control, AC220 alone, and cytarabine alone.

[0024] FIG. 3 is a graph showing the efficacy of AC220 plus Azacitidine (overlapping administration) in controlling tumor growth as compared to control, AC220 alone, and Azacitidine alone.

[0025] FIG. 4 is a graph showing the efficacy of AC220 plus Azacitidine (sequential administration) in controlling tumor growth as compared to control, AC220 alone, and Azacitidine alone.

[0026] FIG. 5A shows the effect of administration of AC220 in combination with etoposide as determined at 10%, 25%, 50%, 75%, 90% and 95% inhibition of MV4-11 cell growth, when administration is concurrent.

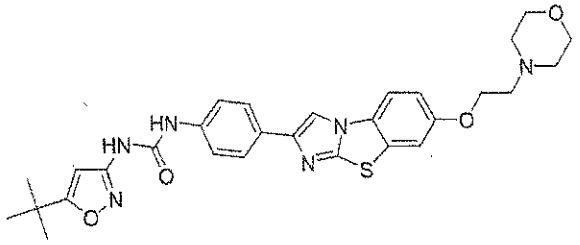
[0027] FIG. 5B shows the effect of administration of AC220 in combination with etoposide as determined at 10%, 25%, 50%, 75%, 90% and 95% inhibition of MV4-11 cell growth, when etoposide is administered 1 day before AC220.

[0028] FIG. 6A shows the effect of AC220 in combination with daunorubicin as determined at 10%, 25%, 50%, 75%, 90% and 95% inhibition of MV4-11 cell growth, when administration is concurrent.

[0029] FIG. 6B shows the effect of administration of AC220 in combination with daunorubicin as determined at 10%, 25%, 50%, 75%, 90% and 95% inhibition of MV4-11 cell growth, when daunorubicin is administered 1 day before AC220.

What is claimed is:

1. Use of a compound of formula A



A

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a proliferative disease in a mammal, wherein said medicament is to be administered to the mammal having or suspected to have the proliferative disease to deliver the compound of formula A or a pharmaceutically acceptable salt thereof in a dose of about 27 to 1000 mg per day, in combination with a second agent selected from azacitidine, cytarabine, etoposide, daunorubicin, cladribine, wherein azacitidine is to be administered in a dose of 50-100 mg/m^2/day, cytarabine is to be administered intravenously or subcutaneously in a dose of 5 mg/m^2/day-3 g/m^2/day, etoposide is to be administered in a dose of 10-150 mg/m^2/day, and daunorubicin is to be administered in a dose of 10-60 mg/m^2/day.

2. The use of claim 1, wherein the compound of formula A or a pharmaceutically acceptable salt thereof is to be administered in a dose of about 40 to 450 mg per day.

3. The use of claim 1, wherein the compound of formula A or a pharmaceutically acceptable salt thereof is to be administered in a dose of about 27, about 30, about 40, about 60, about 90, about 135, about 200, or about 450 mg per day.

4. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof, is to be administered once per day for one week, two weeks, or three weeks.

5. The use of claim 4, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once per day for fourteen days.

6. The use of claim 1, wherein cytarabine is to be administered in a dose of about 100 mg/m^2/day, 200 mg/m^2/day, 750 mg/m^2/day, 1 g/m^2/day or 3 g/m^2/day.

7. The use of claim 20, wherein daunorubicin is to be administered in a dose of about 25, 30, 45, or 60 mg/m^2/day.

8. The use of claim 1, wherein the dose of etoposide is about 35, 50, 100 or 150 mg/m^2/day.

9. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks and etoposide is to be administered once a day for 5 days.

10. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks and etoposide is to be administered once a day on days 1, 3, and 5.

11. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks and cytarabine is to be administered once a day for 7 days.

12. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks and cytarabine is to be administered once a day on days 1, 3 and 5.

13. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks and daunorubicin is to be administered once a day on days 1, 2 and 3.

14. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks, cytarabine is to be administered once a day for 7 days and daunorubicin is to be administered once a day on days 1, 2 and 3.

15. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks and cytarabine is to be administered once a day for 5 days.

16. The use of claim 1, wherein the proliferative disease is cancer.

17. The use of claim 16, wherein the cancer is a leukemia.

18. The use of claim 17, wherein the leukemia is an acute leukemia.

19. The use of claim 17, wherein the leukemia is acute myeloid leukemia.

20. The use of claim 17, wherein the leukemia is promyelocytic leukemia.

21. The use of claim 17, wherein the leukemia is acute lymphoblastic leukemia.

22. The use of claim 17, wherein the leukemia is positive for the FLT3-ITD mutation.

23. The use of claim 17, wherein the leukemia is relapsed or refractory.

24. The use of claim 17, wherein the leukemia is a drug-resistant leukemia.

25. The use of claim 24, wherein the drug-resistant leukemia is resistant to a FLT3 kinase inhibitor.

26. The use of claim 16, wherein the cancer is a solid tumor.

27. The use of claim 26, wherein the cancer is a bladder cancer, breast cancer, cervical cancer, CNS cancer, colon cancer, esophageal cancer, head and neck cancer, liver cancer, lung cancer, nasopharyngeal cancer, neuroendocrine cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, salivary gland cancer, small cell lung cancer, skin cancer, stomach cancer, testicular cancer, thyroid cancer, uterine cancer, or hematologic malignancy.

28. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered orally.

29. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered parenterally.

30. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered intravenously.

31. The use of claim 1, wherein the dose of the compound is to be administered orally for 14 to 32 days, in combination with cytarabine, wherein cytarabine is to be administered intravenously in a dose of 3 g/m^2/day over three hours for every 12 hours on days 1, 3 and 5.

32. A use of claim 1, wherein the dose of the compound is to be administered orally for 14 to 32 days in a dose of 12 mg/day, 20 mg/day, 25 mg/day, 50 mg/day, 60 mg/day, 75 mg/day, 90 mg/day, 100 mg/day, 125 mg/day, 135 mg/day, 200 mg/day, 225 mg/day, 250 mg/day, or 300 mg/day, in combination with cytarabine which is to be administered intravenously or subcutaneously as follows:

5 mg/m^2/day of cytarabine for 7-25 days,
5 mg/m^2/day of cytarabine for 10-14 days,
10 mg/m^2/day of cytarabine for 7-14 days,
10 mg/m^2/day of cytarabine for 7 days,
10 mg/m^2/day of cytarabine for 10 days,
20 mg/m^2/day of cytarabine for 7 -25 days,
20 mg/m^2/day of cytarabine for 10 -14 days,
20 mg/m^2/day of cytarabine for 10 days,
20 mg/m^2/day of cytarabine for 14 days,
20 mg/m^2/day of cytarabine for 21 days,
5 – 30 mg/m^2/day of cytarabine for 1-4 weeks,
100 mg/m^2/day of cytarabine for 7 days,
150 mg/m^2/day of cytarabine for 7 days,
200 mg/m^2/day of cytarabine for 7 days,
100-200 mg/m^2/day of cytarabine for 7 days,
1 g/m^2/day of cytarabine for 7 days,
1 g/m^2/day of cytarabine for 5 days,
1 g/m^2/day of cytarabine for 4 days,
1 g/m^2/day of cytarabine for 3 days,

1 g/m^2/day of cytarabine for 7 days,

1.5 g/m^2/day of cytarabine for 4 days,

1.5 g/m^2/day of cytarabine for 3 days,

2 g/m^2/day of cytarabine for 3 days,

2 g/m^2/day of cytarabine for 4 days,

2 g/m^2/day of cytarabine for 5 days,

2 g/m^2/day of cytarabine for 6 days,

2 g/m^2/day of cytarabine for 12 doses every 12 hours,

3 g/m^2/day of cytarabine for 3 days,

3 g/m^2/day of cytarabine for 4 days,

3 g/m^2/day of cytarabine for 5 days,

3 g/m^2/day of cytarabine for 6 days,

3 g/m^2 of cytarabine for 12 doses every 12 hours,

3 g/m^2 of cytarabine for 8 doses every 12 hours,

3 g/m^2/day of cytarabine for 6 doses every 12 hours,

3 g/m^2 of cytarabine every 12 hours for days 1, 3 and 5,

3 g/m^2/day of cytarabine for 12 doses every 12 hours,

1 g/m^2 of cytarabine every 12 hours for days 1, 3 and 5,

20 mg/day of cytarabine for 10 days, or

40 mg/day of cytarabine for 10 days.

33. A use of claim 1, wherein the dose of the compound is to be administered orally in combination with cytarabine,

wherein compound of formula A or a pharmaceutically acceptable salt thereof is to be administered as follows:

60 mg/day of a compound of formula (I) or A for 14 days,

60 mg/day of a compound of formula (I) or A for 28 days,

60 mg/day of a compound of formula (I) or A for 14-32 days,

90 mg/day of a compound of formula (I) or A for 14 days,

90 mg/day of a compound of formula (I) or A for 28 days,

90 mg/day of a compound of formula (I) or A for 14-32 days,

135 mg/day of a compound of formula (I) or A for 14 days,

135 mg/day of a compound of formula (I) or A for 28 days,

135 mg/day of a compound of formula (I) or Afor 14-32 days,

200 mg/day of a compound of formula (I) or A for 14 days,

200 mg/day of a compound of formula (I) or A for 28 days,

200 mg/day of a compound of formula (I) or A for 14-32 days,

300 mg/day of a compound of formula (I) or A for 14 days,

300 mg/day of a compound of formula (I) or A for 28 days,

300 mg/day of a compound of formula (I) or A for 14-32 days,

450 mg/day of a compound of formula (I) or A for 14 days,

450 mg/day of a compound of formula (I) or A for 28 days; and

450 mg/day of a compound of formula (I) or A for 14-32 days, and

cytarabine is to be administered intravenously or subcutaneously as follows:

5 mg/m^2/day of cytarabine for 7-25 days,

5 mg/m^2/day of cytarabine for 10-14 days,

10 mg/m^2/day of cytarabine for 7-14 days,

10 mg/m^2/day of cytarabine for 7 days,

10 mg/m^2/day of cytarabine for 10 days,

20 mg/m^2/day of cytarabine for 7 -25 days,

20 mg/m^2/day of cytarabine for 10 -14 days,

20 mg/m^2/day of cytarabine for 10 days,

20 mg/m^2/day of cytarabine for 14 days,

20 mg/m^2/day of cytarabine for 21 days,

5 – 30 mg/m^2/day of cytarabine for 1-4 weeks,

100 mg/m^2/day of cytarabine for 7 days,

150 mg/m^2/day of cytarabine for 7 days,

200 mg/m^2/day of cytarabine for 7 days,

100-200 mg/m^2/day of cytarabine for 7 days,

1 g/m^2/day of cytarabine for 7 days,

1 g/m^2/day of cytarabine for 5 days,

1 g/m^2/day of cytarabine for 4 days,

1 g/m^2/day of cytarabine for 3 days,

1 g/m^2/day of cytarabine for 7 days,

1.5 g/m^2/day of cytarabine for 4 days,

1.5 g/m^2/day of cytarabine for 3 days,

2 g/m^2/day of cytarabine for 3 days,

2 g/m^2/day of cytarabine for 4 days,

2 g/m^2/day of cytarabine for 5 days,

2 g/m^2/day of cytarabine for 6 days,

2 g/m^2/day of cytarabine for 12 doses every 12 hours,

3 g/m^2/day of cytarabine for 3 days,

3 g/m^2/day of cytarabine for 4 days,

3 g/m^2/day of cytarabine for 5 days,

3 g/m^2/day of cytarabine for 6 days,

3 g/m^2 of cytarabine for 12 doses every 12 hours,

3 g/m^2 of cytarabine for 8 doses every 12 hours,

3 g/m^2/day of cytarabine for 6 doses every 12 hours,

3 g/m^2 of cytarabine every 12 hours for days 1, 3 and 5,

3 g/m^2/day of cytarabine for 12 doses every 12 hours,

1 g/m^2 of cytarabine every 12 hours for days 1, 3 and 5,

20 mg/day of cytarabine for 10 days, or

40 mg/day of cytarabine for 10 days.

34. The use of claim 1, wherein the compound is to be administered orally to the mammal for 28 days in a treatment cycle, wherein compound is to be administered in a dose of 60 mg/day, 90 mg/day or 135 mg/day in combination with azacytidine, wherein azacytidine is to be administered in a dose of 75 mg/m^2/day for the first 7 days in the same treatment cycle.

35. The use of any of claims 31-34, wherein the proliferative disease is leukemia, or

the proliferative disease is acute myeloid leukemia, or

the proliferative disease is positive for the FLT3-ITD mutation.

36. The use of any of claims 31-34, wherein the mammal is a patient of 65 years or younger with newly diagnosed acute myeloid leukemia.

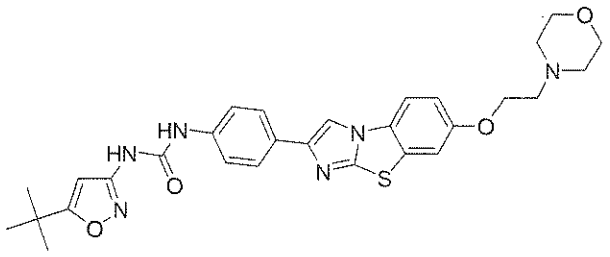
37. The use of any of claims 1 or 31-34, wherein the proliferative disease is hematologic malignancy.

38. The use of claim 38, wherein the hematologic malignancy is myelodysplastic

syndrome.

What is claimed is:

1. Use of a compound of formula A



A

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of leukemia in a mammal, wherein said medicament is to be administered to the mammal having or suspected to have leukemia to deliver the compound of formula A or a pharmaceutically acceptable salt thereof in a dose of about 27 to 1000 mg per day, in combination with a second agent selected from azacitidine, cytarabine, etoposide, daunorubicin, cladribine, wherein azacitidine is administered in a dose of 50-100 mg/m^2/day, cytarabine is administered intravenously or subcutaneously in a dose of 5 mg/m^2/day-3 g/m^2/day, etoposide is administered in a dose of 10-150 mg/m^2/day, and daunorubicin is administered in a dose of 10-60 mg/m^2/day.

2. The use of claim 1, wherein the compound of formula A or a pharmaceutically acceptable salt thereof is to be administered in a dose of about 40 to 450 mg per day.

3. The use of claim 1, wherein the compound of formula A or a pharmaceutically acceptable salt thereof is to be administered in a dose of about 27, about 30, about 40, about 60, about 90, about 135, about 200, or about 450 mg per day.

4. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof, is to be administered once per day for one week, two weeks, or three weeks.

5. The use of claim 4, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once per day for fourteen days.

6. The use of claim 1, wherein cytarabine is to be administered in a dose of about 100 mg/m^2/day, 200 mg/m^2/day, 750 mg/m^2/day, 1 g/m^2/day or 3 g/m^2/day.

7. The use of claim 20, wherein daunorubicin is to be administered in a dose of about 25, 30, 45, or 60 mg/m^2/day.

8. The use of claim 1, wherein the dose of etoposide is about 35, 50, 100 or 150 mg/m^2/day.

9. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks and etoposide is to be administered once a day for 5 days.

10. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks and etoposide is to be administered once a day on days 1, 3, and 5.

11. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks and cytarabine is to be administered once a day for 7 days.

12. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks and cytarabine is to be administered once a day on days 1, 3 and 5.

13. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks and daunorubicin is to be administered once a day on days 1, 2 and 3.

14. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks, cytarabine is to be administered once a day for 7 days and daunorubicin is to be administered once a day on days 1, 2 and 3.

15. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered once a day for one week, two weeks, three weeks, four weeks or five weeks and cytarabine is to be administered once a day for 5 days.

16. The use of claim 1, wherein the leukemia is an acute leukemia.

17. The use of claim 1, wherein the leukemia is acute myeloid leukemia.

18. The use of claim 1, wherein the leukemia is promyelocytic leukemia.

19. The use of claim 1, wherein the leukemia is acute lymphoblastic leukemia.

20. The use of claim 1, wherein the leukemia is positive for the FLT3-ITD mutation.

21. The use of claim 1, wherein the leukemia is relapsed or refractory.

22. The use of claim 1, wherein the leukemia is a drug-resistant leukemia.

23. The use of claim 22, wherein the drug-resistant leukemia is resistant to a FLT3 kinase inhibitor.

24. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered orally.

25. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered parenterally.

26. The use of claim 1, wherein the compound of formula A, or a pharmaceutically acceptable salt thereof is to be administered intravenously.

27. The use of claim 1, wherein the dose of the compound is administered orally for 14 to 32 days, in combination with cytarabine, wherein cytarabine is administered intravenously in a dose of 3 g/m^2/day over three hours for every 12 hours on days 1, 3 and 5.

28. The use of claim 1, wherein the dose of the compound is administered orally for 14 to 32 days in a dose of 12 mg/day, 20 mg/day, 25 mg/day, 50 mg/day, 60 mg/day, 75

mg/day, 90 mg/day, 100 mg/day, 125 mg/day, 135 mg/day, 200 mg/day, 225 mg/day, 250 mg/day, or 300 mg/day, in combination with cytarabine administered intravenously or subcutaneously as follows:

5 mg/m^2/day of cytarabine for 7-25 days,

5 mg/m^2/day of cytarabine for 10-14 days,

10 mg/m^2/day of cytarabine for 7-14 days,

10 mg/m^2/day of cytarabine for 7 days,

10 mg/m^2/day of cytarabine for 10 days,

20 mg/m^2/day of cytarabine for 7 -25 days,

20 mg/m^2/day of cytarabine for 10 -14 days,

20 mg/m^2/day of cytarabine for 10 days,

20 mg/m^2/day of cytarabine for 14 days,

20 mg/m^2/day of cytarabine for 21 days,

5 – 30 mg/m^2/day of cytarabine for 1-4 weeks,

100 mg/m^2/day of cytarabine for 7 days,

150 mg/m^2/day of cytarabine for 7 days,

200 mg/m^2/day of cytarabine for 7 days,

100-200 mg/m^2/day of cytarabine for 7 days,

1 g/m^2/day of cytarabine for 7 days,

1 g/m^2/day of cytarabine for 5 days,

1 g/m^2/day of cytarabine for 4 days,

1 g/m^2/day of cytarabine for 3 days,

1 g/m^2/day of cytarabine for 7 days,

1.5 g/m^2/day of cytarabine for 4 days,

1.5 g/m^2/day of cytarabine for 3 days,

2 g/m^2/day of cytarabine for 3 days,

2 g/m^2/day of cytarabine for 4 days,

2 g/m^2/day of cytarabine for 5 days,

2 g/m^2/day of cytarabine for 6 days,

2 g/m^2/day of cytarabine for 12 doses every 12 hours,

3 g/m^2/day of cytarabine for 3 days,

3 g/m^2/day of cytarabine for 4 days,

3 g/m^2/day of cytarabine for 5 days,

3 g/m^2/day of cytarabine for 6 days,

3 g/m^2 of cytarabine for 12 doses every 12 hours,

3 g/m^2 of cytarabine for 8 doses every 12 hours,

3 g/m^2/day of cytarabine for 6 doses every 12 hours,

3 g/m^2 of cytarabine every 12 hours for days 1, 3 and 5,

3 g/m^2/day of cytarabine for 12 doses every 12 hours,

1 g/m^2 of cytarabine every 12 hours for days 1, 3 and 5,

20 mg/day of cytarabine for 10 days, or

40 mg/day of cytarabine for 10 days.

29. The use of claim 1, wherein the dose of the compound is administered orally in combination with cytarabine,

wherein compound of formula A or a pharmaceutically acceptable salt thereof is administered as follows:

60 mg/day of a compound of formula (I) or A for 14 days,

60 mg/day of a compound of formula (I) or A for 28 days,

60 mg/day of a compound of formula (I) or A for 14-32 days,

90 mg/day of a compound of formula (I) or A for 14 days,

90 mg/day of a compound of formula (I) or A for 28 days,

90 mg/day of a compound of formula (I) or A for 14-32 days,

135 mg/day of a compound of formula (I) or A for 14 days,

135 mg/day of a compound of formula (I) or A for 28 days,

135 mg/day of a compound of formula (I) or Afor 14-32 days,

200 mg/day of a compound of formula (I) or A for 14 days,

200 mg/day of a compound of formula (I) or A for 28 days,

200 mg/day of a compound of formula (I) or A for 14-32 days,

300 mg/day of a compound of formula (I) or A for 14 days,

300 mg/day of a compound of formula (I) or A for 28 days,

300 mg/day of a compound of formula (I) or A for 14-32 days,

450 mg/day of a compound of formula (I) or A for 14 days,

450 mg/day of a compound of formula (I) or A for 28 days; and

450 mg/day of a compound of formula (I) or A for 14-32 days, and

cytarabine is administered intravenously or subcutaneously as follows:

5 mg/m^2/day of cytarabine for 7-25 days,

5 mg/m^2/day of cytarabine for 10-14 days,

10 mg/m^2/day of cytarabine for 7-14 days,

10 mg/m^2/day of cytarabine for 7 days,

10 mg/m^2/day of cytarabine for 10 days,

20 mg/m^2/day of cytarabine for 7 -25 days,

20 mg/m^2/day of cytarabine for 10 -14 days,

20 mg/m^2/day of cytarabine for 10 days,

20 mg/m^2/day of cytarabine for 14 days,

20 mg/m^2/day of cytarabine for 21 days,

5 – 30 mg/m^2/day of cytarabine for 1-4 weeks,

100 mg/m^2/day of cytarabine for 7 days,

150 mg/m^2/day of cytarabine for 7 days,

200 mg/m^2/day of cytarabine for 7 days,

100-200 mg/m^2/day of cytarabine for 7 days,

1 g/m^2/day of cytarabine for 7 days,

1 g/m^2/day of cytarabine for 5 days,

1 g/m^2/day of cytarabine for 4 days,

1 g/m^2/day of cytarabine for 3 days,

1 g/m^2/day of cytarabine for 7 days,

1.5 g/m^2/day of cytarabine for 4 days,

1.5 g/m^2/day of cytarabine for 3 days,

2 g/m^2/day of cytarabine for 3 days,

2 g/m^2/day of cytarabine for 4 days,

2 g/m^2/day of cytarabine for 5 days,

2 g/m^2/day of cytarabine for 6 days,

2 g/m^2/day of cytarabine for 12 doses every 12 hours,

3 g/m^2/day of cytarabine for 3 days,

3 g/m^2/day of cytarabine for 4 days,

3 g/m^2/day of cytarabine for 5 days,

3 g/m^2/day of cytarabine for 6 days,

3 g/m^2 of cytarabine for 12 doses every 12 hours,

3 g/m^2 of cytarabine for 8 doses every 12 hours,

3 g/m^2/day of cytarabine for 6 doses every 12 hours,

3 g/m^2 of cytarabine every 12 hours for days 1, 3 and 5,

3 g/m^2/day of cytarabine for 12 doses every 12 hours,

1 g/m^2 of cytarabine every 12 hours for days 1, 3 and 5,

20 mg/day of cytarabine for 10 days, or

40 mg/day of cytarabine for 10 days.

30. The use of claim 1, wherein the compound is administered orally to the mammal for 28 days in a treatment cycle, wherein compound is administered in a dose of 60 mg/day, 90 mg/day or 135 mg/day in combination with azacytidine, wherein azacytidine is administered in a dose of 75 mg/m^2/day for the first 7 days in the same treatment cycle.

31. The use of any of claims 26-30, wherein the leukemia is acute myeloid leukemia, or the leukemia is positive for the FLT3-ITD mutation.

32. The use of any of claims 26-31, wherein the mammal is a patient of 65 years or younger with newly diagnosed acute myeloid leukemia.

33. The use of claim 1, wherein the second agents are selected from azacitidine, cytarabine and cladribine.