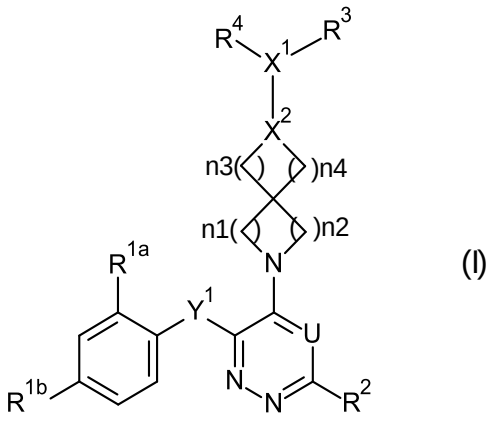
for new treatment modalities for relapsed/refractory (R/R) AML and MDS patients, newly diagnosed AML patients ineligible for induction chemotherapy based on age and co-morbidities, and newly diagnosed intermediate/high/very high risk MDS patients.

[0004] ALL is a hematologic malignancy propagated by impaired differentiation, proliferation, and accumulation of lymphoid progenitor cells in the bone marrow and/or extramedullary sites. ALL represents 12% of all leukemia cases and is the most common childhood acute leukemia, with a worldwide incidence projected to be 1 to 4.75 per 100,000 people. ALL represents about 20% of adult leukemias. Despite high rates of complete remission (CR) (80% to 90%) with current therapies, the majority of adult patients with ALL relapse. The 5-year overall survival rate is approximately 30 to 40% in adults and elderly patients. Therefore, there is an urgent need for new treatment modalities for the treatment of cancer, in particular relapsed/refractory ALL, more particularly in adult and especially elderly patients.

SUMMARY

[0005] The present disclosure relate to novel combinations of a menin-MLL inhibitor of Formula (I), or a pharmaceutically acceptable salt or a solvate thereof; and at least one other therapeutic agent which is a hypomethylating agent, a cytidine deaminase inhibitor, a DNA intercalating agent, a pyrimidine analog, a purine analog, a kinase inhibitor, a CD20 inhibitor, an IDH inhibitor, an immunomodulatory agent or a DHODH inhibitor.

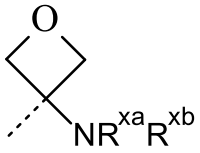
[0005a] In one aspect, there is provided a combination comprising a therapeutically effective amount of a menin-mixed-lineage leukemia 1 (MLL) inhibitor of Formula (I), or a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof; and a therapeutically effective amount of at least one other therapeutic agent, wherein the at least one other therapeutic agent is a hypomethylating agent, cytidine deaminase inhibitor, a DNA intercalating agent, a pyrimidine analog, a purine analog, a kinase inhibitor, a CD20 inhibitor, an isocitrate dehydrogenase inhibitor, an immunomodulatory agent or a dihydroorotate dehydrogenase inhibitor; wherein the menin-MLL inhibitor of Formula (I) has the structure:



(I)

,

wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$; Het; or  ;

Het represents a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety; wherein said 5- or 6-membered monocyclic aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C_{3-6}cycloalkyl and C_{1-4}alkyl;

R^{xa} and R^{xb} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^{1b} represents F or Cl;

Y^1 represents -$CR^{5a}R^{5b}$-, -O- or -NR^{5c}-;

R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and –$NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl; wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH,

and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl; and

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{10c}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl.

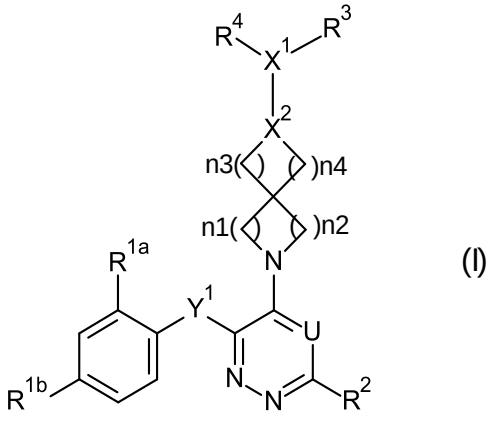
[0005b] In another aspect, there is provided a pharmaceutical composition comprising a combination as defined herein and a pharmaceutically acceptable carrier.

[0005c] In another aspect, there is provided a combination as defined herein or a pharmaceutical composition as defined herein for use as a medicament.

[0006] the present disclosure also relates to uses of such combinations for treating a subject who has been diagnosed with a hematopoietic disorder, including but not limited to, blood cancers, using a menin-MLL inhibitor described herein in combination with at least one other therapeutic agent.

[0006a] In another aspect, there is provided a combination as defined herein or a pharmaceutical composition as defined herein for use in the prevention or treatment, in particular treatment, of a hematopoietic disorder.

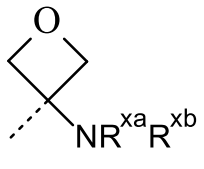
[0006b] In another aspect, there is provided use of a therapeutically effective amount of a menin-mixed lineage leukemia 1 (MLL) inhibitor of Formula (I), or a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof; wherein the menin-MLL inhibitor of Formula (I) has the structure:



(I)

,

wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$; Het; or  ;

Het represents a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety; wherein said 5- or 6-membered monocyclic aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C_{3-6}cycloalkyl and C_{1-4}alkyl;

R^{xa} and R^{xb} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^{1b} represents F or Cl;

Y^1 represents -$CR^{5a}R^{5b}$-, -O- or -NR^{5c}-;

R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and –$NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or

-C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl; wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen;

C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl; and

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{10c}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl,

in the manufacture of a medicament in combination therapy for treating a subject who has been diagnosed with cancer, wherein said menin-MLL inhibitor of Formula (I) is to be administered

in combination with a therapeutically effective amount of at least one other therapeutic agent, wherein the at least one other therapeutic agent is a hypomethylating agent, a cytidine deaminase inhibitor, a DNA intercalating agent, a pyrimidine analog, a purine analog, a kinase inhibitor, a CD20 inhibitor, an IDH inhibitor, an immunomodulatory agent or a DHODH inhibitor.

[0007] The present disclosure also relates to novel methods for treating a subject who has been diagnosed with a hematopoietic disorder using such combinations. Examples of the novel methods comprise administering to the subject a therapeutically effective amount of a menin-MLL inhibitor as described herein; and a therapeutically effective amount of at least one other therapeutic agent; wherein the menin-MLL inhibitor is a compound of Formula (I), or a pharmaceutically acceptable salt or a solvate thereof.

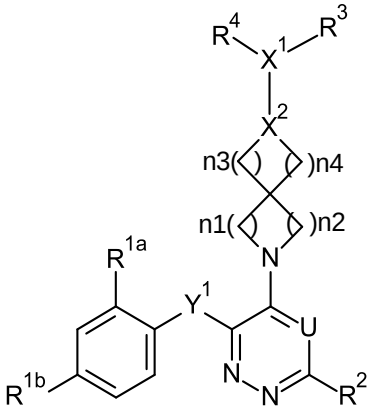
[0008] The present disclosure also relates to novel methods for treating a subject who has been diagnosed with a hematopoietic disorder using such combinations. Examples of the novel methods comprise administering to the subject a therapeutically effective amount of a menin-MLL inhibitor as described herein; and a therapeutically effective amount of at least one other therapeutic agent which is a hypomethylating agent, a cytidine deaminase inhibitor,

a DNA intercalating agent, a pyrimidine analog, a purine analog, a kinase inhibitor, a CD20 inhibitor, an IDH inhibitor, an immunomodulatory agent or a DHODH inhibitor; wherein the menin-MLL inhibitor is a compound of Formula (I), or a pharmaceutically acceptable salt or a solvate thereof.

[0009] In some examples, the present disclosure is directed to methods for treating a subject who has been diagnosed with a hematopoietic disorder, the methods comprising administering to the subject a therapeutically effective amount of a menin-MLL inhibitor of Formula (I), or a pharmaceutically acceptable salt or a solvate thereof; and a therapeutically effective amount of azacitidine or a pharmaceutically acceptable salt or solvate thereof.

[0010] In some examples, the present disclosure is directed to methods for treating a subject who has been diagnosed with a hematopoietic disorder, the methods comprising administering to the subject a therapeutically effective amount of a menin-MLL inhibitor of Formula (I), or a pharmaceutically acceptable salt or a solvate thereof; and a therapeutically effective amount of azacitidine or a pharmaceutically acceptable salt or solvate thereof; wherein the azacitidine, or a pharmaceutically acceptable salt or solvate thereof, is administered to the subject prior to, simultaneous with, or after the administration of the menin-MLL inhibitor.

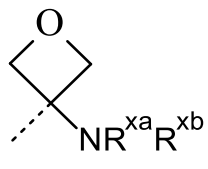
[0011] In examples, the menin-MLL inhibitor of Formula (I) is:



(I)

,

and the tautomers and the stereoisomeric forms thereof, wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$; Het; or 

;

Het represents a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety;

wherein said 5- or 6-membered monocyclic aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C_{3-6}cycloalkyl and C_{1-4}alkyl;

R^{xa} and R^{xb} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^{1b} represents F or Cl;

Y^1 represents $-CR^{5a}R^{5b}-$, -O- or $-NR^{5c}-$;

R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and $-NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

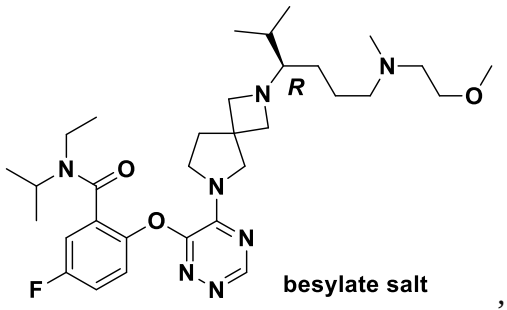
R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl; wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -$S(=O)_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and $-NR^{10c}$-C(=O)-C_{1-4}alkyl; and

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{10c}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

[0012] In particular examples, the menin-MLL inhibitor of Formula (I) is (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide besylate salt (benzenesulfonate salt):



,

and solvates thereof.

[0013] A skilled person will understand that the 'and solvates thereof' refer to the besylate salt of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide.

[0014] In particular examples, the menin-MLL inhibitor of Formula (I) is (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide besylate salt or hydrates thereof.

[0015] In particular examples, the menin-MLL inhibitor of Formula (I) is (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt or solvates thereof.

[0016] In particular examples, the menin-MLL inhibitor of Formula (I) is (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt or hydrates thereof.

[0017] In particular the present disclosure is directed to (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt 0.5-2.0 equivalents hydrate.

[0018] In particular the present disclosure is directed to (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt 2.0 equivalents hydrate.

[0019] In particular examples, the menin-MLL inhibitor of Formula (I) is a crystalline form A of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt hydrate.

[0020] In particular examples, the menin-MLL inhibitor of Formula (I) is a crystalline form A of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-

2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt 0.5-2.0 equivalents hydrate.

[0021] More in particular the present disclosure is directed to a crystalline form A of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt 2.0 equivalents hydrate.

[0022] Additional examples, features, and advantages of the disclosure will be apparent from the following detailed description and through practice of the disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. 1 is an X-ray powder diffraction (XRPD) pattern of Compound **A4**: a crystalline form A of (*R*)-N-ethyl-5-fluoro-N-isopropyl-2-((5-(2-(6-((2-methoxyethyl)(methyl)amino)-2-methylhexan-3-yl)-2,6-diazaspiro[3.4]octan-6-yl)-1,2,4-triazin-6-yl)oxy)benzamide bis-besylate salt hydrate.

[0024] FIG. 2 depicts a comparison of tumor volumes as a function of time for the control group and for the treatment groups treated with a regimen comprising various amounts of Compound **A3**.

[0025] FIG. 3 depicts a comparison of tumor percent survival as a function of time (e.g., Kaplan-Meier survival curves) for the control group and for the treatment groups treated with a regimen comprising various amounts of Compound **A3**.

[0026] FIG. 4A depicts a comparison of percent survival as a function of time of mice bearing established OCI-AML3 tumors following treatment with vehicle, monotherapy with either azacitidine or Compound **A1**, or the doublet combination of Compound **A1** and azacitidine.

[0027] FIG. 4B depicts a comparison of percent survival as a function of time of mice bearing established MOLM-13 tumors following treatment with vehicle, monotherapy with either azacitidine or Compound **A1**, or the doublet combination of Compound **A1** and azacitidine.

[0028] FIG. 5 depicts a comparison of percent survival as a function of time of mice bearing established MOLM-13 tumors following treatment with vehicle, monotherapy with either gilteritinib or Compound **A1**, or the doublet combination of Compound **A1** and gilteritinib.

[0029] FIG. 6A is a contour plot for maxR which illustrates the effect of Compound **A4** in combination with gilteritinib on proliferation of MOLM-13 cells *in vitro*.

[0030] FIG. 6B is a contour plot for maxR which illustrates the effect of Compound **A4** in combination with gilteritinib on proliferation of MV4-11 cells *in vitro*.

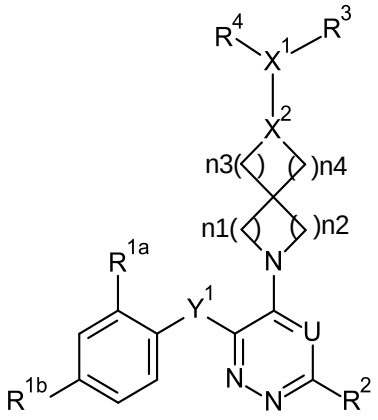
CLAIMS

What is claimed is:

1. A combination comprising:

- a therapeutically effective amount of a menin-mixed-lineage leukemia 1 (MLL) inhibitor of Formula (I), or a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof; and
- a therapeutically effective amount of at least one other therapeutic agent, wherein the at least one other therapeutic agent is a hypomethylating agent, cytidine deaminase inhibitor, a DNA intercalating agent, a pyrimidine analog, a purine analog, a kinase inhibitor, a CD20 inhibitor, an isocitrate dehydrogenase inhibitor, an immunomodulatory agent or a dihydroorotate dehydrogenase inhibitor;

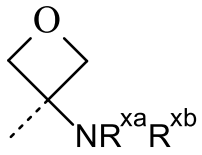
wherein the menin-MLL inhibitor of Formula (I) has the structure:



(I)

,

wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$; Het; or 

;

Het represents a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety; wherein said 5- or 6-membered monocyclic aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C_{3-6}cycloalkyl and C_{1-4}alkyl;

R^{xa} and R^{xb} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^{1b} represents F or Cl;

Y^1 represents -$CR^{5a}R^{5b}$-, -O- or -NR^{5c}-;

R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and –$NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

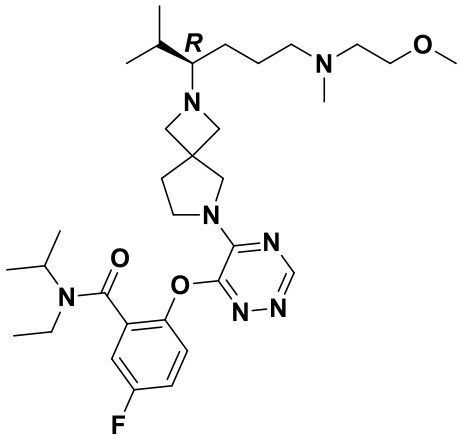
R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or -C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl; wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl; and

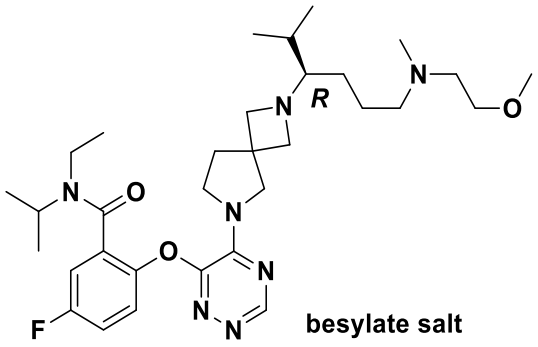
R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{10c}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl.

2. The combination according to claim 1, wherein the menin-MLL inhibitor of Formula (I) is Compound **A**:



or a pharmaceutically acceptable salt or solvate thereof.

3. The combination according to claim 1, wherein the menin-MLL inhibitor of Formula (I) is Compound **A4-a**:



or a solvate thereof.

4. The combination according to any one of claims 1-3, wherein the at least one other therapeutic agent is a hypomethylating agent.

5. The combination according to claim 4, wherein the hypomethylating agent is azacitidine or a pharmaceutically acceptable salt or solvate thereof.

6. The combination according to any one of claims 1-3, wherein the at least one other therapeutic agent is a kinase inhibitor.

7. The combination according to claim 6, wherein the kinase inhibitor is a tyrosine kinase inhibitor.

8. The combination according to claim 7, wherein the tyrosine kinase inhibitor is a FLT-3 inhibitor.

9. The combination according to claim 8, wherein the FLT-3 inhibitor is gilteritinib.

10. The combination according to any one of claims 1-3, wherein the at least one other therapeutic agent is a pyrimidine analog.

11. The combination according to claim 10 wherein the pyrimidine analog is cytarabine.

12. The combination according to any one of claims 1-3, wherein the at least one other

therapeutic agent is a DNA intercalating agent.

13. The combination according to claim 12 wherein the DNA intercalating agent is daunorubicin.

14. The combination according to claim 12 wherein the DNA intercalating agent is doxorubicin.

15. The combination according to claim 12 wherein the DNA intercalating agent is idarubicin.

16. The combination according to any of claims 1-15 wherein the menin-mixed-lineage leukemia 1 (MLL) inhibitor of Formula (I), or the tautomer or the stereoisomeric form thereof, or the pharmaceutically acceptable salt or the solvate thereof and the at least one other therapeutic agent are to be administered sequentially, or simultaneously either in the same or a different pharmaceutical composition.

17. A pharmaceutical composition comprising a combination as claimed in any one of claims 1 to 15 and a pharmaceutically acceptable carrier.

18. A combination as claimed in any one of claims 1 to 16 or a pharmaceutical composition as claimed in claim 17 for use as a medicament.

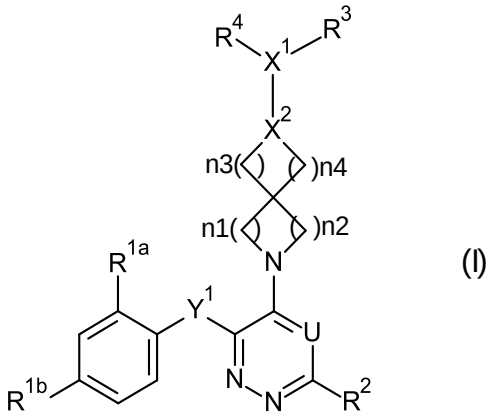
19. A combination as claimed in any one of claims 1 to 16 or a pharmaceutical composition as claimed in claim 17 for use in the prevention or treatment, in particular treatment, of a hematopoietic disorder.

20. The combination or pharmaceutical composition for use according to claim 19 wherein the hematopoietic disorder is a nucleophosmin 1 (NPM1)-mutated leukemia or KMT2A-rearranged leukemia.

21. The combination or pharmaceutical composition for use according to claim 19 wherein the hematopoietic disorder is acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL).

22. The combination or pharmaceutical composition for use according to claim 19 wherein the hematopoietic disorder is AML with KMT2A gene alterations and/or NPM1 mutations.

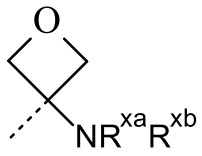
23. Use of a therapeutically effective amount of a menin-mixed lineage leukemia 1 (MLL) inhibitor of Formula (I), or a tautomer or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof;
wherein the menin-MLL inhibitor of Formula (I) has the structure:



(I)

,

wherein

R^{1a} represents -C(=O)-$NR^{xa}R^{xb}$; Het; or 

;

Het represents a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety; wherein said 5- or 6-membered monocyclic aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C_{3-6}cycloalkyl and C_{1-4}alkyl;

R^{xa} and R^{xb} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^{1b} represents F or Cl;

Y^1 represents -$CR^{5a}R^{5b}$-, -O- or -NR^{5c}-;

R^2 is selected from the group consisting of hydrogen, halo, C_{1-4}alkyl, -O-C_{1-4}alkyl, and –$NR^{7a}R^{7b}$;

U represents N or CH;

n1, n2, n3 and n4 are each independently selected from 1 and 2;

X^1 represents CH, and X^2 represents N;

R^4 represents isopropyl;

R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl and C_{3-6}cycloalkyl;

R^3 represents -C_{1-6}alkyl-$NR^{8a}R^{8b}$, -C_{1-6}alkyl-C(=O)-$NR^{9a}R^{9b}$, -C_{1-6}alkyl-OH, or

-C_{1-6}alkyl-NR^{11}-C(=O)-O-C_{1-4}alkyl-O-C(=O)-C_{1-4}alkyl; wherein each of the C_{1-4}alkyl or C_{1-6}alkyl moieties in the R^3 definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C_{1-4}alkyl;

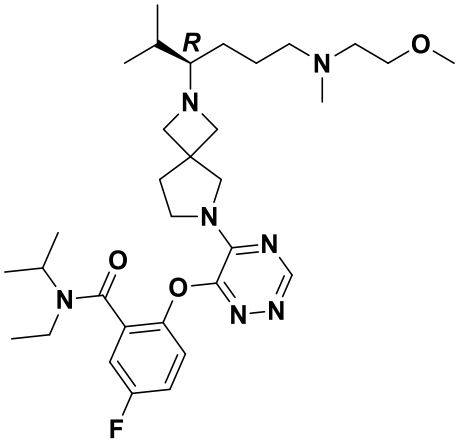
R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen;

C_{1-6}alkyl; -C(=O)-C_{1-4}alkyl; -C(=O)-O-C_{1-4}alkyl; -C(=O)-$NR^{12a}R^{12b}$; and C_{1-6}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)$_2$-C_{1-4}alkyl, -O-C_{1-4}alkyl, -C(=O)-$NR^{10a}R^{10b}$, and -NR^{10c}-C(=O)-C_{1-4}alkyl; and

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{10c}, R^{11}, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl,

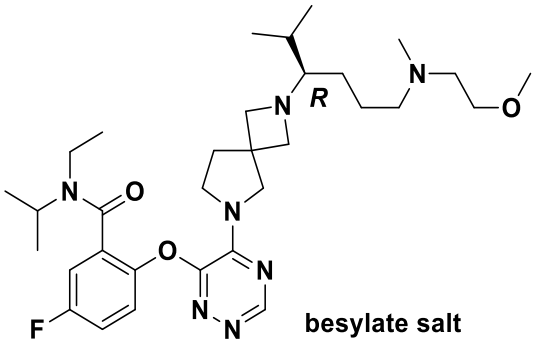
in the manufacture of a medicament in combination therapy for treating a subject who has been diagnosed with cancer, wherein said menin-MLL inhibitor of Formula (I) is to be administered in combination with a therapeutically effective amount of at least one other therapeutic agent, wherein the at least one other therapeutic agent is a hypomethylating agent, a cytidine deaminase inhibitor, a DNA intercalating agent, a pyrimidine analog, a purine analog, a kinase inhibitor, a CD20 inhibitor, an IDH inhibitor, an immunomodulatory agent or a DHODH inhibitor.

24. The use according to claim 23, wherein the menin-MLL inhibitor of Formula (I) is Compound **A**:



or a pharmaceutically acceptable salt or solvate thereof.

25. The use according to claim 23, wherein the menin-MLL inhibitor of Formula (I) is Compound **A4-a**:



or a solvate thereof.

26. The use according to any one of claims 23-25, wherein the at least one other therapeutic agent is a hypomethylating agent.

27. The use according to claim 26, wherein the hypomethylating agent is azacitidine or a pharmaceutically acceptable salt or solvate thereof.

28. The use according to any one of claims 23-25, wherein the at least one other therapeutic agent is a kinase inhibitor.

29. The use according to claim 28, wherein the kinase inhibitor is a tyrosine kinase inhibitor.

30. The use according to claim 29, wherein the tyrosine kinase inhibitor is a FLT-3 inhibitor.

31. The use according to claim 30, wherein the FLT-3 inhibitor is gilteritinib.

32. The use according to any one of claims 23-25, wherein the at least one other therapeutic agent is a pyrimidine analog.

33. The use according to claim 32 wherein the pyrimidine analog is cytarabine.

34. The use according to any one of claims 23-25, wherein the at least one other therapeutic

agent is a DNA intercalating agent.

35. The use according to claim 34 wherein the DNA intercalating agent is daunorubicin.

36. The use according to claim 34 wherein the DNA intercalating agent is doxorubicin.

37. The use according to claim 12-34 wherein the DNA intercalating agent is idarubicin.

38. The use according to any of claims 23-37 wherein the menin-mixed-lineage leukemia 1 (MLL) inhibitor of Formula (I), or the tautomer or the stereoisomeric form thereof, or the pharmaceutically acceptable salt or the solvate thereof and the at least one other therapeutic agent are to be administered sequentially, or simultaneously either in the same or a different pharmaceutical composition.

39. The use according to any of claims 23-38 wherein the menin-mixed-lineage leukemia 1 (MLL) inhibitor of Formula (I), or the tautomer or the stereoisomeric form thereof, or the pharmaceutically acceptable salt or the solvate thereof and the at least one other therapeutic agent are to be administered in separate dosage forms.

40. The use according to any one of claims 23-39, wherein the cancer is a hematopoietic disorder.

41. The use according to claim 40, wherein the hematopoietic disorder is a nucleophosmin 1 (NPM1)-mutated leukemia or MLL-rearranged leukemia.

42. The use according to claim 40, wherein the hematopoietic disorder is acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL).

43. The use according to claim 40 wherein the hematopoietic disorder is AML with KMT2A gene alterations and/or NPM1 mutations.