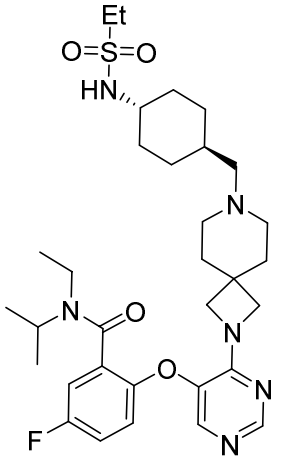
inhibitors of the menin-MLL interaction in the treatment of diabetes (Yang *et al*., 2010, Proc Natl Acad Sci U S A., 107:20358-20363). The interaction between menin and MLL or MLL fusion proteins is an attractive target for therapeutic intervention, and there is a need for novel combination therapeutics that inhibit the menin-MLL interaction for the treatment of various diseases and conditions, including leukemia, other cancers and diabetes.

SUMMARY

In an aspect of the present disclosure, there is provided use of a menin inhibitor of Formula (II):

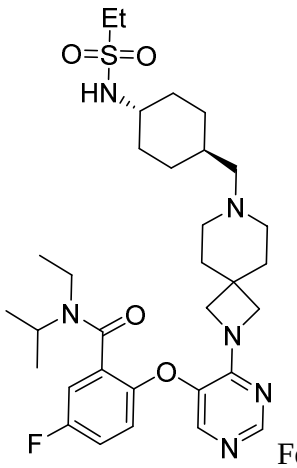


Formula (II),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combinatorial therapy for treating a hematological cancer in an individual in need thereof, wherein the menin inhibitor is to be administered in combination with a strong CYP3A4 inhibitor, and wherein the menin inhibitor is to be administered at a daily dosage of from 280 mg/day to 350 mg/day.

In another aspect of the present disclosure, there is provided use of a pharmaceutical composition comprising a menin inhibitor of Formula (II), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combinatorial therapy for treating a hematological cancer in an individual in need thereof, wherein the menin inhibitor is to be administered in combination with a pharmaceutical composition comprising a strong CYP3A4 inhibitor, and wherein the menin inhibitor is to be administered at a daily dosage of from 280 mg/day to 350 mg/day.

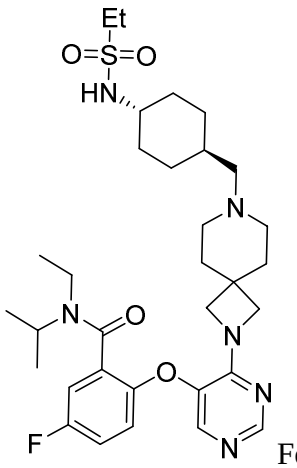
In a further aspect of the present disclosure, there is provided a kit comprising a menin inhibitor of Formula (II):



Formula (II),

or a pharmaceutically acceptable salt thereof, and instructions for use in treating a hematological cancer in combination with a strong CYP3A4 inhibitor, wherein the menin inhibitor is to be administered at a daily dosage of from 280 mg/day to 350 mg/day.

In a further aspect of the present disclosure, there is provided use of a menin inhibitor of Formula (II):



Formula (II),

or a pharmaceutically acceptable salt thereof, and a strong CYP3A4 inhibitor, in the manufacture of a pharmaceutical composition, for use in combinatorial therapy for the treatment of a hematological cancer, wherein the menin inhibitor is to be administered at a daily dosage of from 280 mg/day to 350 mg/day.

The present disclosure provides a combination therapy comprising a menin inhibitor and a CYP3A inhibitor. In certain examples, the present disclosure provides for a pharmaceutical composition comprising: (a) a menin inhibitor, and (b) a CYP3A inhibitor. In some examples, the present disclosure is directed to a method for treating a patient comprising (a) administering a menin inhibitor, and (b) administering a CYP3A inhibitor.

Some examples of this present disclosure are directed to combination therapies designed to treat or manage cancer in a subject, wherein the combination therapies comprise administering a menin inhibitor in combination with a CYP3A inhibitor. In particular, some examples of this present disclosure are directed to methods of treating or managing cancer in a subject, comprising administering a menin inhibitor in combination with a therapeutically effective amount of a CYP3A inhibitor administered simultaneously, separately or sequentially.

In some examples, the present disclosure provides a combination therapy comprising a menin inhibitor and a CYP3A4 inhibitor. In certain examples, the present disclosure provides for a pharmaceutical composition comprising: (a) a menin inhibitor, and (b) a CYP3A4 inhibitor. In some examples, the present

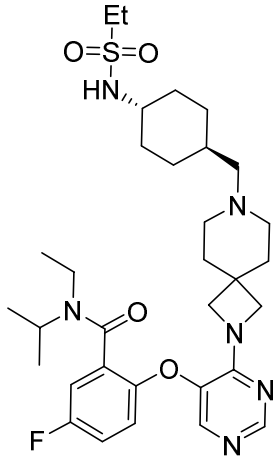
disclosure is directed to a method for treating a patient comprising (a) administering a menin inhibitor, and (b) administering a CYP3A4 inhibitor.

Some examples of this present disclosure are directed to combination therapies designed to treat or manage cancer in a subject, wherein the combination therapies comprise administering a menin inhibitor in combination with a CYP3A4 inhibitor. In particular, some examples of this present disclosure are directed to methods of treating or managing cancer in a subject, comprising administering a menin inhibitor in combination with a therapeutically effective amount of a CYP3A4 inhibitor administered simultaneously, separately or sequentially.

In some examples, the CYP3A inhibitor is: an antiarrhythmic; an antihistamine; an azole antifungal; a benzodiazepine; a calcium channel blocker; a HIV antiviral; a HMG CoA

CLAIMS

1. Use of a menin inhibitor of Formula (II):



Formula (II),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combinatorial therapy for treating a hematological cancer in an individual in need thereof, wherein the menin inhibitor is to be administered in combination with a strong CYP3A4 inhibitor, and wherein the menin inhibitor is to be administered at a daily dosage of from 280 mg/day to 350 mg/day.

2. Use of a pharmaceutical composition comprising a menin inhibitor of Formula (II), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combinatorial therapy for treating a hematological cancer in an individual in need thereof, wherein the menin inhibitor is to be administered in combination with a pharmaceutical composition comprising a strong CYP3A4 inhibitor, and wherein the menin inhibitor is to be administered at a daily dosage of from 280 mg/day to 350 mg/day.

3. The use of claim 1 or 2, wherein the hematological cancer is a leukemia.

4. The use of any one of claims 1-3, wherein the hematological cancer is mixed lineage leukemia (MLL), MLL-related leukemia, MLL-associated leukemia, MLL-positive leukemia, MLL-induced leukemia, rearranged mixed lineage leukemia (MLL-r), leukemia associated with a MLL rearrangement or a rearrangement of the *MLL* gene, acute leukemia, chronic leukemia,

indolent leukemia, lymphoblastic leukemia, lymphocytic leukemia, myeloid leukemia, myelogenous leukemia, childhood leukemia, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute granulocytic leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), therapy related leukemia, myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), myeloproliferative neoplasia (MPN), plasma cell neoplasm, multiple myeloma, myelodysplasia, cutaneous T-cell lymphoma, lymphoid neoplasm, AIDS-related lymphoma, thymoma, thymic carcinoma, mycosis fungoides, Alibert-Bazin syndrome, granuloma fungoides, Sézary Syndrome, hairy cell leukemia, T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia, meningeal leukemia, leukemic leptomeningitis, leukemic meningitis, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma (malignant lymphoma), Waldenstrom's macroglobulinemia or a nucleophosmin (NPM1)-mutated leukemia.

5. The use of any one of claims 1-4, wherein the hematological cancer is an acute lymphocytic leukemia (ALL).

6. The use of any one of claims 1-4, wherein the hematological cancer is an acute myeloid leukemia (AML).

7. The use of any one of claims 1-6, wherein the hematological cancer is NPM1-mutated leukemia.

8. The use of any one of claims 1-6, wherein the hematological cancer is MLL-r leukemia.

9. The use of any one of claims 1-8, wherein the strong CYP3A4 inhibitor is selected from the group consisting of boceprevir, nefazodone, clarithromycin, nelfinavir, conivaptan, posaconazole, grapefruit juice, ritonavir, indinavir, saquinavir, itraconazole, telaprevir, ketoconazole, telithromycin, lopinavir, voriconazole, cobicistat, and mibefradil.

10. The use of any one of claims 1-8, wherein the strong CYP3A4 inhibitor is an azole antifungal.

11. The use of any one of claims 1-8, wherein the strong CYP3A4 inhibitor is posaconazole.

12. The use of any one of claims 1-8, wherein the strong CYP3A4 inhibitor is cobicistat.

13. The use of any one of claims 1-8, wherein the strong CYP3A4 inhibitor is ketoconazole.

14. The use of any one of claims 1-8, wherein the strong CYP3A4 inhibitor is ritonavir.

15. The use of any one of claims 1-8, wherein the strong CYP3A4 inhibitor is itraconazole.

16. The use of any one of claims 1-8, wherein the strong CYP3A4 inhibitor is voriconazole.

17. The use of any one of claims 1-8, wherein the strong CYP3A4 inhibitor is indinavir.

18. The use of any one of claims 1-17, wherein the menin inhibitor and the strong CYP3A4 inhibitor are in a combined dosage form.

19. The use of any one of claims 1-17, wherein the menin inhibitor and the strong CYP3A4 inhibitor are in separate dosage forms.

20. The use of any one of claims 1-19, wherein the menin inhibitor and the strong CYP3A4 inhibitor are to be administered concurrently.

21. The use of any one of claims 1-19, wherein the menin inhibitor and the strong CYP3A4 inhibitor are to be administered simultaneously, essentially simultaneously, or within a treatment protocol.

22. The use of any one of claims 1-17 or 19, wherein the menin inhibitor and the strong CYP3A4 inhibitor are to be administered sequentially.

23. The use of any one of claims 1-22, wherein the menin inhibitor and the strong CYP3A4 inhibitor are to be administered for an initial treatment period, followed by a continued treatment period where the menin inhibitor is to be administered thereafter.

24. The use of any one of claims 1-17 or 21-23, wherein the strong CYP3A4 inhibitor is to be administered before the menin inhibitor is to be administered.

25. The use of any one of claims 1-24, wherein the menin inhibitor is to be administered at a daily dosage of from 300 mg/day to 340 mg/day.

26. The use of any one of claims 1-25, wherein the menin inhibitor is to be administered at a daily dosage of about 310 mg/day.

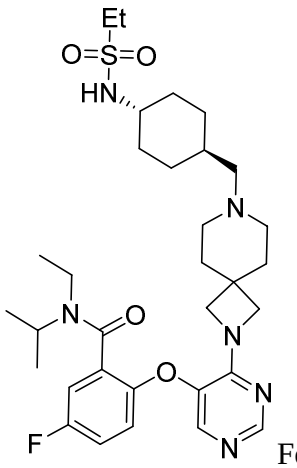
27. The use of any one of claims 1-25, wherein the menin inhibitor is to be administered at a daily dosage of about 320 mg/day.

28. The use of any one of claims 1-25, wherein the menin inhibitor is to be administered at a daily dosage of about 330 mg/day.

29. The use of any one of claims 1-28, wherein the strong CYP3A4 inhibitor is to be administered at a daily dosage of from 50 mg/day up to, and including, 1,000 mg/day.

30. The use of any one of claims 1-29, wherein the daily dosage is divided into multiple administrations which are to be administered twice daily.

31. A kit comprising a menin inhibitor of Formula (II):



Formula (II),

or a pharmaceutically acceptable salt thereof, and instructions for use in treating a hematological cancer in combination with a strong CYP3A4 inhibitor, wherein the menin inhibitor is to be administered at a daily dosage of from 280 mg/day to 350 mg/day.

32. The kit of claim 31, wherein the hematological cancer is a leukemia.

33. The kit of claim 31 or 32, wherein the hematological cancer is mixed lineage leukemia (MLL), MLL-related leukemia, MLL-associated leukemia, MLL-positive leukemia, MLL-induced leukemia, rearranged mixed lineage leukemia (MLL-r), leukemia associated with a MLL rearrangement or a rearrangement of the *MLL* gene, acute leukemia, chronic leukemia, indolent leukemia, lymphoblastic leukemia, lymphocytic leukemia, myeloid leukemia, myelogenous leukemia, childhood leukemia, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute granulocytic leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), therapy related leukemia, myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), myeloproliferative neoplasia(MPN), plasma cell neoplasm, multiple myeloma, myelodysplasia, cutaneous T-cell lymphoma, lymphoid neoplasm, AIDS-related lymphoma, thymoma, thymic carcinoma, mycosis fungoides, Alibert-Bazin syndrome, granuloma fungoides, Sézary Syndrome, hairy cell leukemia, T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia, meningeal leukemia, leukemic leptomeningitis, leukemic meningitis, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma (malignant lymphoma), Waldenstrom's macroglobulinemia or a nucleophosmin (NPM1)-mutated leukemia.

34. The kit of any one of claims 31-33, wherein the hematological cancer is an acute lymphocytic leukemia (ALL).

35. The kit of any one of claims 31-33, wherein the hematological cancer is an acute myeloid leukemia (AML).

36. The kit of any one of claims 31-35, wherein the hematological cancer is a NPM1-mutated leukemia.

37. The kit of any one of claims 31-35, wherein the hematological cancer is a MLL-r leukemia.

38. The kit of any one of claims 31-37, wherein the strong CYP3A4 inhibitor is selected from the group consisting of boceprevir, nefazodone, clarithromycin, nelfinavir, conivaptan, posaconazole, grapefruit juice, ritonavir, indinavir, saquinavir, itraconazole, telaprevir, ketoconazole, telithromycin, lopinavir, voriconazole, cobicistat, and mibefradil.

39. The kit of any one of claims 31-37, wherein the strong CYP3A4 inhibitor is an azole antifungal.

40. The kit of any one of claims 31-37, wherein the strong CYP3A4 inhibitor is posaconazole.

41. The kit of any one of claims 31-37, wherein the strong CYP3A4 inhibitor is cobicistat.

42. The kit of any one of claims 31-37, wherein the strong CYP3A4 inhibitor is ketoconazole.

43. The kit of any one of claims 31-37, wherein the strong CYP3A4 inhibitor is ritonavir.

44. The kit of any one of claims 31-37, wherein the strong CYP3A4 inhibitor is itraconazole.

45. The kit of any one of claims 31-37, wherein the strong CYP3A4 inhibitor is voriconazole.

46. The kit of any one of claims 31-37, wherein the strong CYP3A4 inhibitor is indinavir.

47. The kit of any one of claims 31-46, comprising instructions to administer the menin inhibitor at a daily dosage of from 300 mg/day to 340 mg/day.

48. The kit of any one of claims 31-47, comprising instructions to administer the menin inhibitor at a daily dosage of about 310 mg/day.

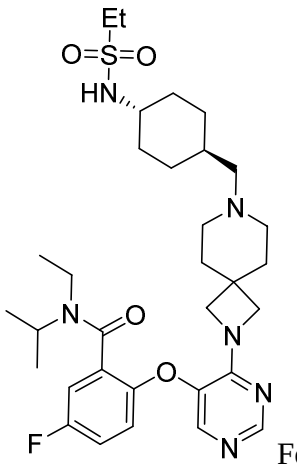
49. The kit of any one of claims 31-47, comprising instructions to administer the menin inhibitor at a daily dosage of about 320 mg/day.

50. The kit of any one of claims 31-47, comprising instructions to administer the menin inhibitor at a daily dosage of about 330 mg/day.

51. The kit of any one of claims 31-50, comprising instructions to administer the strong CYP3A4 inhibitor at a daily dosage of from 50 mg/day up to, and including, 1,000 mg/day.

52. The kit of any one of claims 31-51, comprising instructions to divide the daily dosage into multiple administrations which are given twice daily.

53. Use of a menin inhibitor of Formula (II):



Formula (II),

or a pharmaceutically acceptable salt thereof, and a strong CYP3A4 inhibitor, in the manufacture of a pharmaceutical composition, for use in combinatorial therapy for the treatment of a hematological cancer, wherein the menin inhibitor is to be administered at a daily dosage of from 280 mg/day to 350 mg/day.

54. The use of claim 53, wherein the hematological cancer is a leukemia.

55. The use of claim 53 or 54, wherein the hematological cancer is mixed lineage leukemia (MLL), MLL-related leukemia, MLL-associated leukemia, MLL-positive leukemia, MLL-induced leukemia, rearranged mixed lineage leukemia (MLL-r), leukemia associated with a MLL rearrangement or a rearrangement of the *MLL* gene, acute leukemia, chronic leukemia, indolent leukemia, lymphoblastic leukemia, lymphocytic leukemia, myeloid leukemia, myelogenous leukemia, childhood leukemia, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute granulocytic leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), therapy related leukemia, myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), myeloproliferative neoplasia(MPN), plasma cell neoplasm, multiple myeloma, myelodysplasia, cutaneous T-cell lymphoma, lymphoid neoplasm, AIDS-related lymphoma, thymoma, thymic carcinoma, mycosis fungoides, Alibert-Bazin syndrome, granuloma fungoides, Sézary Syndrome, hairy cell leukemia, T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia, meningeal leukemia, leukemic leptomeningitis, leukemic meningitis, multiple myeloma,

Hodgkin's lymphoma, non-Hodgkin's lymphoma (malignant lymphoma), Waldenstrom's macroglobulinemia or a nucleophosmin (NPM1)-mutated leukemia.

56. The use of any one of claims 53-55, wherein the hematological cancer is an acute lymphocytic leukemia (ALL).

57. The use of any one of claims 53-55, wherein the hematological cancer is an acute myeloid leukemia (AML).

58. The use of any one of claims 53-57, wherein the hematological cancer is a NPM1-mutated leukemia.

59. The use of any one of claims 53-57, wherein the hematological cancer is a MLL-r leukemia.

60. The use of any one of claims 53-59, wherein the strong CYP3A4 inhibitor is selected from the group consisting of boceprevir, nefazodone, clarithromycin, nelfinavir, conivaptan, posaconazole, grapefruit juice, ritonavir, indinavir, saquinavir, itraconazole, telaprevir, ketoconazole, telithromycin, lopinavir, voriconazole, cobicistat, and mibefradil.

61. The use of any one of claims 53-59, wherein the strong CYP3A4 inhibitor is an azole antifungal.

62. The use of any one of claims 53-59, wherein the strong CYP3A4 inhibitor is posaconazole.

63. The use of any one of claims 53-59, wherein the strong CYP3A4 inhibitor is cobicistat.

64. The use of any one of claims 53-59, wherein the strong CYP3A4 inhibitor is ketoconazole.

65. The use of any one of claims 53-59, wherein the strong CYP3A4 inhibitor is ritonavir.

66. The use of any one of claims 53-59, wherein the strong CYP3A4 inhibitor is itraconazole.

67. The use of any one of claims 53-59, wherein the strong CYP3A4 inhibitor is voriconazole.

68. The use of any one of claims 53-59, wherein the strong CYP3A4 inhibitor is indinavir.

69. The use of any one of claims 53-68, wherein the menin inhibitor is for use at a daily dosage of from 300 mg/day to 340 mg/day.

70. The use of any one of claims 53-69, wherein the menin inhibitor is to be administered at a daily dosage of about 310 mg/day.

71. The use of any one of claims 53-69, wherein the menin inhibitor is to be administered at a daily dosage of about 320 mg/day.

72. The use of any one of claims 53-69, wherein the menin inhibitor is to be administered at a daily dosage of about 330 mg/day.

73. The use of any one of claims 53-72, wherein the strong CYP3A4 inhibitor is to be administered at a daily dosage of from 50 mg/day up to, and including, 1,000 mg/day.

74. The use of any one of claims 53-73, wherein the daily dosage is divided into multiple administrations which are to be administered twice daily.

75. The use of any one of claims 53-74, wherein the menin inhibitor and the strong CYP3A4 inhibitor are in combined dosage forms or separate dosage forms.

76. The use of any one of claims 1-30, the kit of any one of claims 31-52, or the use of any one of claims 53-75, wherein the menin inhibitor is to be administered as a pharmaceutically acceptable salt.

77. The use of any one of claims 1-30, the kit of any one of claims 31-52, or the use of any one of claims 53-75, wherein the menin inhibitor is a fumarate salt.

78. The use of any one of claims 1-30, the kit of any one of claims 31-52, or the use of any one of claims 53-75, wherein the menin inhibitor is a sesquifumarate salt.