demonstrating broad activity against MYD88-mutant B-cell lymphomas.

[0006] A need exists to develop dosing and schedules for IRAKIMiD degraders, which synergistically combine the activity of both IRAK4 and IMiD substrate degradation to exploit complimentary pathway signaling, to improve upon the efficacy of IRAK4 kinase inhibitors and other therapies and provide single-agent activity in MYD88-mutant B-cell lymphoma.

SUMMARY ~~OF THE INVENTION~~

[0007] It has been found that certain IRAK4 degraders are suitable for enteral and parental administration in a patient for treating a MYD88-mutated B-cell lymphoma. Accordingly, in one ~~aspect~~example, the present ~~invention~~disclosure provides a method of treating a MYD88-mutant B-cell lymphoma in a patient in need thereof, comprising administering a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof to the patient, wherein Compound A is N-(2-((1r,4r)-4-((6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)-2-azaspiro[3.3]heptan-2-yl)methyl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide.

[0007a] In an aspect of the present disclosure, there is provided a use of Compound A, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a MYD88-mutant B-cell lymphoma in a patient in need thereof; wherein Compound A is N-(2-((1r,4r)-4-((6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)-2-azaspiro[3.3]heptan-2-yl)methyl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide.

[0008] In one ~~aspect~~example, Compound A or a pharmaceutically acceptable salt thereof is administered at a dose of up to 300 mg, up to 400 mg, up to 900 mg, or up to 1600 mg to the patient. In other ~~aspect~~examples, Compound A or a pharmaceutically acceptable salt thereof is administered at a dose of from about 300 mg to about 900 mg or from about 100 mg to about 300 mg. In some instances, Compound A or a pharmaceutically acceptable salt thereof is administered at a dose of from about 30 mg/m^2 to about 90 mg/m^2 or from about 10 mg/m^2 to about 40 mg/m^2.

[0009] In one ~~aspect~~example, Compound A or a pharmaceutically acceptable salt thereof is administered orally to the patient. The oral administration of Compound A to the patient can include Compound A in solutions, suspensions, emulsions, tablets, pills, capsules, powders, or sustained-release formulations. In other ~~aspect~~example, Compound A or a pharmaceutically acceptable salt thereof is administered intravenously to the patient. The intravenous administration of Compound A to the patient can include Compound A in sterile injectable solutions.

[0010] In one ~~aspect~~example, Compound A or a pharmaceutically acceptable salt thereof is

administered to the patient once weekly (QW) or twice weekly (BIW). For biweekly dosing, the administration of Compound A or a pharmaceutically acceptable salt thereof can be on day 1 and day 2 of the week or on day 1 and day 4 of the week. In some ~~embodiment~~examples, Compound A or a pharmaceutically acceptable salt thereof is administered to the patient once or twice weekly in week 1 and week 2 in a 3 week administration cycle. In some ~~embodiment~~examples, Compound A or a pharmaceutically acceptable salt thereof is administered to the patient once or twice weekly in week 1 and week 2 in a 4 week administration cycle. In some ~~embodiment~~examples,

Compound A or a pharmaceutically acceptable salt thereof is administered to the patient once or twice weekly in week 1 and week 2 in a 4 week administration cycle. In some ~~embodiment~~examples, Compound A or a pharmaceutically acceptable salt thereof is administered to the patient once or twice weekly in week 1 and week 3 in a 4 week administration cycle. In some ~~embodiment~~examples, Compound A or a pharmaceutically acceptable salt thereof is administered to the patient once or twice weekly in weeks 1-3 in a 4 week administration cycle.

[0011] Also provided herein, is a pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipient or carrier. In some ~~aspect~~examples, the one or more pharmaceutically acceptable excipient or carrier includes one or more diluents, preservatives, binders, lubricants, disintegrators, swelling agents, fillers, or stabilizers. In other ~~aspect~~examples, the one or more pharmaceutically acceptable excipient or carrier includes one or more buffers, surfactants, dispersants, emulsifiers, or viscosity modifying agents.

[0012] In further ~~aspect~~examples, the MYD88-mutant B-cell lymphoma is selected from ABC DLBCL, primary CNS lymphomas, primary extranodal lymphomas, Waldenström macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma and chronic lymphocytic leukemia. In some ~~embodiment~~examples, the patient receiving Compound A or a pharmaceutically acceptable salt thereof to treat a MYD88-mutant B-cell lymphoma has received at least one prior therapy. In some ~~embodiment~~examples, the patient is a human.

[0013] These and other ~~aspect~~examples of this disclosure will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain background information and procedures and are each hereby incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIG. 1 shows that Compound A is an approximately equipotent degrader of IRAK4 and Ikaros with approximately 70% degradation of both IRAK4 and Ikaros associated with CTG IC_{90}. Short exposure of Compound A (72 hrs) shows cell killing in vitro, differentiated from IMiDs.

[0015] FIG. 2 shows that Compound A leads to more potent regressions than Compound B in OCI-Ly10 tumor xenographs. Compound A shows regressions at 3 mpk x 21d in OCI-Ly10 with higher doses (≥10 mpk) showing more rapid and complete regressions.

[0016] FIG. 3 shows minimum efficacious doses for QW and BIW schedules of Compound A in OCI-Ly10 tumor xenographs.

[0017] FIG. 4 shows that Compound A gives sustained tumor PD effect in OCI-Ly10, supporting target coverage from intermittent dosing.

[0018] FIG. 5 shows lymphopenia results indicating lymphocyte changes are consistent between IV

CLAIMS

1. Use of Compound A, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating a MYD88-mutant B-cell lymphoma in a patient in need thereof~~,~~ ~~comprising administering a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof to the patient~~;

wherein Compound A is N-(2-((1r,4r)-4-((6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)-2-azaspiro[3.3]heptan-2-yl)methyl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide.

2. The ~~method~~use of claim 1, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered at a dose of up to 1600 mg to the patient.

3. The ~~method~~use of claim 1 or claim 2, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered at a dose of up to 900 mg to the patient.

4. The ~~method~~use of any one of claims 1-3, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered at a dose of up to 400 mg to the patient.

5. The ~~method~~use of any one of claims 1-4, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered at a dose of up to 300 mg to the patient.

6. The ~~method~~use of claim 1, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered at a dose of from about 300 mg to about 900 mg.

7. The ~~method~~use of claim 1, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered at a dose of from about 100 mg to about 300 mg.

8. The ~~method~~use of claim 1, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered at a dose of from about 30 mg/m^2 to about 90 mg/m^2.

9. The ~~method~~use of claim 1, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered at a dose of from about 10 mg/m^2 to about 40 mg/m^2.

10. The ~~method~~use of any one of claims 1-9, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered orally to the patient.

11. The ~~method~~use of claim 10, wherein ~~the oral administration of Compound A to the patient comprises~~ solutions, suspensions, emulsions, tablets, pills, capsules, powders, or sustained-release formulations of Compound A are to be orally administered to the patient.

12. The ~~method~~use of any one of claims 1-9, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered intravenously to the patient.

13. The ~~method~~use of claim 12, wherein ~~the intravenous administration of Compound A to the patient comprises~~ sterile injectable solutions of Compound A is to be intravenously administered to the patient.

14. The ~~method~~use of any one of claims 1-13, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered to the patient once weekly.

15. The ~~method~~use of any one of claims 1-13, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered to the patient twice weekly.

16. The ~~method~~use of claim 15, wherein ~~the administration of~~ Compound A or a pharmaceutically acceptable salt thereof is to be administered on day 1 and day 2 of the week.

17. The ~~method~~use of claim 15, wherein ~~the administration of~~ Compound A or a pharmaceutically acceptable salt thereof is to be administered on day 1 and day 4 of the week.

18. The ~~method~~use of any one of claims 1-13, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered to the patient once weekly in week 1 and week 2 in a 3 week administration cycle.

19. The ~~method~~use of any one of claims 1-13, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered to the patient twice weekly in week 1 and week 2 in a 3 week administration cycle.

20. The ~~method~~use of any one of claims 1-13, wherein Compound A or a pharmaceutically acceptable

salt thereof is to be administered to the patient once weekly in week 1 and week 2 in a 4 week administration cycle.

21. The ~~method~~use of any one of claims 1-13, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered to the patient twice weekly in week 1 and week 2 in a 4 week administration cycle.

~~22. The method of any one of claims 1-13, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient once weekly in week 1 and week 2 in a 4 week administration cycle.~~

~~23. The method of any one of claims 1-13, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient twice weekly in week 1 and week 2 in a 4 week administration cycle.~~

~~24~~22. The ~~method~~use of any one of claims 1-13, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered to the patient once weekly in week 1 and week 3 in a 4 week administration cycle.

~~25~~23. The ~~method~~use of any one of claims 1-13, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered to the patient twice weekly in week 1 and week 3 in a 4 week administration cycle.

~~26~~24. The ~~method~~use of any one of claims 1-13, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered to the patient once weekly in weeks 1-3 in a 4 week administration cycle.

~~27~~25. The ~~method~~use of any one of claims 1-13, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient twice weekly in weeks 1-3 in a 4 week administration cycle.

~~28~~26. The ~~method~~use of any one of claims 1-~~27~~25, wherein Compound A or a pharmaceutically acceptable salt thereof is to be administered as a pharmaceutical composition comprising one or more pharmaceutically acceptable excipient or carrier.

~~29~~27. The ~~pharmaceutical composition~~use of claim ~~28~~26, wherein the one or more pharmaceutically acceptable excipient or carrier comprises one or more diluents, preservatives, binders, lubricants, disintegrators, swelling agents, fillers, or stabilizers.

~~30~~28. The ~~pharmaceutical composition~~use of claim ~~28~~26, wherein the one or more pharmaceutically acceptable excipient or carrier comprises one or more buffers, surfactants, dispersants, emulsifiers, or viscosity modifying agents.

~~31~~29. The ~~method~~use of any one of claims 1-~~30~~28, wherein the MYD88-mutant B-cell lymphoma is selected from ABC DLBCL, primary CNS lymphomas, primary extranodal lymphomas, Waldenström macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma and chronic lymphocytic leukemia.

~~32~~30. The ~~method~~use of any one of claims 1-~~31~~29, wherein the patient has received at least one prior therapy.

~~33~~31. The ~~method~~use of any one of claims 1-~~32~~30, wherein the patient is a human.

~~34. Use of Compound A or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a MYD88-mutant B-cell lymphoma in a patient in need thereof;~~

~~wherein Compound A is N-(2-((1r,4r)-4-((6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)-2-azaspiro[3.3]heptan-2-yl)methyl)cyclohexyl)-5-(2-hydroxypropan-2-yl)benzo[d]thiazol-6-yl)-6-(trifluoromethyl)picolinamide.~~

~~35. The use of claim 34, wherein Compound A or a pharmaceutically acceptable salt thereof is administered at a dose of up to 1600 mg to the patient.~~

~~36. The use of claim 34 or claim 35, wherein Compound A or a pharmaceutically acceptable salt thereof is administered at a dose of up to 900 mg to the patient.~~

~~37. The use of any one of claims 34-36, wherein Compound A or a pharmaceutically acceptable salt thereof is administered at a dose of up to 400 mg to the patient.~~

~~38. The use of any one of claims 34-37, wherein Compound A or a pharmaceutically acceptable salt thereof is administered at a dose of up to 300 mg to the patient.~~

~~39. The use of claim 34, wherein Compound A or a pharmaceutically acceptable salt thereof is~~

~~administered at a dose of from about 300 mg to about 900 mg.~~

~~40. The use of claim 34, wherein Compound A or a pharmaceutically acceptable salt thereof is administered at a dose of from about 100 mg to about 300 mg.~~

~~41. The use of claim 34, wherein Compound A or a pharmaceutically acceptable salt thereof is administered at a dose of from about 30 mg/m^2 to about 90 mg/m^2.~~

~~42. The use of claim 34, wherein Compound A or a pharmaceutically acceptable salt thereof is administered at a dose of from about 10 mg/m^2 to about 40 mg/m^2.~~

~~43. The use of any one of claims 34-42, wherein Compound A or a pharmaceutically acceptable salt thereof is administered orally to the patient.~~

~~44. The use of claim 43, wherein the oral administration of Compound A to the patient comprises solutions, suspensions, emulsions, tablets, pills, capsules, powders, or sustained release formulations.~~

~~45. The use of any one of claims 34-42, wherein Compound A or a pharmaceutically acceptable salt thereof is administered intravenously to the patient.~~

~~46. The use of claim 45, wherein the intravenous administration of Compound A to the patient comprises sterile injectable solutions.~~

~~47. The use of any one of claims 34-46, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient once weekly.~~

~~48. The use of any one of claims 34-46, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient twice weekly.~~

~~49. The use of claim 48, wherein the administration of Compound A or a pharmaceutically acceptable salt thereof is on day 1 and day 2 of the week.~~

~~50. The use of claim 48, wherein the administration of Compound A or a pharmaceutically acceptable salt thereof is on day 1 and day 4 of the week.~~

~~51. The use of any one of claims 34-46, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient once weekly in week 1 and week 2 in a 3 week administration cycle.~~

~~52. The use of any one of claims 34-46, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient twice weekly in week 1 and week 2 in a 3 week administration cycle.~~

~~53. The use of any one of claims 34-46, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient once weekly in week 1 and week 2 in a 4 week administration cycle.~~

~~54. The use of any one of claims 34-46, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient twice weekly in week 1 and week 2 in a 4 week administration cycle.~~

~~55. The use of any one of claims 34-46, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient once weekly in week 1 and week 2 in a 4 week administration cycle.~~

~~56. The use of any one of claims 34-46, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient twice weekly in week 1 and week 2 in a 4 week administration cycle.~~

~~57. The use of any one of claims 34-46, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient once weekly in week 1 and week 3 in a 4 week administration cycle.~~

~~58. The use of any one of claims 34-46, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient twice weekly in week 1 and week 3 in a 4 week administration cycle.~~

~~59. The use of any one of claims 34-46, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient once weekly in weeks 1-3 in a 4 week administration cycle.~~

~~60. The use of any one of claims 34-46, wherein Compound A or a pharmaceutically acceptable salt thereof is administered to the patient twice weekly in weeks 1-3 in a 4 week administration cycle.~~

~~61. The use of any one of claims 34-60, wherein Compound A or a pharmaceutically acceptable salt thereof is administered as a pharmaceutical composition comprising one or more pharmaceutically acceptable excipient or carrier.~~

~~62. The pharmaceutical composition of claim 61, wherein the one or more pharmaceutically acceptable excipient or carrier comprises one or more diluents, preservatives, binders, lubricants, disintegrators, swelling agents, fillers, or stabilizers.~~

~~63. The pharmaceutical composition of claim 61, wherein the one or more pharmaceutically acceptable excipient or carrier comprises one or more buffers, surfactants, dispersants, emulsifiers, or viscosity modifying agents.~~

~~64. The use of any one of claims 34-63, wherein the MYD88-mutant B-cell lymphoma is selected from ABC DLBCL, primary CNS lymphomas, primary extranodal lymphomas, Waldenström macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma and chronic lymphocytic leukemia.~~

~~65. The use of any one of claims 34-64, wherein the patient has received at least one prior therapy.~~

~~66. The use of any one of claims 34-65, wherein the patient is a human.~~