[0007a] In one aspect, the present disclosure refers to the use of a c-KIT inhibitor; and one or more MAPKAP pathway inhibitors in the manufacture of a medicament for combination therapy to treat mastocytosis in a patient in need thereof. In another aspect, the present disclosure refers to a c-KIT inhibitor; and one or more MAPKAP pathway inhibitors for use in combination therapy for treating mastocytosis in a patient in need thereof.

[0007b] In yet another aspect, the present disclosure refers to the use of 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2- dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea, or a pharmaceutically acceptable salt thereof; and one or more MAPKAP pathway inhibitors in the manufacture of a medicament for combination therapy to treat mastocytosis in a patient in need thereof. In another aspect, the present disclosure refers to 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea, or a pharmaceutically acceptable salt thereof; and one or more MAPKAP pathway inhibitors for use in combination therapy for treating mastocytosis in a patient in need thereof.

[0007c] In still another aspect, the present disclosure refers to the use of a c-KIT inhibitor; and a RAF inhibitor in the manufacture of a medicament for combination therapy to treat mastocytosis in a patient in need thereof. In another aspect, the present disclosure refers to a c-KIT inhibitor; and a RAF inhibitor for use in combination therapy for treating mastocytosis in a patient in need thereof.

[0008] Also provided in the present disclosure are methods of treating mastocytosis in a patient in need thereof, comprising administering to the patient: an effective amount of a c-KIT inhibitor, *e.g.*, 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea (Compound A as described herein); and an effective amount of an inhibitor of a mitogen-activated protein kinase (MEK inhibitor), and/or an effective amount of an extracellular signal regulated kinase inhibitor (ERK inhibitor).

[0009] For example, provided herein is a method of treating a systemic mastocytosis in a patient in need thereof, comprising administering to the patient: an effective amount of 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea, or a pharmaceutically acceptable salt thereof; and an effective amount of an inhibitor of a mitogen-activated protein kinase (MEK inhibitor) or ERK inhibitor.

[00010] Also contemplated in this disclosure is a method of treating mastocytosis in a patient in need thereof, comprising administering to the patient: an effective amount of a c-KIT inhibitor; and an effective amount of a RAF inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[00011] Figure 1A shows graphical representations of cell proliferation following the indicated drug treatment with Compound A as compared to vehicle control in HMC1.1 V560G (left panel) and HMC1.2 V560G/D816V (right panel) cell lines.

[00012] Figure 1B shows graphical representations of cell proliferation following the indicated drug treatment with Compound B as compared to vehicle control in HMC1.1 V560G (left panel) and HMC1.2 V560G/D816V (right panel) cell lines.

[00013] Figure 2A shows a graphical representation of caspase activity following the indicated various treatments with Compound A and trametinib in the HMC1.2 V560G/D816V cell line.

[00014] Figure 2B provides a synergy matrix chart based on the combination index method for various treatments with Compound A and trametinib in the HMC1.2 V560G/D816V cell line.

[00015] Figure 2C provides a Combination Index Plot for the combination of Compound A with the MEK inhibitor trametinib.

CLAIMS

What is claimed is:

1. Use of a c-KIT inhibitor; and one or more MAPKAP pathway inhibitors in the manufacture of a medicament for combination therapy to treat mastocytosis in a patient in need thereof.

2. The use of claim 1, wherein the MAPKAP pathway inhibitor is selected from the group consisting of a mitogen-activated protein kinase (MEK inhibitor),an extracellular signal regulated kinase inhibitor (ERK inhibitor), and a rapidly accelerated fibrosarcoma (RAF) kinase inhibitor.

3. The use of claim 1 or 2 , wherein the mastocytosis has a c-KIT mutation.

4. The use of any one of claims 1-3, wherein the c-KIT mutation is an activating mutation.

5. The use of any one of claims 1-4, wherein the mastocytosis comprises mast cells having a primary mutation in exon 17 of a *c-KIT* gene.

6. The use of claim 5, wherein the primary mutation is a c-*KIT D816* mutation.

7. The use of claim 5 or 6, wherein the primary mutation is one of D816V, D816Y, D816F, D816H, F522C, K5091, V560G, V559G, and del419.

8. The use of any one of claims 5-6, wherein the primary mutation is D816V.

9. The use of any one of claims 1-8, wherein the mastocytosis comprises mast cells having a secondary *c-KIT* mutation.

10. The use of claim 9, wherein the secondary c-KIT mutation is in one of exon 9, 11, 13 or 17.

11. The use of claim 9 or 10, wherein the secondary c-KIT mutation is one of Y269C, Y503_F504insAY, V560D, or K642E mutation.

12. The use of any one of claims 6-11, further comprising determination if the mastocytosis has the c-KIT primary mutation.

13. The use of any one of claims 6-11, further comprising determination if the mastocytosis has the c-KIT secondary mutation.

14. The use of claims 12 or 13, wherein determination if the mastocytosis has the c-KIT primary or secondary mutation comprises identification of mutations in DNA extracted from a tumor sample.

15. The use of claims 12 or 13, wherein determination if the mastocytosis has the c-KIT primary or secondary mutation comprises identification of mutations in circulating tumor DNA or in circulating peripheral blood leukocytes.

16. The use of any one of claims 1-15, wherein the mastocytosis is systemic mastocytosis.

17. The use of claim 16, wherein the systemic mastocytosis is selected from the group consisting of indolent systemic mastocytosis, systemic smoldering mastocytosis, systemic mastocytosis with associated clonal hematological non-mast cell lineage disease, aggressive systemic mastocytosis, mast cell leukemia, and mast cell sarcoma.

18. The use of claim 16, wherein the mastocytosis is indolent systemic mastocytosis, optionally systemic mastocytosis with recurrent anaphylaxis or vascular collapse in the absence of skin lesions.

19. The use of claim 16, wherein the mastocytosis is systemic smoldering mastocytosis.

20. The use of claim 16, wherein the mastocytosis is systemic mastocytosis with associated clonal hematological non-mast cell lineage disease.

21. The use of claim 16, wherein the mastocytosis is aggressive systemic mastocytosis.

22. The use of claim 16, wherein the mastocytosis is mast cell leukemia or mast cell sarcoma.

23. The use of any one of claims 1-15, wherein the mastocytosis is cutaneous mastocytosis.

24. The use of claim 23, wherein the mastocytosis is selected from the group consisting of: maculopapular cutaneous mastocytosis, mastocytoma, or diffuse cutaneous mastocytosis.

25. The use of any one of claims 1-24, wherein the c-KIT inhibitor is selected from the group consisting of 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea or a pharmaceutically acceptable salt thereof, midostaurin or a pharmaceutically acceptable salt thereof, imatinib mesylate, sunitinab malate, midostaurin, regorafenib, crenolanib, PTX9486, or BLU-285 or a pharmaceutically acceptable salt thereof.

26. The use of any one of claims 2-25, wherein the MEK inhibitor is selected from the group consisting of trametinib, selumetinib, cobimetinib, and binimetinib.

27. The use of any one of claims 2-26 , wherein the MEK inhibitor is binimetinib.

28. The use of any one of claims 2-27, wherein the MEK inhibitor is trametinib.

29. The use of any one of claims 2-25, wherein the ERK inhibitor is selected from the group consisting of ulixertinib, SCH772984, and LY3214996.

30. The use of any one of claims 2-29, wherein the c-KIT inhibitor and the MEK and/or ERK inhibitor are to be administered substantially concurrently or sequentially.

31. The use of any one of claims 1-30, further comprising administration of another cancer-targeted therapeutic agent, cancer-targeted biological, immune checkpoint inhibitor, or chemotherapeutic agent.

32. The use of any one of claims 1-31, wherein after two weeks or more of administration, the patient has at least a partial remission.

33. Use of 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea, or a pharmaceutically acceptable salt thereof; and one or more MAPKAP pathway inhibitors in the manufacture of a medicament for combination therapy to treat mastocytosis in a patient in need thereof.

34. The use of claim 33, wherein the MAPKAP pathway inhibitor is selected from the group consisting of a mitogen-activated protein kinase (MEK inhibitor),and an extracellular signal regulated kinase inhibitor (ERK inhibitor).

35. The use of claim 33 or 34, wherein the systemic mastocytosis has a c-KIT mutation.

36. The use of claim 33 or 34, wherein the mutation is a c-*KIT D816* mutation.

37. The use of claim 36, wherein the mutation is one of D816V, D816Y, D816F, D816H, F522C, K5091, V560G, V559G, and del419.

38. The use of claim 37, wherein the mutation is one of: A553D, C433Y, D419Y,D572A, D816F, D816H,D816I, D816V, D816Y, D820G, del419, dup(501-502), E839K, F522C, I817V, InsFF419, InsV815-I816, K509I, N822I, R815K, T417V, V560G, V559I or Y418Y.

39. The use of any one of claims 34-38, wherein the mutation is D816V.

40. The use of any one of claims 34-38, wherein the mastocytosis has a further c-KITmutation that is one of Y269C, Y503_F504insAY, V560D, or K642E mutation.

41. The use of any one of claims 34-40, wherein the MEK inhibitor is selected from the group consisting of trametinib, selumetinib, cobimetinib, and binimetinib.

42. The use of any one of claims 34-40, wheren the MEK inhibitor is binimetinib.

43. The use of any one of claims 34-40, wheren the MEK inhibitor is trametinib.

44. The use of any one of claims 34-42, wherein the ERK inhibitor is selected from the group consisting of ulixertinib, SCH772984, and LY3214996.

45. Use of a c-KIT inhibitor; and a RAF inhibitor in the manufacture of a medicament for combination therapy to treat mastocytosis in a patient in need thereof.

46. The use of claim 44, wherein the RAF inhibitor is a pan-RAF or B-RAF inhibitor.

47. The use of claim 44 or 45, wherein the c-KIT inhibitor is 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea, or a pharmaceutically acceptable salt thereof.

48. A c-KIT inhibitor; and one or more MAPKAP pathway inhibitors for use in combination therapy for treating mastocytosis in a patient in need thereof.

49. 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea, or a pharmaceutically acceptable salt thereof; and one or more MAPKAP pathway inhibitors for use in combination therapy for treating mastocytosis in a patient in need thereof.

50. A c-KIT inhibitor; and a RAF inhibitor for use in combination therapy for treating mastocytosis in a patient in need thereof.