each patient. The complex c-KIT mutational heterogeneity within individual patients underscores an unmet medical need to identify inhibitors of c-KIT kinase that are effective across a broad spectrum of c-KIT primary and secondary mutations. In addition, there is a need to identify therapies that are cytotoxic, or cytocidal, to c-KIT-mediated GISTs, as opposed to merely being cytostatic, and which result in disease remission and/or reduced disease recurrence.

SUMMARY

[0007] The instant disclosure is drawn to the combination of the c-KIT inhibitor Compound A or the c-KIT inhibitor Compund B with an inhibitor of the MAPKAP kinase signaling pathway. Herein, the MAPKAP pathway is defined as the signaling through the kinases RAF → MEK → ERK. It has been unexpectedly demonstrated that combination of the c-KIT inhibitor Compound A or Compound B with a MEK inhibitor, including trametinib, an ERK inhibitor including ulixertinib, or a RAF inhibitor including LY3009120 leads to cell death, apoptosis, or prolonged cell stasis of GIST cells, enhanced GIST tumor regression in vivo, or eradication of GIST cells in colony formation assays as compared to a combination of imatinib with a MEK inhibitor or to single agent treatment with Compound A, imatinib, or a MEK inhibitor. Additionally it has been demonstrated that combination of the c-KIT inhibitor Compound A with a MEK inhibitor leads to enhanced cell death or apoptosis and eradication of GIST cancer cell lines that are resistant to imatinib in combination with a MEK inhibitor. In colony outgrowth studies in GIST cells, Compound A exhibited superior synergy in combination with a MEK inhibitor compared to imatinib in combination with a MEK inhibitor. This disclosure, in part, relates to methods of treating tumors in patients using Compound A as described herein or a pharmaceutically acceptable salt thereof.

[0007a] In one 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 kinase inhibitors in the manufacture of a medicament for combination therapy to treat a tumor having one or more c-KIT mutations in a patient in need thereof.

[0007b] In 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 in the manufacture of a medicament

for use in combinatorial therapy for treating a solid tumor in an imatinib resistant patient, wherein said medicament is to be administered to the patient with a MAPKAP kinase inhibitor selected from the group consisting of trametinib, binimetinib, cobimetinib, and ulixertinib, wherein the solid tumor is selected from the group consisting of lung adenocarcinoma, squamous cell lung cancer, glioblastoma, pediatric glioma, astrocytoma, sarcoma, gastrointestinal stromal tumor (GIST), and melanoma.

[0007c] 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 in the manufacture of a medicament for use in combinatorial therapy for treating an imatinib resistant gastrointestinal stromal tumor or imatinib resistant melanoma in a patient in need thereof, wherein said medicament is to be administered with a MAPKAP kinase inhibitor selected from the group consisting of trametinib, binimetinib, cobimetinib, and ulixertinib.

[0007d] 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 in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in a patient in need thereof,wherein said medicament is to be administered in combination with a RAF inhibitor.

[0007e] 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 in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in a patient in need thereof, wherein said medicament is to be administered with a MAPKAP kinase inhibitor selected from the group consisting of trametinib, binimetinib, cobimetinib, and ulixertinib, wherein the solid tumor is selected from the group consisting of lung adenocarcinoma, squamous cell lung cancer, glioblastoma, pediatric glioma, astrocytoma, sarcoma, gastrointestinal stromal tumor (GIST), and melanoma.

[0007f] In still 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 in the manufacture of a medicament for use in combinatorial therapy for treating a gastrointestinal stromal tumor or melanoma in a patient in need thereof, wherein said medicament is to be administered in combination with a MAPKAP kinase inhibitor selected from the group consisting of trametinib, binimetinib, cobimetinib, and ulixertinib.

[0007g] In yet 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 kinase inhibitors for use in combination therapy for treating a tumor having one or more c-KIT mutations in a patient in need thereof.

[0007h] In yet 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 a RAF inhibitor for use in combination therapy for treating a solid tumor in a patient in need thereof.

[0008] For example, described herein is a method of treating a tumor having one or more c-KIT mutations 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 a mitogen-activated protein kinase inhibitor (MEK inhibitor) and/or an effective amount of an extracellular signal regulated kinase inhibitor (ERK inhibitor).

[0009] This disclosure also provides a method of treating a solid tumor in an imatinib resistant patient, 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 administering to the patient an effective amount of a MEK or ERK inhibitor selected from the group consisting of trametinib, binimetinib, cobimetinib, and ulixertinib wherein the solid tumor is selected from the group consisting of lung adenocarcinoma, squamous cell lung cancer, glioblastoma, pediatric glioma, astrocytoma, sarcoma, gastrointestinal stromal tumor (GIST), and melanoma.

[00010] A method of treating an imatinib resistant gastrointestinal stromal tumor or imatinib resistant melanoma in a patient in need thereof is also contemplated herein, 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 administering to the patient an effective amount of a MEK or ERK inhibitor selected from the group consisting of trametinib, binimetinib, cobimetinib, and ulixertinib.

[00011] This disclosure also provides a method of treating a solid tumor 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 administering to the patient an effective amount of a MEK or ERK inhibitor selected from the group consisting of trametinib, binimetinib, cobimetinib, and ulixertinib wherein the solid tumor is selected fromthe group consisting of lung adenocarcinoma, squamous cell lung cancer, glioblastoma, pediatric glioma, astrocytoma, sarcoma, gastrointestinal stromal tumor (GIST), and melanoma.

[00012] A method of treating an gastrointestinal stromal tumor or melanoma in a patient in need thereof is also contemplated herein, 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 administering to the patient an effective amount of a MEK or ERK inhibitor selected from the group consisting of trametinib, binimetinib, cobimetinib, and ulixertinib.

[00013] Additionally contemplated herein is a method of treating a solid tumor in a patient 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 administering to the patient an effective amount of a RAF inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[00014] Figure 1A shows a graphical representation of Caspase activity following various treatments with Compound A and trametinib for 24 hours in GIST-T1 cells.

[00015] Figure 1B provides a synergy matrix chart based on the combination index method for various treatments with Compound A and trametinib for 24 hours in GIST-T1 cells and a Combination Index Plot demonstrating synergy graphed as combination index (CI) on the y-axis and Fraction affected (Fa) on the x-axis.

[00016] Figure 1C shows a graphical representation of Caspase activity following various treatments with Compound A and trametinib for 48 hours in GIST-T1 cells.

[00017] Figure 1D provides a synergy matrix chart based on the combination index method for various treatments with Compound A and trametinib for 48 hours in GIST-T1 cells and a Combination Index Plot demonstrating synergy graphed as combination index (CI) on the y-axis and Fraction affected (Fa) on the x-axis.

[00018] Figure 1E shows a graphical representation of Caspase activity following various treatments with Compound A and trametinib for 24 hours in GIST-T1/D816E imatinib resistant cells.

[00019] Figure 1F provides a synergy matrix chart based on the combination index method for various treatments with Compound A and trametinib for 24 hours in GIST-T1/D816E imatinib resistant cells and a Combination Index Plot demonstrating synergy graphed as combination index (CI) on the y-axis and Fraction affected (Fa) on the x-axis.

[00020] Figure 1G shows a graphical representation of Caspase activity following various treatments with Compound A and trametinib for 24 hours in GIST-T1/T670I imatinib resistant cells.

[00021] Figure 1H provides a synergy matrix chart based on the combination index method for various treatments with Compound A and trametinib for 24 hours in GIST-

CLAIMS

What is claimed is:

1. 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 kinase inhibitors in the manufacture of a medicament for combination therapy to treat a tumor having one or more c-KIT mutations in a patient in need thereof.

2. The use of claim 1, wherein the MAPKAP kinase inhibitor is selected from the groups consisting of a mitogen-activated protein kinase inhibitor (MEK inhibitor) and an effective amount of an extracellular signal regulated kinase inhibitor (ERK inhibitor).

3. The use of claim 1 or 2, wherein the c-KIT mutation is a primary mutation in exon 9, exon 11, exon 13, or exon 17 of the *c-KIT* gene.

4. The use of any one of claims 1-3, wherein the tumor has one or more secondary resistance mutations in the *c-KIT* gene.

5. The use of claim 4, wherein the secondary resistance mutation is in exon 13, exon 14, exon 17, or exon 18 of the *c-KIT* gene.

6. The use of claim 5, wherein the secondary resistance mutation is in exon 17 of the *c-KIT* gene.

7. The use of any one of claims 1-6, wherein the c-KIT mutation is a deletion mutation.

8. The use of any one of claims 4-6, wherein the secondary resistance mutation is the substitution of aspartic acid in codon 816 or the substitution of asparagine in codon 822.

9. The use of any one of claims 4-6, wherein the secondary resistance mutation is one of D816V, D816E, D816H, D820A, T670I, or N822V.

10. The use of any one of claims 4-5, wherein the secondary resistance mutation is one of V654A or T670I.

11. The use of any one of claims 4-10, wherein the secondary resistance mutation was acquired after previous administration of imatinib, sunitinib or regorafenib, or a pharmaceutically acceptable salt thereof to the patient.

12. The use of any one of claims 4-11, further comprising determination if the tumor has the c-KIT secondary mutation.

13. The use of any one of claims 4-12, wherein determination if the tumor has the c-KIT secondary mutation comprises identification of mutations in DNA extracted from a tumor sample.

14. The use of any one of claims 4-12, wherein determination if the tumor has the c-KIT secondary mutation comprises identification of mutations in circulating tumor DNA.

15. The use of any one of claims 1-14, wherein the tumor was resistant to treatment with imatinib mesylate, sunitinib malate, or regorafenib.

16. The use of any one of claims 1-15, wherein the tumor is selected from the group consisting of lung adenocarcinoma, squamous cell lung cancer, glioblastoma, pediatric glioma, astrocytoma, sarcoma, gastrointestinal stromal tumor (GIST), and melanoma.

17. The use of claim 16, wherein the tumor is melanoma.

18. The use of claim 16, wherein the tumor is GIST.

19. The use of any one of claims 1-18, further comprising administration to the patient a cancer targeted therapeutic agent, cancer-targeted biological, immune checkpoint inhibitor, immunomodulatory agent, and/or chemotherapeutic agent.

20. The use of any one of claims 1-19, further comprising administration of a RAF inhibitor.

21. The use of any one of claims 1-20, wherein the 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea, or the pharmaceutically acceptable salt thereof, and the MAPKAP kinase inhibitor is to be administered substantially concurrently or sequentially.

22. The use of any one of claims 2-21, wherein the MEK inhibitor is selected from the group consisting of trametinib, selumetinib, cobimetinib, and binimetinib.

23. The use of any one of claims 2-22, wherein the MEK inhibitor is binimetinib.

24. The use of any one of claims 2-22, wherein the MEK inhibitor is trametinib.

25. The use of any one of claims 2-21, wherein the ERK inhibitor is selected from the group consisting of ulixertinib, SCH772984, and LY3214996.

26. The use of any one of claims 2-25, wherein upon administration for two weeks or more, the patient has partial reduction in tumor volume of at least 30%.

27. The use of any one of claims 1-26, wherein the treatment results in a complete reduction in tumor volume.

28. The use of any one of claims 1-27, further comprising determination if the tumor or tumor cells comprise a primary *c-KIT* gene mutation.

29. The use of claim 28, wherein the primary mutation is in exon 11 of the *c-KIT* gene.

30. The use of claim 28, wherein the primary mutation is in exon 9 of the *c-KIT* gene.

31. The use of any of claims 28-30, wherein the primary mutation is a deletion mutation.

32. The use of any one of claims 28-30, wherein the primary mutation is V560D.

33. The use of any one of claims 1-32, wherein one or more additional secondary mutations *c-KIT* mutations are present.

34. 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 in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in an imatinib resistant patient, wherein said medicament is to be administered to the patient with a MAPKAP kinase inhibitor selected from the group consisting of trametinib, binimetinib, cobimetinib, and ulixertinib, wherein the solid tumor is selected from the group consisting of lung adenocarcinoma, squamous cell lung cancer, glioblastoma, pediatric glioma, astrocytoma, sarcoma, gastrointestinal stromal tumor (GIST), and melanoma.

35. The use of claim 34, further comprising administration of a RAF inhibitor.

36. The use of claim 35, wherein the RAF inhibitor is a pan-RAF inhibitor.

37. 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 in the manufacture of a medicament for use in combinatorial therapy for treating an imatinib resistant gastrointestinal stromal tumor or imatinib resistant melanoma in a patient in need thereof, wherein said medicament is to be administered with a MAPKAP kinase inhibitor selected from the group consisting of trametinib, binimetinib, cobimetinib, and ulixertinib.

38. The use of claim 37, further comprising determination whether the tumor has a mutation of the *c-KIT* gene.

39. The use of claim 38, wherein the mutation is in exon 17 of the *c-KIT* gene.

40. The use of claim 38 or 39, wherein the *c-KIT* mutation is the substitution of aspartic acid in codon 816 or the substitution of asparagine in codon 822.

41. The use of claim 38 or 39, wherein the mutation is one of D816V, D816E, D816H, D820A, T670I, or N822V.

42. The use of claim 38, wherein the mutation is an exon 13 V654A mutation or an exon 14 T670I mutation.

43. 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 in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in a patient in need thereof,wherein said medicament is to be administered in combination with a RAF inhibitor.

44. The use of claim 43, wherein the solid tumor is selected from the group consisting of

lung adenocarcinoma, squamous cell lung cancer, GIST, and melanoma.

45. The use of claim 43 or 44, wherein the solid tumor has one or more mutations of the *c-KIT* gene.

46. The use of any one of claims 43-45, wherein the RAF inhibitor is a pan-RAF inhibitor.

47. The use of any one of claims 43-46, wherein the RAF inhibitor is dabrafenib or LY3009120.

48. 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 in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in a patient in need thereof, wherein said medicament is to be administered with a MAPKAP kinase inhibitor selected from the group consisting of trametinib, binimetinib, cobimetinib, and ulixertinib, wherein the solid tumor is selected from the group consisting of lung adenocarcinoma, squamous cell lung cancer, glioblastoma, pediatric glioma, astrocytoma, sarcoma, gastrointestinal stromal tumor (GIST), and melanoma.

49. The use of claim 48, further comprising administration of a RAF inhibitor.

50. The use of claim 49, wherein the RAF inhibitor is a pan-RAF inhibitor.

51. 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 in the manufacture of a medicament for use in combinatorial therapy for treating a gastrointestinal stromal tumor or melanoma in a patient in need thereof, wherein said medicament is to be administered in combination with a MAPKAP kinase inhibitor selected from the group consisting of trametinib, binimetinib, cobimetinib, and ulixertinib.

52. The use of claim 51, further comprising determination whether the tumor has a mutation of the *c-KIT* gene.

53. The use of claim 52, wherein the mutation is in exon 17 of the *c-KIT* gene.

54. The use of claim 52 or 53, wherein the *c-KIT* mutation is the substitution of aspartic acid in codon 816 or the substitution of asparagine in codon 822.

55. The use of claim 52 or 53, wherein the mutation is one of D816V, D816E, D816H, D820A, T670I, or N822V.

56. The use of claim 52, wherein the mutation is an exon 13 V654A mutation or an exon 14 T670I mutation.

57. 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 kinase inhibitors for use in combination therapy for treating a tumor having one or more c-KIT mutations in a patient in need thereof.

58. 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 a RAF inhibitor for use in combination therapy for treating a solid tumor in a patient in need thereof.