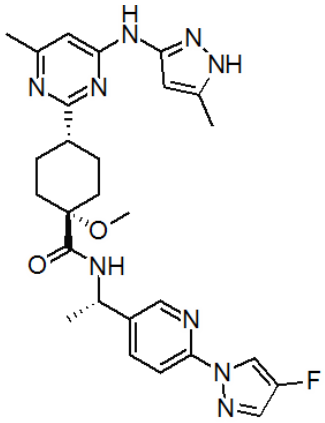
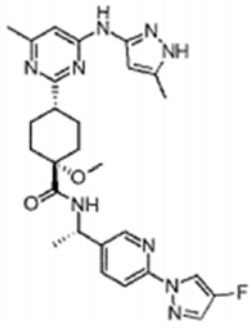


(Compound 1)

[0011] In March 2017, Compound 1 (also known as BLU-667) entered Phase I clinical trials in the United States for the treatment of patients with thyroid cancer, non-small cell lung cancer, and other advanced solid tumors (NCT03037385). WO 2017/079140, incorporated herein by reference, describes the synthesis of Compound 1 (Example Compound 130) and also discloses the therapeutic activity of this molecule to inhibit, regulate, and/or modulate RET kinase (Assays, Example 10 on pp. 72-74).

[0011a] In one aspect of the present disclosure, there is provided a use of Compound 1 in the manufacture of a medicament for treating a subject afflicted with a solid tumor having an activating rearranged during transfection (RET) alteration, wherein 100 mg to 400 mg of Compound 1 or a pharmaceutically acceptable salt thereof is to be administered to the subject once daily, wherein Compound 1 is:



(Compound 1).

BRIEF DESCRIPTION OF THE FIGURES

[0012] FIGs. 1A, 1B, and 1C are a series of bar graphs which show the impact of Compound 1 on expression of DUSP6 and SPRY4 in LC2/ad (FIG. 1A), MZ-CRC-1 (FIG. 1B), and TT (FIG. 1C) cells.

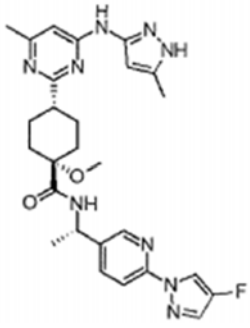
[0013] FIG. 2 is a bar graph which shows the sustained decrease in expression of the MAPK target genes DUSP6 and SPRY4 in a KIF5B-RET NSCLC PDX model.

[0014] FIG. 3 is a graph which shows in vivo anti-tumor activity of Compound 1 in a cabozantinib-resistant tumor model generated from an engineered KIF5B-RET V804L cell line.

[0015] FIG. 4A is a graph which shows tumor size and levels of calcitonin and CEA (carcinoembryonic antigen) decrease over the course of treatment with Compound 1. The RET-mutant MTC patient (RET L629P, D631_R635DELINSG, V637R MTC) was treated with 60 mg once daily and then received successive dose escalation up to 300 mg once daily. FIG. 4B is a CT scan of the same RET-mutant MTC patient of FIG. 4A at baseline (top) and after 8 weeks of Compound 1 treatment (bottom) demonstrating rapid reduction in tumor growth. FIG. 4C is a graph which shows tumor size and the levels of calcitonin and CEA decrease in a patient with RET M918T-mutant MTC over the course of treatment with Compound 1 with 300 mg once daily. FIG. 4D is a CT scan of the RET M918T-mutant patient of FIG. 4C's tumor

Claims:

1. Use of Compound 1 in the manufacture of a medicament for treating a subject afflicted with a solid tumor having an activating rearranged during transfection (RET) alteration, wherein 100 mg to 400 mg of Compound 1 or a pharmaceutically acceptable salt thereof is to be administered to the subject once daily, wherein Compound 1 is:



(Compound 1).

2. The use of claim 1, wherein the amount to be administered is 300 mg.

3. The use of claim 1, wherein the amount to be administered is 400 mg.

4. The use of claim 1, wherein the amount to be administered is 100 mg.

5. The use of any one of claims 1-4, wherein the solid tumor is chosen from papillary thyroid carcinoma (PTC), medullary thyroid cancer (MTC), pheochromocytoma (PCC), pancreatic ductal adenocarcinoma, multiple endocrine neoplasia (MEN2A and MEN2B), metastatic breast cancer, testicular cancer, small cell lung cancer, non-small cell lung cancer (NSCLC), colorectal cancer, ovarian cancer, inflammatory myofibroblastic tumor, and cancer of the salivary gland.

6. The use of any one of claims 1-4, wherein the solid tumor is chosen from esophageal cancer, skin cancer (non-melanoma), endometrial cancer, head and neck cancer, bladder cancer, prostate cancer, hematological cancer, soft tissue sarcoma, renal cell carcinoma (RCC), non-Hodgkin lymphoma, hepatobiliary cancer, adrenocortical carcinoma, myelodysplasia (MDS), uterine sarcoma, germ cell tumor, cervical cancer, central nervous system cancer, bone cancer, ampullary carcinoma, gastrointestinal stromal tumor, small bowel cancer, mesothelioma, rectal cancer, paraganglioma, and intrahepatic bile duct cancer.

7. The use of any one of claims 1-4, wherein the solid tumor is chosen from adenocarcinoma, spitzoid neoplasm, lung adenocarcinoma, adenosquamous carcinoma, colon cancer, metastatic

colon cancer, metastatic papillary thyroid cancer, diffuse sclerosing variant of papillary thyroid cancer, , diffuse gastric cancer, thyroid gland carcinoma, and bronchioles lung cell carcinoma.

8. The use of any one of claims 1-4, wherein the solid tumor is chosen from hepatobiliary cancer, ampullary carcinoma, small bowel cancer, intrahepatic bile duct cancer, metastatic colon cancer, brain cancer associated with lung cancer, brain metastasis associated with lung cancer, and retropentoneal paraganglioma.

9. The use of any one of claims 1-4, wherein the solid tumor is chosen from medullary thyroid cancer (MTC) and non-small cell lung cancer (NSCLC).

10. The use of claim 9, wherein the solid tumor is chosen from sporadic MTC, metastatic RET-altered NSCLC, tyrosine kinase inhibitor (TKI)-refractory KIF5B-RET NSCLC, and KIF5B-RET NSCLC.

11. The use of any one of claims 1-4, wherein the solid tumor is chosen from a brain cancer associated with a lung cancer.

12. The use of claim 11, wherein the brain cancer is brain metastasis.

13. The use of any one of claims 1-12, wherein the activating RET alteration comprises a RET mutation or a RET gene rearrangement (fusion).

14. The use of any one of claims 1-12, wherein the activating RET alteration is a RET mutation.

15. The use of claim 13 or 14, wherein the RET mutation is a point mutation.

16. The use of any one of claims 13-15, wherein the RET mutation is a resistance mutation.

17. The use of any one of claims 1-4, wherein the solid tumor is thyroid cancer or non-small cell lung cancer (NSCLC).

18. The use of any one of claims 1-4, wherein the solid tumor is RET-altered thyroid cancer.

19. The use of claim 18, wherein the RET-altered thyroid cancer has a RET fusion.

20. The use of claim 19, wherein the RET fusion is selected from the group consisting of CCDC6-RET, PTClex9-RET, NCOA4-RET, TRIM33-RET, ERC1-RET, MBD1-RET, RAB61P2-RET, PRKAR1A-RET, TRIM24-RET, KTN1-RET, GOLGA5-RET, HOOK3-RET, KIAA1468-RET, TRIM27-RET, AKAP13-RET, FKBP15-RET, SPECC1L-RET, TBL1XR1-RET, ACBD5-RET, KIAA1217-RET, and MYH13-RET.

21. The use of any one of claims 18-20, wherein the RET-altered thyroid cancer has a RET mutation.

22. The use of claim 21, wherein the RET mutation is V804L, V804M, or V804E.

23. The use of claim 21, wherein the RET mutation is M918T.

24. The use of claim 21, wherein the RET mutation is C609Y, C609S, C609G, C609R, C609F, C609W, C611R, C611S, C611G, C611Y, C611F, C611W, C618S, C618Y, C618R, C618Y, C618G, C618F, C618W, C620S, C620W, C620R, C620G, C620L, C620Y, C620F, C630A, C630R, C630S, C630Y, C630F, C634W, C634Y, C634S, C634F, C634G, C634L, C634A, or C634T.

25. The use of claim 21, wherein the RET mutation is L709F.

26. The use of claim 21, wherein the RET mutation is R844W, R844Q, or R844L.

27. The use of claim 21, wherein the RET mutation is A883F, A883S, or A883T.

28. The use of claim 21, wherein the RET mutation is K666E, K666E, K666M, or K666N

29. The use of any one of claims 18-28, wherein the RET-altered thyroid cancer is papillary thyroid cancer.

30. The use of any one of claims 18-28, wherein the thyroid cancer is radioactive iodine (RAI) refractory.

31. The use of any one of claims 18-28, wherein the RET-altered thyroid cancer is medullary thyroid cancer.

32. The use of any one of claims 18-28, wherein the RET-altered thyroid cancer is selected from differentiated thyroid cancer, follicular thyroid cancer, and anaplastic thyroid cancer.

33. The use of any one of claims 1-4, wherein the solid tumor is RET-mutant medullary thyroid cancer.

34. The use of any one of claims 1-4, wherein the solid tumor is RET-fusion thyroid cancer.

35. The use of any one of claims 1-4, wherein the solid tumor is RET-altered NSCLC.

36. The use of claim 35, wherein the NSCLC is metastatic NSCLC.

37. The use of claim 35 or 36, wherein the NSCLC has a RET mutation or a RET fusion.

38. The use of claim 37, wherein the NSCLC has a RET fusion.

39. The use of claim 38, wherein the RET fusion is selected from the group consisting of KIF5B-RET, CCDC6-RET, NCOA4-RET, TRIM33-RET, KIAA1217-RET, and MPRIP-RET.

40. The use of claim 39, wherein the RET fusion is KIF5B-RET.

41. The use of claim 39, wherein the RET fusion is CCDC6-RET.

42. The use of any one of claims 1-4, wherein the solid tumor is RET-altered intrahepatic bile duct carcinoma.

43. The use of claim 42, wherein the solid tumor is intrahepatic bile duct carcinoma having a NCOA4-RET fusion.

44. The use of any one of claims 1-43, wherein the subject has not received prior treatment with a multikinase RET inhibitor.

45. The use of any one of claims 1-43 wherein the subject has received one or more prior treatments with a multikinase RET inhibitor.

46. The use of claim 45, wherein the multikinase RET inhibitor is chosen from lenvatinib, vandetanib, cabozantinib, and RXDX-105.

47. The use of any one of claims 1-43, wherein the subject has not received prior treatment with platinum.

48. The use of any one of claims 1-43, wherein the subject has received prior treatment with platinum.

49. The use of any one of claims 1-43, wherein the subject has received prior treatment with a selective RET inhibitor.

50. The use of any one of claims 1-43, wherein the subject has not received prior chemotherapy.

51. The use of any one of claims 1-43, wherein the subject has received prior chemotherapy.

52. The use of claim 51, wherein the prior chemotherapy is chosen from carboplatin, pemetrexed, abraxane, cisplatin, bevacizumab, and combinations thereof.

53. The use of any one of claims 1-44, wherein the subject has not received prior immunotherapy.

54. The use of any one of claims 1-44, wherein the subject has received prior immunotherapy.

55. The use of claim 54, wherein the prior immunotherapy is chosen from ipilimumab, pembrolizumab, nivolumab, MPDL3280A, MEDI4736, and combinations thereof.