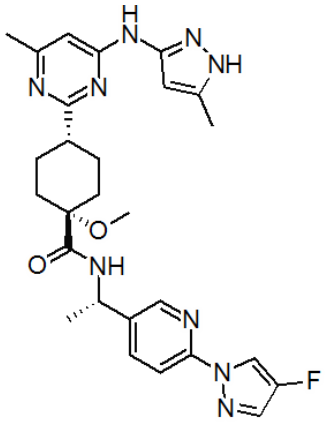
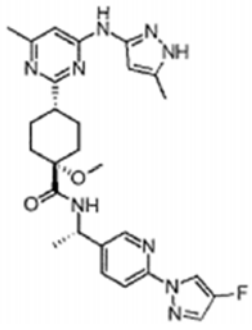


(Compound 1)

[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).

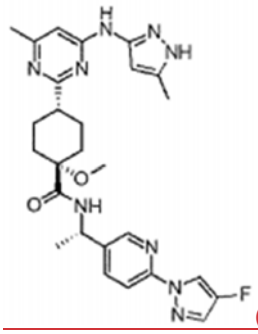
[0011a] In one aspect of the present disclosure, there is provided a use of Compound 1 in the manufacture of a medicament for treating a rearranged during transfection (RET) altered cancer in a subject in need thereof, wherein ~~100~~300 mg ~~to~~or 400 mg of Compound 1 or a pharmaceutically acceptable salt thereof is to be administered to the subject once daily, wherein Compound 1 is:



(Compound 1),

and wherein the RET alteration comprises a RET mutation or a RET fusion, and wherein the RET altered cancer is selected from non-small cell lung cancer (NSCLC) and thyroid cancer.

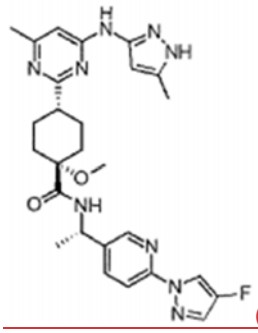
[0011b] In another aspect of the present disclosure, there is provided Use of Compound 1 in the manufacture of a medicament for treating a rearranged during transfection (RET) altered cancer in a subject in need thereof, wherein 400 mg of Compound 1 or a pharmaceutically acceptable salt thereof is to be administered to the subject once daily, wherein Compound 1 is:



(Compound 1),

wherein the RET alteration comprises a RET mutation or a RET fusion, and wherein the RET altered cancer is selected from the group consisting of pancreatic cancer, lung cancer, colorectal cancer, head and neck cancer, hepatobiliary cancer, and sarcoma.

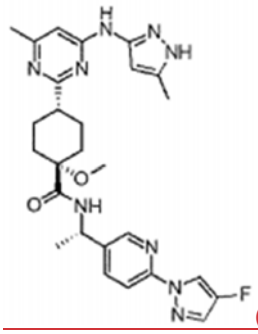
[0011c] In a further aspect of the present disclosure, there is provided Use of Compound 1 in the manufacture of a medicament for treating a rearranged during transfection (RET) altered cancer in a subject in need thereof, wherein 300 mg of Compound 1 or a pharmaceutically acceptable salt thereof is to be administered to the subject once daily, wherein Compound 1 is:



(Compound 1),

wherein the RET alteration comprises a RET mutation or a RET fusion, and wherein the RET altered cancer is selected from non-small cell lung cancer (NSCLC) and thyroid cancer.

[0011d] In another aspect of the present disclosure, there is provided Use of Compound 1 in the manufacture of a medicament for treating a rearranged during transfection (RET) altered cancer in a subject in need thereof, wherein 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),

wherein the RET alteration comprises a RET mutation or a RET fusion, and wherein the RET altered cancer is selected from non-small cell lung cancer (NSCLC) and thyroid cancer.

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.

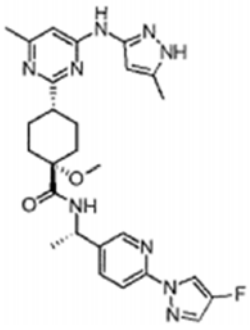
[0013] FIG. 2 is a bar graph which shows the sustained decrease in expression of the MAPK target genes DUSP6 and SPRY4 in a KIF5B-RET NSCLC PDX model.

[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:

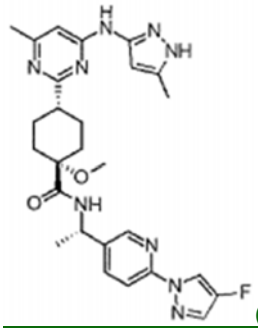
1. Use of Compound 1 in the manufacture of a medicament for treating a rearranged during transfection (RET) altered cancer in a subject in need thereof, wherein ~~100 mg to~~300 mg or 400 mg of Compound 1 or a pharmaceutically acceptable salt thereof is to be administered to the subject once daily, wherein Compound 1 is:



(Compound 1),

~~and~~ wherein the RET alteration comprises a RET mutation or a RET fusion, and wherein the RET altered cancer is selected from non-small cell lung cancer (NSCLC) and thyroid cancer.

2. Use of Compound 1 in the manufacture of a medicament for treating a rearranged during transfection (RET) altered cancer in a subject in need thereof, wherein 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),

wherein the RET alteration comprises a RET mutation or a RET fusion, and wherein the RET altered cancer is selected from the group consisting of pancreatic cancer, lung cancer, colorectal cancer, head and neck cancer, hepatobiliary cancer, and sarcoma.

~~2. The use of claim 1, wherein the cancer is a solid tumor.~~

~~3. The use of claim 1 or 2, wherein the cancer is selected from pancreatic, lung colorectal, ovarian,head and neck, hepatobiliary, sarcoma, and gastrointestinal cancer.~~

~~4~~3. The use of claim ~~3~~2, wherein the lung cancer is selected from small cell lung cancer (SCLC), lung adenocarcinoma, non-small cell lung cancer (NSCLC), bronchioles lung cell carcinoma, and mesothelioma.

~~5~~4. The use of claim ~~3~~2, wherein the head and neck cancer is selected from salivary gland cancer and thyroid cancer

~~6~~5. The use of claim ~~5~~4, wherein the thyroid cancer is selected from differentiated thyroid cancer (DTC), medullary thyroid cancer (MTC), and anaplastic thyroid cancer.

~~7~~6. The use of claim ~~6~~5, wherein the differentiated thyroid cancer is selected from papillary thyroid cancer (PTC) and follicular thyroid cancer.

~~8. The use of claim 3, wherein the hepatobiliary cancer is liver cholangiocarcinoma.~~

~~9~~7. The use of any one of claims 1-~~8~~6, wherein the RET altered cancer comprises a RET fusion.

~~10~~8. The use of claim 1 or 2, wherein the RET-altered cancer is RET-fusion non-small cell lung cancer (NSCLC).

~~11~~9. The use of claim 1 or 2, wherein the RET-altered cancer is a RET-fusion thyroid cancer selected from papillary thyroid cancer (PTC), metastatic papillary thyroid cancer, thyroid gland carcinoma, medullary thyroid cancer (MTC), diffuse sclerosing variant of papillary thyroid cancer and sporadic medullary thyroid cancer.

~~12~~10. The use of any one of claims ~~9-11~~7-9, wherein the RET fusion is selected from the group consisting of CLIP1, PIBF1, BCR, FGFRIOP, CEP55, CUX1, MPRIP, CCDC6, KIF5B, PTClex9, NCOA4, TRIM33, ERC1, MBD1, RAB61P2, PRKAR1A, TRIM24, KTN1, GOLGA5, HOOK3, KIAA1468, TRIM27, AKAP13, FKBP15, SPECC1L, TBL1XR1, ACBD5, KIAA1217, and MYH13.

~~13~~11. The use of claim ~~9~~7, wherein the RET fusion is selected from CCDC6, KIF5B, TRIM33, TRIM24, and NCOA4.

~~14~~12. The use of claim ~~10~~8, wherein the RET fusion is selected from MPRIP, KIF5B, CCDC6, NCOA4, TRIM33, and KIAA1217.

~~15~~13. The use of claim ~~11~~9, wherein the RET fusion is selected from ERC1, GOLGA5, MYH13, PTClex9, MBD1, RAB61P2, PRKAR1A, TRIM24, KTN1, HOOK3, TRIM27, AKAP13, FKBP15, SPECC1L, TBL1XR1, ACBD5, CCDC6, NCOA4, TRIM33, KIAA1468, KIF5B, and KIAA1217.

~~16~~14. The use of any one of claims 1 to ~~8~~6, wherein the RET-altered cancer comprises a RET mutation.

~~17~~15. The use of claim 1 or 2, wherein the RET-altered cancer is a RET-mutant thyroid cancer selected from papillary thyroid carcinoma (PTC), medullary thyroid cancer (MTC), metastatic papillary thyroid cancer, diffuse sclerosing variant of papillary thyroid cancer, thyroid gland carcinoma and sporadic medullary thyroid cancer.

~~18~~16. The use of claim ~~16~~ 14 or ~~17~~15, wherein the RET-altered cancer is a RET mutant thyroid cancer, and wherein the ~~RET mutation or~~ RET mutant is sporadic.

~~19~~17. The use of claim ~~16~~ 14 or ~~17~~15, wherein the RET-altered cancer is a RET mutant thyroid cancer, and wherein the ~~RET mutation or~~ RET mutant is hereditary.

~~20~~18. The use of ~~any one of claims 16 and 17~~claim 14 or 15, wherein the RET mutation or RET mutant is V804L, V804M, V804E, M918T, 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, C634T, L790F, R844W, R844Q, R844L, A883F, A883S, A883T, K666E, K666M, or K666N.

~~21~~19. The use of any one of claims ~~16~~ 14 to ~~20~~18, wherein the cancer is medullary thyroid cancer (MTC).

~~22. The use of any one of claims 7, 11 and 17 wherein the cancer is radioactive iodine (RAI) refractory.~~

~~23~~20. The use of any one of claims ~~1-3, 9, 12-16, 18-20, and 22~~1, 2, 7, 10 to 14, and 16 to 18, wherein the cancer is metastatic and is selected from metastatic papillary thyroid ~~carcinoma~~ cancer (PTC)~~,~~ and metastatic non-small cell lung cancer (NSCLC) ~~and colorectal cancer~~.

21. The use of any one of claims 2, 7, 10 to 14, and 16 to 18, wherein the cancer is metastatic and is metastatic colon cancer.

~~24~~22. The use of any one of claims 1 to ~~23~~21, wherein the subject was previously treated with ~~platinum~~chemotherapy.

~~25~~23. The use of claim ~~24~~22, wherein the ~~platinum~~ previous chemotherapy is selected from cisplatin and carboplatin.

~~26. The compound for use of any one of claims 1 to 25, wherein the subject was previously treated with cabozantinib or vandetanib or both.~~

~~27~~24. The use of any one of claims ~~1 to 26~~1 and 7-23, wherein the subject is to be administered 300 mg of Compound 1 once daily.

~~28~~25. The use of any one of claims 1 to ~~26~~23, wherein the subject is to be administered 400 mg of Compound 1 once daily.

~~29. The use of any one of claims 1 to 26, wherein the subject is to be administered 100 mg of Compound 1 once daily.~~

~~30~~26. The use of claim 1, wherein:

the RET-altered cancer is a RET-mutant thyroid cancer selected from papillary thyroid carcinoma (PTC), medullary thyroid cancer (MTC), metastatic papillary thyroid cancer, diffuse sclerosing variant of papillary thyroid cancer, thyroid gland carcinoma and sporadic medullary thyroid cancer; and
the subject is to be orally administered the~~100 mg to~~ 300 mg or 400 mg of Compound 1 once daily.

~~31~~27. The use of claim 1, wherein:

the RET-altered cancer is RET-fusion non-small cell lung cancer (NSCLC); and

the subject is to be orally administered the ~~100 mg~~300 mg or ~~to~~ 400 mg of Compound 1 once daily.

~~32~~28. The use of claim 1, wherein:

the RET-altered cancer is a RET-fusion thyroid cancer selected from papillary thyroid cancer (PTC), metastatic papillary thyroid cancer, thyroid gland carcinoma, medullary thyroid cancer (MTC), diffuse sclerosing variant of papillary thyroid cancer and sporadic medullary thyroid cancer; and

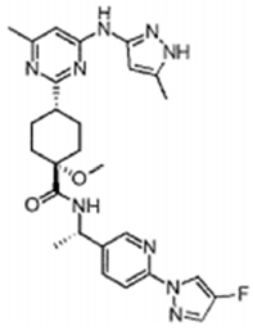
the subject is to be orally administered the ~~100 mg to~~300 mg or 400 mg of Compound 1 once daily.

~~33. The use of any one of claims 1 to 32, wherein the compound is to be administered as one or more solid dosage forms.~~

~~34. The use of claim 33, wherein the one or more solid dosage forms are tablets.~~

~~35. The use of claim 33, wherein the one or more solid dosage forms are capsules.~~

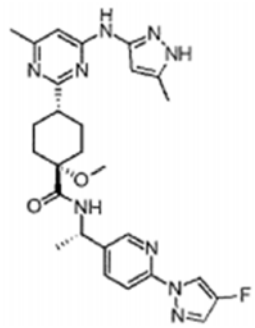
29. Use of Compound 1 in the manufacture of a medicament for treating a rearranged during transfection (RET) altered cancer in a subject in need thereof, wherein 300 mg of Compound 1 or a pharmaceutically acceptable salt thereof is to be administered to the subject once daily, wherein Compound 1 is:



(Compound 1),

wherein the RET alteration comprises a RET mutation or a RET fusion, and wherein the RET altered cancer is selected from non-small cell lung cancer (NSCLC) and thyroid cancer.

30. Use of Compound 1 in the manufacture of a medicament for treating a rearranged during transfection (RET) altered cancer in a subject in need thereof, wherein 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),

wherein the RET alteration comprises a RET mutation or a RET fusion, and wherein the RET altered cancer is selected from non-small cell lung cancer (NSCLC) and thyroid cancer.