

[005] Protein kinases are key regulators for cell growth, proliferation and survival. A variety of diseases, such as cancer, pain, neurological diseases, autoimmune diseases, and inflammation, have been shown to be mediated by receptor tyrosine kinases, such as activating mutated RET or FGFR1/2. For example, genetic and epigenetic alterations can accumulate in cancer cells leading to abnormal activation of signal transduction pathways which drive malignant processes. Manning, G. *et al.*, *Science* 2002, 298, 1912-1934. Pharmacological inhibition of these signaling pathways presents promising intervention opportunities for targeted cancer therapies. Sawyers, C., *Nature* 2004, 432, 294-297.

[006] While Compound I has found application in treating disease associated with receptor tyrosine kinases, such as RET activating mutations, it is advantageous to have polymorphic forms having improved properties, such as improved crystallinity, dissolution properties, and/or decreased hygroscopicity, while maintaining chemical and enantiomeric stability properties.

SUMMARY

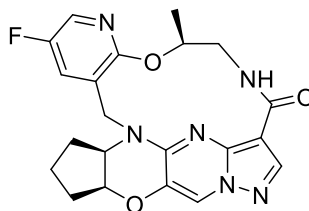
[007] In one example aspect, the present disclosure provides a crystalline form of (3aR,11S,20aS)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1H,5H-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-i]pyrazolo[4,3-f]pyrido[3,2-l][1,4,8,10]oxatriazacyclotridecin-14(11H)-one, or a hydrate thereof.

[007a] In one aspect, the present disclosure provides a crystalline polymorph form of (3aR,11S,20aS)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1H,5H-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-i]pyrazolo[4,3-f]pyrido[3,2-l][1,4,8,10]oxatriazacyclotridecin-14(11H)-one, or a hydrate thereof.

[008] In another embodiment example, the crystalline polymorph form of (3aR,11S,20aS)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1H,5H-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-i]pyrazolo[4,3-f]pyrido[3,2-l][1,4,8,10]oxatriazacyclotridecin-14(11H)-one is a hydrate.

[009] In another embodiment example, the crystalline polymorph form of (3aR,11S,20aS)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1H,5H-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-i]pyrazolo[4,3-f]pyrido[3,2-l][1,4,8,10]oxatriazacyclotridecin-14(11H)-one is anhydrous.

[010] In another embodiment example, the crystalline polymorph form A or D of compound I can be represented by the formula



I.

[010a] In another aspect, the present disclosure provides a crystalline polymorph form A of (3a*R*,11*S*,20a*S*)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1*H*,5*H*-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-*i*]pyrazolo[4,3-*f*]pyrido[3,2-*l*][1,4,8,10]oxatriazacyclotridecin-14(11*H*)-one having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 20.1 ± 0.1 .

[011] In a further **embodimentexample**, the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 20.1 ± 0.1 . In a further **embodimentexample**, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at

diffraction angles (2θ) of 11.3 ± 0.1 and 20.1 ± 0.1 . In a further embodimentexample, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 11.3 ± 0.1 , 20.1 ± 0.1 , and 23.9 ± 0.1 . In a further exampleembodiment, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 11.3 ± 0.1 , 18.0 ± 0.1 , 20.1 ± 0.1 , and 23.9 ± 0.1 . In a further embodimentexample, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 10.3 ± 0.1 , 11.3 ± 0.1 , 18.0 ± 0.1 , 20.1 ± 0.1 , and 23.9 ± 0.1 . In a further embodimentexample, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 10.3 ± 0.1 , 11.3 ± 0.1 , 16.6 ± 0.1 , 18.0 ± 0.1 , 20.1 ± 0.1 , and 23.9 ± 0.1 . In a further embodimentexample, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 10.3 ± 0.1 , 11.3 ± 0.1 , 16.6 ± 0.1 , 18.0 ± 0.1 , 20.1 ± 0.1 , 20.5 ± 0.1 , and 23.9 ± 0.1 .

[012] In a further aspectexample, the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) essentially the same as shown in FIG. 1.

[012a] In another aspect, the present disclosure provides a crystalline polymorph form D of (3aR,11S,20aS)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1H,5H-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-i]pyrazolo[4,3-f]pyrido[3,2-l][1,4,8,10]oxatriazacyclotridecin-14(11H)-one having, a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 18.8 ± 0.1 .

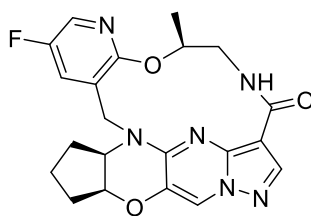
[013] In a further embodimentexample, the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 18.8 ± 0.1 . In a further exampleembodiment, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 18.8 ± 0.1 and 20.9 ± 0.1 . In a further exampleembodiment, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.3 ± 0.1 , 18.8 ± 0.1 , and 20.9 ± 0.1 . In a further exampleembodiment, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.3 ± 0.1 , 18.8 ± 0.1 , 19.4 ± 0.1 , and 20.9 ± 0.1 . In a further embodimentexample, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.3 ± 0.1 , 13.1 ± 0.1 , 18.8 ± 0.1 , 19.4 ± 0.1 , and 20.9 ± 0.1 . In a further exampleembodiment, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 12.3 ± 0.1 , 13.1 ± 0.1 , 15.3 ± 0.1 , 18.8 ± 0.1 , 19.4 ± 0.1 , and 20.9 ± 0.1 . In a further exampleembodiment, the crystalline polymorph form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 9.4 ± 0.1 , 12.3 ± 0.1 , 13.1 ± 0.1 , 15.3 ± 0.1 , 18.8 ± 0.1 , 19.4 ± 0.1 , and 20.9 ± 0.1 .

[013a] In yet another aspect, the present disclosure refers to a crystalline polymorph form of (3aR,11S,20aS)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1H,5H-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-i]pyrazolo[4,3-f]pyrido[3,2-l][1,4,8,10]oxatriazacyclotridecin-14(11H)-one having a powder X-ray diffraction pattern substantially the same as shown in FIG. 1.

[013b] In yet another aspect, the present disclosure refers to a crystalline polymorph form of (3aR,11S,20aS)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1H,5H-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-i]pyrazolo[4,3-f]pyrido[3,2-l][1,4,8,10]oxatriazacyclotridecin-14(11H)-one having a powder X-ray diffraction pattern substantially the same as shown in FIG. 3.

[014] In a further ~~example, aspect~~ the crystalline form has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) essentially the same as shown in FIG. 3.

[015] The present disclosure further provides a pharmaceutical composition comprising a polymorph form A or form D of Compound I of the formula



I.

[016] The present disclosure further provides a capsule comprising pharmaceutical compositions as described herein.

[016a] In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising the crystalline polymorph form as defined above.

[016b] In yet another aspect, the present disclosure refers to a use of a crystalline polymorph form as defined above in the manufacture of a medicament for treating disease in a mammal.

[017] In another aspectexample, the disclosure provides a method of treating disease, especially cancer, in a mammal, including a human, the method comprising administering to the mammal a therapeutically effective amount of polymorph form A or D of (3aR,11S,20aS)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1*H*,5*H*-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-*i*]pyrazolo[4,3-*f*]pyrido[3,2-*l*][1,4,8,10]oxatriazacyclotridecin-14(11*H*)-one, as described herein, or a pharmaceutical composition comprising polymorph form A or D of (3aR,11S,20aS)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1*H*,5*H*-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-*i*]pyrazolo[4,3-*f*]pyrido[3,2-*l*][1,4,8,10]oxatriazacyclotridecin-14(11*H*)-one, as described herein.

[018] In one embodimentexample, the present disclosure provides a method of treating abnormal cell growth in a mammal, including a human, in need of such treatment comprising, administering to said mammal a therapeutically effective amount of the free base polymorph form A or D of Compound I. In some examplesembodiments, the abnormal cell growth is mediated by at least one genetically altered tyrosine kinase.

[019] In some embodimentexamples, the abnormal cell growth is mediated by RET, SRC, FGFR1/2 or a combination thereof. In some examplesembodiments, the abnormal cell growth is mediated by wild-type or mutant RET. In some examplesembodiments, the abnormal cell growth is mediated by wild-type or mutant SRC. In some examplesembodiments, the abnormal cell growth is mediated by wild-type or mutant FGFR1/2.

[020] In some embodimentexamples, the present disclosure provides a method of treating abnormal cell growth in a patient in need of such treatment comprising, administering a therapeutically effective amount of Compound I. In some embodimentexamples, the present

disclosure provides a method of treating abnormal cell growth in a patient in need of such treatment comprising, administering a therapeutically effective amount of the free base polymorph form A or D of Compound I. In some ~~embodiments~~examples, the abnormal cell growth is cancer mediated by a genetically altered RET. In some ~~embodiments~~examples, the abnormal cell growth is cancer mediated by a genetically altered RET comprising at least one point mutation selected from the group

consisting of A883F, E762Q, G691S, L790F, M918T, R749T, R813Q, S891A, S904A, S904F, V778I, V804L, V804M, Y791F, and Y806H.

[021] In some [embodimentsexamples](#), the present disclosure provides a method of treating abnormal cell growth in a patient in need of such treatment comprising, administering a therapeutically effective amount of Compound I. In some [embodimentsexamples](#), the present disclosure provides a method of treating abnormal cell growth in a patient in need of such treatment comprising, administering a therapeutically effective amount of the free base polymorph form A or D of Compound I. In some [embodimentsexamples](#), the abnormal cell growth is cancer mediated by a fusion protein comprising a fragment of a protein encoded by an RET gene and a fragment of a protein which can form coiled-coil interaction to facilitate the protein dimerization or oligomerization. In some [embodimentsexamples](#), the abnormal cell growth is cancer mediated by a fusion protein comprising a fragment of a protein encoded by an RET gene and a fragment of a protein encoded by a gene selected from the group consisting of KIF5B, CCDC6, NCOA4, TRIM24, TRIM33, PRKAR1A, GOLGA5, KTN1, ERC1, MBD1, and TRIM27. In some [embodimentsexamples](#), the fusion protein comprises a fragment of a protein encoded by an RET gene and a fragment of a protein encoded by a KIF5B gene. In some [examplesembodiments](#), the genetically altered RET is a KIF5B-RET, CCDC6-RET, NCOA4-RET, TRIM24-RET, TRIM33-RET, PRKAR1A -RET, GOLGA5-RET, KTN1-RET, ERC1-RET, MBD1-RET, or TRIM27-RET fusion protein. In some [examplesembodiments](#), the genetically altered RET is a KIF5B-RET fusion protein. In some [examplesembodiments](#), the KIF5B-RET fusion protein is a wild-type protein. In some [examplesembodiments](#), the KIF5B-RET fusion protein comprises at least one resistance mutation. In some [examplesembodiments](#), the KIF5B-RET fusion protein comprises at least one gate keeper resistance mutation. In some [examplesembodiments](#), the KIF5B-RET fusion protein comprises at least one solvent front resistance mutation. In some [examplesembodiments](#), the KIF5B-RET fusion protein comprises at least one mutation selected from the group consisting of A883F, E762Q, G691S, L790F, M918T, R749T, R813Q, S891A, S904A, S904F, V778I, V804L, V804M, Y791F, Y806H , V804M, G810R, G810C, and G810S. In some [examplesembodiments](#), the KIF5B-RET fusion protein comprises at least one mutation selected from the group consisting of V804M, G810R, G810C, and G810S.

[022] In some [examplesembodiments](#), the abnormal cell growth is cancer. In some [examplesembodiments](#), the cancer is selected from the group consisting of lung cancer, non-small cell lung cancer, small cell lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, hepatocellular carcinoma, cutaneous or intraocular melanoma,

uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, gastric and esophago-gastric cancers,

cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, such as anaplastic large cell lymphoma, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), glioblastoma, primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, inflammatory myofibroblastic tumors, and combinations thereof.

[023] Additional ~~example embodiments~~, features, and advantages of the disclosure will be apparent from the following detailed description and through practice of the disclosure. The compounds of the present disclosure can be described as ~~example embodiments~~ in any of the following enumerated clauses. It will be understood that any of the ~~example embodiments~~ described herein can be used in connection with any other ~~example embodiments~~ described herein to the extent that the ~~example embodiments~~ do not contradict one another.

[024] 1. A crystalline polymorph form of (3a*R*,11*S*,20a*S*)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1*H*,5*H*-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-*i*]pyrazolo[4,3-*f*]pyrido[3,2-*l*][1,4,8,10]oxatriazacyclotridecin-14(11*H*)-one, or a hydrate thereof.

[025] 2. The crystalline polymorph form of clause 1, wherein the crystalline form is a polymorph form of the free base of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a hydrate thereof.

[026] 3. The crystalline polymorph of clause 1 or 2, wherein the crystalline form is a monohydrate.

[027] 4. The crystalline polymorph of clause 1 or 2, wherein the crystalline form is anhydrous.

[028] 5. A crystalline polymorph form A of (3a*R*,11*S*,20a*S*)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1*H*,5*H*-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-*i*]pyrazolo[4,3-*f*]pyrido[3,2-*l*][1,4,8,10]oxatriazacyclotridecin-14(11*H*)-one having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 20.1 ± 0.1 .

[029] 6. The crystalline polymorph form of clause 5, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 11.3 ± 0.1 and 20.1 ± 0.1 .

[030] 7. The crystalline polymorph form of clause 5 or 6, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 11.3 ± 0.1 , 20.1 ± 0.1 , and 23.9 ± 0.1 .