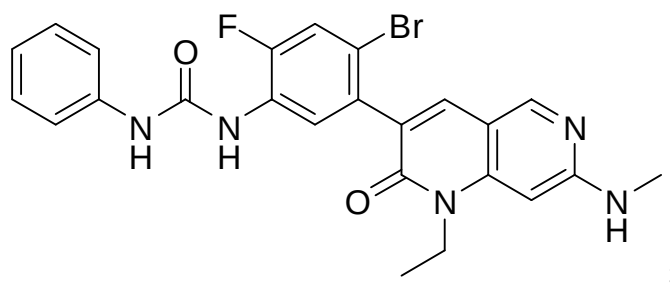


[0006] Despite significant improvement in outcomes compared with those in the pre-mutation-driven/TKI therapy era, response to imatinib is not experienced by all patients, and most patients with GIST will ultimately develop resistance to imatinib, most commonly due to the development of secondary mutations in KIT. Secondary resistance mutations usually arise in the catalytic domain of the kinase: 1) at the switch pocket, which typically occur in KIT exons 13 and 14 or PDGFRA exons 14 and 15 and sterically disrupt drug binding or conformationally activate KIT, and 2) in the activation loop switch encoded by KIT exons 17 and 18 and PDGFRA 18. Activation loop mutations act by shifting the kinase into an activated Type I or on-state conformation that is less amenable to drug binding by any of the approved Type II TKIs. Although uncommon in primary GIST (1%-2% of newly diagnosed cases), mutations in exons 13, 14 and 17 are often responsible for acquired imatinib resistance, with exon 17 mutations alone accounting for as many as 50% of the acquired resistance cases to imatinib, and later to sunitinib. A need exists for a TKI that can inhibit clinically relevant KIT and PDGFRA mutations.

SUMMARY

[0007] The present disclosure provides, in an example, methods of treating gastrointestinal stromal tumors to a subject in need thereof, comprising administering to the subject a therapeutically effective amount of ripretinib or a pharmaceutically acceptable salt thereof.

[0008] Disclosed herein, in an example, is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, where the patient has a) a *KIT* exon 17 and/or a *KIT* exon 18 mutation and/or b) a *KIT* exon 11 mutation, comprising: administering to the patient 150 mg of a compound represented by:

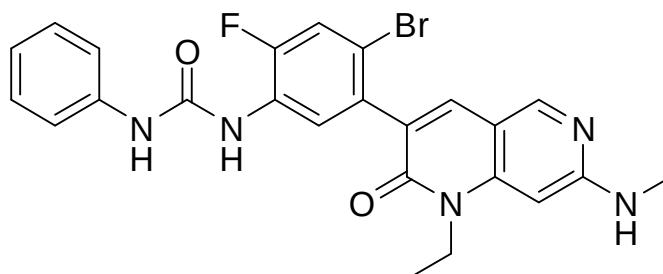


Formula (I)

daily or twice daily, and where before the administration of the compound, the patient has progressed on or was intolerant to imatinib; and wherein upon administration of the compound the patient achieves significantly more progression free survival time as

determined by mRECIST1.1, and significantly more overall survival time, as compared to a patient with a *KIT* exon 17 and/or a *KIT* exon 18 mutation and/or a *KIT* exon 11 mutation suffering from an advanced gastrointestinal stromal tumor who has progressed on or was intolerant to imatinib and was then administered 50 mg sunitinib once daily.

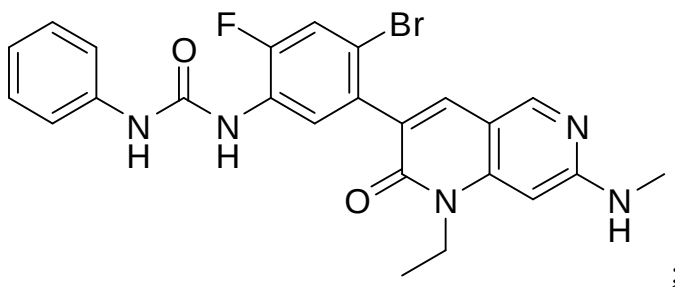
[0008a] In one aspect, the present disclosure refers to use of a compound represented by:



Formula (I),

in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, where the patient has a) a *KIT* exon 17 and/or a *KIT* exon 18 mutation and b) a *KIT* exon 11 mutation, wherein: 150mg of the compound is to be administered to the patient daily or twice daily, and where before the administration of the compound, the patient has progressed on or was intolerant to imatinib; and wherein upon administration of the compound the patient achieves significantly more progression free survival time as determined by mRECIST1.1, and significantly more overall survival time, as compared to a patient with a *KIT* exon 17 and/or a *KIT* exon 18 mutation and a *KIT* exon 11 mutation suffering from an advanced gastrointestinal stromal tumor who has progressed on or was intolerant to imatinib and was then administered 50 mg sunitinib once daily.

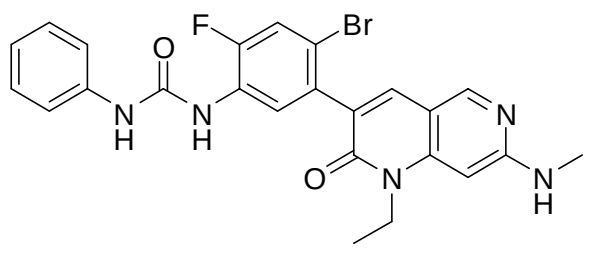
[0009] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor who has a *KIT* exon 17 and/or a *KIT* exon 18 mutation, does not have *KIT* exon 13 and/or 14 mutation, and does not have a *KIT* exon 9 mutation, and where the patient has progressed on or was intolerant to imatinib, comprising administering to the patient 150 mg of a compound represented by:



Formula (I)

daily or twice daily.

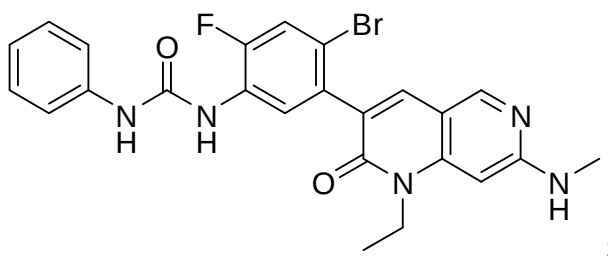
[0009a] In one aspect, the present disclosure refers to use of a compound represented by:



Formula (I),

in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor who has a *KIT* exon 17 and/or a *KIT* exon 18 mutation, does not have *KIT* exon 13 and/or 14 mutation, and does not have a *KIT* exon 9 mutation, and where the patient has progressed on or was intolerant to imatinib, wherein: 150mg of the compound is to be administered to the patient daily or twice daily.

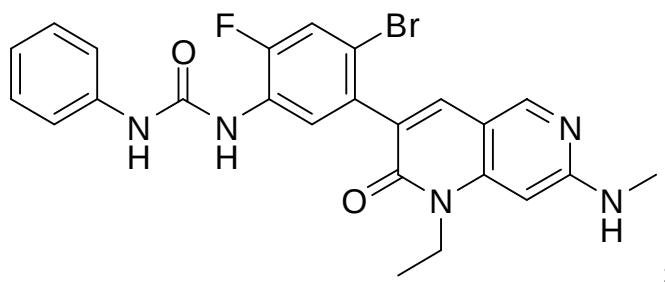
[0010] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor where the patient has progressed on or was intolerant to imatinib, and the patient's circulating tumor DNA has a *KIT* exon 17 and/or a *KIT* exon 18 mutation and does not have a *KIT* exon 9 mutation, comprising administering to the patient 150 mg of a compound represented by:



Formula (I)

daily or twice daily.

[0010a] In one aspect, the present disclosure refers to use of a compound represented by:

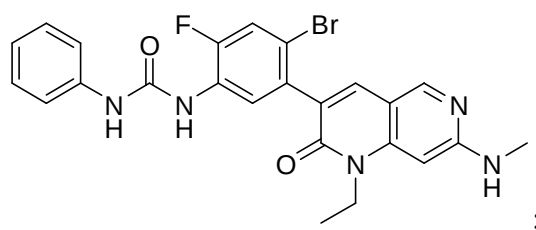


Formula (I),

in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor where the patient has progressed on or was intolerant to imatinib, and the patient's circulating tumor DNA has a *KIT* exon 17 and/or a *KIT* exon 18 mutation and does not have a *KIT* exon 9 mutation, wherein: 150 mg of the compound is to be administered to the patient daily or twice daily.

[0011] In another example, described herein is a method of treating an advanced gastrointestinal stromal tumor where the patient has progressed on or was intolerant to

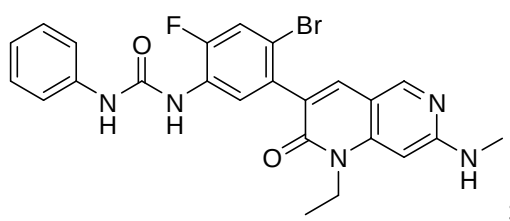
imatinib in a patient in need thereof, comprising: selecting a patient having a circulating tumor DNA *KIT* exon 17 and/or a *KIT* exon 18 mutation and without one or more of a *KIT* exon 9, 13, and 14 mutation to obtain a selected patient; administering to the selected patient 150 mg of a compound represented by:



Formula (I)

daily or twice daily; or if the patient is not a selected patient, administering to the patient one or more different kinase inhibitors.

[0011a] In one aspect, the present disclosure refers to use of a compound represented by:



Formula (I),

in the manufacture of a medicament for treating an advanced gastrointestinal stromal tumor where the patient has progressed on or was intolerant to imatinib in a patient in need thereof, wherein: a patient having a circulating tumor DNA *KIT* exon 17 and/or a *KIT* exon 18 mutation and without one or more of a *KIT* exon 9, 13, and 14 mutation is to be selected to obtain a selected patient; 150mg of the compound is to be administered to the selected patient daily or twice daily; or if the patient is not a selected patient, the patient is to be administered one or more different kinase inhibitors.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] **FIG. 1** depicts a flow chart for the ctDNA sample evaluability conducted from randomized patient population with advanced GIST and have taken imatinib as the 1st line of treatment, as described in Example 1.

[0013] **FIG. 2** depicts a flow chart of detecting *KIT* or PDGFRA exon mutations by ctDNA test as described in Example 1.

[0014] **FIG. 3** depicts PFS by IRR for GIST patients with *KIT* mutations at exon 11 and exons 17/18 upon treatment with ripretinib or sunitinib.

[0015] **FIG. 4** depicts PFS by IRR for GIST patients with *KIT* mutations at exons 17/18 upon treatment with ripretinib or sunitinib.

[0016] **FIG. 5** depicts a plot of a GIST interim analysis (Interim Analysis 1) of overall survivals from patients who have been administered ripretinib or sunitinib and exhibits *KIT* mutations at exon 11 and exon 17/18.

[0017] **FIG. 6** depicts a plot of an extended GIST interim analysis (Interim Analysis 2) of overall survival from patients who have been administered ripretinib or sunitinib and exhibits *KIT* mutations at exon 11 and exon 17/18.