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 broadly inhibit clinically relevant KIT and PDGFRA mutations.

SUMMARY

[0006a] In a first aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 100 mg to 300 mg of ripretinib is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[0006b] In another aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 100 mg to 600 mg of ripretinib is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[0006c] In yet another aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 100 mg to 250 mg of ripretinib is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib, or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

[0006d] In a further aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein one or more tablets comprising ripretinib is to be orally administered

to the patient daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[0006e] In another aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein one or more tablets comprising ripretinib is to be orally administered to the patient, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

[0006f] In yet another aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of ripretinib is to be orally administered to the patient once daily, and wherein the patient was previously administered three or more kinase inhibitors before administration of the ripretinib.

[0006g] In a further aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg ripretinib is to be orally administered daily to the patient, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib.

[0006h] In another aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of ripretinib is to be orally administered to the patient once or twice daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[0006i] In yet another aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a CYP3A4 inhibitor, wherein

100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, is to be orally administered to the patient once or twice daily, and wherein upon administration of the ripretinib and the CYP3A4 inhibitor, an increased ripretinib area under the plasma concentration curve ($AUC_{0\text{-}inf}$) of 80% or more in the patient is to be provided as compared to administration of ripretinib without concurrent treatment of the CYP3A4 inhibitor, and therefore the patient is at higher risk of an adverse event; and

the patient is to be monitored more frequently, as compared to a patient not being treated with a CYP3A4 inhibitor, for the adverse event.

[0007] Described herein are methods of treating a gastrointestinal stromal tumor in a patient in need thereof comprising administering to the patient a therapeutically effective amount of ripretinib or a pharmaceutically acceptable salt thereof.

[0008] For example, in one example described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 300 mg, e.g., 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[0009] For example, in one example described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 250 mg, e.g., 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[00010] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg, e.g., 100 mg to 250 mg, e.g., 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[00011] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient one or more tablets comprising ripretinib, e.g., tablets each comprising 50 mg to

100 mg of ripretinib, daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib. In some examples, the tablets comprise 50 mg of ripretinib. In some examples, the tablets comprise 75 mg of ripretinib. In some examples, the tablets comprise 100 mg of ripretinib.

[00012] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient one or more tablets comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib, a previous second line administration of sunitinib, and a previous third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib. In some examples, the tablets comprise 50 mg of ripretinib. In some example, the tablets comprise 75 mg of ripretinib. In some example, the tablets comprise 100 mg of ripretinib. In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 250 mg of ripretinib daily, e.g., 150 mg, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

[00013] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg of ripretinib daily, e.g., 100 mg to 250 mg, e.g., 100 mg to 500 mg, e.g., 100 mg to 250 mg, e.g., 150 mg, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

[00014] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient to the patient, on a daily basis, one or more tablets each comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or

wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib. In some example, the tablets comprise 50 mg of ripretinib. In some example, the tablets comprise 75 mg of ripretinib. In some example, the tablets comprise 100 mg of ripretinib.

[00015] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg of ripretinib daily, e.g., 100 mg to 250 mg, e.g., 100 mg to 500 mg, e.g., 100 mg to 250 mg, e.g., 150 mg, e.g., 300 mg, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.

[00016] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once daily, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.

[00017] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient, on a daily basis, one or more tablets each comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib. In some example, the tablets comprise 50 mg of ripretinib. In some example, the tablets comprise 75 mg of ripretinib. In some example, the tablets comprise 100 mg of ripretinib.

[00018] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once daily, wherein the patient was previously administered three or more kinase inhibitors before administration of the ripretinib. In some examples, after at least 4 weeks of the daily ripretinib administration, the patient has at least a 5-month progression-free survival as measured using mRECIST v1.1. In some examples, orally administering to the patient 150 mg of ripretinib once daily comprises administering to the patient three tablets each tablet comprising 50 mg of ripretinib. In some examples, one of the three or more kinase inhibitors is imatinib. In some examples, the patient was previously administered imatinib, sunitinib and regorafenib.

[00019] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg daily ripretinib, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib.

[00020] In another example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once or twice daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[00021] In another example, described herein is a method for achieving at least 5 months of progression free survival as determined by mRECIST 1.1 in a patient having an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100, 150 200, or 300 mg of ripretinib daily or twice daily for at least 28 days.

[00022] In another example, described herein is a method for achieving at least 5 months of progression free survival as determined by mRECIST 1.1 in a patient having an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100, 150, or 200 mg of ripretinib daily or twice daily for at least 28 days.

[00023] In another example, descried herein is a method of treating a patient suffering from Grade 3 palmer-plantar erythrodysesthia syndrome while being administered 150 mg ripretinib daily or twice daily, comprising withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantarplantar erythrodysesthia syndrome, then administering to the patient 100 mg daily (e.g., 100 mg once daily) ripretinib for at least 28 days.

[00024] In another example, descried herein is a method of treating a patient suffering from Grade 2 palmer-plantarplantar erythrodysesthia syndrome upon administration of 150 mg ripretinib daily or twice daily, comprising a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily

ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.

[00025] In another example, described herein is a method of treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a CYP3A4 inhibitor, the method comprising: orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, and wherein upon administration of the ripretinib and the CYP3A4 inhibitor, provides an increased ripretinib area under the plasma concentration curve ($AUC_{0\text{-}inf}$) of 80% or more in the patient as compared to administration of ripretinib without concurrent treatment of the CYP3A4 inhibitor, and therefore the patient is at higher risk of an adverse event; and monitoring the patient more frequently, as compared to a patient not being treated with a CYP3A4 inhibitor, for the adverse event.

[00026] In another example, described herein is a method of treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a proton pump inhibitor, the method comprising: orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, and wherein administration of the ripretinib and proton pump inhibitor to the patient provides no clinically significant difference in the plasma exposure of ripretinib in the patient as compared to administration of ripretinib without concurrent treatment of the proton pump inhibitor.

[00027] In another example, described herein is a method of treating a gastrointestinal stromal tumor in a patient in need thereof, the method comprising orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, wherein the ripretinib is administered to the patient with food or without food.

BRIEF DESCRIPTION OF THE DRAWINGS

[00028] **FIG. 1** depicts a plot of survival probability with respect to progression-free survival (PFS) for patients on ripretinib and patients on placebo as described in Example 2.

[00029] **FIG. 2** depicts a plot of survival probability with respect to overall survival (OS) for patients on ripretinib and patients on placebo as described in Example 2.

CLAIMS

What is claimed is:

1. Use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 100 mg to 300 mg of ripretinib is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

2. Use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 100 mg to 600 mg of ripretinib is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

3. The use of claim 1 or 2, wherein the patient is to be administered 150 mg of ripretinib daily.

4. The use of claim 1 or 2, wherein the patient is to be administered 150 mg of ripretinib once daily.

5. The use of claim 2, wherein the patient is to be administered 150 mg of ripretinib twice daily.

6. The use of any one of claims 1-5, wherein the tumor has, a KIT exon 9 mutation, a PDGFRA exon 18 mutation, a PDGFRA exon 12 mutation, or a PDGFRA exon 18 activation loop mutation.

7. Use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 100 mg to 250 mg of ripretinib is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib, or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

8. The use of claim 7, wherein the patient is to be administered 150 mg of ripretinib daily.

9. The use of claim 7, wherein the patient is to be administered 150 mg of ripretinib once daily.

10. Use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein one or more tablets comprising ripretinib is to be orally administered to the patient daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

11. The use of claim 10, wherein the patient is to be administered three tablets each comprising 50 mg of ripretinib once daily.

12. Use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein one or more tablets comprising ripretinib is to be orally administered to the patient, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

13. The use of claim 12, wherein the patient is to be administered, once daily, three tablets each comprising 50 mg of ripretinib.

14. Use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of ripretinib is to be orally administered to the patient once daily, and wherein the patient was previously administered three or more kinase inhibitors before administration of the ripretinib.

15. The use of claim 14, wherein the patient was previously administered imatinib, sunitinib and regorafenib.

16. The use of claim 14 or 15, wherein if the patient suffers from a Grade 3 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, a) administration of ripretinib is to be withheld for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome, then 100 mg ripretinib is to be administered to the patient daily for at least 28 days.

17. The use of claim 14 or 15, wherein if the patient suffers from a Grade 2 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, a) administration of ripretinib is to be withheld until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythroysesthesia syndrome within 7 days of withholding administration, then 150 mg ripretinib is to be administered daily to the patient; or c) if the patient has not recovered, then 100mg ripretinib is to be administered daily to the patient for at least 28 days.

18. Use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg ripretinib is to be orally administered daily to the patient, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib.

19. The use of claim 18, wherein if the patient suffers from a Grade 3 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, a) administration of ripretinib is to be withheld for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome, then 100 mg ripretinib is to be administered to the patient daily for at least 28 days.

20. The use of claim 18, wherein if the patient suffers from a Grade 2 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, a) administration of ripretinib is to be withheld until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythrodysesthesia syndrome within 7 days of withholding administration, then 150 mg ripretinib is to be administered to the patient daily; or c) if the patient has not recovered, then 100mg ripretinib is to be administered to the patient daily for at least 28 days.

21. Use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of ripretinib is to be orally administered to the patient once or twice daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

22. The use of claim 21, wherein if the patient suffers from Grade 3 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, a) administration of ripretinib is to be withheld for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome, then 100 mg ripretinib is to be administered to the patient daily for at least 28 days.

23. The use of any one of claims 3-7, wherein if the patient suffers from Grade 3 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, a) administration of ripretinib is to be withheld for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome, then 100 mg ripretinib is to be administered to the patient daily for at least 28 days.

24. The use of any one of claims 3-7, wherein if the patient suffers from Grade 2 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, a) administration of ripretinib is to be withheld until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythroysesthesia syndrome within 7 days of withholding administration, then 150 mg ripretinib is to be administered to the patient daily; or c) if the patient has not recovered, then 100mg ripretinib is to be administered to the patient daily for at least 28 days.

25. The use of any one of claims 3-7, wherein if the patient suffers from a Grade 3 adverse disorder selected from arthralgia or myalgia upon administration of the ripretinib, a) administration of ripretinib is to be withheld until the patient has less than or equal to Grade 1 adverse disorder, then 100 mg ripretinib is to be administered to the patient daily for at least 28 days.

26. The use of any one of claims 3-7, wherein if the patient suffers from Grade 3 hypertension upon administration of the ripretinib, administration of ripretinib is to be withheld until the patient's blood pressure is controlled, and if the patient has less than or equal to Grade 1 blood pressure is, 150 mg ripretinib is to be administered to the patient daily, or if the patient has more than Grade 1 blood pressure, 100 mg ripretinib is to be administered to the patient daily.

27. Use of ripretinib in the manufacture of a medicament for treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a CYP3A4 inhibitor, wherein

100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, is to be orally administered to the patient once or twice daily, and wherein upon administration of the ripretinib and the CYP3A4 inhibitor, an increased ripretinib area under the plasma concentration curve ($AUC_{0\text{-}inf}$) of 80% or more in the patient is to be provided as compared to administration of ripretinib without concurrent treatment of the CYP3A4 inhibitor, and therefore the patient is at higher risk of an adverse event; and

the patient is to be monitored more frequently, as compared to a patient not being treated with a CYP3A4 inhibitor, for the adverse event.