CLAIMS

What is claimed is:

1. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 300 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.

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

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

4. The method of claim 2, wherein the patient is administered 500 mg of ripretinib daily.

5. The method of claim 1 or 2, wherein the patient is administered 150 mg of ripretinib once daily.

6. The method of claim 2, wherein the patient is administered 150 mg of ripretinib twice daily.

7. The method of claim 2, wherein the patient is administered 250 mg of ripretinib twice daily.

8. The method of any one of claims 1-7, wherein the patient was only previously treated with the first line administration of imatinib.

9. The method of claim 8, wherein the patient was not previously given a second line administration of sunitinib therapy and/or a third-line administration of regorafenib therapy.

10. The method of any one of claims 1-9, wherein the patient has a non-nodal tumor lesion greater than or equal to 1.0 cm in the long axis or greater than or equal to double the slide thickness in the long axis, within 21 days prior to the first dose of ripretinib.

11. The method of any one of claims 1-10, wherein administering ripretinib is a 42-day cycle comprising daily administration of ripretinib without administering sunitinib.

12. The method of claim 11, wherein, after at least one 42-day cycle, the patient has a progression-free survival as measured using mRECIST v1.1.

13. The method of claim 11 or 12, wherein the patient has a significant progression free survival as compared to a second-line daily administration of 50 mg sunitinib for four weeks followed by two weeks without daily administrations on a 42-day cycle, wherein the patient's tumor has progressed from, or the patient was intolerant to, the previous first line administration of imatinib.

14. The method of any one of claims 1-13, 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.

15. The method of claim 14, wherein the mutation is a PDGFRA D842V mutation.

16. The method of any one of claims 1-15, wherein the tumor has an imatinib resistant mutation selected from the group consisting of a KIT exon 17 activation loop mutation, a KIT exon 18 activation loop mutation, a KIT exon 13 mutation, a KIT exon 14 mutation, a KIT exon 18 mutation, a PDGFRA exon 12 mutation, a PDGFRA exon 14 mutation, a PDGRFA exon 15 mutation, and a PDGFRA exon 18 activation loop mutation.

17. The method of claim 16, wherein the imatinib resistant mutation is a PDGFRA D842V mutation.

18. The method of claim 16 or 17, wherein the tumor has an imatinib resistant mutation selected from the group consisting of KIT exon 13 or 14 mutation, PDGFRA exon 14 or 15 mutation, a KIT 17 or 18 activation loop mutation, and a PDGFRA 18 activation loop mutation.

19. The method of any one of claims 15-18, wherein the tumor has an imatinib resistant KIT exon 17 mutation.

20. 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,

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.

21. 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, 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.

22. The method of claim 20 or 21, wherein the patient is administered 150 mg of ripretinib daily.

23. The method of claim 21, wherein the patient is administered 500 mg of ripretinib daily.

24. The method of claim 20 or 21, wherein the patient is administered 150 mg of ripretinib once daily.

25. The method of claim 21, wherein the patient is administered 150 mg of ripretinib twice daily.

26. The method of claim 21, wherein the patient is administered 250 mg of ripretinib twice daily.

27. The method of any one of claims 20-26, wherein the patient has at least one measurable tumor lesion according to modified RECIST Version 1.1 within 21 days prior to the first dose of ripretinib.

28. The method of any one of claims 20-27, wherein the patient has a non-nodal tumor lesion of greater than or equal to 1.0 cm in the long axis or greater than or equal to double the slide thickness in the long axis, within 21 days prior to the first dose of ripretinib.

29. The method of any one of claims 20-28, 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.

30. The method of claim 29, wherein the mutation is a PDGFRA D842V mutation.

31. The method of any one of claims 20-30, wherein the tumor has an imatinib resistant, sunitinib resistant, and/or regorafenib resistant mutation selected from the group consisting of a KIT exon 17 activation loop mutation, a KIT exon 18 activation loop mutation, a KIT exon 13 mutation, a KIT exon 14 mutation, a KIT exon 18 mutation, a PDGFRA exon 12 mutation, a PDGFRA exon 14 mutation, a PDGRFA exon 15 mutation and a PDGFRA exon 18 activation loop mutation.

32. The method of claim 31, wherein the resistant mutation is a PDGFRA D842V mutation.

33. The method of claim 31 or 32, wherein the tumor has a drug resistant mutation selected from the group consisting of KIT exon 13 or 14 mutation, PDGFRA exon 14 or 15 mutation, a KIT 17 or 18 activation loop mutation, and a PDGFRA 18 activation loop mutation.

34. The method of any one of claims 20-33, wherein the tumor has a drug resistant KIT exon 17 mutation.

35. The method of any one of claims 20-34, wherein administering ripretinib is a 42-day cycle comprising daily administration of ripretinib without administering sunitinib.

36. The method of claim 35, wherein, after at least one 42-day cycle, the patient has a progression-free survival as measured using mRECIST v1.1.

37. The method of any one of claims 20-36, wherein the patient has at least a 5 or 6 month progression-free survival as compared to placebo after at least 4 weeks of daily administration of ripretinib.

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

39. The method of claim 38, wherein the patient is administered three tablets each comprising 50 mg of ripretinib once daily.

40. The method of claim 38, wherein the patient is administered two tablets each comprising 50 mg of ripretinib once daily.

41. The method of claim 38, wherein the patient is administered one tablet comprising 50 mg of ripretinib once daily.

42. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient to the patient one or more tablets comprising 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.

43. The method of claim 42, wherein the patient is administered, once daily, three tablets each comprising 50 mg of ripretinib.

44. The method of claim 42, wherein the patient is administered, once daily two tablets each comprising 50 mg of ripretinib.

45. The method of claim 42, wherein the patient is administered one tablet comprising 50 mg of ripretinib once daily.

46. 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, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.

47. 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.

48. 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.

49. The method of claim 48, wherein the patient is administered, once daily, three tablets each comprising 50 mg of ripretinib.

50. The method of any one of claims 46-49, wherein the patient has previously been administered two separate tyrosine kinase inhibitors, each selected from the group consisting of imatinib, sunitinib, regorafenib, lapatinib, gefitinib, erlotinib, vatalanib, crenolanib, and pharmaceutically acceptable salts thereof.

51. 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.

52. The method of claim 51, wherein 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.

53. The method of claim 51 or 52, wherein 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.

54. The method of any one of claims 51-53, wherein one of the three or more kinase inhibitors is imatinib.

55. The method of any one of claims 51-54, wherein the patient was previously administered imatinib, sunitinib and regorafenib.

56. The method of any one of claims 51-55, wherein if the patient suffers from a Grade 3 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises a) withholding administration of ripretinib for at least 7 days or

until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.

57. The method of any one of claims 51-55, wherein if the patient suffers from a Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises: 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.

58. 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.

59. The method of claim 58, wherein if the patient suffers from a Grade 3 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.

60. The method of claim 58, wherein if the patient suffers from a Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises: 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.

61. 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.

62. The method of 61, wherein if the patient suffers from Grade 3 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.

63. The method of any one of claims 3-20, wherein if the patient suffers from Grade 3 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.

64. The method of any one of claims 3-20, wherein if the patient suffers from Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises: 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.

65. The method of any one of claims 3-20, wherein if the patient suffers from a Grade 3 adverse disorder selected from arthralgia or myalgia upon administration of the ripretinib, the method further comprises: a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 adverse disorder, then administering to the patient 100 mg daily ripretinib for at least 28 days.

66. The method of any one of claims 3-20, wherein if the patient suffers from Grade 3 hypertension upon administration of the ripretinib, the method further comprises withholding administration of ripretinib until the patient's blood pressure is controlled, and if the patient has less than or equal to Grade 1 blood pressure is, administering to the patient 150 mg daily ripretinib, or if the patient has more than Grade 1 blood pressure, administering 100 mg daily ripretinib.

67. 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.

68. The method of claim 67, wherein the patient has been administered at least one previous kinase inhibitor.

69. The method of claim 67-68, wherein the patient has been administered at least three previous kinase inhibitors.

70. The method of claim 68 or 69, wherein the at least one previous kinase inhibitor is imatinib.

71. The method of any one of claims 67-70, comprising orally administering to the patient 100, 150 or 200 mg of ripretinib daily or twice daily for at least 4 months.

72. 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-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.

73. A method of treating a patient suffering from Grade 2 palmer-plantar 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.

74. 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.

75. The method of claim 74, wherein if the patient suffers from a Grade 3 palmer-plantar erythrodysesthia syndrome adverse event, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.

76. The method of claim 75, wherein if the patient suffers from Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises: 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.

77. The method of any one of claims 74-76, wherein the CYP3A4 inhibitor is selected from the group consisting of itraconazole, ketoconazole, clarithromycin, and indinavir.

78. The method of any one of claims 74-77, wherein the CYP3A4 inhibitor is itraconazole.

79. The method of any one of claims 74-78, wherein the patient has previously been administered one or more tyrosine kinase inhibitors, each selected from the group consisting of imatinib, sunitinib, regorafenib, lapatinib, gefitinib, erlotinib, vatalanib, crenolanib, and pharmaceutically acceptable salts thereof.

80. 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 upon administration of the ripretinib and proton pump inhibitor, 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.

81. The method of claim 80, wherein the proton pump inhibitor is selected from the group consisting of pantoprazole, omeprazole, lansoprazole, rabeprazole, esomeprazole, and dexlansoprazole.

82. The method of claim 80 or 81, wherein the proton pump inhibitor is pantoprazole.

83. The method of any one of claims 80-82, wherein the patient is being treated concurrently with 40 mg of the proton pump inhibitor once daily.

84. 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.

85. The method of claim 83, wherein the food comprises a high-fat meal.