symptoms and may increase overall survival, but it does not reverse fibrosis in most cases and can lead to anemia and low platelet counts. Surprisingly, ruxolitinb works equally as well in reducing splenomegaly and controlling symptoms in MF patients lacking the JAK2V617 driver mutation; confounding initial therapeutic expectations. However, ruxolitinib is not disease modifying because it has no effect on reducing the malignant CD34+ cell numbers or the Jak allele burden. Nonetheless, with a better understanding of the cellular and molecular events that lead to the development of MF, the possibility exists for safer and more efficacious targeted therapies, such as BTK inhibitors, to treat myeloproliferative neoplasms with splenomegaly through the modulation of cell trafficking, homing and adhesion.

SUMMARY

[0006a] In one aspect, the present disclosure refers to use of a Bruton's Tyrosine Kinase (BTK) inhibitor in the manufacture of a medicament for the treatment of a myeloproliferative neoplasm (MPN) in a human subject in need thereof, wherein the BTK inhibitor is selected from 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one, or pharmaceutically acceptable salts thereof, wherein the human subject has an accumulation of malignant CD34+ myeloid cells in their hematopoietic tissue.

[0006b] In another aspect, the present disclosure refers to the use of a BTK inhibitor in the manufacture of a medicament for stimulating migration of malignant CD34+ myeloid cells from hematopoietic tissue to the peripheral blood in a human subject suffering from a myeloproliferative neoplasm (MPN), wherein the BTK inhibitor is selected from 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one, or pharmaceutically acceptable salts thereof.

[0007] The disclosure relates to a method of treating splenomegaly in a human subject in need thereof comprising administering a Bruton's Tyrosine Kinase inhibitor to the human subject. In some examples, the human subject has an accumulation of malignant CD34+ myeloid cells in the spleen. In some examples, the malignant CD34+ myeloid cells have decreased expression of CXCR4 relative to normal myeloid cells. In some examples, the human subject is suffering from myelofibrosis. In some examples, the myelofibrosis is selected from the group consisting of primary myelofibrosis, (PMF), post-polycythemia vera myelofibrosis (post PV-MF), and post-essential thrombocythemia myelofibrosis (post ET-MF). In some examples, the human subject did not respond to ruxolitinib therapy. In some examples, the human subject has a JAK2V617F mutation and optionally has acute myeloid leukemia (AML) secondary to a myeloproliferative neoplasm (MPN). In some examples, the human subject does not have a JAK2V617F mutation and optionally has acute myeloid leukemia secondary to a myeloproliferative neoplasm.

[0008] In some examples, the BTK inhibitor is administered in an amount sufficient to stimulate migration of the malignant CD34+ myeloid cells to peripheral blood of the human subject. In some examples, the BTK inhibitor is administered in an amount sufficient to stimulate apoptosis of the malignant CD34+ myeloid cells in the spleen of the human subject. In some examples, the BTK inhibitor is administered in an amount sufficient to decrease activity of VLA-4 in the malignant CD34+ myeloid cells. In some examples, the BTK inhibitor is administered in an amount sufficient to decrease expression of VLA-4 in the malignant CD34+ myeloid cells.

[0009] The disclosure also relates to a method of stimulating migration of malignant CD34+ myeloid cells from the spleen to the peripheral blood in a human subject suffering from splenomegaly,

comprising administering a BTK inhibitor to the human subject. In some examples, the human subject has an accumulation of malignant CD34+ myeloid cells in the spleen. In some examples, the method encompasses stimulating apoptosis of malignant CD34+ myeloid cells in the spleen by administering a BTK inhibitor. In some examples, the malignant CD34+ myeloid cells have decreased expression of CXCR4 relative to normal myeloid cells. In some examples, the human subject is suffering from myelofibrosis. In some examples, the myelofibrosis is selected from the group consisting of primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis. In some examples, the human subject did not respond to ruxolitinib therapy. In some examples, the human subject has a JAK2V617F mutation and optionally has acute myeloid leukemia secondary to a myeloproliferative neoplasm. In some examples, the human subject does not have a JAK2V617F mutation and optionally has acute myeloid leukemia secondary to a myeloproliferative neoplasm.

[0010] The methods of the disclosure encompass treatment of the human subject who has not been treated with a JAK2 inhibitor. The methods of the disclosure also encompass treatment of the human subject who is intolerant to a JAK2 inhibitor. The methods of the disclosure encompass treatment of the human subject who is ineligible for treatment with a JAK2 inhibitor. The methods of the disclosure encompass treatment of the human subject who is relapsed following JAK2 inhibitor treatment or is refractory to JAK2 inhibitor treatment.

[0011] In the methods of the disclosure, the BTK inhibitor is administered once daily at a dose selected from the group consisting of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 90 mg, 100 mg, 120 mg, 150 mg, 175 mg, 180 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, 480 mg and 560 mg.

[0012] In the methods of the disclosure, the BTK inhibitor is administered twice daily at a dose selected from the group consisting of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 90 mg, 100 mg, 120 mg, 150 mg, 175 mg, 180 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, 480 mg and 560 mg.

[0013] In the methods of the disclosure, the BTK inhibitor is orally administered.

[0014] In the methods of the disclosure, the BTK inhibitor is a covalent BTK inhibitor.

[0015] In the methods of the disclosure, the BTK inhibitor is a non-covalent BTK inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figures 1A and 1B are graphs showing inhibition of cell migration towards SDF-1.

CLAIMS

1. Use of a Bruton's Tyrosine Kinase (BTK) inhibitor in the manufacture of a medicament for the treatment of a myeloproliferative neoplasm (MPN) in a human subject in need thereof, wherein the BTK inhibitor is selected from
   1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one,
   or pharmaceutically acceptable salts thereof, wherein the human subject has an accumulation of malignant CD34+ myeloid cells in their hematopoietic tissue.

2. The use of claim 1, wherein the hematopoietic tissue is extramedullary hematopoietic tissue.

3. The use of claim 1, wherein the hematopoietic tissue is bone marrow.

4. The use of claim 1, wherein the hematopoietic tissue is spleen.

5. The use of claim 1, wherein the hematopoietic tissue is liver.

6. The use of any preceding claim, wherein the malignant CD34+ myeloid cells have decreased expression of CXCR4 relative to normal myeloid cells.

7. The use of any preceding claim, wherein the BTK inhibitor is administered in an amount sufficient to stimulate migration of the malignant CD34+ myeloid cells to peripheral blood of the human subject.

8. The use of any preceding claim, wherein the BTK inhibitor is administered in an amount sufficient to decrease activity of VLA-4 in the malignant CD34+ myeloid cells.

9. The use of any preceding claim, wherein the BTK inhibitor is administered in an amount sufficient to decrease expression of VLA-4 in the malignant CD34+ myeloid cells.

10. The use of any preceding claim wherein the human subject is suffering from myelofibrosis.

11. Use of a BTK inhibitor in the manufacture of a medicament for stimulating migration of malignant CD34+ myeloid cells from hematopoietic tissue to the peripheral blood in a human subject suffering from a myeloproliferative neoplasm (MPN), wherein the BTK inhibitor is selected from

1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one,
or pharmaceutically acceptable salts thereof.

12. The use of claim 11, wherein the human subject has an accumulation of malignant CD34+ myeloid cells in the spleen.

13. The use of claim 11, wherein the malignant CD34+ myeloid cells have decreased expression of CXCR4 relative to normal myeloid cells.

14. The use of claim 11, wherein the human subject is suffering from myelofibrosis.

15. The use of claim 10 or 14, wherein the myelofibrosis is primary myelofibrosis (PMF).

16. The use of claim 10 or 14, wherein the myelofibrosis is post-polycythemia vera myelofibrosis (post PV-MF).

17. The use of claim 10 or 14, wherein the myelofibrosis is post essential thrombocythemia myelofibrosis (post ET-MF).

18. The use of any preceding claim, wherein the human subject did not respond to ruxolitinib therapy.

19. The use of any preceding claim, wherein the human subject has a JAK2V617F mutation.

20. The use of claim 19, wherein the human subject has acute myeloid leukemia (AML) secondary to a myeloproliferative neoplasm (MPN).

21. The use of any of claims 1-18, wherein the human subject does not have a JAK2V617F mutation.

22. The use of claim 21, wherein the human subject has acute myeloid leukemia secondary to a myeloproliferative neoplasm.

23. The use of any preceding claim, wherein the human subject has not been treated with a JAK2 inhibitor.

24. The use of any preceding claim, wherein the human subject is intolerant to a JAK2 inhibitor.

25. The use of any preceding claim, wherein the human subject is ineligible for treatment with a JAK2 inhibitor.

26. The use of any preceding claim, wherein the human subject is relapsed following JAK2 inhibitor treatment or is refractory to JAK2 inhibitor treatment.

27. The use of any preceding claim, wherein the BTK inhibitor is to be administered once daily at a dose selected from the group consisting of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 90 mg, 100 mg, 120 mg, 150 mg, 175 mg, 180 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, 480 mg and 560 mg.

28. The use of any preceding claim, wherein the BTK inhibitor is to be administered twice daily at a dose selected from the group consisting of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 90 mg, 100 mg, 120 mg, 150 mg, 175 mg, 180 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, 480 mg and 560 mg.

29. The use of any preceding claim, wherein the BTK inhibitor is to be orally administered.

30. The use of claim 11, wherein the hematopoietic tissue is extramedullary hematopoietic tissue.

31. The use of claim 11, wherein the hematopoietic tissue is bone marrow.

32. The use of claim 11, wherein the hematopoietic tissue is the spleen.

33. The use of claim 11, wherein the hematopoietic tissue is liver.