

form (where the entire lining of the joint is involved). Treatment is surgical excision of the tumor. However, it is often difficult to perform a marginal excision for the diffuse form of TGCT resulting in a high recurrence rate. It can be characterized by overexpression of CSF1.

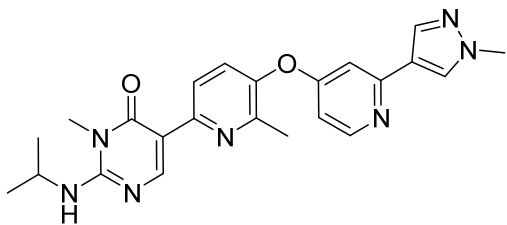
5 [0005] There is a need for selective small-molecule CSF1R inhibitors that are useful in the treatment of disorders associated with the proliferation of TAMs including solid tumors of various cancers and treatment of mesenchymal tumors including TGCT and diffuse-type tenosynovial giant cell tumor (DTGCT).

## SUMMARY

10 [0006] Provided herein, in part, are methods of treating disorders such as tenosynovial giant cell tumors and/or or cancers in a patient in need thereof, comprising orally administering to the patient a therapeutically effective amount of the compound 2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3H)-one or a pharmaceutically acceptable salt thereof.

15 [0007] For example, described herein is a method of treating a cancer selected from the group consisting of solid tumors, acute myeloid leukemia, myelodysplastic syndrome, acute lymphocytic leukemia, and chronic lymphocytic leukemia, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound 2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3H)-one or a pharmaceutically acceptable salt thereof, 20 wherein administering comprises: administering a loading dose of the compound daily for a first time period; and administering a maintenance dose of the compound once a week, twice a week (also described as biweekly), or three times a week for a second time period.

[0007a] In one aspect of the present disclosure, there is provided a use of a compound 25 represented by:



~~2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3H)-one~~ or a pharmaceutically acceptable salt thereof, in the

manufacture of a medicament for treating a tenosynovial giant cell tumor in a patient in need thereof, wherein the compound is to be orally administered to the patient.

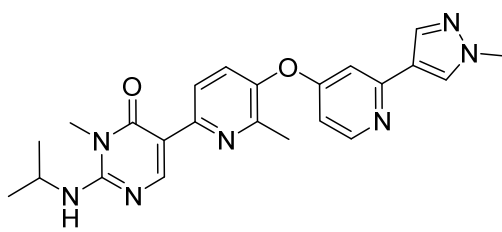
~~{0007b} In another aspect of the present disclosure, there is provided a use of a compound 2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3H)-one or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a cancer selected from the group consisting of solid tumors, acute myeloid leukemia, myelodysplastic syndrome, acute lymphocytic leukemia,~~

~~and chronic lymphocytic leukemia, in a patient in need thereof, wherein the compound is to be administered to the patient, and wherein:~~

~~a loading dose of the compound is to be administered daily for a first time period; and~~

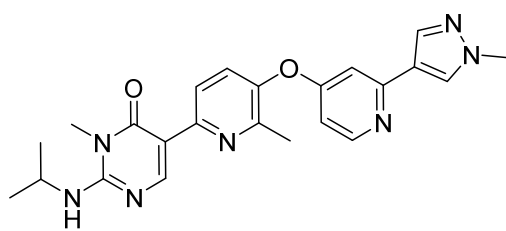
5 ~~———— a maintenance dose of the compound is to be administered daily, once a week,~~  
~~twice a week, or three times a week for a second time period.~~

**[0007b]** In another aspect of the present disclosure, there is provided a use of a compound represented by:



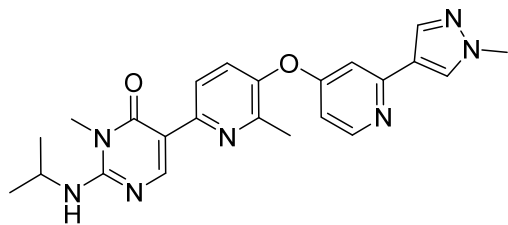
10 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating  
a tenosynovial giant cell tumor in a patient in need thereof, wherein 2 mg to 50 mg of the  
compound is to be orally administered to the patient twice weekly.

[0007c] In a further aspect of the present disclosure, there is provided Use of a compound  
represented by:



15 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a tenosynovial giant cell tumor in a patient in need thereof, wherein 30 mg of the compound is to be orally administered to the patient twice weekly.

[0007d] In another aspect of the present disclosure, there is provided a use of a compound  
20 represented by:



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating tumors known to have expression of the receptor colony-stimulating factor 1 receptor (CSF1R) or its ligands, colony stimulating factor-1 (CSF1) or interleukin (IL)-34 in a patient in need thereof, wherein 2 mg to 60 mg of the compound is to be orally administered to the patient.

~~[0007c] In a further aspect of the present disclosure, there is provided a use of a compound 2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3H)-one or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating tumors known to have expression of the receptor colony-stimulating factor 1 receptor (CSF1R) or its ligands, colony-stimulating factor 1 (CSF1) or interleukin (IL)-34, in a patient in need thereof, wherein the compound is to be administered to the patient, and wherein:~~

~~a loading dose of the compound is to be administered daily for a first time period; and~~

~~—a maintenance dose of the compound is to be administered once a week, twice a week, or three times a week for a second time period.~~

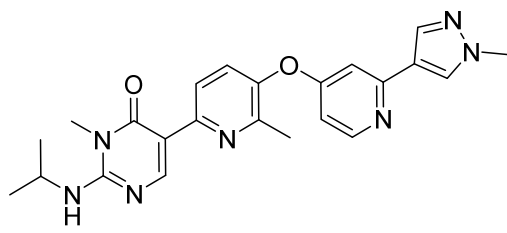
[0008] The disclosure also provides for a method of treating tumors, e.g., GCTTS, PVNS, TGCT or DTGCT, comprising administering to the patient a therapeutically effective amount of the compound 2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3H)-one or a pharmaceutically acceptable salt thereof, wherein administering comprises: administering a loading dose of the compound daily for a first time period; and administering a maintenance dose of the compound once a week, twice a week, or three times a week for a second time period.

[0009] A method of inhibiting the proliferation of a cell known to have expression of the receptor colony-stimulating factor 1 receptor (CSF1R) or its ligands, colony-stimulating factor 1 (CSF1) or interleukin (IL)-34 in a patient in need thereof is also contemplated herein,

## CLAIMS

What is claimed is:

1. Use of a compound represented by:



- 5      ~~2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3H)-one~~ or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a tenosynovial giant cell tumor in a patient in need thereof, wherein the compound is to be orally administered to the patient.
- 10      2. The use of claim 1, wherein the tenosynovial giant cell tumor is diffuse-type tenosynovial giant cell tumor.
3. The use of claim 1, wherein the tumor is benign.
4. The use of any one of claims 1-3, wherein ~~about 2 mg to about 60 mg~~ of the compound is to be administered to the patient daily, once a week, twice a week, or
- 15      three times a week.
5. The use of any one of claims 1-3, wherein ~~about 10 to about 90 mg~~ of the compound is to be administered to the patient daily, once a week, twice a week, or three times a week.
6. The use of any one of claims 1-3, wherein
- 20      a loading dose of the compound is to be administered daily for a first time period; and
- a maintenance dose of the compound is to be administered daily, twice weekly, or three times a week for a second time period.

7. The use of claim 6, wherein the loading dose is ~~about~~10 to ~~about~~80mg/day.
8. The use of claim 6 or 7 wherein the loading dose is ~~about~~20 to ~~about~~60mg/day.
9. The use of any one of claims 6-8, wherein the loading dose is ~~about~~20mg, ~~about~~30mg/day, ~~about~~40mg/day, ~~about~~50mg/day or ~~about~~60mg/day.
- 5 10. The use of any one of claims 6-9, wherein the maintenance dose is ~~about~~2mg to ~~about~~60mg.
11. The use of any one of claims 6-10, wherein the maintenance dose is ~~about~~2mg, ~~about~~10 mg, ~~about~~20mg, ~~about~~25mg, ~~about~~30mg, ~~about~~40mg or ~~about~~50mg each administered twice or three times a week.
- 10 12. The use of any one of claims 6-11, wherein the first time period is ~~about~~one or two weeks.
13. The use of any one of claims 6-12, wherein the first time period is ~~about~~4 days, ~~about~~5 days, ~~about~~6 days, or ~~about~~10 days.
14. The use of any one of claims 6-13, wherein the second time period is one month to  
15 ~~about~~two months, three months or more.
15. The use of any one of claims 6-14, wherein the second time period is ~~about~~one month to ~~about~~nine months or more.
16. The use of any one of claims 6-14, wherein an additional loading dose is to be further administered during a third time period.
- 20 17. The use of claim 16, wherein an additional maintenance dose is to be further administered during a fourth time period.
18. The use of claim 15 or 16, wherein the third and/or fourth time period occurs after the first and second time period.
19. The use of any one of claims 1-17, wherein after 1 month or more of administration,  
25 the patient has an improved tumor response as measured by CT, MRI and/or RECIST.

20. The use of any one of claims 1-18, wherein the compound is to be administered for 1 month or more, and after 1 month or more of administration, the patient has an improved range of motion.
21. The use of any one of claims 1-19, wherein the compound is to be administered for 1 month or more, and after 1 month or more of administration, the patient has reduced macrophage infiltration in the affected joint and/or circulating chemokine/cytokines associated with inflammation as compared to the amounts before administration.
22. The use of any one of claims 6-21, wherein the compound is to be administered, and wherein the size of the tenosynovial giant cell tumor decreases to 90% to 10% of its size prior to administering.
- ~~23. Use of a compound 2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3H)-one or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a cancer selected from the group consisting of solid tumors, acute myeloid leukemia, myelodysplastic syndrome, acute lymphocytic leukemia, and chronic lymphocytic leukemia, in a patient in need thereof, wherein the compound is to be administered to the patient, and wherein:  
  
a loading dose of the compound is to be administered daily for a first time period;  
and  
  
a maintenance dose of the compound is to be administered daily, once a week, twice a week, or three times a week for a second time period.~~
- ~~24. The use of claim 23, wherein the solid tumor is one of breast, cervix, pancreas, bladder, prostate, gastric, ovarian, melanoma, glioma, glioblastoma multiforme, osteosarcoma, osteolytic cancers, chondrosarcoma, histiocytosis, or lung cancer.~~
- ~~25. The use of claim 23 or 24, wherein the solid tumor has progressed after prior administration of another cancer therapy.~~
- ~~26. The use of any one of claims 23-25, wherein the solid tumor is metastatic breast or prostate cancer with bone disease.~~

- ~~27.—The use of any one of claims 23–25, wherein the solid tumor is gastric, ovarian or non-small cell lung cancer that has malignant associated ascites or effusion(s).~~
- ~~28.—The use of any one of claims 23–27, wherein the tumor expresses one or more of: CSF1R or its ligands, CSF1, and IL-34.~~
- 5     ~~29.—The use of any one of claims 23–27, further comprising identifying the tumor or tumor microenvironment as expressing CSF1R, CSF1, or IL-34.~~
- ~~30.—The use of any one of claims 23–29, wherein each maintenance dose is lower than or equal to each loading dose.~~
- 10     ~~31.—The use of any one of claims 23–30, wherein the loading dose is about 10 to about 80mg/day.~~
- ~~32.—The use of any one of claims 23–31, wherein the loading dose is about 20 to about 60mg/day.~~
- ~~33.—The use of any one of claims 23–32, wherein the loading dose is about 20mg, about 30mg/day, about 40mg/day, about 50mg/day or about 60mg/day.~~
- 15     ~~34.—The use of any one of claims 23–33, wherein the maintenance dose is about 2mg to about 60mg.~~
- ~~35.—The use of any one of claims 23–33, wherein the maintenance dose is about 2 mg, about 10 mg, about 20mg, about 25mg, about 30mg, about 40mg or about 50mg twice or three times a week.~~
- 20     ~~36.—The use of any one of claims 23–35, wherein the first time period is about one or two weeks.~~
- ~~37.—The use of any one of claims 23–36, wherein the first time period is about 4 days, about 5 days, about 6 days, or about 10 days.~~
- ~~38.—The use of any one of claims 23–37, wherein the second time period is one month to about two months, three months or more.~~
- 25     ~~39.—The use of any one of claims 23–38, wherein an additional loading dose is to be further administered during a third time period.~~

40. — ~~The use of claim 39, wherein an additional maintenance dose is to be further administered during a fourth time period.~~
41. — ~~The use of claim 39 or 40, wherein the third and/or fourth time period occurs after the first and second time period.~~
- 5 42. — ~~The use of any one of claims 23–41, wherein the compound is to be administered for 1 month or more, and after 1 month or more of administration, the patient has an improved tumor response as measured by RECIST.~~
- 10 43. — ~~The use of any one of claims 23–42, wherein the compound is to be administered for 1 month or more, and after 1 week, or 1 month, or more of administration, the patient has one of: reduced levels of circulating CD16+ or CSF1R+ monocytes in blood by flow cytometry, increased levels of CSF1 or IL-34 in plasma, reduced levels of bone turnover markers wherein the turnover markers can include collagen fragments C-terminal fragment of collagen in serum and urine N-terminal fragment of collagen, and reduced macrophage content and/or re-polarization of pro-tumor M2 macrophages~~
- 15 ~~to an anti-tumoral M1 phenotype in the tumor or tumor-associated ascites/effusion fluids, as compared to the associated level before administration.~~
44. — ~~The use of any one of claims 23–42, wherein another immunomodulatory therapeutic is to be further administered.~~
- 20 45. — ~~The use of claim 44, wherein the other immunomodulatory therapeutic is an anti-PD-1 therapeutic, an anti-PD-L1 therapeutic, a CD40 agonist therapeutic, an anti-CD47 therapeutic, an anti-LAG3 therapeutic, an anti-CD20 therapeutic, an anti-CD38 therapeutic, and/or an anti-TIM3 therapeutic.~~
46. — ~~The use of any one of claims 23–42, wherein a chemotherapeutic agent is to be further administered.~~
- 25 47. — ~~The use of claim 46, wherein the chemotherapeutic agent is selected from the group consisting of paclitaxel, eribulin, docetaxel, gemcitabine, vemurafenib, dabrafenib, trametinib, cobimetinib, and binimetinib.~~
48. — ~~The use of any one of claims 23–42, wherein an immunomodulatory therapeutic and another chemotherapeutic agent is to be further administered.~~

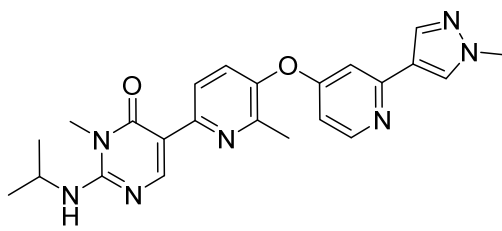
49. ~~Use of a compound 2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)-2,5,8-triazine-4-yl)oxy)pyridine-2-yl)pyrimidin-4(3H)-one or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating tumors known to have expression of the receptor colony-stimulating factor-1 receptor (CSF1R) or its ligands, colony stimulating factor-1 (CSF1) or interleukin (IL)-34, in a patient in need thereof, wherein the compound is to be administered to the patient, and wherein:~~

~~a loading dose of the compound is to be administered daily for a first time period; and~~

~~a maintenance dose of the compound is to be administered once a week, twice a week, or three times a week for a second time period.~~

50. ~~The use of claim 49, comprising determining if the tumor, its microenvironment, expresses CSF1R, CSF1, or IL-34 from the patient's extracted tumor sample, or patient's extracellular fluid.~~

23. Use of a compound represented by:



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a tenosynovial giant cell tumor in a patient in need thereof, wherein 2 mg to 50 mg of the compound is to be orally administered to the patient twice weekly.

24. The use of claim 23, wherein 5 mg to 30 mg of the compound is to be administered to the patient twice weekly.

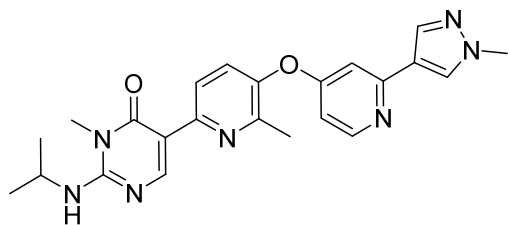
25. The use of claim 23 or 24, wherein 20 mg of the compound is to be administered to the patient twice weekly.

26. The use of claim 23 or 24, wherein 14 mg of the compound is to be administered to the patient twice weekly.

27. The use of any one of claims 23-26, wherein the tenosynovial giant cell tumor is a diffuse-type tenosynovial giant cell tumor.

28. The use of any one of claims 23-27, wherein the tumor is benign.

29. Use of a compound represented by:



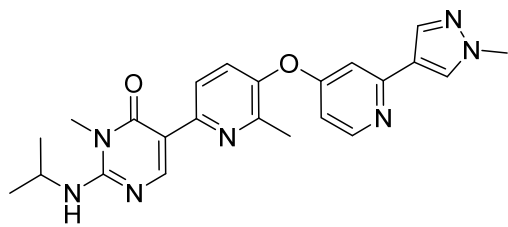
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a tenosynovial giant cell tumor in a patient in need thereof, wherein 30 mg of the compound is to be orally administered to the patient twice weekly.

30. The use of claim 29, wherein the tumor is benign.

10 31. The use of claim 29 or 30, wherein the compound is to be administered to the patient twice weekly for at least 6 months.

32. The use of claim 29 or 30, wherein the compound is to be administered to the patient twice weekly for 1 year.

33. Use of a compound represented by:



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating tumors known to have expression of the receptor colony-stimulating factor 1 receptor (CSF1R) or its ligands, colony stimulating factor-1 (CSF1) or interleukin (IL)-34 in a patient in need thereof, wherein 2 mg to 60 mg of the compound is to be orally administered to the patient.

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34. The use of claim 33, wherein 5 mg to 30 mg of the compound is to be administered to the patient twice weekly.
35. The use of claim 33, wherein 30 mg of the compound is to be administered to the patient twice weekly.
- 5 36. The use of any one of claims 33-35, wherein the tenosynovial giant cell tumor is a diffuse-type tenosynovial giant cell tumor.
37. The use of any one of claims 33-36, wherein the tumor is benign.
38. The use of any one of claims 33-37, wherein expression of CSF1R, CSF1, or IL-34 in the tumor is to be determined from the patient's extracted tumor sample, or patient's extracellular fluid.
- 10 39. The use of any one of claims 33-37, wherein expression of CSF1R, CSF1, or IL-34 in the tumor's microenvironment is to be determined from the patient's extracted tumor sample, or patient's extracellular fluid.
40. The use any one of claims 1-39, wherein the tenosynovial giant cell tumor is additionally to be surgically treated in the patient.
- 15 41. The use of claim 40, wherein the compound is to be administered to the patient as an adjuvant after surgically treating the tenosynovial giant cell tumor in the patient.
42. The use of claim 40, wherein the compound is to be administered to the patient as a neo-adjuvant prior to surgically treating the tenosynovial giant cell tumor in the patient.
- 20 43. The use of any one of claims 1-42, wherein after 1 month or more of administration, the patient has: (i) an improved tumor response as measured by CT, MRI and/or RECIST; and/or (ii) an improved range of motion; and/or (iii) reduced macrophage infiltration in the affected joint and/or circulating chemokine/cytokines associated with inflammation as compared to the amounts before administration.
- 25 44. The use of claim 43, wherein the size of the tenosynovial giant cell tumor decreases to 90% to 10% of its size prior to administering.

45. The use of claim 29 or 30, wherein the compound is to be administered to the patient twice weekly for at least 3 months.

46. The use of claim 29 or 30, wherein the compound is to be administered to the patient twice weekly for at least 1 month.