SUMMARY OF THE DISLCOSURE

[0007] A first aspect of the present disclosure is directed to a method of treating gastrointestinal stromal tumor (GIST). The method entails administering to a subject a therapeutically effective amount of a Menin inhibitor. In some embodiments, the method also entails administering to the subject a therapeutically effective amount of a tyrosine kinase inhibitor (TKI) and/or a therapeutically effective amount of a MOZ inhibitor.

[0007a] In one aspect, there is provided a use of a Menin inhibitor in the manufacture of a medicament for treating gastrointestinal stromal tumor (GIST) in a subject.

[0008] Another aspect of the present disclosure is a method of reducing KIT activity *in vitro* or *in vivo*. The method entails contacting a cell having an activating mutation in or around the *KIT* gene with a Menin inhibitor. In some embodiments, the method entails administering to the subject a therapeutically effective amount of a TKI and/or a therapeutically effective amount of a MOZ inhibitor.

[0008a] In another aspect, the present disclosure provides a use of a Menin inhibitor in the manufacture of a medicament for reducing KIT activity *in vitro* or *in vivo*, wherein a cell having an activating mutation in or around the *KIT* gene is to be contacted with a Menin inhibitor.

[0009] Yet another aspect of the present disclosure is directed to a kit containing a therapeutically effective amount of a Menin inhibitor, a pharmaceutically acceptable carrier disposed in a suitable container, and printed instructions for using the Menin inhibitor in the treatment of GIST in a subject. In some embodiments, the kit also contains a therapeutically effective amount of a TKI and printed instructions for using the TKI in the treatment of GIST in a subject, wherein the Menin inhibitor and the TKI are contained in the same dosage form or different dosage forms that are disposed in the same or different containers. In some embodiments, the kit also contains a therapeutically effective amount of a MOZ inhibitor and printed instructions for using the MOZ inhibitor in the treatment of GIST in a subject, wherein the Menin inhibitor and the MOZ inhibitor are contained in the same dosage form or different dosage forms that are disposed in the same or different containers.

[0010] As shown in the working examples, the present inventors have shown that the Menin-MLL and MOZ chromatin regulatory complexes were enriched at GIST-relevant genes, regulated their transcription, and the transcription of the GIST epigenome. Inhibition of the Menin-MLL complex, alone or in combination with MOZ complex inhibition, decreased GIST cell proliferation by disrupting interactions with transcriptional and chromatin regulators, such as DOT1L. Menin and MOZ inhibition caused significant reductions in tumor burden *in vivo*, with even greater effects observed with combined Menin and KIT inhibition.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIGs. 1A-1G are a series of scatter, bar, and dot plots that illustrate the identification of GIST epigenetic dependencies through genome-scale CRISPR dependency screens. FIGs. 1A and 1B are scatter plots showing correlation β-scores. FIG. 1A shows the correlation

What is claimed is:

1. Use of a Menin inhibitor in the manufacture of a medicament for treating gastrointestinal stromal tumor (GIST) in a subject.

2. The use of claim 1, wherein the Menin inhibitor is JNJ-75276617, KO-539, SNDX-5613, DS-1594, or DSP-5336, MI-3454, M-808, BMF-219, A300-105A, VTP-50469, a short interfering RNA (siRNA), or a combination of two or more thereof.

3. The use of claim 2, wherein the Menin inhibitor is SNDX-5613.

4. The use of claim 2, wherein the Menin inhibitor is VTP-50469.

5. The use of claim 2, wherein the Menin inhibitor is M-808.

6. The use of any one of claims 1-5, wherein the Menin inhibitor is to be administered orally, intramuscularly, subcutaneously, or intravenously.

7. The use of any one of claims 1-6, wherein a therapeutically effective amount of a tyrosine kinase inhibitor (TKI) is to be administered to the subject.

8. The use of claim 7, wherein the TKI is imatinib, sunitinib, regorafenib, ripretinib, nilotinib, pazopanib, cabozantinib, avapritinib, or a combination of two or more thereof.

9. The use of claim 8, wherein the TKI is imatinib.

10. The use of any one of claims 7-9, wherein the TKI is to be administered subsequent to administration of the Menin inhibitor.

11. The use of any one of claims 7-9, wherein the TKI is to be administered substantially simultaneously with administration of the Menin inhibitor.

12. The use of any one of claims 7-9, wherein the TKI is to be administered prior to administration of the Menin inhibitor.

13. The use of any one of claims 1-12, wherein a therapeutically effective amount of a MOZ inhibitor is to be administered to the subject.

14. The use of claim 13, wherein the MOZ inhibitor is WM-1119, WM-8014, PF-9363, a siRNA, or a combination of two or more thereof.

15. The use of claim 14, wherein the MOZ inhibitor is WM-1119.

16. The use of any one of claims 13-15, wherein the MOZ inhibitor is to be administered orally, intramuscularly, subcutaneously, or intravenously.

17. The use of any one of claims 13-16, wherein the MOZ inhibitor is to be administered subsequent to administration of the Menin inhibitor.

18. The use of any one of claims 13-16, wherein the MOZ inhibitor is to be administered simultaneously with administration of the Menin inhibitor.

19. The use of any one of claims 13-16, wherein the MOZ inhibitor is to be administered prior to administration of the Menin inhibitor.

20. The use of claim 17, wherein the MOZ inhibitor is to be administered subsequent to administration of the TKI.

21. The use of claim 18, wherein the MOZ inhibitor is to be administered substantially simultaneously with administration of the TKI.

22. The use of any one of claim 19, wherein the MOZ inhibitor is to be administered prior to administration of the TKI.

23. The use of any one of claims 1-22, wherein the subject is diagnosed with an activating mutation in or around the receptor tyrosine kinase (*KIT*) gene.

24. The use of any one of claims 1-23, wherein the GIST is metastatic.

25. Use of a Menin inhibitor in the manufacture of a medicament for reducing KIT activity *in vitro* or *in vivo*,

wherein a cell having an activating mutation in or around the *KIT* gene is to be contacted with a Menin inhibitor.

26. The use of claim 25, wherein the Menin inhibitor is MI-3454, M-808, JNJ-75276617, KO-539, SNDX-5613, DS-1594, or DSP-5336, BMF-219, A300-105A, VTP-50469, or a combination of two or more thereof.

27. The use of claim 26, wherein the Menin inhibitor is SNDX-5613.

28. The use of claim 26, wherein the Menin inhibitor is VTP-5613.

29. The use of any one of claims 25-28, wherein the cell is to be contacted with a TKI.

30. The use of claim 29, wherein the TKI is imatinib, sunitinib, regorafenib, ripretinib, nilotinib, pazopanib, cabozantinib, avapritinib, or a combination of two or more thereof.

31. The use of claim 30, wherein the TKI is imatinib.

32. The use of any one of claims 25-31, wherein the cell is to be contacted with a therapeutically effective amount of a MOZ inhibitor.

33. The use of claim 32, wherein the MOZ inhibitor is WM-1119.

34. A kit comprising a therapeutically effective amount of a Menin inhibitor, a pharmaceutically acceptable carrier disposed in a suitable container and printed instructions for using the Menin inhibitor in the treatment of GIST in a subject.

35. The kit of claim 34, wherein the Menin inhibitor is SNDX-5613.

36. The kit of claim 34 or 35, further comprising a therapeutically effective amount of a TKI and printed instructions for using the TKI in the treatment of GIST in a subject, wherein

the Menin inhibitor and the TKI are contained in the same dosage form or different dosage forms that are disposed in the same or different containers.

37. The kit of claim 36, wherein the TKI is imatinib.

38. The kit of any one of claims 34-37, further comprising a therapeutically effective amount of a MOZ inhibitor and printed instructions for using the MOZ inhibitor in the treatment of GIST in a subject, wherein the Menin inhibitor and the MOZ inhibitor are contained in the same dosage form or different dosage forms that are disposed in the same or different containers.