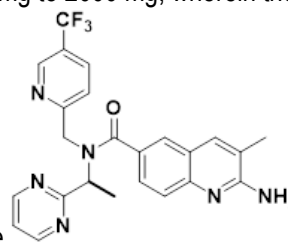
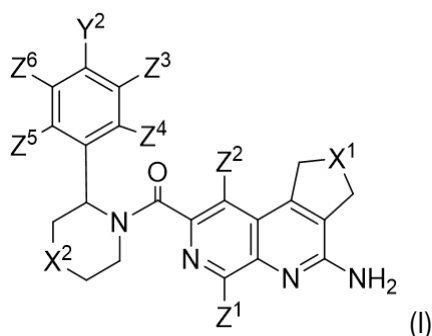


(a) a PRMT5 inhibitor in an amount ranging from 40 mg to 2000 mg, wherein the PRMT5 inhibitor



comprises a compound set forth in Formula (I) or having a structure , or a pharmaceutically acceptable salt thereof;

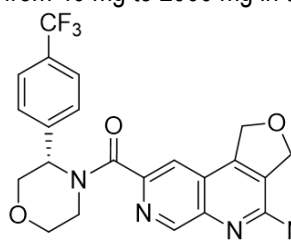


wherein

X¹ is NH, N(C₁-C₆alkyl), O, or S;
X² is N(C₁-C₆alkyl), O, or S;
Y² is H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;
each of Z¹ and Z² is independently H, F, or C₁-C₆ alkyl; and
each of Z³, Z⁴, Z⁵, and Z⁶ is independently H, C₁-C₆alkyl, or chloride; and

(b) a second therapeutic agent selected from a PARP inhibitor, a KRAS inhibitor, or a Kinase-like protein 18A (KIF18A) inhibitor, or a kinase inhibitor.

[0003a] In one aspect, the present disclosure refers to the use of (a) a PRMT5 inhibitor in an amount ranging from 40 mg to 2000 mg in the manufacture of a first medicament, wherein the PRMT5 inhibitor has a structure of



or a pharmaceutically acceptable salt thereof ; and (b) use of a second therapeutic agent selected from a PARP inhibitor, a KRAS inhibitor, a Kinase-like protein 18A (KIF18A) inhibitor, or a kinase inhibitor in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination therapy for treating a MTAP-null cancer in a patient.

BRIEF DESCRIPTION OF THE FIGURES

[0004] Figure 1 is a graph showing that the combination of Compound G and sotorasib resulted in significant anti-tumor activity versus either single agent alone in LU99 NSCLC xenografts.

[0005] Figure 2 is a graph showing that the combination of Compound B and sotorasib resulted in significant anti-tumor activity versus either single agent alone in LU99 NSCLC xenografts.

[0006] Figure 3 is a graph showing that the combination of Compound B and sotorasib resulted in significant anti-tumor activity versus either single agent alone in LU5268 NSCLC patient-derived xenografts.

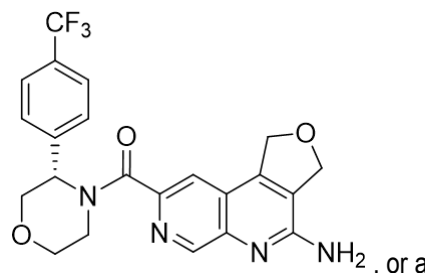
[0007] Figure 4 is a graph showing that the combination of Compound B and sotorasib resulted in decreased pancreatic cancer (MIAPACA2) cell viability.

[0008] Figure 5 is a graph showing that the combination of Compound B and sotorasib significantly reduced pancreatic cancer (MIAPACA2) cell counts.

What is claimed is:

1. Use of

- (a) a PRMT5 inhibitor in an amount ranging from 40 mg to 2000 mg in the manufacture of a first



medicament, wherein the PRMT5 inhibitor has a structure of pharmaceutically acceptable salt thereof ; and

(b) use of a second therapeutic agent selected from a PARP inhibitor, a KRAS inhibitor, a Kinase-like protein 18A (KIF18A) inhibitor, or a kinase inhibitor in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination therapy for treating a MTAP-null cancer in a patient.

2. The use of claim 1, wherein the second therapeutic agent is a PARP inhibitor.

3. The use of claim 2, wherein the PARP inhibitor is olaparib, niraparib, rucaparib or talazoparib.

4. The use of claim 3, wherein the PARP inhibitor is olaparib.

5. The use of any one of claims 1-4, comprising that

(a) 40-2000 mg of the PRMT5 inhibitor; and

(b) 300 mg olaparib are to be administered to the patient twice daily.

6. The use of claim 1, wherein the second therapeutic is a KRAS inhibitor.

7. The use of claim 6, wherein the KRAS inhibitor is sotorasib, adagrasib, JNJ-74699157, LY3537982, BI1823911, BI1701963, GDC-6036, JAB-2122, ARS-3248, AZD4625, or MRTX1133.

8. The use of claim 6 or 7, wherein the KRAS inhibitor is sotorasib.

9. The use of claim 8, comprising that

(a) 40-2000 mg of the PRMT5 inhibitor; and

(b) 960 mg sotorasib are to be administered to the patient once daily.

10. The use of claim 8, comprising that

(a) 40-2000 mg of the PRMT5 inhibitor; and

(b) 240 mg sotorasib are to be administered to the patient once daily.

11. The use of claim 1, wherein the second therapeutic agent is kinase-like protein 18A inhibitor.

12. The use of claim 11, wherein the kinase-like protein 18A inhibitor is KIF18A.

13. The use of claim 12, wherein the KIF18A inhibitor is N-(2-(4,4-difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide.
14. The use of claim 1, wherein the second therapeutic agent is a kinase inhibitor.
15. The use of claim 14, wherein the kinase inhibitor is palbociclib or trametinib.
16. The use of claim 15, wherein the kinase inhibitor is palbociclib.
17. The use of claim 16, comprising that
 - (a) 40-2000 mg of the PRMT5 inhibitor; and
 - (b) 125 mg palbociclib is to be administered to the patient once daily.
18. The use of claim 15, wherein the kinase inhibitor is trametinib.
19. The use of claim 18, comprising that
 - (a) 40-2000 mg of the PRMT5 inhibitor; and
 - (b) 2 mg trametinib is to be administered to the patient once daily.
20. The use of any one of claims 1-19 wherein the MTAP-null cancer is a solid tumor.
21. The use of claim 20, wherein the tumor is malignant.
22. The use of any one of claims 1-19, wherein the MTAP-null cancer is lung cancer.
23. The use of any one of claims 1-19, wherein the MTAP-null cancer is pancreatic cancer.
24. The use of claim 22, wherein the MTAP-null lung cancer is non-small cell lung cancer (NSCLC).
25. The use of claim 24, wherein the NSCLC is squamous.
26. The use of claim 24, wherein the NSCLC is non-squamous.
27. The use of any one of claims 1-19, wherein the MTAP-null cancer is biliary tract cancer.
28. The use of any one of claims 1-19, wherein the MTAP-null cancer is head and neck squamous cell carcinoma.
29. The use of claim 23, wherein the MTAP-null cancer is pancreatic adenocarcinoma.
30. The use of any one of claims 1-19, wherein the MTAP-null cancer is gallbladder cancer.
31. The use of any one of claims 1-19, wherein the MTAP-null cancer is mesothelioma.
32. The use of any one of claims 1-19, wherein the MTAP-null cancer is not a primary brain tumor or lymphoma.

33. The use of any one of claims 1-19, wherein the MTAP-null cancer is esophageal cancer or gastric cancer.