the compound of Formula (I) or a pharmaceutically acceptable salt thereof and the DNA synthesis inhibitor is further combined with a taxane in the treatment of MTAP-deficient pancreatic cancer, including PDAC. Examples of a taxane are docetaxel and paclitaxel including nanoparticle-albumin bound paclitaxel. In still further embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt thereof and a taxane are believed to provide a therapeutic advantage when used in combination for the treatment of MTAP-deficient esophageal cancer. In a still further aspect, the compound of Formula (I), or pharmaceutically acceptable salts thereof, provides a therapeutic advantage when used in combination with at least one antimetabolite agent in treating MTAP-deficient lung or MTAP-deficient pancreatic cancer, including MTAP-deficient NSCLC or MTAP-deficient PDAC or MTAP-deficient esophageal cancer. In another embodiment, the compound of Formula (I), or pharmaceutically acceptable salts thereof, may provide a therapeutic advantage when used in combination with at least one antimetabolite agent in treating MTAP-deficient mesothelioma. One example of an antimetabolite agent is pemetrexed disodium ("pemetrexed"). In yet further embodiments, any of the foregoing treatment methods may incorporate one or more additional therapeutic agents as detailed herein.

[0012a] In one aspect there is provided a use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of MTAP-deficient non-small cell lung cancer (NSCLC) in a patient in need thereof, wherein the medicament is to be administered with a therapeutically effective amount of a taxane.

[0012b] In another aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating MTAP-deficient non-small cell lung cancer (NSCLC) in combination with a therapeutically effective amount of a taxane.

[0012c] In yet another aspect, there is provided a use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of MTAP-deficient pancreatic cancer in a patient in need thereof, wherein the medicament is to be administered with a therapeutically effective amount of a taxane.

[0012d] In a further aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating MTAP-deficient pancreatic cancer, in combination with a therapeutically effective amount of a taxane.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Figure 1 is an illustration of a cell cycle analysis in synchronized HCT116 $MTAP^{-/-}$, which demonstrates that a compound of Formula (I), or a pharmaceutically acceptable salt thereof, inhibits cell cycle progression.

[0014] Figure 2 illustrates a Western blot analysis for levels of Aurora B and phospho-Ser10-H3 during cell cycle progression.

[0015] Figures 3A and 3B illustrate the results of an immunofluorescence analysis demonstrating that the compound of Formula (I) leads to increased γH2AX in HCT116 $MTAP^{-/-}$ cells.

[0016] Figures 4A and 4B illustrate a DAPI staining analysis that demonstrates an increased number of micronuclei formation.

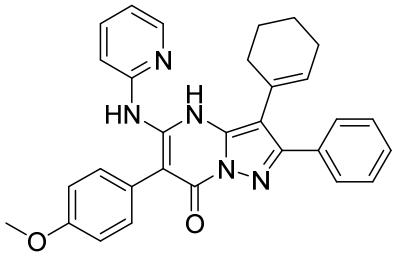
[0017] Figure 5A illustrates the results of an immunofluorescence analysis that demonstrates mitotic defects upon treatment with a compound of Formula (I). Figure 5B illustrates the results of an γH2AX staining analysis to demonstrate that a compound of Formula (I) induces DNA damage in HCT116 $MTAP^{-/-}$ cells.

[0018] Figure 6 illustrates Loewe Synergy Scores, as herein defined, displayed as a scatter plot and ranked by median score across the cell line panel as described.

[0019] Figure 7 illustrates the results of a combination index assessment with the compound of Formula (I) and two different taxane compounds: docetaxel and paclitaxel.

What is claimed is:

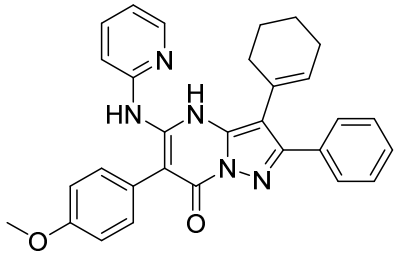
1. Use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of MTAP-deficient non-small cell lung cancer (NSCLC) in a patient in need thereof,



Formula (I)

wherein the medicament is to be administered with a therapeutically effective amount of a taxane.

2. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating MTAP-deficient non-small cell lung cancer (NSCLC) in combination with a therapeutically effective amount of a taxane:



Formula (I).

3. The use of claim 1 or compound of claim 2, wherein the taxane is docetaxel, paclitaxel, or nab-paclitaxel.

4. The use or compound of claim 3, wherein the taxane is docetaxel.

5. The use of claim 1, 3, or 4, wherein one or more additional therapeutic agents is to be further administered.

6. The compound of any one of claims 2-4, wherein the combination further comprises one or more additional therapeutic agents.

7. The use of claim 5 or compound of claim 6, wherein the additional therapeutic agent is a platinum-based chemotherapeutic.

8. The use or compound of claim 7, wherein the platinum-based chemotherapeutic is cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetra nitrate, phenanthriplatin, picoplatin, or satraplatin.

9. The use or compound of claim 7 or 8, wherein the platinum-based chemotherapeutic is carboplatin or cisplatin.

10. The use of any one of claims 1, 3-5, or 7 – 9, wherein the patient failed to respond, ceased responding, or experienced disease progression after one or more prior lines of therapy for treating MTAP-deficient NSCLC.

11. The use or compound of claim 10, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is a second line of therapy for treating MTAP-deficient NSCLC.

12. The use or compound of claim 10, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is a third line of therapy for treating MTAP-deficient NSCLC.

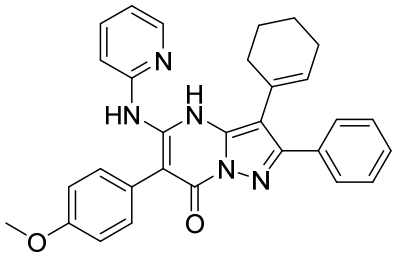
13. The use of claims 1, 3-5 or 7-12, or compound of any one of claims 2-4, 6-9 and 11 – 12, wherein the MTAP-deficient NSCLC is newly diagnosed.

14. The use of any one of claims 1, 3-5 or 7-13, or compound of any one of claims 2-4, 6-9 and 11–13, wherein the dosage of the compound of Formula (I) or a pharmaceutically acceptable salt thereof is about 20 mg to about 800 mg.

15. The use of any one of claims 1, 3-5 or 7-14, or compound of any one of claims 2-4, 6-9 or 11–14, wherein the dosage of the compound of Formula (I) or a pharmaceutically acceptable salt thereof is once or twice daily dosing.

16. The use of any one of claims 1, 3-5 or 7-15, or compound of any one of claims 2-4, 6-9 and 11–15, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is to be administered orally, or formulated for oral administration.

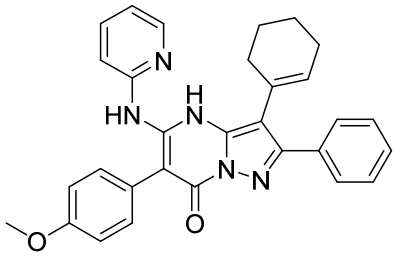
17. Use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of MTAP-deficient pancreatic cancer in a patient in need thereof,



Formula (I)

wherein the medicament is to be administered with a therapeutically effective amount of a taxane.

18. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating MTAP-deficient pancreatic cancer, in combination with a therapeutically effective amount of a taxane:



Formula (I).

19. The use of claim 17 or compound of claim 18, wherein the taxane is paclitaxel, nab-paclitaxel, or docetaxel.

20. The use or compound of claim 19, wherein the taxane is nab-paclitaxel.

21. The use of any one of claims 17, 19, or 20, wherein a therapeutically effective amount of a DNA synthesis inhibitor to be further administered.

22. The compound of any one of claims 18 – 20, wherein the combination further comprises a therapeutically effective amount of a DNA synthesis inhibitor.

23. The use of claim 21 compound of claim 22, wherein the DNA synthesis inhibitor is gemcitabine.

24. The use of any one of claims 17, 19-21, or 23, wherein the patient failed to respond, ceased responding, or experienced disease progression after one or more prior lines of therapy for treating MTAP-deficient pancreatic cancer.

25. The use or compound of claim 24, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is a second line of therapy for treating MTAP-deficient pancreatic cancer.

26. The use or compound of claim 25, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is a third line of therapy for treating MTAP-deficient pancreatic cancer.

27. The use of any one of claims 17, 19-21 or 23-26, or compound of any one of claims 18-20, 22-23 and 25 – 26, wherein the MTAP-deficient pancreatic cancer is newly diagnosed.

28. The use of any one of claims 17, 19-21 or 23-27, or compound of any one of claims 18-20, 22-23 and 25– 27, wherein the dosage of the compound of Formula (I) or a pharmaceutically acceptable salt thereof is about 20 mg to about 800 mg.

29. The use of any one of claims 17, 19-21 and 23-28 or compound of any one of claims 18-20, 22-23 and 25-28, wherein the dosage of the compound of Formula (I) or a pharmaceutically acceptable salt thereof is selected from once or twice daily dosing.

30. The use of any one of claims 17, 19-21 and 23-29 or compound of any one of 18-20, 22-23 and 25– 29, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is to be administered orally or the compound is formulated for oral administration.

31. The use of any one of claims 17, 19-21 and 23-27 or compound of any one of claims 18-20, 22-23 and 25 – 27, wherein the pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC).

32. The use of any one of claims 17, 19-21 and 23-31 or compound of any one of claims 18-20, 22-23 and 25 – 31, wherein the pancreatic cancer is unresected, locally advanced or metastatic.

33. The use of any one of claims 1, 3-5, 7-17, 19-21, or 23 – 32, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof and the taxane are to be administered concurrently.

34. The use of any one of claims 1, 3-5, 7-17, 19-21, or 23 – 32, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof and the taxane are to be administered sequentially.