[0006] Chk1 inhibitors, either as single agents or in combination, are useful, as an example, in treating tumor cells in which constitutive activation of DNA damage and checkpoint pathways drives genomic instability. Various attempts have been made to develop inhibitors of Chk1 kinase. For example, PCT Application Publication Nos. WO 2003/010444 and WO 2005/072733 disclose aryl/heteroaryl urea compounds as Chk1 kinase inhibitors. U.S. Patent Application Publication No. US 2005/0215556 discloses macrocyclic ureas as kinase inhibitors. PCT Application Publication Nos. WO 2002/070494, WO 2006/014359, and WO 2006/021002 disclose aryl and heteroaryl ureas as Chk1 inhibitors. PCT Application Publication Nos. WO 2011/141716 and WO 2013/072502 both disclose substituted pyrazinyl-phenyl ureas as Chk1 kinase inhibitors. PCT Application Publication Nos. WO 2005/009435 and WO 2010/077758 disclose aminopyrazoles as Chk1 kinase inhibitors.

[0007] Despite the aforementioned efforts, there remains a need for cell cycle checkpoint inhibitors that can be used as therapeutic agents to render cancer cells more susceptible to DNA damage and the activation of apoptosis pathways, and to make cancer cells less likely to become resistant to other chemotherapy and radiotherapy treatments. The present invention satisfies this need and provides related advantages as well.

SUMMARY

[0008] In some examples, the present disclosure provides a method for preventing or treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of Compound 1 and a therapeutically effective amount of a Wee1 inhibitor. In some examples, the Wee1 inhibitor is adavosertib (i.e., AZD-1775).

[0008a] In one aspect, the present disclosure refers to use of Compound I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for preventing or treating cancer in a subject, wherein the medicament is to be administered with a Wee1 inhibitor or a pharmaceutically acceptable salt thereof.

[0008b] In one aspect, the present disclosure refers to use of a Wee1 inhibitor or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for preventing or treating cancer in a subject, wherein the medicament is to be administered with Compound 1 or a pharmaceutically acceptable salt thereof.

[0009] In some examples, the cancer is selected from the group consisting of acute myeloid leukemia, esophageal cancer, gastric cancer, mantle cell lymphoma, non-small cell lung cancer (NSCLC), ovarian cancer, head and neck cancer, liver cancer, pancreatic cancer, prostate cancer, and a central nervous system cancer. In other examples, the cancer is a metastatic cancer. In some other examples, the cancer is a multidrug-resistant cancer.

[0010] In some examples, the dose of Compound 1 is between about 1 mg and 100 mg per kg of the subject's body weight. In some examples, the dose of Compound 1 is about 12.5 mg per kg of the subject's body weight. In other examples, the dose of Compound 1 is about 25 mg per kg of the subject's body weight. In some other examples, the dose of Compound 1 is about 50 mg per kg of the subject's body weight. In other examples, the dose of AZD-1775 is about 30 mg per kg of the subject's body weight. In particular

examples, the dose of Compound 1 is about 25 mg per kg of the subject's body weight and the dose of AZD-1775 is about 30 mg per kg of the subject's body weight.

[0011] In some examples, Compound 1 and the Wee1 inhibitor are co-administered. In other examples, Compound 1 and the Wee1 inhibitor are co-administered simultaneously or sequentially. In particular examples, Compound 1 or the Wee1 inhibitor are administered orally, intravenously, intramuscularly, subcutaneously, or intratumorally.

[0012] In some examples, treating the subject results in a reduction of tumor volume. In other examples, treating the subject results in a decrease or elimination of one or more signs or symptoms of cancer. In some other examples, treating the subject results in an increased survival time. In particular examples, the administration is for prevention and the subject does not have cancer.

[0013] In other examples, the present disclosure provides a pharmaceutical composition comprising Compound 1 and a pharmaceutically acceptable carrier. In some examples, the pharmaceutical composition further comprises a Wee1 inhibitor. In some examples, the Wee1 inhibitor is AZD-1775.

[0013a] In another aspect, the present disclosure refers to a pharmaceutical composition comprising: (i) Compound I or a pharmaceutically acceptable salt thereof; (ii) a Wee1 inhibitor or a pharmaceutically acceptable salt thereof; and (iii) a pharmaceutically acceptable carrier.

[0014] In some examples, Compound 1 is present at a concentration between about 0.1 nM and 2,000 nM. In some examples, the Wee1 inhibitor (*e.g.*, AZD-1775) is present at a concentration between about 0.1 nM and 1,000 nM.

[0015] In yet other aspects, the present disclosure refers to a kit for preventing or treating cancer in a subject, the kit comprising a pharmaceutical composition of the present disclosure. In some examples, the kit further comprises instructions for use. In some examples, the kit further comprises one or more reagents.

[0016] Other objects, features, and advantages of the present disclosure will be apparent to one of skill in the art from the following detailed description and figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIG. 1 depicts the DNA damage response and cell cycle control axis in cancer.

[0018] FIG. 2 presents various drug properties of Compound 1.

[0019] FIGS. 3A-3D show that Compound 1 is a potent and selective inhibitor of Chk1. FIG. 3A depicts different kinase families. FIG. 3B shows the enzymatic selectivity of

WHAT IS CLAIMED IS:

1. Use of Compound 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for preventing or treating cancer in a subject, wherein the medicament is to be administered with a Wee1 inhibitor or a pharmaceutically acceptable salt thereof.

2. Use of a Wee1 inhibitor or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for preventing or treating cancer in a subject, wherein the medicament is to be administered with Compound 1 or a pharmaceutically acceptable salt thereof.

3. The use of claim 1 or 2, wherein the Wee1 inhibitor is AZD-1775.

4. The use of any of claims 1-3, wherein the cancer is selected from the group consisting of acute myeloid leukemia, esophageal cancer, gastric cancer, mantle cell lymphoma, non-small cell lung cancer (NSCLC), ovarian cancer, head and neck cancer, liver cancer, pancreatic cancer, prostate cancer, and a central nervous system cancer.

5. The use of any one of claims 1 to 4, wherein the cancer is a metastatic cancer.

6. The use of any one of claims 1 to 5, wherein the cancer is a multidrug-resistant cancer.

7. The use of any one of claims 1 to 6, wherein the dose of Compound 1 is between about 1 mg and 100 mg per kg of the subject's body weight.

8. The use of claim 7, wherein the dose of Compound 1 is about 12.5 mg per kg of the subject's body weight.

9. The use of claim 7, wherein the dose of Compound 1 is about 25 mg per kg of the subject's body weight.

10. The use of claim 7, wherein the dose of Compound 1 is about 50 mg per kg of the subject's body weight.

11. The use of any one of claims 3 to 10, wherein the dose of AZD-1775 is about 30 mg per kg of the subject's body weight.

12. The use of any one of claims 7 to 11, wherein the dose of Compound 1 is about 25 mg per kg of the subject's body weight and the dose of AZD-1775 is about 30 mg per kg of the subject's body weight.

13. The use of any one of claims 1 to 12, wherein Compound 1 and the Wee1 inhibitor are to be co-administered.

14. The use of claim 13, wherein Compound 1 and the Wee1 inhibitor are to be co-administered simultaneously or sequentially.

15. The use of any one of claims 1 to 14, wherein Compound 1 or the Wee1 inhibitor are to be administered orally, intravenously, intramuscularly, subcutaneously, or intratumorally.

16. The use of any one of claims 1 to 15, wherein treating the subject results in a reduction of tumor volume.

17. The use of any one of claims 1 to 16, wherein treating the subject results in a decrease or elimination of one or more signs or symptoms of cancer.

18. The use of any one of claims 1 to 17, wherein treating the subject results in an increased survival time.

19. The use of any one of claims 1 to 15, wherein the subject does not have cancer.

20. The use of any one of claims 1 to 15, wherein the medicament is to be administered with a DNA-damaging agent.

21. A pharmaceutical composition comprising:

(i) Compound 1 or a pharmaceutically acceptable salt thereof;

(ii) a Wee1 inhibitor or a pharmaceutically acceptable salt thereof; and

(iii) a pharmaceutically acceptable carrier.

22. The pharmaceutical composition of claim 21, wherein the Wee1 inhibitor is AZD-1775.

23. The pharmaceutical composition of claim 21 or 22, wherein Compound 1 is present at a concentration between about 0.1 nM and 2,000 nM.

24. The pharmaceutical composition of claim 22 or 23, wherein AZD-1775 is present at a concentration between about 0.1 nM and 1,000 nM.

25. The pharmaceutical composition of any of claims 20 to 23, wherein the composition comprises a DNA-damaging agent.

26. A kit for preventing or treating cancer in a subject, the kit comprising a pharmaceutical composition of any one of claims 21 to 24.

27. The kit of claim 26, further comprising instructions for use.

28. The kit of claim 26 or 27, further comprising one or more reagents.

29. The kit of any of claims 26 to 28, wherein the composition comprises a DNA-damaging agent.