## CLAIMS

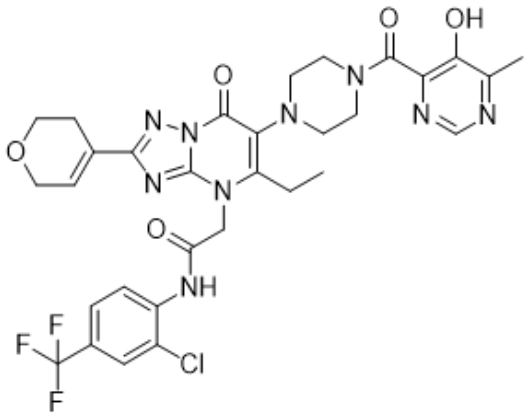
1. Use of a WRN inhibitor in the manufacture of a medicament for the treatment of cancer, wherein the use further comprises:

**i.** temozolomide to be administered,

and optionally wherein the use further comprises:

**ii.** irinotecan to be administered,

wherein the WRN inhibitor is Compound A:



, or a pharmaceutically acceptable salt thereof.

2. The use as claimed in claim 1, wherein the cancer is MSS (microsatellite stable) cancer.

3. The use as claimed in claims 1 or 2, further comprising i. temozolomide and ii. Irinotecan, to be administered.

4. The use as claimed in any of claims 1 to 3, wherein the cancer is selected from colorectal cancer (CRC), gastric cancer, prostate cancer, endometrial cancer, adrenocortical cancer, cervical cancer, uterine cancer, esophageal ccancer, breast cancer, kidney cancer, ovarian cancer, glioma, glioblastoma, neuroendocrine tumors, melanoma, small cell lung cancer and sarcoma.

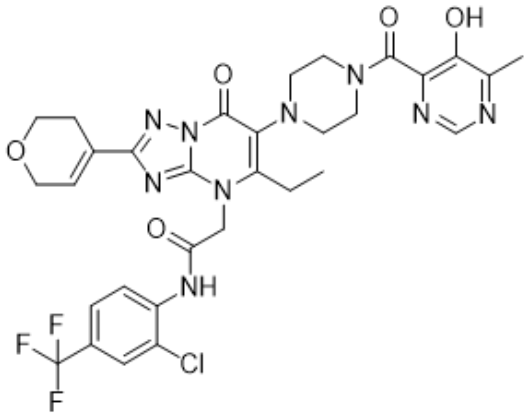
5. The use as claimed in claim 4, wherein the cancer is colorectal cancer or small cell lung cancer.

6.The use as claimed in any of claims 1 to 5, wherein the cancer is selected from MSS (microsatellite stable) MGMT-defective, or MSS (microsatellite stable) MGMT-deficient, or MSS (microsatellite stable) MGMT-silenced, or MGMT-methylated MSS (microsatellite stable) cancer.

7. The use as claimed in any of claims 1 to 6, wherein the agent i. is temozolomide, and temozolomide is to be administered:

- as a pre-treatment before administration of the WRN inhibitor, or
- in combination with the WRN inhibitor, without pre-treatment with temozolomide, or
- as a pre-treatment before administration of the WRN inhibitor, followed by combination treatment including temozolomide and the WRN inhibitor.

8. A combination comprising i) a WRN inhibitor and ii) temozolomide, and optionally iii) irinotecan, wherein the WRN inhibitor is Compound A:




, or a pharmaceutically acceptable salt thereof.

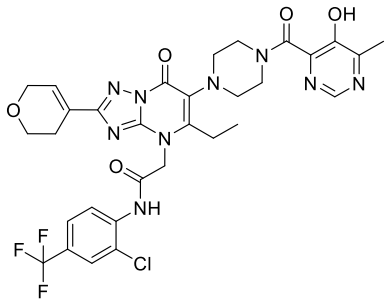
9. Use of the combination according to claim 8 in the manufacture of a medicament for the treatment of MSS cancer.

10. The use according to claim 9, wherein the cancer is selected from colorectal cancer (CRC), gastric cancer, prostate cancer, endometrial cancer, adrenocortical cancer, cervical cancer, uterine cancer, esophageal cancer, breast cancer, kidney cancer, ovarian cancer, glioma, glioblastoma, neuroendocrine tumors, melanoma, small cell lung cancer and sarcoma.

11. The use according to claim 10, wherein the cancer is colorectal cancer or small cell lung cancer.

12. The use according to any of claims 9 to 11, wherein the cancer is selected from MSS (microsatellite stable) MGMT-defective, or MSS (microsatellite stable) MGMT-deficient, or MSS (microsatellite stable) MGMT-silenced, or MGMT-methylated MSS (microsatellite stable) cancer.

13. Use of a WRN inhibitor in the manufacture of a medicament for the treatment of cancer, in particular microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer, wherein the use further comprises at least one therapeutically active agent selected from the group consisting of a Wee1 inhibitor, an ATR inhibitor, a DNA-PK inhibitor, ionising radiation based therapy selected from i) external beam radiation, ii) brachytherapy and iii) a radiopharmaceutical, a MEK inhibitor, an MDM2 inhibitor, a G4-quadruplex stabilizer, an ATM inhibitor, and a CHK1 or CHK2 inhibitor, including dual CHK1 and CHK2 inhibitor to be administered, wherein the WRN inhibitor is Compound A:



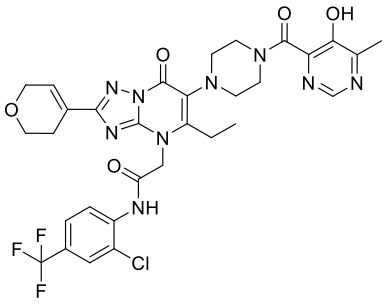

or a pharmaceutically acceptable salt thereof.

14. A combination comprising:

i) a WRN inhibitor, and ii) at least one therapeutically active agent selected from the group consisting of a Wee1 inhibitor, an ATR inhibitor, a DNA-PK inhibitor, ionising radiation selected from i) external beam radiation, ii) brachytherapy and iii) a radiopharmaceutical, a MEK inhibitor, an MDM2 inhibitor, a G4-quadruplex stabilizer, an ATM inhibitor, a CHK1 or CHK2 inhibitor, including dual CHK1 and CHK2 inhibitor,

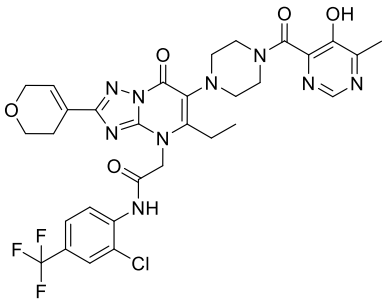
or a combination comprising a WRN inhibitor and a chemotherapy agent, wherein the chemotherapy agent is selected from epirubicin and mitomycin C,

wherein the WRN inhibitor is Compound A:



or a pharmaceutically acceptable salt thereof.

15. Use of a WRN inhibitor in the manufacture of a medicament for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer, wherein the use further comprises a chemotherapy agent to be administered, wherein the chemotherapy agent is selected from epirubicin (Ellence®, Pharmorubicin®), oxaliplatin (Eloxatin®), and mitomycin C and wherein the WRN inhibitor is Compound A:



or a pharmaceutically acceptable salt thereof.

16. The use according to claim 13, or the combination according to claim 14, wherein the (at least one) therapeutically active agent is a WEE1 inhibitor, and the WEE1 inhibitor is adavosertib.

17. The use according to claim 13, or the combination according to claim 14, wherein the (at least one) therapeutically active agent is the ATR inhibitor elimusertib (also known as BAY-1895344).

18. The use according to claim 13, or the combination according to claim 14, wherein the (at least one) therapeutically active agent is the DNA-PK inhibitor AZD7648 or NU7441.

19. The use according to claim 13, or the combination according to claim 14, wherein the (at least one) therapeutically active agent is an ionising radiation based therapy selected from i) external beam radiation, ii) brachytherapy and iii) a radiopharmaceutical.

20. The use according to claim 13, or the combination according to claim 14, wherein the ionising radiation is external beam radiation.

21. The use according to claim 13, or the combination according to claim 14, wherein the (at least one) therapeutically active agent is the MEK inhibitor trametinib.

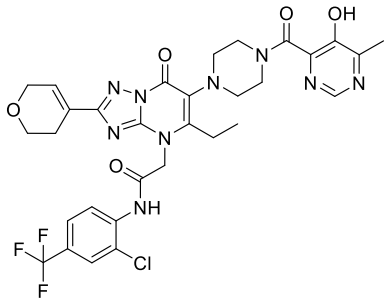
22. The use according to claim 13, or the combination according to claim 14, wherein the (at least one) therapeutically active agent is the MDM2 inhibitor HDM201 (also known as siremadlin), or a pharmaceutically acceptable salt thereof.

23. The use according to claim 13 or 15 to 22, wherein the cancer is selected from colorectal cancer (CRC), such as colon adenocarcinoma or rectal adenocarcinoma, gastric cancer, such as stomach adenocarcinoma, prostate cancer, endometrial cancer, adrenocortical cancer, such as

adrenocortical carcinoma, cervical cancer, such as cervical squamous cell carcinoma or endocervical adenocarcinoma, uterine cancer, such as uterine corpus endometrial carcinoma and uterine carcinosarcoma, esophageal cancer, such as esophageal carcinoma, breast cancer, such as breast carcinoma or triple negative breast cancer, kidney cancer, such as kidney renal clear cell carcinoma, ovarian cancer, such as ovarian serous cystadenocarcinoma, glioma, glioblastoma, neuroendocrine tumors, melanoma, small cell lung cancer and sarcoma.

24. The use according to claim 23, wherein the cancer is colorectal cancer (CRC) or gastric cancer, particularly colorectal cancer (CRC).

25. A WRN inhibitor or a combination according any one of claims 8, 14, 16 to 22, for use in therapy, wherein the WRN inhibitor is Compound A:



or a pharmaceutically acceptable salt thereof.