Claims

1. Use of a histone-lysine N-methyltransferase EZH2 (enhancer of zeste homolog 2) inhibitor and an enhancer of interferon-gamma receptor activity in the manufacture of a pharmaceutical composition for treating a patient having cancer, wherein said inhibitor is selected from the group consisting of (-)-1-[(1R,4R,5S)-3-(Hydroxymethyl)-4,5-dihydroxy-2-cyclopenten-1-yl]4-aminoimidazo[4,5-c]pyridine hydrochloride (DZNep; 3-deazaneplanocin A);
1-{[4-amino-5-(2,2-dimethylpropanoyl)-1,3-thiazol-2-yl]sulfanyl}-3,3-dimethylbutan-2-one;
2-{[(3,4-dichlorophenyl)carbamoyl]amino}benzoic acid;
(2E)-2-(1,3-benzothiazol-2-yl)-3-(4-chlorophenyl)prop-2-enenitrile;
1-(4-fluorophenyl)-3-(1-phenyl-5-propyl-1H-pyrazol-4-yl)urea;
5-(4-chlorophenyl)-3-(2,2-dichloroacetamido)thiophene-2-carboxamide;
3-(5-tert-butyl-1,2-oxazol-3-yl)-1-phenylurea;
1-benzoyl-3-2,3-dihydro-1H-inden-5-ylthiourea;
N,5-diphenyl-1,3,4-oxadiazole-2-carboxamide; and
2,4-dihydroxy-5,7-diphenylpyrano[2,3-d]pyrimidin-8-ium perchlorate.

2. The use of claim 1, wherein the interferon-gamma receptor is interferon-gamma receptor 1 (IFNGR1) encoding for interferon-gamma receptor (IFNGR1) subunit 1.

3. The use according to claim 1 or claim 2, the pharmaceutical composition further comprising one or more pharmaceutically acceptable excipients, vehicles or carriers.

4. The use of any of the preceding claims, wherein said inhibitor is (-)-1-[(1R,4R,5S)-3-(Hydroxymethyl)-4,5-dihydroxy-2-cyclopenten-1-yl]4-aminoimidazo[4,5-c]pyridine hydrochloride (DZNep; 3-deazaneplanocin A).

5. The use according to claim 1 or 2 or 3, wherein said inhibitor is an EZH2-binding protein.

6. The use according to claim 5, wherein said EZH2-binding protein is an antibody or fragment thereof.

7. The use according to claim 1 or 2 or 3, wherein said inhibitor is a nucleic acid molecule or conjugate thereof.

8. The use according to claim 7, wherein said nucleic acid molecule is a small interfering RNA.

9. The use according to claim 1 or 2 or 3, wherein said enhancer is interferon-gamma (IFN-γ).

10. The use according to claim 1 or 2 or 3, wherein said inhibitor is DZNep and said enhancer is IFN-γ.

11. The use according to any one of the preceding claims wherein said inhibitor is in amount of less than 3 mg/kg, or less than 2mg/kg, or less than 1 mg/kg, or less than 0.8 mg/kg, or less than 0.5 mg/kg, or less than 0.2 mg/kg, or between 0.1 mg/kg to 3 mg/kg.

12. The use according to any one of the preceding claims, wherein said enhancer is in an amount of less than $5x10^6$ IU/kg, or less than 10^6 IU/kg, or less than $5x10^5$ IU/kg, or less than $2x10^5$ IU/kg, or in an amount of between $1x10^5$ IU/kg to 10^6 IU/kg.

13. The use according to any one of the preceding claims, wherein the cancer is a metastatic cancer.

14. The use according to claim 13, wherein said metastatic cancer is a prostate cancer.

15. The use according to any one of claims 1 to 12, wherein the cancer is selected from the group consisting of liver, ovarian, lung, acute lymphoblastic leukemia, breast particularly luminal B breast, bladder, and lymphoma mantle-cell cancer.

16. The use according to any one of claims 1 to 15, wherein said patient is characterized by an increased level of EZH2 in a tumor sample relative to the level in other tissues and a decreased level of IFNGR1 in a tumor sample relative to the level in other tissues.

17. An *in vitro* method for determining susceptibility of a patient suffering from cancer to a treatment with a pharmaceutical composition as defined in any one of claims 1 to 16, wherein the method comprises:

a. comparing a first level of EZH2 selected from the group consisting of EZH2 mRNA level in a tumor sample, EZH2 cDNA level made from mRNA from said tumor sample, and EZH2 protein level from said tumor sample, with a second level of EZH2 selected from the group consisting of EZH2 mRNA level from a non-tumor sample from said patient, EZH2 cDNA level made from mRNA from said non-tumor sample, and EZH2 protein level from said non-tumor sample;

b. comparing a first level of IFNGR1 selected from the group consisting of IFNGR1 mRNA level from said tumor sample, IFNGR1 cDNA level made from mRNA from said tumor sample, and IFNGR1 protein level from said tumor sample with the level of IFNGR1 selected from the group consisting of IFNGR1 mRNA level from a non-tumor sample from said patient, IFNGR1 cDNA level made from mRNA from said non-tumor sample, and IFNGR1 protein level from said non-tumor sample; and

c. wherein a patient characterized by an increased level of EZH2 in said tumor sample and a decreased level of IFNGR1 in said tumor sample is susceptible to a treatment with said pharmaceutical composition.

18. The use of any one of claims 1 to 16, wherein the patient is characterized by a difference in the level of EZH2 mRNA, and/or EZH2 cDNA, and/or EZH2 protein and IFNGR1 mRNA, and/or IFNGR1 cDNA, and/or IFNGR1 protein in a tumor

sample, and the level of EZH2 mRNA, and/or EZH2 cDNA, and/or EZH2 protein and IFNGR1 mRNA, and/or IFNGR1 cDNA, and/or IFNGR1 protein from a non-tumor sample, wherein the level of EZH2 mRNA, and/or EZH2 cDNA, and/or EZH2 protein are at least 2-fold higher in the tumor sample and the IFNGR1 mRNA, and/or IFNGR1 cDNA, and/or IFNGR1 protein level is at least 2-fold lower in the tumor sample.

19. The method of claim 17, wherein the cancer is selected from the group consisting of prostate, liver, ovarian, lung, acute lymphoblastic leukemia, breast particularly luminal B breast, bladder, and lymphoma mantle-cell.

20. The method of claim 17, wherein the first level of EZH2 protein from said tumor sample and the second level of EZH2 protein from said non-tumor sample, and wherein a first level of IFNGR1 protein from said tumor sample with the level of IFNGR1 protein from said non-tumor sample is examined by immunohistochemistry.

21. The method of claim 17, wherein the level of EZH2 expression from said tumor sample and from said non-tumor sample, and wherein the level of IFNGR1 expression from said tumor sample and from said non-tumor sample is examined by q-PCR, wherein q-PCR comprises selecting primers comprising SEQ ID Nos 1 to 4.

22. An *in vitro* method for determining susceptibility of a patient suffering from advanced prostate cancer to a treatment with a pharmaceutical composition as defined in any one of claims 1 to 16, wherein the method comprises:

a. comparing a first level of IFNGR1 selected from the group consisting of IFNGR1 mRNA level in a tumor sample, IFNGR1 cDNA level made from mRNA from said tumor sample, and IFNGR1 protein level from said tumor sample with the level of IFNGR1 selected from the group consisting of IFNGR1 mRNA level from a non-tumor sample from said patient, IFNGR1 cDNA level made from mRNA from said non-tumor sample, and IFNGR1 protein level from said non-tumor sample; and

b. wherein a patient characterized by a decreased level of IFNGR1 in said tumor sample is susceptible to a treatment with said pharmaceutical composition.

23. An *in vitro* method for determining susceptibility of a patient suffering from breast cancer to a treatment with a pharmaceutical composition as defined in any one of claims 1 to 16, wherein the method comprises:

a. comparing a first level of IFNGR1 selected from the group consisting of IFNGR1 mRNA level in a tumor sample, IFNGR1 cDNA level made from mRNA from said tumor sample, and IFNGR1 protein level from said tumor sample with the level of IFNGR1 selected from the group consisting of IFNGR1 mRNA level from a non-tumor sample from said patient, IFNGR1 cDNA level made from mRNA from said non-tumor sample, and IFNGR1 protein level from said non-tumor sample;

b. wherein a patient suffering from basal breast cancer is characterized by an increased level of INFGR1 in said tumor sample is not susceptible to a treatment with said pharmaceutical composition ; and

c. wherein a patient suffering from luminal breast cancer is characterized by a decreased level of INFGR1 in said tumor sample is susceptible to a treatment with said pharmaceutical composition.

24. An *in vitro* method for making a prognosis with respect to the clinical outcome of a patient suffering from cancer comprising:

a. comparing a first level of EZH2 selected from the group consisting of EZH2 mRNA level in a tumor sample, EZH2 cDNA level made from mRNA from said tumor sample, and EZH2 protein level from said tumor sample, with a second level of EZH2 selected from the group consisting of EZH2 mRNA level from a non-tumor sample from said patient, EZH2 cDNA level made from mRNA from said non-tumor sample, and EZH2 protein level from said non-tumor sample;

b. comparing a first level of IFNGR1 selected from the group consisting of IFNGR1 mRNA level from said tumor sample, IFNGR1 cDNA level made from mRNA from said tumor sample, and IFNGR1 protein level from said tumor sample with the level of IFNGR1 selected from the group consisting of IFNGR1 mRNA level

from a non-tumor sample from said patient, IFNGR1 cDNA level made from mRNA from said non-tumor sample, and IFNGR1 protein level from said non-tumor sample; and

c. making a prognosis with respect to the clinical outcome of a patient suffering from cancer.

25. The method as claimed in claim 24, wherein said clinical outcome indicates the susceptibility to treatment with said pharmaceutical composition as defined in any one of claims 1-16.

26. The method as claimed in claim 24 or 25, wherein the cancer is selected from the group consisting of prostate, liver, ovarian, lung, particularly small cell lung, acute lymphoblastic leukemia, breast particularly luminal B breast, bladder, and lymphoma mantle-cell cancer.

27. A pharmaceutical composition comprising a histone-lysine N-methyltransferase EZH2 (enhancer of zeste homolog 2) inhibitor and an enhancer of interferon-gamma receptor activity, wherein said inhibitor is selected from the group consisting of (-)-1-[(1R,4R,5S)-3-(Hydroxymethyl)-4,5-dihydroxy-2-cyclopenten-1-yl]4-aminoimidazo[4,5-c]pyridine hydrochloride (DZNep; 3-deazaneplanocin A);
1-{[4-amino-5-(2,2-dimethylpropanoyl)-1,3-thiazol-2-yl]sulfanyl}-3,3-dimethylbutan-2-one;
2-{[(3,4-dichlorophenyl)carbamoyl]amino}benzoic acid;
(2E)-2-(1,3-benzothiazol-2-yl)-3-(4-chlorophenyl)prop-2-enenitrile;
1-(4-fluorophenyl)-3-(1-phenyl-5-propyl-1H-pyrazol-4-yl)urea;
5-(4-chlorophenyl)-3-(2,2-dichloroacetamido)thiophene-2-carboxamide;
3-(5-tert-butyl-1,2-oxazol-3-yl)-1-phenylurea;
1-benzoyl-3-2,3-dihydro-1H-inden-5-ylthiourea;
N,5-diphenyl-1,3,4-oxadiazole-2-carboxamide; and
2,4-dihydroxy-5,7-diphenylpyrano[2,3-d]pyrimidin-8-ium perchlorate.

28. The pharmaceutical composition of claim 27, wherein said inhibitor is DZNep and said enhancer is IFN-γ.