markers have been reported, that could help determine the dose and clinical outcomes in patients receiving anti-cancer treatments.

[0006] Recent introduction of targeted therapy and increasing numbers of available chemotherapeutic regimens, such as platinum and derivatives, taxanes and gemcitabine, do not effectively cure cancer patients, with varied response towards treatment and occurrence of drug toxicity. In addition, prognosis remains dismal in advanced cancer patients albeit careful evaluation of clinico-pathological factors that determine patient response to therapy, such as tumor, nodes and metastasis (TNM) staging, performance status, gender and weight loss.

[0007] Accordingly, there is a need for developing new therapeutic targets and pharmaceutical compositions for the treatment of cancer patients.

SUMMARY OF THE INVENTION

[0008] In a first aspect, the present invention provides 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.

In a second aspect, the present invention provides an *in vitro* method for determining susceptibility of a patient suffering from cancer to a treatment with a pharmaceutical composition as defined herein, wherein the method comprises, 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; 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 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.

In a third aspect, the present invention provides an *in vitro* method for determining susceptibility of a patient suffering from advanced prostate cancer to a treatment with a pharmaceutical composition as defined herein, wherein the method comprises, 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 wherein a patient characterized by a decreased level of IFNGR1 in said tumor sample is susceptible to a treatment with said pharmaceutical composition.

In a fourth aspect, the present invention provides an *in vitro* method for determining susceptibility of a patient suffering from breast cancer to a treatment with a pharmaceutical composition as defined herein, wherein the method comprises, 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; 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 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.

In a fifth aspect, the present invention provides an *in vitro* method for making a prognosis with respect to the clinical outcome of a patient suffering from cancer comprising, 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; 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 making a prognosis with respect to the clinical outcome of a patient suffering from cancer.

In a sixth aspect, the present invention provides a pharmaceutical composition comprising a histone-lysine N-methyltransferase EZH2 (enhancer of zeste homolog 2) inhibitor and an enhancer of interferon-gamma receptor activity.

In ~~a first aspect~~one example, the present ~~invention~~disclosure provides a pharmaceutical composition

comprising a histone-lysine N-methyltransferase EZH2 (enhancer of zeste homolog 2) inhibitor and an enhancer of interferon-gamma receptor activity.

[0009] In ~~a second aspect~~another example, the present ~~invention~~disclosure provides a method of treating a patient having cancer comprising administration of the pharmaceutical composition as defined herein.

[0010] In ~~a third aspect~~yet another example, the present ~~invention~~disclosure provides a method for determining susceptibility of a patient suffering from cancer to a treatment with a pharmaceutical composition as defined herein, wherein the method comprises, comparing a first level of EZH2 comprising but not limited to 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 comprising but not limited to 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; comparing a first level of IFNGR1 comprising but not limited to 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 comprising but not limited to 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 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.

[0011] In ~~a fourth aspect~~one example, the present ~~invention~~disclosure provides a method for treating cancer in a patient with 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, wherein the method comprises administration of a pharmaceutical composition as defined herein to the patient.

[0012] In ~~a fifth aspect~~another example, disclosed herein is a method for determining susceptibility of a patient suffering from advanced prostate cancer to a treatment with a pharmaceutical composition as defined herein, wherein the method comprises comparing a first level of IFNGR1 comprising but not limited to 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 comprising but not limited to 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 wherein a patient characterized by a decreased level of IFNGR1 in said tumor sample is susceptible to a treatment with said pharmaceutical composition.

[0013] In ~~a sixth aspect~~one example, disclosed herein is a method for determining susceptibility of a patient suffering from breast cancer to a treatment with a pharmaceutical composition as defined herein, wherein the method comprises comparing a first level of IFNGR1 comprising but not limited to 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 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

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.

[0014] In ~~a seventh aspect~~another example, disclosed herein is a method for making a prognosis with respect to the clinical outcome of a patient suffering from cancer comprising comparing a first level of EZH2 comprising but not limited to 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 comprising but not limited to 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, comparing a first level of IFNGR1 comprising but not limited to 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 comprising but not limited to 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 making a prognosis with respect to the clinical outcome of a patient suffering from cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

[0016] **Figure 1** is a series of drawings, graphs and western-blot analysis showing that oncogenic transformation by MYC and PI3K induced transcriptional inactivation of IFN-γ-JAK-STAT1 signaling pathway.

[0017] Figure 1(A) is an unsupervised hierarchical clustering showing 610 genes that were differentially regulated in either RWPE1-MYC and RWPE1-PI3K cells compared to RWPE1-vector control cells (2-fold cutoff, $P<0.01$) The colored scale bar represents the absolute fold change.

[0018] Figure 1(B) is a table summarizing an Ingenuity Pathway Analysis (IPA) that shows interferon signaling pathway as the top gene network enriched in downregulated genes in transformed RWPE1 cells.

Claims

1. A pharmaceutical composition comprising a histone-lysine N-methyltransferase EZH2 (enhancer of zeste homolog 2) inhibitor and an enhancer of interferon-gamma receptor activity.

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

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

4. The pharmaceutical composition according any one of the preceding claims, wherein said inhibitor is selected from a 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;
4-[4-(4-methyl-1,3-thiazol-2-yl)phenyl]-1,2,3-thiadiazole;
2-{[(3,4-dichlorophenyl)carbamoyl]amino}benzoic acid;
N-(2-methylquinolin-6-yl)quinoxaline-2-carboxamide;
2-[(4-tert-butylphenyl)carbonyl]-1H-imidazole;
1-(2-hydroxyphenyl)-3-[4-(methoxymethoxy)phenyl]propane-1,3-dione;
N-(3-acetylphenyl)-8-methoxy-2-oxo-2H-chromene-3-carboxamide;
1-{3-[4-(2-phenylethynyl)phenyl]-1H-pyrazol-1-yl}ethan-1-one;
3-(thiophen-2-yl)benzoic acid;
5-(6-methoxynaphthalen-2-yl)-1H-pyrazole;
4-methyl-5-[3-(methylsulfanyl)-1H-pyrazol-5-yl]-2-(thiophen-2-yl)-1,3-thiazole;
2-{[(2-chloro-6-fluorophenyl)methyl]sulfanyl}-1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethan-1-one;
3-(3-chlorophenyl)-5-(thiophen-3-yl)-1,2,4-oxadiazole;

2,3-dihydro-1-benzofuran-5-ylmethanimidamido thiophene-2-carboxylate;
N-(2,3-dihydro-1,4-benzodioxin-6-yl)[(furan-2-ylmethyl)carbamothioyl]formamide;
N-[4-(diethylamino)phenyl]-3-methylbenzamide;
3-[5-(1,2-oxazol-3-yl)thiophen-2-yl]-5-phenyl-1,2,4-oxadiazole;
ethyl(2E)-2-cyano-3-{[(E)-{[4-dimethylamino)phenyl]methylidene}amino](methane) sulfinimidamido}prop-2-enoate;
(2Z)-2-(4-ethylphenyl)-3-(4-methoxyphenyl)prop-2-enenitrile;
5-tert-butyl-3-methyl-N-phenylthieno[3,2-b]thiophene-2-carboxamide;
5-(1-butyl-2-oxo-2,3-dihydro-1H-indol-3-ylidene)-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one;
(2E,6E)-2,6-bis(thiophen-2-ylmethylidene)cyclohexan-1-one;
2-[(E)-2-(3,4-dimethoxyphenyl)ethenyl]-1,3-benzothiazole;
2-chloro-N-[3-hydroxy-4-(5-methyl-1,3-benzoxazol-2-yl)phenyl]-5-nitrobenzamide;
6-chloro-2-phenyl-4H-thiochromen-4-one methyl 2-(3,4-dihydro-2H-1,5-benzodioxepine-7-amido)benzoate;
3-chloro-N,N-dimethyl-4-[(1 E)-[2-(quinoxalin-2-yl)hydrazin-1-ylidene]methyl]aniline;
(2E)-1-(2-methyl-1H-indol-3-yl)-3-(thiophen-2-yl)prop-2-en-1-one;
N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(thiophen-2-yl)-1,3-thiazole-4-carboxamide;
4-[(E)-2-(1-methyl-1H-1,3-benzodiazol-2-yl)ethenyl]-1,3-thiazole;
3-(4-bromophenyl)-3,4-dihydro-1,2,3-benzotriazin-4-one;
N-(2,4-dichlorophenyl)-3,4-dihydro-2H-1-benzopyran-2-carboxamide;
N,N-dimethyl-4-[(E)-2-phenylethenyl]aniline;
2-(3,4-dichlorophenyl)quinoxaline;
N-(3-tert-butyl-1H-pyrazol-5-yl)-2,3-dihydro-1,4-benzodioxine-2-carboxamide;
(2E)-2-(1,3-benzothiazol-2-yl)-3-(4-chlorophenyl)prop-2-enenitrile;
(4-tert-butylphenyl)methanimidamido 2-(thiophen-2-yl)acetate;
5-[4-(3-methyl-1-benzothiophen-2-yl)-1,3-thiazol-2-yl]-1,2-oxazole;
1-(4-fluorophenyl)-3-(1-phenyl-5-propyl-1H-pyrazol-4-yl)urea;
2-[(2Z)-2-phenyl-2-[(2E)-2-(thiophen-2-ylmethylidene)hydrazin-1-ylidene]ethyl]-1H-1,3-benzodiazole;

N-{7-oxo-8-oxa-4-thiatricyclo[7.4.0.0^{2,6}]trideca-1(9),2,5,10,12-pentaen-5-yl}thiophene-2-carboxamide;

2-(2-chlorophenyl)-1-[4-(dimethylamino)phenyl]ethan-1-one ethyl 4-cyano-1-(4-methylphenyl)-1H-pyrazole-3-carboxylate;

3-hydrazinylquinoxaline-2-thiol;

1-[(5-tert-butylthiophen-2-yl)carbonyl]piperidine;

3-[5-(2-phenylethynyl)thiophen-2-yl]-1-(thiophen-2-ylcarbonyl)-1H-pyrazole;

2,5-dichloro-N-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)thiophene-3-carboxamide;

1-tert-butyl-N-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-methyl-1H-pyrazole-3-carboxamide;

4-(5-propylpyridin-2-yl)benzonitrile;

5-(4-chlorophenyl)-3-(2,2-dichloroacetamido)thiophene-2-carboxamide;

(4-methanesulfonamidophenyl)methanimidamido thiophene-2-carboxylate;

ethyl 7-methyl-2-phenylpyrazolo[1,5-a]pyrimidine-6-carboxylate;

6-(4-chlorophenyl)-3-phenylthieno[2,3-e][1,2,4]triazine;

1-{1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-2,3-dihydro-1H-indole;

5-(4-chlorophenyl)-2-(4-methylphenyl)-2H-1,2,3,4-tetrazole;

4-[(1 E)-[2-(3,5-dichloropyridin-4-yl)hydrazin-1-ylidene]methyl]-N,N-dimethylaniline;

3-(5-tert-butyl-1,2-oxazol-3-yl)-1-phenylurea;

(4-chlorophenyl)methanimidamido 3-chlorothiophene-2-carboxylate;

N-{4-[(E)-2-phenyldiazen-1-yl]phenyl}acetamide;

methyl 4-[(pyrimidin-2-ylsulfanyl)methyl]benzoate;

2-phenylimidazo[1,2-a]pyridine;

6-chloro-2-phenyl-4H-thiochromen-4-one;

2-{[(4-methylphenyl)methyl]sulfanyl}-5-(pyrazin-2-yl)-1,3,4-thiadiazole;

5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one;

(E)-[I-(1H-pyrrol-2-yl)ethylidene]amino N-(4-chlorophenyl)carbamate;

1-benzoyl-3-2,3-dihydro-1H-inden-5-ylthiourea;

1-{1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-2,3-dihydro-1H-indole;

N,5-diphenyl-1,3,4-oxadiazole-2-carboxamide;

(3Z)-3-(2,3-dihydro-1-benzofuran-5-ylmethylidene)-2,3-dihydro-1H-indol-2-one;

[(3-methylbutyl)sulfanyl]-N-phenylformamide;
2,4-dihydroxy-5,7-diphenylpyrano[2,3-d]pyrimidin-8-ium perchlorate;
ethyl 7-hydroxy-9-oxo-9H-xanthene-2-carboxylate;
[({[3,5-Dimethyl-1-(2-methyl-2-propanyl)-1H-pyrazol-4-yl]methylene}amino)oxy]{[3-(trifluoromethyl)phenyl]amino}methanone;
5-[(4-iodophenyl)amino]-3-phenyl-1,3-thiazolidine-2,4-dione;
N-(furan-2-ylmethyl)-2-[methane(4-phenoxyphenyl)sulfonamido]acetamide
N-(3-methoxyphenyl)-6-phenylpyridazin-3-amine;
ethyl (2E)-3-[(2-chlorophenyl)amino]-2-cyanoprop-2-enoate;
1-[3-chloro-1-benzothiophen-2-yl)carbonyl]-1H,2H,3H,4H,6H,10bH-pyrimido[2,1-a]isoindol-6-one;
2-(4-chlorophenyl)-5-[(cyclopropylmethyl)sulfanyl]-1,3,4-oxadiazole;
1-[6-(benzyloxy)-3-tert-butyl-2-hydroxyphenyl]ethan-1-one;
3-[(1 E)-1-[(2,2-dichloroethenyl)imino]-2,2-dimethylpropyl]-1-(4-methylphenyl)thiourea;
6,7-dimethyl-2-phenylquinoxaline;
5-(2,3-dihydro-1-benzofuran-5-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole;
2-{4-[(4-methylphenyl)methoxy]phenyl}acetonitrile;
1-cyclohexyl-3-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3,5,10,12-hexaen-5-ylurea;
5-(1,2,3-thiadiazol-4-yl)-3-[4-(trifluoromethyl)phenyl]-1,2,4-oxadiazole;
N-(2-methylquinolin-6-yl)-2-phenylacetamide;
3-(piperidin-1-ylcarbonyl)-5-(thiophen-2-yl)-1,2-oxazole;
N-(3,4-dimethylphenyl)[(E)-N'-(thiophen-2-ylmethylidene)hydrazinecarbonyl]formamide;
2-(2,3-dimethoxyphenyl)-2,3-dihydro-1,3-benzothiazole;
2-methyl-5-(naphthalen-2-yl)-1,3-thiazole hydrobromide;
(cyclohexylcarbamothioyl)-N-(4-fluorophenyl)formamide;
4-(1,3-benzothiazol-2-yl)-1-methyl-1H-pyrazol-3-amine;
(4-tert-butylphenyl)methanimidamido 5-methyl-1,2-oxazole-3-carboxylate;
N-[2-(methylsulfanyl)-1,3-benzothiazol-6-yl]thiophene-2-carboxamide;
N-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-2H-1,3-benzodioxole-5-carboxamide;

(2E)-3-(2-chlorophenyl)-N-(2-methylbut-3-yn-2-yl)prop-2-enamide;
1-naphthalen-1-yl-3-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(13),2,4,6,9,11-hexaen-5-ylthiourea;
3-methyl-N-phenyl-1-benzothiophene-2-carbothioamide;
5-(2,5-dichlorophenyl)-N-[2-(trifluoromethyl)phenyl]furan-2-carboxamide;
3-(5-methyl-1,2-oxazol-3-yl)-5-(thiophen-2-yl)-1,2,4-oxadiazole;
N-(1H-indazol-3-yl)-3-methoxybenzamide;
2-(4-tert-butylphenyl)-5-[(propane-1-sulfonyl)methyl]-1,3,4-oxadiazole;
1-[2-(4-chlorophenoxymethyl)-4-methyl-1,3-thiazol-5-yl]ethan-1-one;
(4-methanesulfonamidophenyl)methanimidamido N-(4-methylphenyl)carbamate;
N-phenyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine hydrochloride;
7-nitro-N-(2-phenylethyl)-1H-indole-2-carboxamide;
2-{[(2E)-4-(pyridin-2-ylsulfanyl)but-2-en-1-yl]sulfanyl}pyridine;
4-[(E)-2-(3-methylthiophen-2-yl)ethenyl]-2-[(3-nitropyridin-2-yl)sulfanyl]pyrimidine;
4-(4-chlorophenyl)-2-[(4-methoxyphenyl)methyl]-1,3-thiazole;
(3Z)-3-{[5-(thiophen-2-yl)thiophen-2-yl]methylidene}-2,3-dihydro-1H-indol-2-one;
N-(4-bromo-2,5-difluorophenyl)-2,3-dimethylbenzamide;
sodium N-phenyl(phenylamino)carboximidate;
2-(benzylsulfanyl)-N-(2,3-dihydro-1H-inden-2-yl)acetamide;
(5Z)-5-[(5-methylfuran-2-yl)methylidene]-3-phenyl-1,3-thiazolidine-2,4-dione;
N-{4-[(3-chlorophenyl)carbamoyl]phenyl}thiophene-2-carboxamide;
N-[(3-chlorophenyl)methyl]-5-(methylsulfanyl)-1,3,4-thiadiazol-2-amine;
(E)-2-(phenylamino)-3-(phenylimino)guanidine;
(2Z)-3-methyl-2-[2-(3-methyl-2,3-dihydro-1,3-benzoxazol-2-ylidene)hydrazin-1-ylidene]-2,3-dihydro-1,3-benzoxazole;
3-[2-(2H-1,4-benzothiazin-3-yl)hydrazin-1-yl]-2H-1,4-benzothiazine;
3-(3,4-dimethyl-1,2-oxazol-5-yl)-1-[4-(dimethylamino)-3,5-difluorophenyl]carbonylurea;
(3Z)-3-[2-(2,5-difluorophenyl)hydrazin-1-ylidene]piperidin-2-one;
N'-[(E)-[1-(1-benzofuran-2-yl)ethylidene]amino](methylsulfanyl)methanimidamide;
(2Z)-3-(9H-fluoren-2-ylcarbamoyl)prop-2-enoic acid;
4-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)diazen-1-yl]-N,N-diethylaniline;

4,5-dichloro-N-(3-chloro-4-fluorophenyl)-1,2-thiazole-3-carboxamide;
5-[4-(4-methoxyphenoxy)phenyl]-1H-pyrazole;
1-cyclohexyl-3-[(Z)-(1H-pyrazol-3-ylmethylidene)amino]thiourea;
[5-(4-chlorophenyl)-3-methyl-2-sulfanylidene-1,3,4-thiadiazinan-6-ylidene]amino 5-tert-butylthiophene-2-carboxylate;
N-(2-phenylethyl)benzenecarbothioamide;
5-amino-3-methyl-2-N-phenylthiophene-2,4-dicarboxamide;
3-amino-5-(thiophen-3-yl)thiophene-2-carboxamide;
(2E)-2-{[4-(trifluoromethoxy)phenyl]imino}-3,4-dihydro-2H-1,3-benzoxazin-4-one;
3-hydroxy-9H-xanthen-9-one;
4-[(E)-2-(3,5-dihydroxyphenyl)ethenyl]benzene-1,2-diol;
(3-chlorophenyl)methanimidamido 6-(2,2,2-trifluoroethoxy)pyridine-3-carboxylate;
5-phenyl-3-(pyrrolidin-1-yl)-1,2-thiazole-4-carbonitrile;
7-hydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one;
2-(4-fluorophenyl)-2H,3H,5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyrimidin-3-one;
(4-chlorophenyl)methanimidamido 2,6-difluorobenzoate;
2-(2-amino-3-methoxyphenyl)-4H-chromen-4-one;
6,7-dimethoxy-2-phenylquinoxaline;
6-methoxy-3-phenyl-[1,2,4]triazolo[4,3-a]pyridazine;
5-[4-(furan-2-ylcarbonyl)piperazin-1-yl]-3-(thiophen-2-yl)-1,2,4-thiadiazole;
(E)-{1-[2-(4-chlorophenoxymethyl)-1,3-thiazol-4-yl]ethylidene}amino benzoate;
N-[(2-chloro-6-fluorophenyl)carbonyl]-N'-(4-methylpyridin-2-yl)ethanediamide;
(E)-hydroxy[1-(2-phenyl-1,3-thiazol-4-yl)ethylidene]amine;
ethyl 1-{[4-(trifluoromethoxy)phenyl]carbamoyl}piperidine-4-carboxylate;
3-(3-methyl-1H-indol-1-yl)-N-[4-(morpholin-4-yl)phenyl]propanamide;
6,8-dimethyl-1-methylidene-2-(4-methylphenyl)-1,4-dihydronaphthalene;
N'-[(2-methyl-1,3-thiazol-4-yl)methoxy]-4-(trifluoromethyl)benzene-1-carboximidamide;
1-[4-(benzyloxy)phenyl]-3-[(3-cyanopyridin-2-yl)amino]urea;
2-phenylimidazo[1,2-a]pyridine;
3-(morpholin-4-yl)-5-[4-(trifluoromethyl)phenyl]-1,2-thiazole-4-carbonitrile;
N-(2-chlorophenyl)-2-[(3-cyano-6-acetylpyridin-2-yl)sulfanyl]acetamide;

3-[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]-5-methyl-1,2-oxazole;
N-(3-bromo-5-methylpyridin-2-yl)-4-ethylbenzamide;
2-(5-methyl-1,2-oxazol-3-yl)-5-[3-(trifluoromethyl)phenyl]-1,3,4-oxadiazole;
(E)-[1-(3-methyl-1-benzothiophen-2-yl)ethylidene]amino N-phenylcarbamate;
N-(2,3-dihydro-1H-inden-2-yl)-3-(3-methyl-1H-indol-1-yl)propanamide;
1,3-dimethanesulfonyl-2,3-dihydro-1H-1,3-benzodiazole;
methyl 2-[5-methyl-2-(thiophene-2-amido)-1,3-thiazol-4-yl]acetate;
4-[(5-{[(4-chlorophenyl)sulfanyl]methyl}furan-2-yl)carbonyl]morpholine;
2-oxo-2-phenylethyl 2,3-dimethoxybenzoate;
N-(4-chlorophenyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide;
(2,4-dichlorophenyl)methyl N-[(2-fluorophenyl)carbonyl]carbamate;
2-[(4-chlorophenyl)carbonyl]-1-benzofuran;
4-chlorophenyl 2,3-dihydro-1-benzofuran-5-carboxylate;
2-[4-(dimethylamino)phenyl]-1,2,3,4-tetrahydroquinolin-4-one;
[6-(ethylsulfanyl)pyridin-3-yl]methanimidamido thiophene-2-carboxylate;
N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-6-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1-(propan-2-yl)-1H-indazole-4-carboxamide (GSK343);
N-[(4,6-dimethyl-2-oxo-1,2-dihydro-3-pyridinyl)methyl]-3-methyl-1-((1S)-1-methylpropyl)-6-[6-(1-piperazinyl)-3-pyridinyl]-1H-indole-4-carboxamide (GSK126);
N-[(4,6-Dimethyl-2-oxo-1,2-dihydro-3-pyridinyl)methyl]-1-(1-methylethyl)-6-[6-(4-methyl-1-piperazinyl)-3-pyridinyl]-1H-indazole-4-carboxamide (GSK926)

5. The pharmaceutical composition 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).

6. The pharmaceutical composition according to claim 1 or 2 or 3, wherein said inhibitor is an EZH2-binding protein.

7. The pharmaceutical composition according to claim 6, wherein said EZH2-binding protein is an antibody or fragment thereof.

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

9. The pharmaceutical composition according to claim 8, wherein said nucleic acid molecule is a small interfering RNA.

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

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

12. The pharmaceutical composition according to any of the preceding claims for use in therapy.

13. A method of treating a patient having cancer comprising administration of the pharmaceutical composition as defined in any one of claims 1-12.

14. The method of claim 13, wherein the pharmaceutical composition is as defined in claim 11.

15. The method according to any one of claims 12 to 14 wherein said inhibitor is used 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 about 0.1 mg/kg to about 3 mg/kg.

16. The method according to any one of claims 12 to 15, wherein said enhancer is used 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 about $1x10^5$ IU/kg to about 10^6 IU/kg.

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

18. The method according to claim 17, wherein said metastatic cancer is a prostate cancer.

19. The method according to claim 13 to 16, wherein cancer is selected from a group comprising liver, ovarian, lung, acute lymphoblastic leukemia, breast particularly luminal B breast, bladder, or lymphoma mantle-cell cancer.

20. The method according to any one of claims 12 to 19, wherein said patient is characterized by an increased level of EZH2 in a tumor sample and a decreased level of IFNGR1 in a tumor sample.

21. A 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 11, 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.

22. A method for treating cancer in a patient with 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, wherein the method comprises administration of a pharmaceutical composition according to any one of claims 1-12 to the patient.

23. The method of claim 21 or claim 22, wherein cancer is selected from a group comprising prostate, liver, ovarian, lung, acute lymphoblastic leukemia, breast particularly luminal B breast, bladder, or lymphoma mantle-cell.

24. The method of claim 21 or claim 22, 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.

25. The method of claim 21 or claim 22, 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.

26. A 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 11, 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.

27. A 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 11, 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.

28. A 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.

29. The method as claimed in claim 28, wherein said clinical outcome indicates the susceptibility to treatment with said pharmaceutical composition as claimed in any one of claims 1-11.

30. The method as claimed in claim 28 or 29, wherein the cancer is selected from a group comprising prostate, liver, ovarian, lung, particularly small cell lung, acute lymphoblastic leukemia, breast particularly luminal B breast, bladder, or lymphoma mantle-cell cancer.

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.

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 according any one of the preceding claims, 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;
4-[4-(4-methyl-1,3-thiazol-2-yl)phenyl]-1,2,3-thiadiazole;
2-{[(3,4-dichlorophenyl)carbamoyl]amino}benzoic acid;
N-(2-methylquinolin-6-yl)quinoxaline-2-carboxamide;
2-[(4-tert-butylphenyl)carbonyl]-1H-imidazole;
1-(2-hydroxyphenyl)-3-[4-(methoxymethoxy)phenyl]propane-1,3-dione;
N-(3-acetylphenyl)-8-methoxy-2-oxo-2H-chromene-3-carboxamide;
1-{3-[4-(2-phenylethynyl)phenyl]-1H-pyrazol-1-yl}ethan-1-one;
3-(thiophen-2-yl)benzoic acid;
5-(6-methoxynaphthalen-2-yl)-1H-pyrazole;
4-methyl-5-[3-(methylsulfanyl)-1H-pyrazol-5-yl]-2-(thiophen-2-yl)-1,3-thiazole;
2-{[(2-chloro-6-fluorophenyl)methyl]sulfanyl}-1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethan-1-one;
3-(3-chlorophenyl)-5-(thiophen-3-yl)-1,2,4-oxadiazole;
2,3-dihydro-1-benzofuran-5-ylmethanimidamido thiophene-2-carboxylate;

N-(2,3-dihydro-1,4-benzodioxin-6-yl)[(furan-2-ylmethyl)carbamothioyl]formamide;
N-[4-(diethylamino)phenyl]-3-methylbenzamide;
3-[5-(1,2-oxazol-3-yl)thiophen-2-yl]-5-phenyl-1,2,4-oxadiazole;
ethyl(2E)-2-cyano-3-{[(E)-{[4-dimethylamino)phenyl]methylidene}arnino](rnethane)
sulfinirnidamido}prop-2-enoate;
(2Z)-2-(4-ethylphenyl)-3-(4-methoxyphenyl)prop-2-enenitrile;
5-tert-butyl-3-methyl-N-phenylthieno[3,2-b]thiophene-2-carboxamide;
5-(1-butyl-2-oxo-2,3-dihydro-1H-indol-3-ylidene)-2-(piperidin-1-yl)-4,5-dihydro-1,3-thiazol-4-one;
(2E,6E)-2,6-bis(thiophen-2-ylmethylidene)cyclohexan-1-one;
2-[(E)-2-(3,4-dimethoxyphenyl)ethenyl]-1,3-benzothiazole;
2-chloro-N-[3-hydroxy-4-(5-methyl-1,3-benzoxazol-2-yl)phenyl]-5-nitrobenzamide;
6-chloro-2-phenyl-4H-thiochromen-4-one methyl 2-(3,4-dihydro-2H-1,5-benzodioxepine-7-amido)benzoate;
3-chloro-N,N-dimethyl-4-[(1 E)-[2-(quinoxalin-2-yl)hydrazin-1-ylidene]methyl]aniline;
(2E)-1-(2-methyl-1H-indol-3-yl)-3-(thiophen-2-yl)prop-2-en-1-one;
N-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(thiophen-2-yl)-1,3-thiazole-4-carboxamide;
4-[(E)-2-(1-methyl-1H-1,3-benzodiazol-2-yl)ethenyl]-1,3-thiazole;
3-(4-bromophenyl)-3,4-dihydro-1,2,3-benzotriazin-4-one;
N-(2,4-dichlorophenyl)-3,4-dihydro-2H-1-benzopyran-2-carboxamide;
N,N-dimethyl-4-[(E)-2-phenylethenyl]aniline;
2-(3,4-dichlorophenyl)quinoxaline;
N-(3-tert-butyl-1H-pyrazol-5-yl)-2,3-dihydro-1,4-benzodioxine-2-carboxamide;
(2E)-2-(1,3-benzothiazol-2-yl)-3-(4-chlorophenyl)prop-2-enenitrile;
(4-tert-butylphenyl)methanimidamido 2-(thiophen-2-yl)acetate;
5-[4-(3-methyl-1-benzothiophen-2-yl)-1,3-thiazol-2-yl]-1,2-oxazole;
1-(4-fluorophenyl)-3-(1-phenyl-5-propyl-1H-pyrazol-4-yl)urea;
2-[(2Z)-2-phenyl-2-[(2E)-2-(thiophen-2-ylmethylidene)hydrazin-1-ylidene]ethyl]-1H-1,3-benzodiazole;
N-{7-oxo-8-oxa-4-thiatricyclo[7.4.0.0^{2,6}]trideca-1(9),2,5,10,12-pentaen-5-yl}thiophene-2-carboxamide;

2-(2-chlorophenyl)-1-[4-(dimethylamino)phenyl]ethan-1-one ethyl 4-cyano-1-(4-methylphenyl)-1H-pyrazole-3-carboxylate;
3-hydrazinylquinoxaline-2-thiol;
1-[(5-tert-butylthiophen-2-yl)carbonyl]piperidine;
3-[5-(2-phenylethynyl)thiophen-2-yl]-1-(thiophen-2-ylcarbonyl)-1H-pyrazole;
2,5-dichloro-N-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)thiophene-3-carboxamide;
1-tert-butyl-N-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-methyl-1H-pyrazole-3-carboxamide;
4-(5-propylpyridin-2-yl)benzonitrile;
5-(4-chlorophenyl)-3-(2,2-dichloroacetamido)thiophene-2-carboxamide;
(4-methanesulfonamidophenyl)methanimidamido thiophene-2-carboxylate;
ethyl 7-methyl-2-phenylpyrazolo[1,5-a]pyrimidine-6-carboxylate;
6-(4-chlorophenyl)-3-phenylthieno[2,3-e][1,2,4]triazine;
1-{1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-2,3-dihydro-1H-indole;
5-(4-chlorophenyl)-2-(4-methylphenyl)-2H-1,2,3,4-tetrazole;
4-[(1 E)-[2-(3,5-dichloropyridin-4-yl)hydrazin-1-ylidene]methyl]-N,N-dimethylaniline;
3-(5-tert-butyl-1,2-oxazol-3-yl)-1-phenylurea;
(4-chlorophenyl)methanimidamido 3-chlorothiophene-2-carboxylate;
N-{4-[(E)-2-phenyldiazen-1-yl]phenyl}acetamide;
methyl 4-[(pyrimidin-2-ylsulfanyl)methyl]benzoate;
2-phenylimidazo[1,2-a]pyridine;
6-chloro-2-phenyl-4H-thiochromen-4-one;
2-{[(4-methylphenyl)methyl]sulfanyl}-5-(pyrazin-2-yl)-1,3,4-thiadiazole;
5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one;
(E)-[I-(1H-pyrrol-2-yl)ethylidene]amino N-(4-chlorophenyl)carbamate;
1-benzoyl-3-2,3-dihydro-1H-inden-5-ylthiourea;
1-{1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-2,3-dihydro-1H-indole;
N,5-diphenyl-1,3,4-oxadiazole-2-carboxamide;
(3Z)-3-(2,3-dihydro-1-benzofuran-5-ylmethylidene)-2,3-dihydro-1H-indol-2-one;
[(3-methylbutyl)sulfanyl]-N-phenylformamide;
2,4-dihydroxy-5,7-diphenylpyrano[2,3-d]pyrimidin-8-ium perchlorate;

ethyl 7-hydroxy-9-oxo-9H-xanthene-2-carboxylate;
[({[3,5-Dimethyl-1-(2-methyl-2-propanyl)-1H-pyrazol-4-yl]methylene}amino)oxy]{[3-(trifluoromethyl)phenyl]amino}methanone;
5-[(4-iodophenyl)amino]-3-phenyl-1,3-thiazolidine-2,4-dione;
N-(furan-2-ylmethyl)-2-[methane(4-phenoxyphenyl)sulfonamido]acetamide
N-(3-methoxyphenyl)-6-phenylpyridazin-3-amine;
ethyl (2E)-3-[(2-chlorophenyl)amino]-2-cyanoprop-2-enoate;
1-[3-chloro-1-benzothiophen-2-yl)carbonyl]-1H,2H,3H,4H,6H,10bH-pyrimido[2,1-a]isoindol-6-one;
2-(4-chlorophenyl)-5-[(cyclopropylmethyl)sulfanyl]-1,3,4-oxadiazole;
1-[6-(benzyloxy)-3-tert-butyl-2-hydroxyphenyl]ethan-1-one;
3-[(1 E)-1-[(2,2-dichloroethenyl)imino]-2,2-dimethylpropyl]-1-(4-methylphenyl)thiourea;
6,7-dimethyl-2-phenylquinoxaline;
5-(2,3-dihydro-1-benzofuran-5-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole;
2-{4-[(4-methylphenyl)methoxy]phenyl}acetonitrile;
1-cyclohexyl-3-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7),3,5,10,12-hexaen-5-ylurea;
5-(1,2,3-thiadiazol-4-yl)-3-[4-(trifluoromethyl)phenyl]-1,2,4-oxadiazole;
N-(2-methylquinolin-6-yl)-2-phenylacetamide;
3-(piperidin-1-ylcarbonyl)-5-(thiophen-2-yl)-1,2-oxazole;
N-(3,4-dimethylphenyl)[(E)-N'-(thiophen-2-ylmethylidene)hydrazinecarbonyl]formamide;
2-(2,3-dimethoxyphenyl)-2,3-dihydro-1,3-benzothiazole;
2-methyl-5-(naphthalen-2-yl)-1,3-thiazole hydrobromide;
(cyclohexylcarbamothioyl)-N-(4-fluorophenyl)formamide;
4-(1,3-benzothiazol-2-yl)-1-methyl-1H-pyrazol-3-amine;
(4-tert-butylphenyl)methanimidamido 5-methyl-1,2-oxazole-3-carboxylate;
N-[2-(methylsulfanyl)-1,3-benzothiazol-6-yl]thiophene-2-carboxamide;
N-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-2H-1,3-benzodioxole-5-carboxamide;
(2E)-3-(2-chlorophenyl)-N-(2-methylbut-3-yn-2-yl)prop-2-enamide;

1-naphthalen-1-yl-3-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(13),2,4,6,9,11-hexaen-5-ylthiourea;

3-methyl-N-phenyl-1-benzothiophene-2-carbothioamide;

5-(2,5-dichlorophenyl)-N-[2-(trifluoromethyl)phenyl]furan-2-carboxamide;

3-(5-methyl-1,2-oxazol-3-yl)-5-(thiophen-2-yl)-1,2,4-oxadiazole;

N-(1H-indazol-3-yl)-3-methoxybenzamide;

2-(4-tert-butylphenyl)-5-[(propane-1-sulfonyl)methyl]-1,3,4-oxadiazole;

1-[2-(4-chlorophenoxymethyl)-4-methyl-1,3-thiazol-5-yl]ethan-1-one;

(4-methanesulfonamidophenyl)methanimidamido N-(4-methylphenyl)carbamate;

N-phenyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine hydrochloride;

7-nitro-N-(2-phenylethyl)-1H-indole-2-carboxamide;

2-{[(2E)-4-(pyridin-2-ylsulfanyl)but-2-en-1-yl]sulfanyl}pyridine;

4-[(E)-2-(3-methylthiophen-2-yl)ethenyl]-2-[(3-nitropyridin-2-yl)sulfanyl]pyrimidine;

4-(4-chlorophenyl)-2-[(4-methoxyphenyl)methyl]-1,3-thiazole;

(3Z)-3-{[5-(thiophen-2-yl)thiophen-2-yl]methylidene}-2,3-dihydro-1H-indol-2-one;

N-(4-bromo-2,5-difluorophenyl)-2,3-dimethylbenzamide;

sodium N-phenyl(phenylamino)carboximidate;

2-(benzylsulfanyl)-N-(2,3-dihydro-1H-inden-2-yl)acetamide;

(5Z)-5-[(5-methylfuran-2-yl)methylidene]-3-phenyl-1,3-thiazolidine-2,4-dione;

N-{4-[(3-chlorophenyl)carbamoyl]phenyl}thiophene-2-carboxamide;

N-[(3-chlorophenyl)methyl]-5-(methylsulfanyl)-1,3,4-thiadiazol-2-amine;

(E)-2-(phenylamino)-3-(phenylimino)guanidine;

(2Z)-3-methyl-2-[2-(3-methyl-2,3-dihydro-1,3-benzoxazol-2-ylidene)hydrazin-1-ylidene]-2,3-dihydro-1,3-benzoxazole;

3-[2-(2H-1,4-benzothiazin-3-yl)hydrazin-1-yl]-2H-1,4-benzothiazine;

3-(3,4-dimethyl-1,2-oxazol-5-yl)-1-[4-(dimethylamino)-3,5-difluorophenyl]carbonylurea;

(3Z)-3-[2-(2,5-difluorophenyl)hydrazin-1-ylidene]piperidin-2-one;

N'-[(E)-[1-(1-benzofuran-2-yl)ethylidene]amino](methylsulfanyl)methanimidamide;

(2Z)-3-(9H-fluoren-2-ylcarbamoyl)prop-2-enoic acid;

4-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)diazen-1-yl]-N,N-diethylaniline;

4,5-dichloro-N-(3-chloro-4-fluorophenyl)-1,2-thiazole-3-carboxamide;

5-[4-(4-methoxyphenoxy)phenyl]-1H-pyrazole;
1-cyclohexyl-3-[(Z)-(1H-pyrazol-3-ylmethylidene)amino]thiourea;
[5-(4-chlorophenyl)-3-methyl-2-sulfanylidene-1,3,4-thiadiazinan-6-ylidene]amino 5-tert-butylthiophene-2-carboxylate;
N-(2-phenylethyl)benzenecarbothioamide;
5-amino-3-methyl-2-N-phenylthiophene-2,4-dicarboxamide;
3-amino-5-(thiophen-3-yl)thiophene-2-carboxamide;
(2E)-2-{[4-(trifluoromethoxy)phenyl]imino}-3,4-dihydro-2H-1,3-benzoxazin-4-one;
3-hydroxy-9H-xanthen-9-one;
4-[(E)-2-(3,5-dihydroxyphenyl)ethenyl]benzene-1,2-diol;
(3-chlorophenyl)methanimidamido 6-(2,2,2-trifluoroethoxy)pyridine-3-carboxylate;
5-phenyl-3-(pyrrolidin-1-yl)-1,2-thiazole-4-carbonitrile;
7-hydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one;
2-(4-fluorophenyl)-2H,3H,5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyrimidin-3-one;
(4-chlorophenyl)methanimidamido 2,6-difluorobenzoate;
2-(2-amino-3-methoxyphenyl)-4H-chromen-4-one;
6,7-dimethoxy-2-phenylquinoxaline;
6-methoxy-3-phenyl-[1,2,4]triazolo[4,3-a]pyridazine;
5-[4-(furan-2-ylcarbonyl)piperazin-1-yl]-3-(thiophen-2-yl)-1,2,4-thiadiazole;
(E)-{1-[2-(4-chlorophenoxymethyl)-1,3-thiazol-4-yl]ethylidene}amino benzoate;
N-[(2-chloro-6-fluorophenyl)carbonyl]-N'-(4-methylpyridin-2-yl)ethanediamide;
(E)-hydroxy[1-(2-phenyl-1,3-thiazol-4-yl)ethylidene]amine;
ethyl 1-{[4-(trifluoromethoxy)phenyl]carbamoyl}piperidine-4-carboxylate;
3-(3-methyl-1H-indol-1-yl)-N-[4-(morpholin-4-yl)phenyl]propanamide;
6,8-dimethyl-1-methylidene-2-(4-methylphenyl)-1,4-dihydronaphthalene;
N'-[(2-methyl-1,3-thiazol-4-yl)methoxy]-4-(trifluoromethyl)benzene-1-carboximidamide;
1-[4-(benzyloxy)phenyl]-3-[(3-cyanopyridin-2-yl)amino]urea;
2-phenylimidazo[1,2-a]pyridine;
3-(morpholin-4-yl)-5-[4-(trifluoromethyl)phenyl]-1,2-thiazole-4-carbonitrile;
N-(2-chlorophenyl)-2-[(3-cyano-6-acetylpyridin-2-yl)sulfanyl]acetamide;
3-[4-(4-methoxyphenyl)-1,3-thiazol-2-yl]-5-methyl-1,2-oxazole;

N-(3-bromo-5-methylpyridin-2-yl)-4-ethylbenzamide;
2-(5-methyl-1,2-oxazol-3-yl)-5-[3-(trifluoromethyl)phenyl]-1,3,4-oxadiazole;
(E)-[1-(3-methyl-1-benzothiophen-2-yl)ethylidene]amino N-phenylcarbamate;
N-(2,3-dihydro-1H-inden-2-yl)-3-(3-methyl-1H-indol-1-yl)propanamide;
1,3-dimethanesulfonyl-2,3-dihydro-1H-1,3-benzodiazole;
methyl 2-[5-methyl-2-(thiophene-2-amido)-1,3-thiazol-4-yl]acetate;
4-[(5-{[(4-chlorophenyl)sulfanyl]methyl}furan-2-yl)carbonyl]morpholine;
2-oxo-2-phenylethyl 2,3-dimethoxybenzoate;
N-(4-chlorophenyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide;
(2,4-dichlorophenyl)methyl N-[(2-fluorophenyl)carbonyl]carbamate;
2-[(4-chlorophenyl)carbonyl]-1-benzofuran;
4-chlorophenyl 2,3-dihydro-1-benzofuran-5-carboxylate;
2-[4-(dimethylamino)phenyl]-1,2,3,4-tetrahydroquinolin-4-one;
[6-(ethylsulfanyl)pyridin-3-yl]methanimidamido thiophene-2-carboxylate;
N-[(6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl]-6-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1-(propan-2-yl)-1H-indazole-4-carboxamide (GSK343);
N-[(4,6-dimethyl-2-oxo-1,2-dihydro-3-pyridinyl)methyl]-3-methyl-1-((1S)-1-methylpropyl)-6-[6-(1-piperazinyl)-3-pyridinyl]-1H-indole-4-carboxamide (GSK126); and
N-[(4,6-Dimethyl-2-oxo-1,2-dihydro-3-pyridinyl)methyl]-1-(1-methylethyl)-6-[6-(4-methyl-1-piperazinyl)-3-pyridinyl]-1H-indazole-4-carboxamide (GSK926)

5. 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).

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

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

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

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

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

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

12. 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.

13. 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.

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

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

16. The use according to any one of claims 1 to 13, 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.

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

18. 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 17, 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.

19. The use of any one of claims 1 to 17, 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.

20. The method of claim 18, 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.

21. The method of claim 18, 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.

22. The method of claim 18, 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.

23. 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 17, 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.

24. 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 17, 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.

25. 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.

26. The method as claimed in claim 25, wherein said clinical outcome indicates the susceptibility to treatment with said pharmaceutical composition as defined in any one of claims 1-17.

27. The method as claimed in claim 25 or 26, 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.

28. A pharmaceutical composition comprising a histone-lysine N-methyltransferase EZH2 (enhancer of zeste homolog 2) inhibitor and an enhancer of interferon-gamma receptor activity.

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