WHAT IS CLAIMED IS:

1. An *in vitro* method of predicting the response of a human subject having a cyclin-dependent kinase 2 (CDK2)-associated cancer to a CDK2 inhibitor, comprising:

(i) determining the presence or absence of functional p16 gene expression by determining, from a biological sample obtained from the human subject by:

(a) the nucleotide sequence of a cyclin dependent kinase inhibitor 2A (CDKN2A) gene;

(b) the presence of a CDKN2A gene lacking one or more inactivating nucleic acid substitutions and/or deletions, which inactivating nucleic acid substitutions and/or deletions would, if present, result in dysfunctional p16 gene expression; and/or

(c) the presence of a p16 protein; and

(ii) determining the presence or absence of higher CCNE1 gene expression by determining, from a biological sample obtained from the human subject:

(a) the copy number of the cyclin E1 (CCNE1) gene; and/or

(b) the expression level of CCNE1,

wherein

(1)

(a) the presence of a CDKN2A gene encoding a p16 protein comprising the amino acid sequence of SEQ ID NO:1;

(b) the presence of a CDKN2A gene lacking one or more inactivating nucleic acid substitutions and/or deletions, which inactivating nucleic acid substitutions and/or deletions would, if present, result in dysfunctional p16 gene expression; and/or

(c) the presence of a p16 protein; and

(2) an amplification of the CCNE1 gene and/or an expression level of CCNE1 that is higher than a control expression level of CCNE1,

is predictive that the human subject will respond to the CDK2 inhibitor;

wherein the control expression level of CCNE1 is the expression level of CCNE1 in a sample or samples obtained from one or more subjects that have not responded to treatment with the CDK2 inhibitor; and

wherein the CDK2 inhibitor is:

4-((8-cyclopentyl-6,6-dimethyl-7-oxo-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-2-

yl)amino)benzenesulfonamide,

8-cyclopentyl-6,6-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-5,8-dihydropyrido[2,3-d]pyrimidin-7(6H)-one,

6,6-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-8-phenyl-5,8-dihydropyrido[2,3-d]pyrimidin-7(6H)-one,

8-(1,1-difluorobutan-2-yl)-6,6-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one,

6,6-dimethyl-8-((1-methyl-1*H*-pyrazol-5-yl)methyl)-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one,

6,6-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-8-(tetrahydrofuran-3-yl)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one,

8-((1R,2R)-2-hydroxy-2-methylcyclopentyl)-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one,

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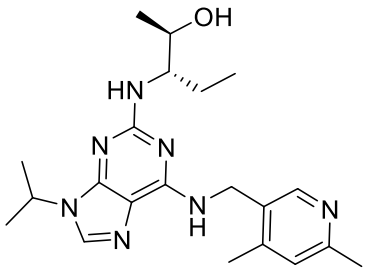
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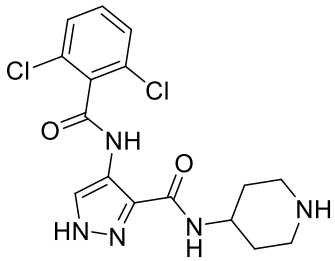
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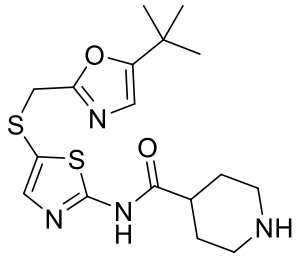
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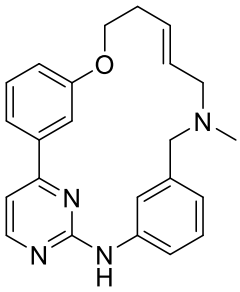
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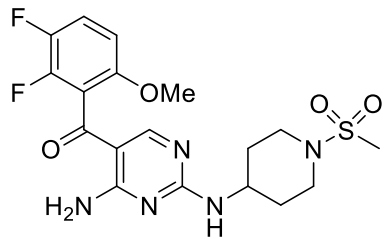
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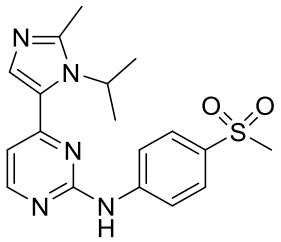
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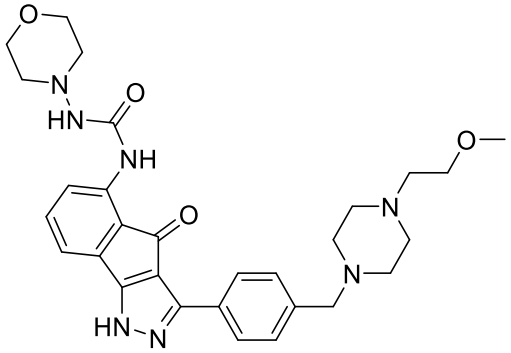
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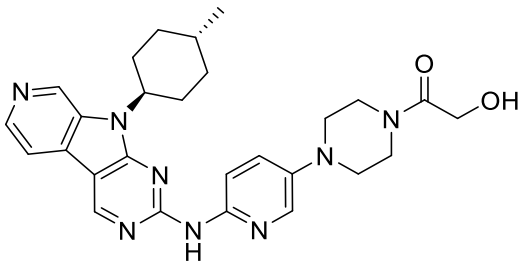
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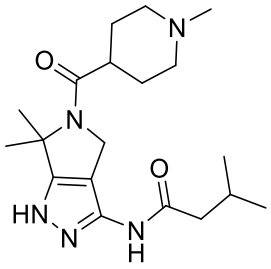
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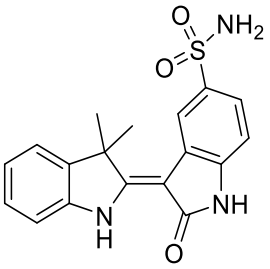
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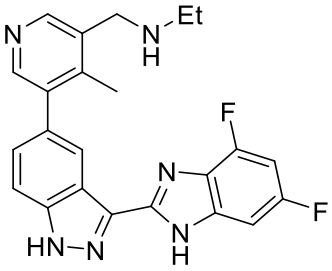
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or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, comprising:

(i) determining, from a biological sample obtained from the human subject:

(a) the nucleotide sequence of a CDKN2A gene and/or the presence of a CDKN2A gene lacking one or more inactivating nucleic acid substitutions and/or deletions, which inactivating nucleic acid substitutions and/or deletions would, if present, result in dysfunctional p16 gene expression; and

(ii) determining, from a biological sample obtained from the human subject:

(a) the copy number of the CCNE1 gene,

wherein

(1)

(a) the presence of a CDKN2A gene encoding a p16 protein comprising the amino acid sequence of SEQ ID NO:1; and/or the

(b) presence of a CDKN2A gene lacking one or more inactivating nucleic acid substitutions and/or deletions, which inactivating nucleic acid substitutions and/or deletions would, if present, result in dysfunctional p16 gene expression, and

(2) an amplification of the CCNE1 gene,

is predictive that the human subject will respond to the CDK2 inhibitor.

3. Use of a CDK2 inhibitor in the manufacture of a medicament for the treatment of a human subject having a cyclin-dependent kinase 2 (CDK2)-associated cancer, wherein the human subject has been previously determined, according to the *in vitro* method of Claim 1 or Claim 2, to:

(i)

(a) have a nucleotide sequence encoding a p16 protein comprising the amino acid sequence of SEQ ID NO:1;

(b) have a cyclin dependent kinase inhibitor 2A (CDKN2A) gene lacking one or more inactivating nucleic acid substitutions and/or deletions, which inactivating nucleic acid substitutions and/or deletions would, if present, result in dysfunctional p16 gene expression; and/or

(c) express a p16 protein; and

(ii)

(a) have an amplification of the cyclin E1 (CCNE1) gene; and/or

(b) have an expression level of CCNE1 in a biological sample obtained from the human subject that is higher than a control expression level of CCNE1;

wherein the control expression level of CCNE1 is the expression level of CCNE1 in a sample or samples obtained from one or more subjects that have not responded to treatment with the CDK2 inhibitor; and

wherein the CDK2 inhibitor is:

4-((8-cyclopentyl-6,6-dimethyl-7-oxo-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-2-yl)amino)benzenesulfonamide,

8-cyclopentyl-6,6-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-5,8-dihydropyrido[2,3-d]pyrimidin-7(6H)-one,

6,6-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-8-phenyl-5,8-dihydropyrido[2,3-d]pyrimidin-7(6H)-one,

8-(1,1-difluorobutan-2-yl)-6,6-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one,

6,6-dimethyl-8-((1-methyl-1*H*-pyrazol-5-yl)methyl)-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one,

6,6-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-8-(tetrahydrofuran-3-yl)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one,

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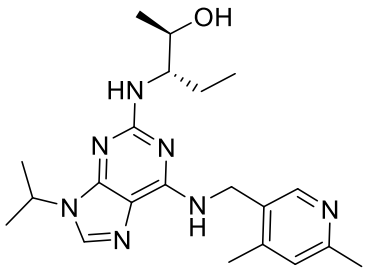
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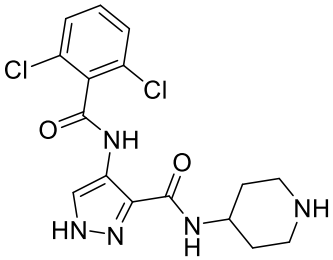
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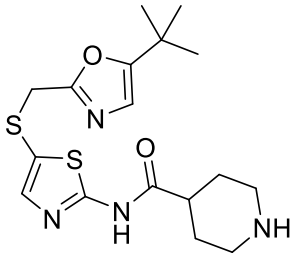
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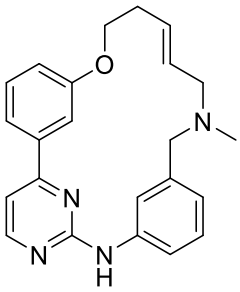
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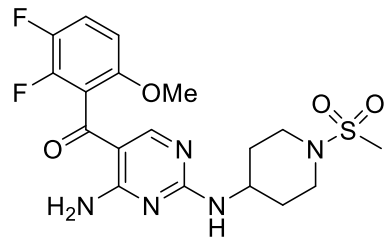
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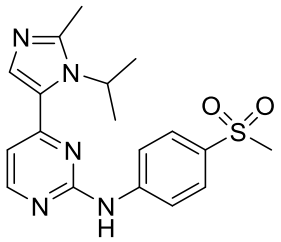
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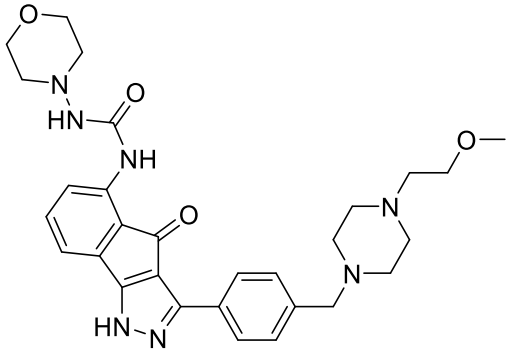
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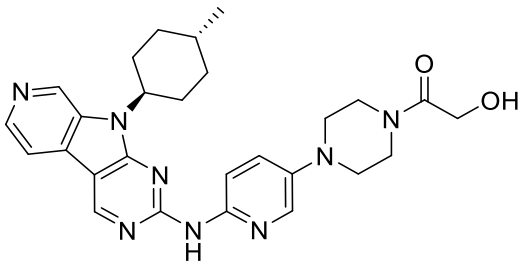
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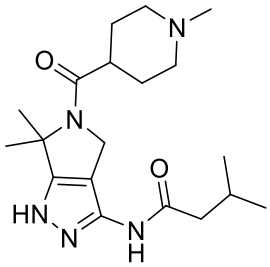
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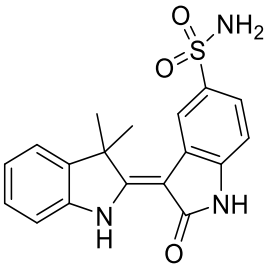
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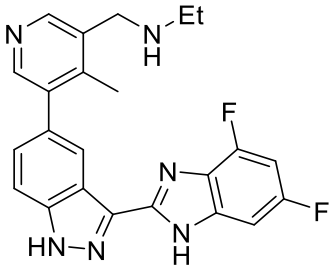
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or a pharmaceutically acceptable salt thereof.

4. The use of claim 3, wherein the human subject has been previously determined to:

(i)

(a) have a nucleotide sequence encoding a p16 protein comprising the amino acid sequence of SEQ ID NO:1; and/or

(b) a CDKN2A gene lacking one or more inactivating nucleic acid substitutions and/or deletions, which inactivating nucleic acid substitutions and/or deletions would, if present, result in dysfunctional p16 gene expression; and

(ii) have an amplification of the CCNE1 gene in a biological sample obtained from the human subject.

5. The use of claim 3, wherein the expression level of CCNE1 in the biological sample is at least 1.5, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 20, at least 25, at least 50, at least 75, or at least 100 times higher than the control expression level of CCNE1.

6. Use of a CDK2 inhibitor in the manufacture of a medicament for the treatment of a human subject having a cyclin-dependent kinase 2 (CDK2)-associated cancer, wherein, according to the *in vitro* method of Claim 1 or Claim 2:

(i) in a biological sample obtained from the human subject:

(a) a nucleotide sequence encoding a p16 protein comprising the amino acid sequence of SEQ ID NO:1 is present;

(b) a cyclin dependent kinase inhibitor 2A (CDKN2A) gene lacking one or more inactivating nucleic acid substitutions is present, which inactivating nucleic acid substitutions and/or deletions would, if present, result in dysfunctional p16 gene expression; and/or

(c) a p16 protein is present; and

(ii) in a biological sample obtained from the human subject:

(a) there is present an amplification of the cyclin E1 (CCNE1) gene; and/or

(b) there is present an expression level of CCNE1 that is higher than a control expression level of CCNE1;

wherein the control expression level of CCNE1 is the expression level of CCNE1 in a sample or samples obtained from one or more subjects that have not responded to treatment with the CDK2 inhibitor; and

wherein the CDK2 inhibitor is:

4-((8-cyclopentyl-6,6-dimethyl-7-oxo-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-2-yl)amino)benzenesulfonamide,

8-cyclopentyl-6,6-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-5,8-dihydropyrido[2,3-d]pyrimidin-7(6H)-one,

6,6-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-8-phenyl-5,8-

dihydropyrido[2,3-d]pyrimidin-7(6H)-one,

8-(1,1-difluorobutan-2-yl)-6,6-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one,

6,6-dimethyl-8-((1-methyl-1*H*-pyrazol-5-yl)methyl)-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one,

6,6-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-8-(tetrahydrofuran-3-yl)-5,8-dihydropyrido[2,3-*d*]pyrimidin-7(6*H*)-one,

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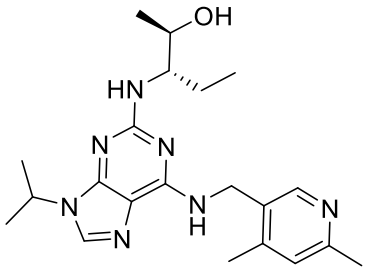
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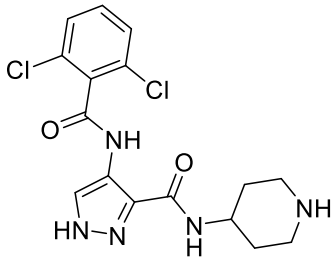
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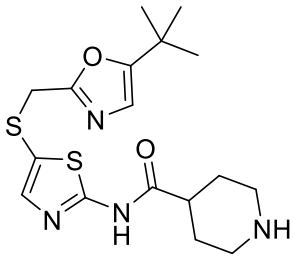
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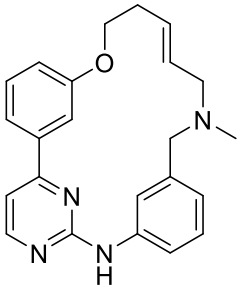
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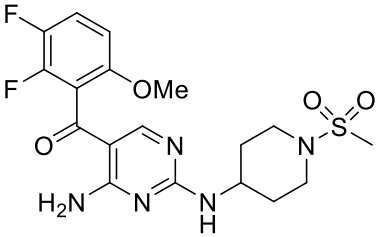
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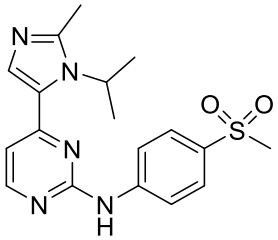
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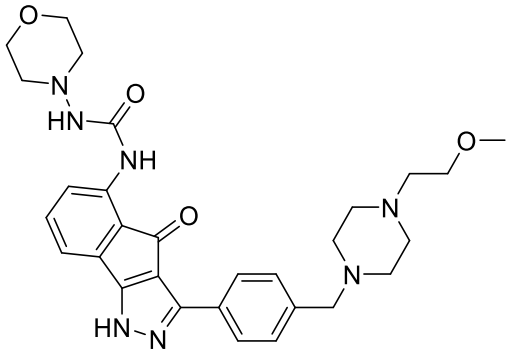
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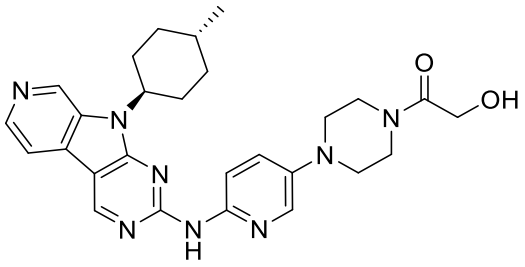


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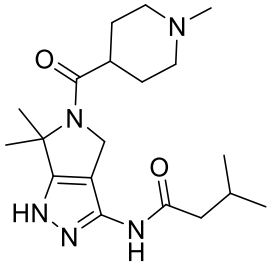
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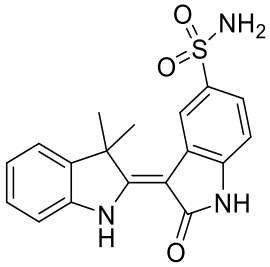
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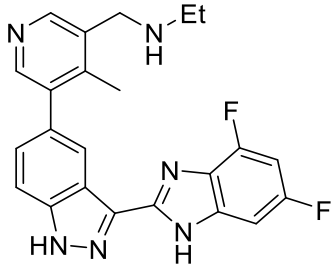
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or a pharmaceutically acceptable salt thereof.

7. The use of claim 6, comprising:

(i) in a biological sample obtained from the human subject:

(a) a nucleotide sequence encoding a p16 protein comprising the amino acid sequence of SEQ ID NO:1 is present;

(b) a CDKN2A gene lacking one or more inactivating nucleic acid substitutions and/or deletions is present, which inactivating nucleic acid substitutions and/or deletions would, if present, result in dysfunctional p16 gene expression; and/or

(c) a p16 protein is present; and

(d) there is present an amplification of the CCNE1 gene.

8. The use of claim 6, wherein the expression level of CCNE1 in the biological sample is at least 1.5, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 20, at least 25, at least 50, at least 75, or at least 100 times higher than the control expression level of CCNE1.

9. The use of any one of claims 3-7, wherein the medicament comprises a second therapeutic agent.

10. The use of claim 9, wherein the second therapeutic agent is a BCL2 inhibitor or a CDK4/6 inhibitor.

11. The *in vitro* method of claim 1 or claim 2 or the use of any one of claims 3-10 or, wherein the amplification of the CCNE1 gene comprises a gene copy number of at least 3; at least 5; or at least 21.

12. The *in vitro* method of any one of claims 1, 2, and 11 or the use of any one of claims 3-10, , wherein the expression level of CCNE1 is the expression level of CCNE1 mRNA; or wherein the expression level of CCNE1 is the expression level of CCNE1 protein.

13. The *in vitro* method of claim 14 or the use of claim 14, , wherein the expression level of CCNE1 is measured by RNA sequencing, quantitative polymerase chain reaction (PCR), in situ hybridization, nucleic acid array or RNA sequencing; or wherein the expression level of CCNE1 is measured by western blot, enzyme-linked immunosorbent assay, or immunohistochemistry staining.

14. The *in vitro* method of any one of claims 1, 2, and 11-13 or the use of any one of claims 3-13, wherein the CDK2-associated cancer is lung squamous cell carcinoma, lung adenocarcinoma, pancreatic adenocarcinoma, breast invasive carcinoma, uterine carcinosarcoma, ovarian serous cystadenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, bladder urothelial carcinoma, mesothelioma, or sarcoma.

15. The *in vitro* method of any one of claims 1, 2 and 11-13 or the use of any one of claims 3-13, wherein the CDK2-associated cancer is lung adenocarcinoma, breast invasive carcinoma, uterine carcinosarcoma, ovarian serous cystadenocarcinoma, or stomach adenocarcinoma.

16. The *in vitro* method of any one of claims 1, 2 and 11-13 or the use of any one of claims 3-13, wherein the CDK2-associated cancer is an adenocarcinoma, carcinoma, or cystadenocarcinoma.

17. The *in vitro* method of any one of claims 1, 2 and 11-13 or the use of any one of claims 3-13, wherein the CDK2-associated cancer is uterine cancer, ovarian cancer, stomach cancer, esophageal cancer, lung cancer, bladder cancer, pancreatic cancer, or breast cancer.

18. The *in vitro* method of any one of claims 1, 2 and 11-13 or the use of any one of claims 3-13, wherein the CDK2-associated cancer is ovarian cancer, uterine carcinosarcoma, or breast cancer.

19. The *in vitro* method of any one of claims 1, 2 and 11-13 or the use of any one of claims 3-13, wherein the CDK2-associated cancer is endometrial cancer.

20. The *in vitro* method of any one of claims 1, 2 and 11-13 or the use of any one of claims 3-13, wherein the CDK2-associated cancer comprises p27 inactivation.

21. The *in vitro* method of any one of claims 1, 2 and 11-13 or the use of any one of claims 3-13, wherein the CDK2-associated cancer is a N-myc amplified neuroblastoma, a K-Ras mutant lung cancer, or a cancer with a FBW7 mutation and CCNE1 overexpression.