

[0011] Precision medicine is aimed at improving cancer patient response rates by reducing toxicities to normal tissues and utilizing stratification markers to enrich for patients most likely to benefit from therapy treatment or importantly to exclude patients unlikely to benefit. A biomarker guided approach has the potential to customizing cancer patient treatment to achieve higher response rates and to drive improvement in patient outcomes and quality of life. There is a lack of established stratification markers (biomarkers) available for selecting patients most likely to benefit from current anti-mitotic therapies.

[0012] Thus, there is a need for biomarkers to identify patients will benefit from KIF18A inhibitor treatment.

SUMMARY

[0013] Presented herein for the first time are data evidencing biomarkers of sensitivity to KIF18A inhibitor treatment. Cancer cells exhibiting an inactivated *TP53* gene and/or at least one of: (i) an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene, gene copy number gain of the *CCNE1* gene, or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof, demonstrated sensitivity to treatment with a KIF18A inhibitor. Also provided herein are data demonstrating that KIF18A inhibitor-sensitive cancer cells exhibit a reduced or lost sensitivity or resistance to CDK4/6 inhibitors. The data further support that CDK4/6 inhibitor-sensitive cancer cells exhibit a reduced or lost sensitivity or resistance to KIF18A inhibitors.

[0014] The present disclosure provides methods of determining a treatment for a subject with a neoplastic disease (e.g., cancer). In one aspect, the present disclosure provides a method of determining a treatment for a subject having a neoplastic disease, comprising assaying a sample obtained from the subject for (a) an inactivated *TP53* gene and/or (b) at least one of: (i) an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof, wherein the treatment determined for the subject comprises a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene and/ or positive for at least one of an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof.

In another aspect, the present disclosure provides the use of a KIF18A inhibitor in the manufacture of a medicament for treating a subject having a neoplastic disease, wherein the subject comprises cells that are positive for (a) an inactivated *TP53* gene and/or (b) at least one of: (i) an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof. In another aspect, the present disclosure provides a method of identifying a subject having a neoplastic disease as sensitive to treatment with a KIF18A inhibitor, comprising assaying a sample obtained from the subject for (a) an inactivated *TP53* gene and/or (b) at least one of: (i) an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof, wherein the subject is identified as sensitive to treatment with a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene and/or positive for at least one of an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof. In another aspect, the present disclosure provides a method of determining a treatment for a subject having a neoplastic disease, comprising determining sensitivity of the neoplastic disease to treatment with a CDK4/6 inhibitor, wherein the treatment for the subject is determined as a treatment comprising a KIF18A inhibitor, when the neoplastic disease is insensitive to the CDK4/6 inhibitor, or determining sensitivity of the neoplastic disease to treatment with a KIF18A inhibitor, wherein the treatment for the subject is determined as a treatment comprising a CDK4/6 inhibitor, when the neoplastic disease is insensitive to the KIF18A inhibitor. In another aspect, the present disclosure provides a method of identifying a subject having a cancer as responsive to treatment with a KIF18A inhibitor, comprising determining the sensitivity of the neoplastic disease to treatment with a KIF18A inhibitor, wherein the subject is identified as responsive to treatment with a KIF18A inhibitor, when the cancer cells of the sample are insensitive to the CDK4/6 inhibitor. In another aspect, the present disclosure provides the use of a KIF18A inhibitor in the manufacture of a medicament for (A) treating a subject having a neoplastic disease, wherein the neoplastic disease is resistant to treatment with a CDK4/6 inhibitor or the subject is or has been treated with the CDK4/6 inhibitor or (B) maintaining sensitivity of a neoplastic disease to treatment with a CDK4/6 inhibitor in a subject, optionally, wherein the KIF18A inhibitor is to be used together with the CDK4/6 inhibitor. In another aspect, the present disclosure provides a pharmaceutical combination comprising a CDK4/6 inhibitor and a KIF18A inhibitor.

In another aspect, the present disclosure provides the use of a KIF18A inhibitor in the manufacture of a medicament for treating a subject having a neoplastic disease, inducing or increasing tumor regression in a subject with a tumor, reducing tumor or cancer growth in a subject with a tumor, and/or inducing or increasing death of tumor or cancer cells in a subject. In another aspect, the present disclosure provides the use of a KIF18A inhibitor in the manufacture of a medicament for treating a neoplastic disease in a subject who is or has been treated with an anti-mitotic agent or anthracycline antibiotic, optionally, wherein the KIF18A inhibitor (A) reduces expression of a KIF18A gene and/or a KIF18A gene product (B) is a non-coding RNA, optionally, wherein the KIF18A inhibitor mediates RNAi, and/or (C) is an siRNA, optionally, comprising a sequence of any one of SEQ ID NOs: 12-18. In exemplary embodimentexamples, the method comprises assaying a sample obtained from the subject for (a) an inactivated *TP53* gene and/or (b) at least one of: (i) an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene, gene copy number gain of the *CCNE1* gene, or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof. In various aspectsexamples, the treatment determined for the subject comprises of a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene and/or positive for at least one of an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene, gene copy number gain of the *CCNE1* gene, or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof. In exemplary embodimentexample, the method comprises determining sensitivity of the neoplastic disease to treatment with a CDK4/6 inhibitor. In various aspectsexamples, the treatment for the subject is determined as a treatment comprising a KIF18A inhibitor, when the neoplastic disease is insensitive or resistant to the CDK4/6 inhibitor. In exemplary embodimentexamples, the method comprises determining sensitivity of the neoplastic

disease to treatment with a KIF18A inhibitor. In various [aspectsexamples](#), the treatment for the subject is determined as a treatment comprising a CDK4/6 inhibitor, when the neoplastic disease is insensitive or resistant to the KIF18A inhibitor.

[0015] Methods of identifying a subject with a neoplastic disease as sensitive to treatment with a KIF18A inhibitor are provided herein. In exemplary [embodimentexamples](#), the method comprises assaying a sample obtained from the subject for (a) an inactivated *TP53* gene and/or (b) at least one of: (i) an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene, gene copy number gain of the *CCNE1* gene, or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof. In various instances, the subject is identified as sensitive to treatment with a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene and/or positive for at least one of an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof.

[0016] The present disclosure additionally provides a method of identifying a subject with a neoplastic disease as responsive to treatment with a KIF18A inhibitor. In exemplary [embodimentexamples](#), the method comprises determining the sensitivity of the neoplastic disease to treatment with a KIF18A inhibitor. In various [aspectsexamples](#), the subject is identified as responsive to treatment with a KIF18A inhibitor, when the cancer cells of the sample are insensitive to the CDK4/6 inhibitor.

[0017] Methods of maintaining sensitivity of a neoplastic disease to treatment with a CDK4/6 inhibitor in a subject are provided herein. In exemplary [embodimentexamples](#), the method comprises administering to the subject a KIF18A inhibitor.

[0018] Methods of treating a subject with a neoplastic disease, e.g., methods of treating the neoplastic disease in a subject, are provided herein. In exemplary [embodimentexamples](#), the method comprises administering a KIF18A inhibitor to treat the patient. Optionally, the neoplastic disease is resistant to treatment with a CDK4/6 inhibitor. In various instances, the subject is or has been treated with a CDK4/6 inhibitor. In various [aspectsexamples](#), the KIF18A inhibitor is co-administered with the CDK4/6 inhibitor. In various instances, the method comprises administering a pharmaceutical combination comprising a CDK4/6 inhibitor and a KIF18A inhibitor. Accordingly, a pharmaceutical combination comprising a KIF18A inhibitor and a CDK4/6 inhibitor is provided herein.

[0019] Methods of inducing or increasing tumor regression in a subject with a tumor are additionally provided herein. In exemplary [embodimentexamples](#), the method comprises administering to the subject a KIF18A inhibitor in an amount effective to induce or increase tumor regression. The present disclosure also provides methods of reducing tumor growth or cancer growth in a subject. In exemplary [embodimentexamples](#), the method comprises administering to the subject a KIF18A inhibitor in an amount effective to reduce tumor or cancer growth. Methods of inducing or increasing death of tumor cells or cancer cells in a subject are provided herein. The method in exemplary [embodimentexamples](#) comprises administering to the subject a KIF18A inhibitor in an amount effective to induce or increase death of the tumor cells or cancer cells. In various [aspectexamples](#), the neoplastic disease is a cancer, optionally, breast cancer, ovarian cancer, or prostate cancer. In various instances, the neoplastic disease is triple-negative breast cancer (TNBC), non-luminal breast cancer, or high-grade serous ovarian cancer (HGSOC). In exemplary [aspectexamples](#), the neoplastic disease is an endometrial cancer, optionally, serous endometrial cancer. Optionally, the cancer comprises cells that are positive for an inactivated *TP53* gene and/or positive for at least one of an inactivated *Rb* gene, (ii) an amplified *CCNE1* gene or overexpressed *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof. In some [aspectexamples](#), the cancer comprises cells that are positive for a mutant *TP53* gene. In various instances, the cancer comprises cells that are positive for an amplified *CCNE1* gene, a silenced *BRCA1* gene, a deficient *Rb1* gene, or a combination thereof. Optionally, the KIF18A inhibitor is administered for oral administration, optionally once a day. In exemplary [aspectexamples](#), the amount of the KIF18A inhibitor is effective to induce at least 50% or at least 75% (e.g., at least 80% or 85% or at least 90% or 95%) tumor regression, compared to a control. In various instances, the KIF18A inhibitor selectively treats the neoplastic disease, selectively induces or increases tumor regression, selectively reduces tumor or cancer growth, and/or selectively induces or increases death of tumor or cancer cells and the KIF18A inhibitor is not toxic to normal somatic cells. In various [aspectexamples](#), the KIF18A inhibitor treats the neoplastic disease, induces or increases tumor regression, reduces tumor or cancer growth, and/or induces or increases death of tumor or cancer cells and the proliferation of the normal somatic cells in the subject is substantially the same as the proliferation of the normal somatic cells of a control subject. In exemplary instances, the KIF18A inhibitor treats the neoplastic disease, induces or increases tumor regression, reduces tumor or cancer growth, and/or induces or increases death of tumor or cancer cells and the level of apoptosis of normal somatic cells is not increased in the subject, relative to the level of apoptosis of normal somatic cells of a

control subject, optionally, wherein the level of apoptosis of normal somatic cells is substantially the same as the level of apoptosis of the normal somatic cells of a control subject.

[0020] In various [aspectexamples](#) of the present disclosure, the KIF18A inhibitor is a compound of formula (I). In exemplary [aspectexamples](#), the KIF18A inhibitor is Compound C1, Compound C2, Compound C3, Compound C4, Compound C5, Compound C6, Compound C7, Compound C8, Compound C9, Compound C10, Compound C11, Compound C12, Compound C13, or Compound C14, or any pharmaceutically-acceptable salt thereof, as described herein.

[0021] In alternative [aspectexamples](#), the KIF18A inhibitor is a large molecule KIF18A inhibitor, such as a non-coding RNA, e.g., an siRNA.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] Figures 1A-1C provide tables referenced in Example 1. Figure 1A provides Table 1A which lists tissue culture growth conditions for the indicated cell line originating from the indicated tissue. Figure 1B provides Table 1B which lists the seeding density for the NCA for each tested cell line. Figure 1C provides Table 1C which lists cancer cell lines and their sensitivity to a first KIF18A inhibitor.

[0023] Figures 2A to 2F are graphs of POC plotted as a function of concentration of KIF18A inhibitor (solid squares) or CDK4/6 inhibitor (open circles). Figures 2A-2C demonstrate KIF18A inhibitor-sensitive, CDK4/6 inhibitor-insensitive cells. cells and Figures 2D-2F demonstrate KIF18A inhibitor insensitive cells, CDK4/6 inhibitor-sensitive cells.

[0024] Figure 3A is a graph plotting the POC as a function of concentration of KIF18A inhibitor for the OVCAR-8 HGSOC cell line. Figure 3B is a graph plotting the POC as a function of concentration of KIF18A inhibitor for the MX-1 TNBC cell line. Figure 3C is a graph plotting the POC as a function of concentration of KIF18A inhibitor for the MAX401NL TNBC cell line. Figure 3D is a graph plotting the POC as a function of concentration of KIF18A inhibitor for the HCC-1937 TNBC cell line. Figure 3E is a graph plotting the POC as a function of concentration of KIF18A inhibitor Compound C14, Olaparib, Paclitaxel, Doxorubicin, or Carboplatin for the OVCAR-8 cancer cell line.

[0025] Figure 4A provides Table 2 which lists cancer cell lines and their sensitivity to a second KIF18A inhibitor. Figure 4B provides Table 3 which lists cancer cell lines and their sensitivity to a second KIF18A inhibitor. Figure 4C is a graph plotting the POC as a function of concentration of KIF18A inhibitor for breast and ovarian cancer cell lines which demonstrated sensitivity to KIF18A inhibitor treatment. Figure 4D is a graph plotting the POC as a function of

WHAT IS CLAIMED IS:

1. A method of determining a treatment for a subject having a neoplastic disease, comprising assaying a sample obtained from the subject for (a) an inactivated *TP53* gene and/or (b) at least one of: (i) an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof, wherein the treatment determined for the subject comprises a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene and/ or positive for at least one of an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof.
2. [Use of Aa](#) KIF18A inhibitor ~~for use in~~ [the manufacture of a medicament for](#) treating a subject having a neoplastic disease, wherein the subject comprises cells that are positive for (a) an inactivated *TP53* gene and/or (b) at least one of: (i) an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof.
3. A method of identifying a subject having a neoplastic disease as sensitive to treatment with a KIF18A inhibitor, comprising assaying a sample obtained from the subject for (a) an inactivated *TP53* gene and/or (b) at least one of: (i) an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof, wherein the subject is identified as sensitive to treatment with a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene and/or positive for at least one of an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof.
4. A method of determining a treatment for a subject having a neoplastic disease, comprising determining sensitivity of the neoplastic disease to treatment with a CDK4/6 inhibitor, wherein the treatment for the subject is determined as a treatment comprising a KIF18A inhibitor, when the neoplastic disease is insensitive to the CDK4/6 inhibitor, or determining sensitivity of the neoplastic disease to treatment with a KIF18A inhibitor, wherein the treatment for the subject is determined as a treatment comprising a CDK4/6 inhibitor, when the neoplastic disease is insensitive to the KIF18A inhibitor.

5. A method of identifying a subject having a cancer as responsive to treatment with a KIF18A inhibitor, comprising determining the sensitivity of the neoplastic disease to treatment with a KIF18A inhibitor, wherein the subject is identified as responsive to treatment with a KIF18A inhibitor, when the cancer cells of the sample are insensitive to the CDK4/6 inhibitor.
6. Use of Aa KIF18A inhibitor ~~for use in the manufacture of a medicament for~~ in (A) treating a subject having a neoplastic disease, wherein the neoplastic disease is resistant to treatment with a CDK4/6 inhibitor or the subject is or has been treated with the CDK4/6 inhibitor or (B) maintaining sensitivity of a neoplastic disease to treatment with a CDK4/6 inhibitor in a subject, optionally, wherein the KIF18A inhibitor is ~~for use to be used~~ together with the CDK4/6 inhibitor.
7. The method of any one of claims 4-~~6~~5 wherein determining sensitivity comprises assaying a sample obtained from the subject for the absence of (i) an inactivated *Rb1* gene, (ii) an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, or (iii) a combination thereof.
8. The method of any one of ~~the preceding~~ claims 1 and 3 to 5, wherein the sample comprises cancer cells, tumor cells, non-tumor cells, blood, blood cells, or plasma, optionally, wherein the sample comprises germline cancer cells or somatic cancer cells.
9. A pharmaceutical combination comprising a CDK4/6 inhibitor and a KIF18A inhibitor.
10. The method of any one of claims 1 and 3 to 5 or the pharmaceutical combination of ~~any one of claims 4-9~~claim 9 wherein the CDK4/6 inhibitor is palbociclib, ribociclib, and/or abemaciclib.
11. Use of Aa KIF18A inhibitor ~~for use in~~ the manufacture of a medicament for treating a subject having a neoplastic disease, inducing or increasing tumor regression in a subject with a tumor, reducing tumor or cancer growth in a subject with a tumor, and/or inducing or increasing death of tumor or cancer cells in a subject.
12. The method of any one of claims 1 and 3 to 5 and 7 to 8 and 10 or KIF18A inhibitor for the use of any one of ~~the preceding~~ claims 2 or 6 or 11, wherein the neoplastic disease is a cancer, optionally, breast cancer, ovarian cancer, endometrial cancer, lung cancer, or prostate cancer.

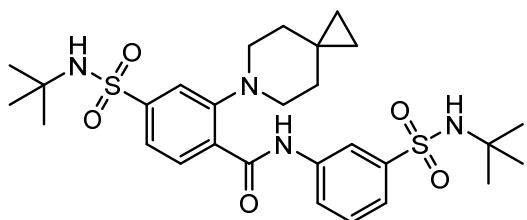
13. The method ~~of any one of claims 1 and 3 to 5 and 7 to 8 and 10~~ or ~~KIF18A inhibitor for the~~ use of ~~claim 12~~any one of claims 2 or 6 or 11, wherein the neoplastic disease is triple-negative breast cancer (TNBC), non-luminal breast cancer, or high-grade serous ovarian cancer (HGSOC) or an endometrial cancer, optionally, serous endometrial cancer.
14. The method or ~~KIF18A inhibitor for~~ use of ~~any one of the preceding claims~~claim 12, wherein the cancer comprises cells that are positive for an inactivated *TP53* gene and/or positive for at least one of an inactivated *Rb* gene, (ii) an amplified *CCNE1* gene or overexpressed *CCNE1* gene product, (iii) an inactivated *BRCA* gene or (iv) a combination thereof.
15. The method or ~~KIF18A inhibitor for~~ use of claim 14, wherein the cancer comprises cells that are positive for a mutant *TP53* gene and/or comprises cells that are positive for an amplified *CCNE1* gene, a silenced *BRCA1* gene, a deficient *Rb1* gene, or a combination thereof.
16. The method ~~of any one of claims 1 and 3 to 5 and 7 to 8 and 10 and 12 to 15~~ or ~~KIF18A inhibitor for the~~ use of any one of ~~the claims 2 or 6 or 11 to 15~~preceding claims, wherein the KIF18A inhibitor treats the neoplastic disease, induces or increases tumor regression, reduces tumor or cancer growth, and/or induces or increases death of tumor or cancer cells and (A) the proliferation of the normal somatic cells in the subject is substantially the same as the proliferation of the normal somatic cells of a control subject and/or (B) the level of apoptosis of normal somatic cells is not increased in the subject, relative to the level of apoptosis of normal somatic cells of a control subject, optionally, wherein the level of apoptosis of normal somatic cells is substantially the same as the level of apoptosis of the normal somatic cells of a control subject.
17. The method or ~~KIF18A inhibitor for the~~ use of claim 16, wherein the normal somatic cells are human bone marrow mononuclear cells, human mammary epithelial cells, or human foreskin fibroblast cells and/or the normal somatic cells are not TP53^{MUT} or wherein the normal somatic cells are TP53^{WT}.
18. The method ~~of any one of claims 1 and 3 to 5 and 7 to 8 and 10 and 12 to 17~~ or ~~KIF18A inhibitor for the~~ use of any one of ~~claims 2 or 6 or 11 to 17~~the preceding claims, wherein (i) the neoplastic disease is a multidrug resistant neoplastic disease, (ii) the tumor or cancer cells are multidrug resistant tumor or cancer cells, (iii) the tumor or cancer cells exhibit increased expression of the Multidrug resistance 1 (MDR-1) gene and/or a gene product thereof, (iv) the

tumor or cancer cells exhibit increased expression of a P-glycoprotein (P-gp), or (v) any combination thereof.

19. The method [of any one of claims 1 and 3 to 5 and 7 to 8 and 10 and 12 to 18](#) or ~~KIF18A inhibitor for the~~ use of any one of [claims 2 or 6 or 11 to 18](#)~~the preceding claims~~, wherein the neoplastic disease is resistant to treatment with an anti-mitotic agent or anthracycline antibiotic, optionally, wherein the anti-mitotic agent or anthracycline antibiotic is paclitaxel or doxorubicin.

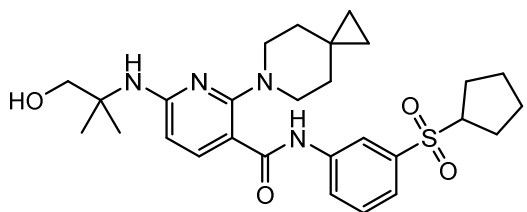
20. The ~~method or KIF18A inhibitor for use~~ [of any one of claims 2 or 6 or 11 to 18](#), ~~or pharmaceutical combination of any one of the preceding claims~~, wherein the KIF18A inhibitor is [to be](#) administered for oral administration, optionally once a day.

21. The method [of any one of claims 1 and 3 to 5 and 7 to 8 and 10 and 12 to 19](#) or ~~KIF18A inhibitor for the~~ use of any one of [claims 2 or 6 or 11 to 20](#)~~the preceding claims~~, wherein the KIF18A inhibitor is KIF18A inhibitor Compound C9, also known as 4-(*N*-(*tert*-butyl)sulfamoyl)-*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide, having the structure:



; or any pharmaceutically acceptable salt thereof.

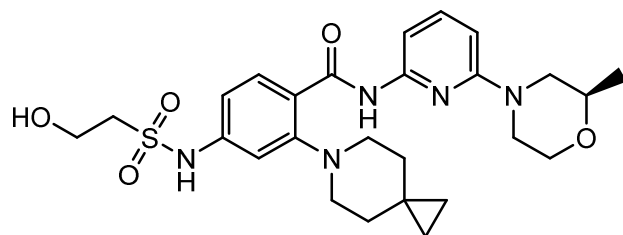
22. The method [of any one of claims 1 and 3 to 5 and 7 to 8 and 10 and 12 to 19](#) or ~~KIF18A inhibitor for the~~ use of any one of [claims 2 or 6 or 11 to 20](#)~~the preceding claims~~, wherein the KIF18A inhibitor is KIF18A inhibitor Compound C11, also known as *N*-(3-(cyclopentylsulfonyl)phenyl)-6-((1-hydroxy-2-methylpropan-2-yl)amino)-2-(6-azaspiro[2.5]octan-6-yl)nicotinamide, having the structure:



; or any pharmaceutically acceptable salt thereof.

23. The method [of any one of claims 1 and 3 to 5 and 7 to 8 and 10 and 12 to 19](#) or ~~KIF18A inhibitor for the~~ use of any one of [claims 2 or 6 or 11 to 20](#)~~the preceding claims~~, wherein the

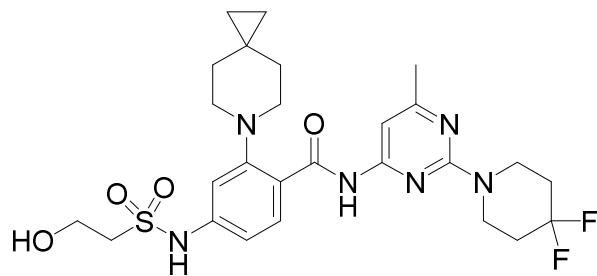
KIF18A inhibitor is KIF18A inhibitor Compound C12, also known as (*R*)-4-((2-Hydroxyethyl)sulfonamido)-*N*-(6-(2-methylmorpholino)pyridin-2-yl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide, having the structure:



; or any pharmaceutically acceptable salt

thereof.

24. The method [of any one of claims 1 and 3 to 5 and 7 to 8 and 10 and 12 to 19](#) or ~~KIF18A inhibitor for the~~ use of any one of [claims 2 or 6 or 11 to 20](#)~~the preceding claims~~, wherein the KIF18A inhibitor is KIF18A inhibitor Compound C14, also known as *N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide, having the structure:



; or any pharmaceutically acceptable salt thereof.

25. [Use of Aa](#) KIF18A inhibitor ~~for use in~~ [the manufacture of a medicament for](#) treating a neoplastic disease in a subject who is or has been treated with an anti-mitotic agent or anthracycline antibiotic, optionally, wherein the KIF18A inhibitor (A) reduces expression of a KIF18A gene and/or a KIF18A gene product (B) is a non-coding RNA, optionally, wherein the KIF18A inhibitor mediates RNAi, and/or (C) is an siRNA, optionally, comprising a sequence of any one of SEQ ID NOs: 12-18.