

[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 neoplastic disease in a subject, comprising assaying a sample obtained from the subject for an inactivated *TP53* gene, wherein the treatment determined for the subject comprises a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene. 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, wherein the subject comprises cells in a sample that have been determined to be positive for an inactivated *TP53* gene. In another aspect, the present disclosure provides a method of identifying a neoplastic disease in a subject as sensitive to treatment with a KIF18A inhibitor, comprising assaying a sample obtained from the subject for an inactivated *TP53* gene, wherein the disease is identified as sensitive to treatment with a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene. In exemplary examples, 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 examples, 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 examples, the method comprises determining sensitivity of the neoplastic disease to treatment with a CDK4/6 inhibitor. In various examples, 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 examples, the method comprises determining sensitivity of the neoplastic

WHAT IS CLAIMED IS:

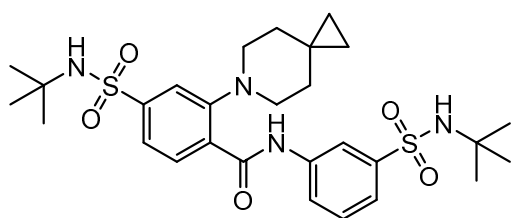
1. A method of determining a treatment for a neoplastic disease in a subject, comprising assaying a sample obtained from the subject for an inactivated *TP53* gene, wherein the treatment determined for the subject comprises a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene.
2. Use of a KIF18A inhibitor in the manufacture of a medicament for treating a neoplastic disease in a subject, wherein the subject comprises cells in a sample that have been determined to be positive for an inactivated *TP53* gene.
3. A method of identifying a neoplastic disease in a subject as sensitive to treatment with a KIF18A inhibitor, comprising assaying a sample obtained from the subject for an inactivated *TP53* gene, wherein the disease is identified as sensitive to treatment with a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene.
4. The method of any one of claim 1 or 3, wherein the sample comprises cancer cells, tumor cells, non-tumor cells, blood, blood cells, or plasma.
5. The method of claim 4, wherein the sample comprises germline cancer cells or somatic cancer cells.
6. The method of any one of claims 1 and 3 to 5 or the use of claim 2, wherein the neoplastic disease is a cancer.
7. The method or use of claim 6, wherein the neoplastic disease is breast cancer, ovarian cancer, endometrial cancer, lung cancer, or prostate cancer.
8. The method of any one of claims 1 and 3 to 7 or the use of any one of claims 2, 6, and 7, 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.
9. The method or use of claim 8, wherein the endometrial cancer is serous endometrial cancer.
10. The method or use of claim 6, wherein the cancer comprises cells that have been determined to be positive for an inactivated *TP53* gene.

11. The method or use of claim 10, wherein the cancer comprises cells that have been determined to be positive for a mutant *TP53* gene.
12. The method of any one of claims 1 and 3 to 11 or the use of any one of claims 2 and 6 to 11, wherein the KIF18A inhibitor is to be administered to the subject, 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.
13. The method or use of claim 12, wherein:
 - (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.
14. The method or use of claim 13, 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.
15. The method or the use of any one of claims 12 to 14, 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}.
16. The method of any one of claims 1 and 3 to 15 or the use of any one of claims 2 and 6 to 15, wherein (i) the neoplastic disease is a multidrug resistant neoplastic disease, (ii) the sample comprises multidrug resistant tumor or cancer cells, (iii) the sample comprises tumor or cancer cells that exhibit increased expression of the Multidrug resistance 1 (MDR-1) gene and/or a gene product thereof, (iv) the sample comprises tumor or cancer cells that exhibit increased expression of a P-glycoprotein (P-gp), or (v) any combination thereof.
17. The method of any one of claims 1 and 3 to 16 or the use of any one of claims 2 and 6 to 16, wherein the neoplastic disease is resistant to treatment with an anti-mitotic agent or anthracycline antibiotic.
18. The method or use of claim 17, wherein the anti-mitotic agent or anthracycline antibiotic is paclitaxel or doxorubicin.

19. The method or use of any one of claims 12 to 18, wherein the KIF18A inhibitor is to be administered by oral administration.

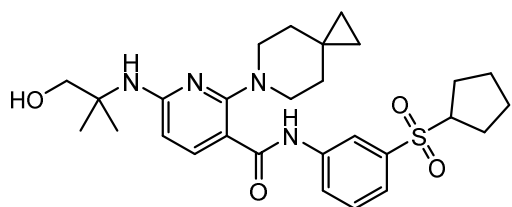
20. The method or use of claim 19, wherein the KIF18A inhibitor is to be administered once a day.

21. The method of any one of claims 1 and 3 to 20 or the use of any one of claims 2 and 6 to 20, 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:



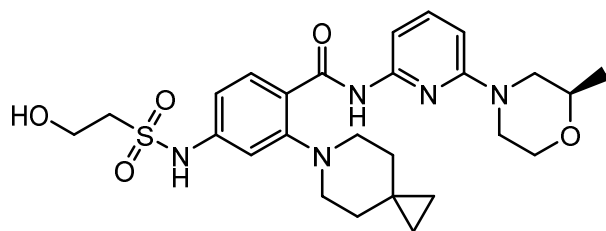
; or any pharmaceutically acceptable salt thereof.

22. The method of any one of claims 1 and 3 to 20 or the use of any one of claims 2 and 6 to 20, 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.

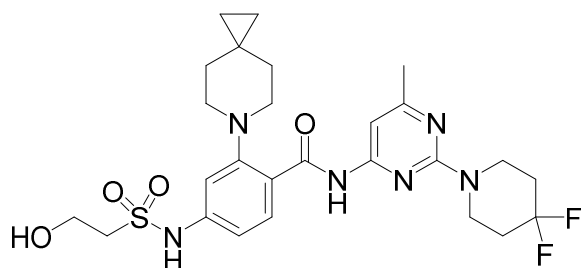
23. The method of any one of claims 1 and 3 to 20 or the use of any one of claims 2 and 6 to 20, wherein the KIF18A inhibitor is KIF18A inhibitor Compound C12, also known as (*R*)-4-((2-Hydroxyethyl)sulfonamido)-*N*-(6-(2-methylmorpholino)pyridin-2-yl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide, having the structure:



; or any pharmaceutically acceptable salt

thereof.

24. The method of any one of claims 1 and 3 to 20 or the use of any one of claims 2 and 6 to 20, 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. The method of any one of claims 1 and 3 to 24 or the use of any one of claims 2 and 6 to 24, wherein the subject is or has been treated with an anti-mitotic agent or anthracycline antibiotic.

26. The method or use of claim 25, wherein the KIF18A inhibitor (A) reduces expression of a KIF18A gene and/or a KIF18A gene product (B) is a non-coding RNA, and/or (C) is an siRNA.

27. The method or use of claim 26, wherein the KIF18A inhibitor is a non-coding RNA that mediates RNAi.

28. The method or use of any one of claims 25-27, wherein the KIF18A inhibitor comprises a sequence of any one of SEQ ID NOs: 12-18.

29. The method of any one of claims 1 and 3 to 28 or the use of any one of claims 2 and 6 to 28, further comprising assaying the sample obtained from the subject for 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 sample is positive for an inactivated *TP53* gene and 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.

30. The method of any one of claims 1 and 3 to 29 or the use of any one of claims 2 and 6 to 29, wherein the sample comprises cells that have been determined to be positive for an amplified *CCNE1* gene, a silenced *BRCA1* gene, a deficient *Rb1* gene, or a combination thereof.

31. The method or use of claim 29 or 30, comprising assaying the sample obtained from the subject for an inactivated *Rb1* gene, wherein the treatment determined for the subject comprises a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene and an inactivated *Rb1* gene.

32. The method or use of claim 29 or 30, comprising assaying the sample obtained from the subject for an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product, wherein the treatment determined for the subject comprises a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene and an amplified *CCNE1* gene or overexpression of a *CCNE1* gene product.

33. The method or use of claim 29 or 30, comprising assaying the sample obtained from the subject for an inactivated *BRCA* gene, wherein the treatment determined for the subject comprises a KIF18A inhibitor, when the sample is positive for an inactivated *TP53* gene and an inactivated *BRCA* gene.