

recent addition to the anti-cancer arsenal. Certain PARP inhibitors work as catalytic inhibitors as well as PARP poisons by trapping PARP-DNA complexes (Murai *et al.*, *Cancer Res.* 2012; 72:5588-99). Talazoparib (BMN 673) is the most potent PARP inhibitor reported to date in terms of tumor cytotoxicity and PARP trapping activities (Shen *et al.*, *Clin. Cancer Res.* 2013;19:5003-15; Murai *et al.*, *Mol. Cancer Ther.* 2014;13:433-43). Talazoparib has demonstrated significant clinical activity in ovarian and breast cancer patients with deleterious germline BRCA1/2 mutations (De Bono *et al.*, ASCO 2013, Abstract 2580). However, BRCA mutations have not been shown to predict greater sensitivity of SCLC to PARP inhibitors. Antitumor responses to talazoparib were also reported in SCLC patients (Wainberg *et al.*, ASCO 2014, Abstract 7522). Previous studies identified a slate of DNA repair protein markers that correlates with talazoparib sensitivity in SCLC (Cardnell *et al.*, *Clin. Cancer Res.* 2013, 19(22), 6322-6328), but these have not been validated clinically. In addition, an *in vitro* screen in the NCI60 cell line panel revealed that increased expression of Schlafen 11 (SLFN11) is correlated with increased cellular sensitivity to talazoparib exposure in a range of tumor cell lines (Murai *et al.*, AACR 2014, Abstract 1718). However, the NCI60 panel lacks any SCLC-derived cell lines, so the question of whether any particular genetic features correlated with increased sensitivity of SCLC cells to PARP inhibitors or talazoparib was left unanswered. In sum, there are no validated genetic profiles in SCLC patients that predict responsiveness to PARP inhibitors. Identification of such determinants will allow for the identification of patients who may respond well to a PARP inhibitor, or to talazoparib in particular.

[0005] There remains a need for methods of treatment of certain genetically-sensitive SCLC patients with PARP inhibitors. Further, identifying validated, clinically relevant biomarkers for SCLC will allow for earlier detection and appropriate therapeutic targeting.

SUMMARY

[0006] A study of a collection of 38 SCLC cell lines demonstrated that sensitivity to single-agent treatment of talazoparib correlates well with expression of each of the following genes: SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, and GULP1. The *in vitro* sensitivity results were confirmed *in vivo* in several SCLC cell line-derived xenograft (CDX) models. Notably, an *in vivo* study using 12 patient-derived xenograft (PDX) samples of SCLC revealed a correlation between SLFN11 expression (both at the messenger RNA level and at the

protein level) and the sensitivity of the tumors to PARP inhibitor treatment.

[0006a] In one aspect of the present disclosure, there is provided a use of a PARP inhibitor in the manufacture of a medicament for treating small cell lung cancer in a subject expressing SLFN11.

[0006b] In another aspect of the present disclosure, there is provided a use of a PARP inhibitor in the manufacture of a medicament for treating a small cell lung cancer subject, wherein one or more of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, or GULP1 is to be detected in a tumor cell sample from the subject.

[0006c] In yet another aspect of the present disclosure, there is provided a method of selecting a small cell lung cancer subject for PARP inhibitor chemotherapy, wherein one or more of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, and GULP1 is to be detected in a small cell lung cancer tumor sample of the subject, and an effective amount of a PARP inhibitor is to be administered to the subject.

[0006d] In a further aspect of the present disclosure, there is provided a use of talazoparib or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating small cell lung cancer in a subject expressing SLFN11.

[0007] Thus, the present disclosure includes methods of treating a SLFN11-, SIL1-, SLC25A3-, MAF-, AP3B1-, C1orf50-, BCL2-, DDX6-, and/or GULP1-positive SCLC patient comprising administering to the patient an effective amount of a PARP inhibitor. The

present disclosure relates to a method of treating a SLFN11-positive SCLC patient comprising administering to the patient an effective amount of a PARP inhibitor. The present disclosure relates to a method of treating a SLFN11-, SIL1-, SLC25A3-, MAF-, AP3B1-, C1orf50-, BCL2-, DDX6-, and/or GULP1-positive SCLC patient comprising administering to the patient an effective amount of talazoparib or a pharmaceutically acceptable salt thereof. The present disclosure relates to a method of treating a SLFN11-positive SCLC patient comprising administering to the patient an effective amount of talazoparib or a pharmaceutically acceptable salt thereof.

[0008] The present disclosure relates to a method of treating SCLC in a subject expressing SLFN11, comprising administering to the subject an effective amount of a PARP inhibitor. The present disclosure relates to a method of treating SCLC in a subject expressing SLFN11, comprising administering to the subject an effective amount of talazoparib or a pharmaceutically acceptable salt thereof.

[0009] The present disclosure relates to a method of treating SCLC in a subject expressing one or more of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, or GULP1, comprising administering to the subject an effective amount of a PARP inhibitor, or an effective amount of talazoparib or a pharmaceutically acceptable salt thereof. In some embodiments, the subject expresses SLFN11, and optionally expresses one or more of SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, or GULP1.

[0010] The present disclosure also relates to a method of treating a small cell lung cancer subject, comprising detecting one or more of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, and GULP1, in a tumor cell sample from the subject, and administering an effective amount of a PARP inhibitor to the subject.

[0011] The present disclosure relates to a method of selecting a small cell lung cancer subject for PARP inhibitor chemotherapy, comprising detecting one or more of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, or GULP1 in a small cell lung cancer tumor sample of the subject. The method optionally further comprises administering an effective amount of the PARP inhibitor to the subject. The present disclosure relates to a method of selecting a small cell lung cancer subject for PARP inhibitor chemotherapy, comprising detecting SLFN11 expression in the subject, and optionally further comprising administering an effective amount of a PARP inhibitor to the subject. The present disclosure relates to a method of selecting a small cell lung cancer subject for talazoparib chemotherapy, comprising detecting one or more of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, or GULP1 in a SCLC tumor sample from the subject. The method optionally further comprises administering an effective amount of talazoparib or a pharmaceutically acceptable salt thereof to

the subject. The present disclosure relates to a method of selecting a small cell lung cancer subject for talazoparib chemotherapy, comprising detecting SLFN11 expression in the subject, and optionally further comprising administering an effective amount of talazoparib or a pharmaceutically acceptable salt thereof to the subject.

[0012] The present disclosure relates to a method of treating a human subject having small cell lung cancer with a PARP inhibitor, comprising:

- (a) performing a nucleic acid-based detection assay to detect the mRNA expression level of one or more genes selected from the group consisting of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, and GULP1, in cells of a biological sample from the human subject by detecting mRNA expression;
- (b) determining that the cells from the human subject express said one or more genes at a level greater than the expression level of the respective genes in cells of a biological sample from a healthy human control; and
- (c) administering an effective amount of a PARP inhibitor to the human subject expressing the one or more genes at a level greater than the expression level of the respective genes in cells of a biological sample from a healthy human control, thereby treating small cell lung cancer in said human subject.

[0013] The present disclosure relates to a method for diagnosing and treating SCLC in a human subject, the method comprising:

- (a) performing a nucleic acid-based detection assay to detect the mRNA expression level of one or more genes selected from the group consisting of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, and GULP1, in cells of a biological sample from the human subject by detecting mRNA expression;
- (b) determining that the cells from the human subject express said one or more genes at a level greater than the expression level of the respective genes in cells of a biological sample from a healthy human control; and
- (c) administering an effective amount of a PARP inhibitor to the human subject expressing the one or more genes at a level greater than the expression level of the respective genes in cells of a biological sample from a healthy human control, thereby treating small cell lung cancer in the human subject.

[0014] The present disclosure relates to a method of diagnosing SCLC in a subject, comprising detecting expression of SLFN11 in the subject. The method optionally further comprises detecting one or more of SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, or GULP1 in the subject.

[0015] The present disclosure relates to a method of treating a small cell lung cancer subject with a reduced expression level of ATM, comprising administering to the subject an effective amount of a PARP inhibitor or talazoparib or a pharmaceutically acceptable salt thereof. In other embodiments, ATM expression in the subject is detected in addition to the one or more detection targets described herein. In other embodiments, ATM expression in the subject is reduced.

[0016] Additional embodiments, features, and advantages of the disclosure will be apparent from the following detailed description and through practice of the disclosure.

[0017] For the sake of brevity, the disclosures of the publications cited in this specification, including patents, are herein incorporated by reference.

BRIEF DESCRIPTION OF THE FIGURES

[0018] The present application can be understood by reference to the following description taken in conjunction with the accompanying figures.

[0019] FIG. 1 illustrates the correlation of GI_{50} values between talazoparib and cisplatin sensitivity in various small-cell lung cancer (SCLC) cell lines. GI_{50} values in log10 scale for talazoparib appear along the x-axis and for cisplatin along the y-axis. A linear regression line is shown, and the Spearman correlation and p-value are listed as R and P, respectively.

[0020] FIG. 2 illustrates the sensitivity of cell lines to talazoparib. Circles without arrows indicate cell lines that were studied for five days; circles with arrows indicate cell lines that were studied for seven days. The size of the data points is set based on the $\log_{10}(GI_{50})$ (lower GI_{50} = smaller size circles).

[0021] FIG. 3A illustrates the robust multi-array average (RMA) scores for SLFN11 expression in various small-cell lung cancer lines. Cell lines with an RMA score above 6 (above the line, designated “high” RMA) are differentiated from cell lines with an RMA score below 6 (below the line, designated “low” RMA). FIG. 3B illustrates boxplots of maximum growth inhibition and GI_{50} for the cell lines treated with talazoparib, pooled by high or low RMA score. The p-values shown are based on an Anova test. FIG. 3C illustrates a Waterfall plot of small-cell lung cancer (SCLC) cell lines ranked by maximum growth inhibition by talazoparib. Bars without arrows correspond to cell lines designated as “high” RMA and bars with arrows correspond to cell lines designated as “low” RMA. FIG. 3D illustrates the correlation between SLFN11 RMA expression score and GI_{50} for talazoparib for the tested cell lines. A linear regression line is shown, and the Spearman correlation and p-value are listed as R and P, respectively. FIG. 3E illustrates the correlation between SLFN11 RMA expression score and

CLAIMS

1. Use of a PARP inhibitor in the manufacture of a medicament for treating small cell lung cancer in a subject expressing SLFN11.
2. Use of a PARP inhibitor in the manufacture of a medicament for treating a small cell lung cancer subject, wherein one or more of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, or GULP1 is to be detected in a tumor cell sample from the subject.
3. A method of selecting a small cell lung cancer subject for PARP inhibitor chemotherapy, wherein one or more of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, and GULP1 is to be detected in a small cell lung cancer tumor sample of the subject, and an effective amount of a PARP inhibitor is to be administered to the subject.
4. The use or method of any one of claims 1-3, wherein the PARP inhibitor is talazoparib, olaparib, rucaparib, veliparib, CEP9722, MK4827, or BGB-290, or a pharmaceutically acceptable salt thereof.
5. The use or method of claim 4, wherein the PARP inhibitor is talazoparib or a pharmaceutically acceptable salt thereof.
6. The use or method of claim 5, wherein the PARP inhibitor is the tosylate salt of talazoparib.
7. Use of talazoparib or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating small cell lung cancer in a subject expressing SLFN11.

8. The use or method of any one of claims 1-7, wherein talazoparib or a pharmaceutically acceptable salt thereof is to be administered orally, once daily, at a dose of about 0.5 to about 2 mg per day, or of about 1 mg/day, or about 0.10 to 0.75 mg/kg/day, or about 0.25-0.30 mg/kg/day.

9. The use or method of any one of claims 1-8, wherein the subject expresses one or more of SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, or GULP1.

10. The use or method of any one of claims 1-9, wherein the subject has an increased expression level of one or more of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, or GULP1.

11. The use or method of any one of claims 1-10, wherein the PARP inhibitor or talazoparib or a pharmaceutically acceptable salt thereof is to be administered in combination with one or more chemotherapeutic agents, surgery, and/or radiation.

12. The use or method of claim 11, wherein the one or more chemotherapeutic agents is a DNA damaging agent, temozolomide, a topoisomerase 1 inhibitor, irinotecan, topotecan, a topoisomerase 2 inhibitor, etoposide, enzalutamide, an ATR inhibitor, an EGFR inhibitor, a platinum drug, cisplatin, carboplatin, or etoposide.

13. The use or method of any one of claims 1-12, wherein the subject has previously been treated with a platinum drug, or with cisplatin, or with carboplatin, optionally in combination with etoposide.

14. The use or method of any one of claims 1-13, wherein the subject expresses a reduced level of ATM.

15. The use or method of claim 2 or claim 3, wherein one of the detected biomarkers is SLFN11.

16. The use or method of any one of claims 2-6 or 8-15, wherein the detecting step comprises detection by an immunohistological assay, an immunohistochemistry staining (IHC) assay, an in-situ LC/MS assay, a promoter methylation assay, a cytological assay, an mRNA expression assay, an RT-PCR assay, a northern blot assay, a protein expression immunosorbent assay (ELISA), an enzyme-linked immunospot assay (ELISPOT), a lateral flow test assay, an enzyme immunoassay, a fluorescent polarization immunoassay, a chemiluminescent immunoassay (CLIA), or a fluorescence activated sorting assay (FACS).

17. The use or method of any one of claims 1 or 4-16, wherein the subject expresses an increased level of one or more of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, or GULP1.

18. The use or method of any one of claims 2-6 or 8-16, wherein the detecting step comprises detecting an increased level of one or more of SLFN11, SIL1, SLC25A3, MAF, AP3B1, C1orf50, BCL2, DDX6, or GULP1.

19. The use or method of claim 17, wherein the subject expresses a reduced level of ATM.

20. The use or method of claim 18, wherein the detecting step further comprises detecting ATM, or detecting a reduced level of expression of ATM.

21. The use or method of any one of the preceding claims, wherein the subject expresses the TP53 and/or RB1 mutation.

22. The use or method of any one of the preceding claims, wherein the RMA score for SLFN11 in the subject is 4 or higher, or is 5 or higher, or is 6 or higher, or is 7 or higher, or is 8 or higher.

23. The use or method of any one of the preceding claims, wherein the subject has a Myriad HRD score of 40 or lower, or of 35 or lower, or of 30 or lower, or of 25 or lower, or of 20 or lower.