

ALISERTIB AND PACLITAXEL FOR TREATING SMALL CELL LUNG CANCER

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/587,628 filed October 3, 2023, the disclosure of which is incorporated herein by reference in its entirety.

FIELD

[0002] Provided herein are methods for the treatment of small cell lung cancer (SCLC) comprising administering alisertib. Specific patient populations are contemplated in the methods and compositions disclosed herein, including patients with certain biomarkers and/or genetic profiles as well as resistant or refractory patients with certain biomarkers and/or genetic profiles. Also provided herein are methods for the treatment of small cell lung cancer (SCLC) comprising administering alisertib and a taxane. Further, provided herein are pharmaceutical compositions and dosage forms of alisertib. Further provided herein are methods for using the pharmaceutical compositions, and dosage forms of alisertib for treating and/or managing SCLC.

BACKGROUND

[0003] Small cell lung cancer (SCLC) is an aggressive malignancy, accounting for 13% to 18% of all lung cancer diagnoses (Alvarado-Luna G, *et al.*, *Transl Lung Cancer Res.* 2016;5:26–38. 3; Sorensen M, *et al.*, *Ann Oncol.* 2010;21(suppl 5):v120–v125; Arcaro A. *Crit Rev Oncol Hematol.* 2015;95:154–164). In treated extensive-stage SCLC, the median overall survival (OS) is just 7 to 12 months. (Hamilton G, *et al.*, *Transl Lung Cancer Res.* 2016;5:71–77.) The prognosis for relapsed or refractory SCLC is more dismal, with a median OS of 4 to 5 months. (Jett JR, *et al.*, *Chest.* 2013;143:e400S–e419S.) Response rates are particularly poor ($\leq 10\%$) in patients with resistant or refractory disease who relapse 3 months or less from the end of initial therapy. (*Chest.* 2013;143:e400S–e419S). Patients with platinum-sensitive disease (relapse >3 months from end of initial therapy) have a relatively better outcome (response rate approximately 25%).

[0004] Aurora A kinase (AAK), is a key regulator of mitosis. (Barr AR, *et al.* *J Cell Sci.* 2007;120:2987–2996). AAK is amplified or overexpressed in several solid tumors, including

SCLC, and may play a role in tumorigenesis.. Knocking down the expression of Aurora-A gene inhibits cell proliferation and induces G2/M phase arrest in human small cell lung cancer cells. (*Oncol Rep.* 2014;32:243–249; Marumoto T, *et al. J Biol Chem.* 2003;278:51786–51795). Inhibition of AAK leads to disrupted mitosis and cell death, reduced proliferation, and induction of apoptosis in SCLC cells. (*Oncol Rep.* 2014;32:243–249; Cowley DO, *et al., Mol Cell Biol.* 2009;29:1059–1071.)

[0005] Amplification of v-myc avian myelocytomatosis viral oncogene homolog gene (*MYC*) in SCLC cell lines is associated with improved sensitivity to Aurora kinase inhibitors. (Hook KE, *et al. Mol Cancer Ther.* 2012;11:710–719; Sos ML, *et al. Proc Natl Acad Sci USA.* 2012;109:17034–17039). Amplification and overexpression of the *MYC* gene family occurs in 18% to 31% of SCLCs and is more common in chemorefractory disease. The gene product, c-Myc (a transcription factor), binds directly to AAK, and inhibition of this interaction by AAK inhibitors results in c-Myc degradation and cell death. (Brockmann M, *et al. Cancer Cell.* 2013;24:75–89; Dauch D, *et al. Nat Med.* 2016;22:744–753). Thus, the Myc–AAK protein complex represents an actionable drug target for AAK inhibitors.

[0006] Alisertib (MLN8237) is a selective, oral, small molecule AAK inhibitor that has been studied in various solid tumors and hematologic malignancies. (Barr PM, *et al. J Clin Oncol.* 2015;33:2399–2404; Falchook G, *et al. JAMA Oncol.* 2019;5:e183773; Falchook GS, *et al. Drugs R D.* 2016;16:45–52; Goldberg SL, *et al. Leuk Res Rep.* 2014;3:58–61; Matulonis UA, *et al. Gynecol Oncol.* 2012;127:63–69; Melichar B, *et al. Lancet Oncol.* 2015;16:395–405.) Single-agent activity of alisertib was demonstrated in a phase II study of patients with relapsed or refractory solid tumors, including SCLC (n = 48); in patients with SCLC, the objective response rate (ORR) was 21% and the median progression-free survival (PFS) was 2.1 months. (Melichar B, *et al. Lancet Oncol.* 2015;16:395–405.)

[0007] Alisertib plus paclitaxel was evaluated in patients with breast and ovarian cancer and showed promise over paclitaxel alone (*JAMA Oncol.* 2019;5:e183773). A Phase II study of paclitaxel plus alisertib versus paclitaxel plus placebo as second line therapy for SCLC was

conducted. (*Journal of Thoracic Oncology* Vol. 15 No. 2: 274-287). The study did not assess the treatment of patients with particular genetic mutations.

[0008] Because of poor responses to current treatments, there is a critical unmet medical need in patients with SCLC.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1A illustrates the Kaplan-Meier (KM) curve for PFS for c-Myc positive SCLC.

[0010] FIG. 1B illustrates the KM curve for OS for c-Myc positive SCLC.

[0011] FIG. 2A illustrates the KM curve for PFS for RB1 mutant SCLC.

[0012] FIG. 2B illustrates the KM curve for OS for RB1 mutant SCLC.

[0013] FIG. 3A illustrates the KM curve for PFS for c-Myc positive and RB1 mutant SCLC.

[0014] FIG. 3B illustrates the KM curve for OS for c-Myc positive and RB1 mutant SCLC.

[0015] FIG. 4A illustrates the KM curve for PFS for TP53 mutant SCLC.

[0016] FIG. 4B illustrates the KM curve for OS for TP53 mutant SCLC.

[0017] FIG. 5A illustrates the KM curve for PFS for TP53 mutant and c-Myc positive SCLC.

[0018] FIG. 5B illustrates the KM curve for OS for TP53 mutant and c-Myc positive SCLC.

[0019] FIG. 6A illustrates the KM curve for PFS for RB1 mutant and TP53 mutant SCLC.

[0020] FIG. 6B illustrates the KM curve for OS for RB1 mutant and TP53 mutant SCLC.

[0021] FIG. 7A illustrates the KM curve for PFS for c-Myc positive, RB1 mutant, and TP53 mutant SCLC.

[0022] FIG. 7B illustrates the KM curve for OS for c-Myc positive, RB1 mutant, and TP53 mutant SCLC.

DETAILED DESCRIPTION

[0023] 1. *General Description*

[0024] Provided herein, is a method of treating small cell lung cancer (SCLC) comprising administering alisertib to a patient having SCLC. Provided herein is alisertib for use in a method of treating SCLC. In one embodiment, the SCLC is c-Myc positive and has a retinoblastoma 1

gene (RB1) mutation. In one embodiment, the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC has a retinoblastoma 1 gene (RB1) mutation and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is c-Myc positive and/or has a retinoblastoma 1 gene (RB1) mutation, and/or has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation.

[0025] Provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and a taxane. Provided herein is alisertib and a taxane for use in a method of treating SCLC. In one embodiment, the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation. In one embodiment, the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC has a retinoblastoma 1 gene (RB1) mutation and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is c-Myc positive and/or has a retinoblastoma 1 gene (RB1) mutation, and/or has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation.

[0026] Also, provided herein, is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and a taxane to a patient having SCLC, wherein the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation. Provided herein is alisertib and a taxane for use in method of treating small cell lung cancer (SCLC) comprising administering alisertib and a taxane to a patient having SCLC, wherein the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation.

[0027] Also, provided herein, is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation. Provided herein is alisertib and paclitaxel for use in method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation.

[0028] Also, provided herein, is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and nab-paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation. Provided herein is alisertib and nab-paclitaxel for use in method of treating small cell lung cancer (SCLC) comprising administering alisertib and nab-paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation.

[0029] Also, provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and a taxane to a patient having SCLC, wherein the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation. Provided herein is alisertib and a taxane for use in a method of treating small cell lung cancer (SCLC) comprising administering alisertib and a taxane to a patient having SCLC, wherein the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation.

[0030] Also, provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation. Provided herein is alisertib and paclitaxel for use in a method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation.

[0031] Also, provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and nab-paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation. Provided herein is alisertib and nab-paclitaxel for use in a method of treating small cell lung cancer (SCLC) comprising administering alisertib and nab-paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation.

[0032] Also, provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and a taxane to a patient having SCLC, wherein the SCLC has a retinoblastoma 1 gene (RB1) mutation and a tumor protein p53 gene (TP53) mutation.

Provided herein is alisertib and a taxane for use in a method of treating small cell lung cancer (SCLC) comprising administering alisertib and a taxane to a patient having SCLC, wherein the SCLC has a retinoblastoma 1 gene (RB1) mutation and a tumor protein p53 gene (TP53) mutation.

[0033] Also, provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC has a retinoblastoma 1 gene (RB1) mutation and a tumor protein p53 gene (TP53) mutation.

Provided herein is alisertib and paclitaxel for use in a method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC has a retinoblastoma 1 gene (RB1) mutation and a tumor protein p53 gene (TP53) mutation.

[0034] Also, provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and nab-paclitaxel to a patient having SCLC, wherein the SCLC has retinoblastoma 1 gene (RB1) mutation and a tumor protein p53 gene (TP53) mutation. Provided herein is alisertib and nab-paclitaxel for use in a method of treating small cell lung cancer (SCLC) comprising administering alisertib and nab-paclitaxel to a patient having SCLC, wherein the SCLC has a retinoblastoma 1 gene (RB1) mutation and a tumor protein p53 gene (TP53) mutation.

[0035] Provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and a taxane to a patient having SCLC, wherein the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation. Provided herein is alisertib and a taxane for use in a method of treating small cell lung cancer (SCLC) comprising administering alisertib and a taxane to a patient having SCLC, wherein the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation.

[0036] Provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, the SCLC is c-Myc positive, has

a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation. Provided herein is alisertib and paclitaxel for use in a method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation.

[0037] Provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and nab-paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation. Provided herein is alisertib and nab-paclitaxel for use in a method of treating small cell lung cancer (SCLC) comprising administering alisertib and nab-paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation.

[0038] Methods for detecting c-Myc expression and the presence of genetic alterations, including mutations, are well known in the art. Such methods include, without limitation, immunohistochemical analysis, such as a c-Myc immunohistochemistry assay clinically validated from PhenoPath (Seattle, WA, USA). Genetic alterations can be determined by methods well known in the art, including, without limitation, next-generation sequencing (NGS) analysis of circulating tumor DNA (ctDNA) and/or analysis of primary tumor tissue samples by methods known in the art.

[0039] In one embodiment, the distribution of specific amino acid alterations in key mutated genes identified are compared with those identified in SCLC primary tumor tissue samples. Visualization of the distribution of mutations across each gene can be performed using MutationMapper from cBioPortal (Cerami E, *et al. Cancer Discov.* 2012;2:401-404. <https://doi.org/10.1158/2159-8290.Cd-12-0095>; Gao J, *et al. Sci Signal.* 2013;6:pl1) among other methods known in the art. All known methods for detecting and identifying genetic mutations are contemplated herein.

[0040] In one embodiment, provided herein are pharmaceutical compositions comprising an effective amount of alisertib, and a pharmaceutically acceptable carrier, excipient or vehicle. In some embodiments the pharmaceutical composition comprising alisertib is suitable for oral, parenteral, mucosal, transdermal or topical administration.

[0041] Further provided herein are methods for using the pharmaceutical compositions, and dosage forms of alisertib for treating SCLC, as described herein. Also provided herein is a pharmaceutical composition of alisertib for use in a method for treating SCLC, as described herein. Also provided herein is a dosage form of alisertib for use in a method for treating SCLC, as described herein.

[0042] Also provided herein is a kit comprising one or more pharmaceutical compositions or dosage forms comprising (i) alisertib; and (ii) paclitaxel. Also provided herein is a kit comprising one or more pharmaceutical compositions or dosage forms comprising (i) alisertib; and (ii) nab-paclitaxel.

[0043] 2. *Definitions*

[0044] As used herein, the terms “small cell lung cancer” or “SCLC” refer to a neuroendocrine carcinoma that exhibits aggressive behavior, rapid growth, early spread to distant sites, exquisite sensitivity to chemotherapy and radiation, and frequent association with distinct paraneoplastic syndromes, including hypercalcemia, Eaton-lambert syndrome, syndrome of inappropriate antidiuretic hormone (SIADH) secretion, and many others. SCLC is divided into the 2 subtypes: oat cell carcinoma and combined-SCLC. Combined SCLC is defined as SCLC with non-small cell components such as squamous cell or adenocarcinoma. (*StatPearls Publishing*; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482458/>). Nearly 60% of SCLC patients present with metastatic disease. Most common sites of metastases include the brain, liver, adrenal glands, bone, and bone marrow. If left untreated, SCLC is characterized by rapid tumor progression with a median survival of 2 to 4 months. Treatment is highly dependent on stage. Patients with limited-stage SCLC are candidates for curative-intent radiation therapy and chemotherapy. Patients with extensive-stage disease are treated with chemotherapy with radiation (RT) reserved for select candidates and palliation. **Limited Stage:** While the majority of patients present with locally advanced disease, a small minority may

present with T1-2N0 disease. These patients may be candidates for lobectomy with mediastinal sampling or dissection. If surgery demonstrates mediastinal nodal involvement, adjuvant chemoradiation is indicated. If they are not surgical candidates, stereotactic ablative body therapy (SABR) may be employed. Adjuvant cisplatin-based systemic therapy typically follows both local approaches. The remainder of limited stage patients is treated with concurrent chemotherapy and radiation. Cisplatin and etoposide is the current standard of care. The addition of radiation to chemotherapy significantly increases local control and overall survival. The early incorporation of RT with CT has been shown to further increase overall survival compared to late incorporation. Prophylactic cranial irradiation (PCI) is indicated for patients with a complete or partial response to therapy. PCI significantly increases overall survival and decreases the incidence of brain metastases. **Extensive Stage:** The mainstay of therapy for patients with the extensive stage is systemic chemotherapy. Patients who have a complete or partial response to therapy can be evaluated for consolidative thoracic RT. This therapy has been associated with an increase in overall survival and is typically well tolerated. PCI is also indicated for ES and has been associated with an increase in survival with a decrease in brain metastases incidence. There is currently no role for the addition of consolidation radiation to limited volume metastatic sites. The efficacy of platinum-based chemotherapy for frontline therapy has been established in randomized clinical trials with objective responses in approximately 70% of patients with limited stage SCLC and in 50% of patients with extensive stage disease (*Oncology (Williston Park)* 1998;12:647–58. discussion 661–3; *Oncology (Williston Park)* 2008;22:1495–6; . *N Engl J Med.* 2002;346:85–91.) Despite this high initial response, the majority of SCLC patients require salvage therapy for disease progression within several months following frontline therapy. (*J Thorac Oncol.* 2012 May; 7(5): 866–872.)

[0045] As used herein, the term “patient” means an animal, in one embodiment a mammal, and in another embodiment a human. In some embodiments, the patient has a pathologically (histologically or cytologically) confirmed diagnosis of SCLC. In one embodiment, the patient has progressed within 180 days of last platinum dose, after receiving a standard platinum-based chemotherapy regimen as first-line treatment and has measurable disease per the Response Evaluation Criteria in Solid Tumors version 1.1. In one embodiment, the patient has not received prior treatment with an Aurora A kinase inhibitor (*e.g.*, alisertib), a pan-Aurora-targeted

agent, paclitaxel, or any other taxane. In one embodiment, the patient has not received prior treatment with any other investigational agent for relapsed disease. In one embodiment, the patient has limited stage SCLC. In one embodiment, the patient has extensive stage SCLC.

[0046] The term “mutation” as used herein refers to an alteration in a gene or protein which is not present in the wild-type gene or protein. The terms “mutant,” “mutation,” or “mutations” as used herein are interchangeable. In one embodiment, the term “mutant” as used herein encompasses one or more mutations and is not limited to a single mutational status.

[0047] The terms “sensitive,” “sensitive relapse,” or “platinum sensitive” as used herein refer to SCLC in which progression of disease is observed >90 days from the last dose of first-line platinum-based chemotherapy.

[0048] The term “resistant” or “resistant relapse” as used herein refers to SCLC in which progression of disease is observed ≤ 90 days after first-line platinum-based chemotherapy.

[0049] The term “refractory” or “refractory relapse” as used herein refers to SCLC in which no objective response is achieved and disease progression occurs either during or immediately after first-line platinum-based chemotherapy.

[0050] It will be understood that encompassed herein is SCLC which is resistant/refractory or relapsed SCLC, resistant/refractory SCLC, platinum sensitive SCLC, platinum-resistant SCLC, platinum resistant or refractory SCLC, and sensitive relapse SCLC.

[0051] The term “c-Myc positive” as used herein refers to SCLC positive for c-Myc expression. In one embodiment, c-Myc positive as used herein refers to c-Myc expression measured by immunohistochemistry analysis in which modal intensity is 1+, 2+, or 3+. In one embodiment, c-Myc positive includes c-Myc overexpression and/or amplification, and/or c-Myc alteration.

[0052] An improvement in SCLC can be characterized as a complete or partial response. “Complete response” (CR) refers to disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to about < 10 mm. “Partial response” (PR) refers to at least about a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or

90% decrease in all measurable tumor burden (i.e., decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) in the absence of new lesions. The term “treatment” contemplates both a complete and a partial response. “Progressive Disease” (PD): refers to at least about a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of about 20%, the sum must also demonstrate an absolute increase of at least about 5 mm. The appearance of one or more new lesions is also considered progression. “Stable Disease” (SD) refers to neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

[0053] As used herein, and unless otherwise specified, the term “sensitivity” and “sensitive” when made in reference to treatment with a compound disclosed herein is a relative term which refers to the degree of effectiveness of the compound in lessening or decreasing the progress of SCLC. For example, the term “increased sensitivity” when used in reference to treatment of SCLC in connection with a compound disclosed herein refers to an increase of, at least a 5%, or more, in the effectiveness of the SCLC treatment.

[0054] As used herein, and unless otherwise specified, the terms “determining”, “measuring”, “evaluating”, “assessing” and “assaying” as used herein generally refer to any form of measurement, and include determining if an element is present or not. These terms include both quantitative and/or qualitative determinations. Assessing may be relative or absolute. “Assessing the presence of” can include determining the amount of something present, as well as determining whether it is present or absent.

[0055] The expressions “therapeutically effective” and “therapeutic effect” refer to a benefit including, but not limited to, the treatment or amelioration of symptoms of a disorder discussed herein. It will be appreciated that the therapeutically effective amount or the amount of agent required to provide a therapeutic effect will vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (e.g., nature of the severity of

the condition to be treated, the particular inhibitor, the route of administration and the age, weight, general health, and response of the individual patient), which can be readily determined by a person of skill in the art. For example, an amount of a selective inhibitor of Aurora A kinase such as alisertib with an amount of a taxane such as paclitaxel is therapeutically effective if it is sufficient to effect the treatment or amelioration of symptoms of a disorder discussed herein.

[0056] The expressions “prophylactically effective” and “prophylactic effect” refer to a benefit including, but not limited to, the prophylaxis of symptoms of SCLC discussed herein. It will be appreciated that the prophylactically effective amount or the amount of agent required to provide a prophylactic effect will vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being prevented (e.g., nature of the severity of the condition to be prevented, the particular inhibitor, the route of administration and the age, weight, general health, and response of the individual patient), which can be readily determined by a person of skill in the art. For example, an amount of alisertib with an amount of a taxane such as paclitaxel is prophylactically effective if it is sufficient to effect the prophylaxis of symptoms of SCLC discussed herein. In one embodiment, the symptom is neutropenia. In another embodiment, a prophylactically effective amount of an agent is an amount effective to reduce grade 3 or higher neutropenia. In one embodiment, the agent is Granulocyte-Colony-Stimulating Factor (G-CSF). In one embodiment, provided herein is a method of treating SCLC, comprising administering a prophylactically effective amount of alisertib, wherein the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation. In one embodiment, the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC has a retinoblastoma 1 gene (RB1) mutation and a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is c-Myc positive and/or has a retinoblastoma 1 gene (RB1) mutation, and/or has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation. In one embodiment, provided herein is a method of treating SCLC,

comprising administering a prophylactically effective amount of alisertib and a taxane, wherein the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation. In one embodiment, the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC has a retinoblastoma 1 gene (RB1) mutation and a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is c-Myc positive and/or has a retinoblastoma 1 gene (RB1) mutation, and/or a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation. In one embodiment, provided herein is a method of treating SCLC, comprising administering a prophylactically effective amount of alisertib and paclitaxel, wherein the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation. In one embodiment, the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC has a retinoblastoma 1 gene (RB1) mutation and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is c-Myc positive and/or has a retinoblastoma 1 gene (RB1) mutation, and/or has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation. In one embodiment, provided herein is a method of treating SCLC, comprising administering a prophylactically effective amount of alisertib and nab-paclitaxel, wherein the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation. In one embodiment, the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC has a retinoblastoma 1 gene (RB1) mutation and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is c-Myc positive and/or has a retinoblastoma 1 gene (RB1) mutation, and/or has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation.

[0057] As used herein, the term “taxane” refers to a class of diterpenes produced by the plants of the genus *Taxus* (yews). Examples of taxanes include, but are not limited to, paclitaxel

(TAXOL®), docetaxel (TAXOTERE®), ABRAXANE® (Paclitaxel Injection), and nab-paclitaxel (nanoparticle albumin-bound paclitaxel).

[0058] As used herein, the term “in combination” refers to use of both alisertib and a taxane in the treatment of the same disease or condition in the same patient and may include a further therapeutic agent (*e.g.*, G-CSF). As further described below, unless explicitly specified, the term “in combination” does not restrict the timing and mode of administration of alisertib, the taxane, or other therapeutic agent.

[0059] As used herein, and unless otherwise specified, the term “about” or “approximately” means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term “about” or “approximately” means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term “about” or “approximately” means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

[0060] As used herein, the term “or” is to be interpreted as an inclusive “or” meaning any one or any combination. Therefore, “A, B or C” means any of the following: “A; B; C; A and B; A and C; B and C; A, B and C”. An exception to this definition will occur only when a combination of elements, functions, steps or acts are in some way inherently mutually exclusive.

CLINICAL TRIAL ENDPOINTS FOR SCLC APPROVAL

[0061] “Overall survival” (OS) is defined as the time from first dose until death from any cause, and is measured in the intent-to-treat population. Overall survival should be evaluated in randomized controlled studies. Demonstration of a statistically significant improvement in overall survival can be considered to be clinically significant if the toxicity profile is acceptable, and has often supported new drug approval. In one embodiment, patients are followed for overall survival (OS) every 2 months (± 2 weeks) until approximately 80% of all patients in the intent-to-treat (ITT) population have died or 14 months after the last patient was randomized, whichever occurred first.

[0062] Several endpoints are based on SCLC assessments. These endpoints include disease free survival (DFS), objective response rate (ORR), including complete response, time to progression (TTP), progression-free survival (PFS), event-free survival (EFS), duration of response (DOR), disease control rate (DCR), time-to-treatment failure (TTF), safety and/or tolerability. The collection and analysis of data on these time-dependent endpoints are based on indirect assessments, calculations, and estimates. In one embodiment, end points such as safety and/or tolerability, OS, ORR including complete response, and DCR as used herein are secondary end points. Generally, “disease free survival” (DFS) is defined as the time from randomization until recurrence of cancer or death from any cause. Although overall survival is a conventional endpoint for most adjuvant settings, DFS can be an important endpoint in situations where survival may be prolonged, making a survival endpoint impractical. DFS can be a surrogate for clinical benefit or it can provide direct evidence of clinical benefit. This determination is based on the magnitude of the effect, its risk-benefit relationship, and the disease setting. The definition of DFS can be complicated, particularly when deaths are noted without prior cancer progression documentation. These events can be scored either as disease recurrences or as censored events. Although all methods for statistical analysis of deaths have some limitations, considering all deaths (deaths from all causes) as recurrences can minimize bias. DFS can be overestimated using this definition, especially in patients who die after a long period without observation. Bias can be introduced if the frequency of long-term follow-up visits is dissimilar between the study arms or if dropouts are not random because of toxicity.

[0063] “Objective response rate” (ORR) is defined as the sum of the percentage of patients who achieve complete and partial responses. Response duration usually is measured from the time of initial response until documented cancer progression. Generally, the FDA has defined ORR as the sum of partial responses plus complete responses. When defined in this manner, ORR is a direct measure of drug anticancer activity, which can be evaluated in a single-arm study. If available, standardized criteria should be used to ascertain response. A variety of response criteria have been considered appropriate (e.g., RECIST criteria) (Therasse et al.,

(2000) *J. Natl. Cancer Inst*, 92: 205-16). The significance of ORR is assessed by its magnitude and duration, and the percentage of complete responses (no detectable evidence of cancer).

[0064] “Duration of response” (DOR) is the time from achieving a response until relapse or disease progression.

[0065] “Time to progression” (TTP) and “progression-free survival” (PFS) have served as primary endpoints for drug approval. TTP is defined as the time from randomization until objective cancer progression; TTP does not include deaths. PFS is defined as the time from randomization until objective cancer progression or death. Compared with TTP, PFS is the preferred regulatory endpoint. PFS includes deaths and thus can be a better correlate to overall survival. PFS assumes patient deaths are randomly related to cancer progression. However, in situations where the majority of deaths are unrelated to cancer, TTP can be an acceptable endpoint.

[0066] As an endpoint to support drug approval, PFS can reflect cancer growth and be assessed before the determination of a survival benefit. Its determination is not confounded by subsequent therapy. For a given sample size, the magnitude of effect on PFS can be larger than the effect on overall survival. However, the formal validation of PFS as a surrogate for survival for the many different malignancies that exist can be difficult. Data are sometimes insufficient to allow a robust evaluation of the correlation between effects on survival and PFS. Cancer trials are often small, and proven survival benefits of existing drugs are generally modest. The role of PFS as an endpoint to support licensing approval varies in different cancer settings. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit of the new treatment compared to available therapies. In one embodiment, PFS as contemplated herein, is a primary end point. In one such embodiment, PFS is measured as time from randomization to progressive disease or death. In one such embodiment, patients are stratified by type of relapse after primary treatment (sensitive versus resistant or refractory disease) and presence of brain metastases. In one embodiment, PFS is also analyzed in patient subgroups according to baseline characteristics.

[0067] “Event-free survival” (EFS) is the time from study entry until any treatment failure, including disease progression, treatment discontinuation for any reason, or death.

[0068] “Time-to-treatment failure” (TTF) is defined as a composite endpoint measuring time from randomization to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. TTF is not recommended as a regulatory endpoint for drug approval. TTF does not adequately distinguish efficacy from these additional variables. A regulatory endpoint should clearly distinguish the efficacy of the drug from toxicity, patient or physician withdrawal, or patient intolerance.

[0069] “Disease control rate” (DCR) is defined as complete response, partial response, or stable disease ≥ 8 weeks.

[0070] In one embodiment, encompassed herein are exploratory end points including correlative biomarker studies to evaluate the impact of c-Myc expression and/or genetic alterations on clinical outcomes (PFS and OS).

[0071] In certain embodiments, the methods provided herein are useful for achieving one or more of these clinical trial endpoints in a patient. In certain embodiments, the methods provided herein are useful for improving one or more of these clinical trial endpoints in a patient. In certain embodiments, the methods provided herein increase PFS relative to treatment of SCLC with a taxane. In some embodiments, the method of treating SCLC comprising alisertib and paclitaxel as provided herein increases PFS relative to treatment of SCLC with paclitaxel. In some embodiments, such increase in PFS is 2 fold, 3 fold, or 4 fold, or by 10%, 20%, 25%, 30%, 35, or 40%. In certain embodiments, the methods provided herein increase OS relative to treatment of SCLC with a taxane. In some embodiments, the method of treating SCLC comprising alisertib and paclitaxel as provided herein increases OS relative to treatment of SCLC with paclitaxel. In some embodiments, such increase in OS is 2 fold, 3 fold, or 4 fold, or by 10%, 20%, 25%, 30%, 35%, or 40%. In some such embodiments, the taxane is paclitaxel or nab-paclitaxel.

[0072] 3. *Detailed Description*

[0073] ***A. Alisertib - Inhibitor of Aurora A Kinase***

[0074] Alisertib (MLN8237) is a selective Aurora A kinase inhibitor also known as 4-{[9-Chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino}-2-methoxybenzoic acid or sodium 4-{[9-Chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino}-2-methoxybenzoate. Alisertib or a pharmaceutically acceptable salt thereof and their methods of preparation are described in US Patent No. 8,026,246; US Patent No. 9,765,076; and US Patent No. 10,836,766, each of which is herein incorporated by reference in their entirety. Formulations of alisertib are disclosed in US Patent No. 9,173,846; US Patent No. 9,655,856; US Patent No. 10,888,523; US Patent No. 9,127,011; US Patent No. 9,504,693, the entirety of each of which is incorporated herein by reference. The compound can be also synthesized according to other methods apparent to those of skill in the art based upon the teaching of these publications.

[0075] In one embodiment, provided herein is sodium 4-{[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino}-2-methoxybenzoate monohydrate. In another embodiment, provided herein is sodium 4-{[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino}-2-methoxybenzoate polymorph Form 2, as described in US Patent No. 8,026,246, and US Patent No. 8,653,064, each of which is hereby incorporated by reference in their entirety.

[0076] Throughout this application and unless specified otherwise, the terms 4-{[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino}-2-methoxybenzoic acid; 4-{[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino}-2-methoxybenzoic acid or a pharmaceutically acceptable salt thereof; sodium 4-{[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino}-2-methoxybenzoate; sodium 4-{[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino}-2-methoxybenzoate monohydrate; and sodium 4-{[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino}-2-methoxybenzoate polymorph Form 2, collectively are referred to herein as “alisertib.”

[0077] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A “pharmaceutically acceptable salt” means any non-toxic salt or salt of an ester of a compound disclosed herein that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound disclosed herein or an inhibitorily active metabolite or residue thereof. As used herein, the term “inhibitorily active metabolite or residue thereof” means that a metabolite or residue thereof is also a selective inhibitor of Aurora A kinase.

[0078] If a pharmaceutically acceptable salt of the selective inhibitor of Aurora A kinase is utilized in pharmaceutical compositions, the salt preferably is derived from an inorganic or organic acid or base. For reviews of suitable salts, see, e.g., Berge et al, *J. Pharm. Sci.* 66:1-19 (1977) and *Remington: The Science and Practice of Pharmacy, 20th Ed.*, ed. A. Gennaro, Lippincott Williams & Wilkins, 2000.

[0079] Nonlimiting examples of suitable acid addition salts include the following: acetate, adipate, alginate, aspartate, benzoate, benzene sulfonate, bisulfate, butyrate, citrate, camphorate, camphor sulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, lucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate.

[0080] Suitable base addition salts include, without limitation, ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine, *N*-methyl-D-glucamine, *t*-butylamine, ethylene diamine, ethanolamine, and choline, and salts with amino acids such as arginine, lysine, and so forth.

[0081] Also, basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

[0082] ***B. Dosages and Administration of Alisertib and Taxanes***

[0083] The therapeutically effective amounts or suitable dosages of alisertib depends upon a number of factors, including the nature of the severity of the condition to be treated, the particular inhibitor, the route of administration and the age, weight, general health, and response of the individual patient. In certain embodiments, the suitable dose level is one that achieves an effective exposure as measured by increased skin mitotic index, or decreased chromosome alignment and spindle bipolarity in tumor mitotic cells, or other standard measures of effective exposure in cancer patients. In certain embodiments, the suitable dose level is one that achieves a therapeutic response as measured by tumor regression, or other standard measures of disease progression, progression free survival or overall survival. In other embodiments, the suitable dose level is one that achieves this therapeutic response and also minimizes any side effects associated with the administration of the therapeutic agent. All dosages and routes of administration provided herein refer to the particular patient population described herein, including patients with certain biomarkers and/or genetic profiles as well as resistant or refractory patients with certain biomarkers and/or genetic profiles.

[0084] Suitable daily dosages of alisertib can generally range, in single or divided or multiple doses, from about 20 mg to about 120 mg per day. Other suitable daily dosages of alisertib can generally range, in single or divided or multiple doses, from about 40 mg to about 80 mg per day. Other suitable daily dosages of alisertib can generally range, in single or divided or multiple doses, from about 60 mg to about 80 mg per day. In certain embodiments, the suitable dosages are from about 10 mg twice daily to about 40 mg twice daily. In some other embodiments, the suitable dosages are from about 20 mg twice daily to about 40 mg twice daily.

In some other embodiments, the suitable dosages are from about 30 mg twice daily to about 50 mg twice daily. In some other embodiments, the suitable dosages are from about 30 mg twice daily to about 40 mg twice daily. In some other embodiments, the suitable dosages are from about 40 mg twice daily to about 50 mg twice daily. In other embodiments, suitable dosages are about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg per day, about 95 mg per day, about 100 mg per day, about 105 mg per day, about 110 mg per day, about 115 mg per day, or about 120 mg per day. In certain other embodiments, suitable dosages are about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, or about 60 mg twice daily. In some embodiments, suitable dosages are about 20 mg twice daily. In some embodiments, suitable dosages are about 30 mg twice daily. In some embodiments, suitable dosages are about 40 mg twice daily. In some embodiments, suitable dosages are about 50 mg twice daily.

[0085] It will be understood that a suitable dosage of alisertib may be taken at any time of the day or night. In some embodiments, a suitable dosage of alisertib is taken in the morning. In some other embodiments, a suitable dosage of alisertib is taken in the evening. In some other embodiments, a suitable dosage of alisertib is taken both in the morning and the evening. It will be understood that a suitable dosage of alisertib may be taken with or without food. In some embodiments a suitable dosage of alisertib is taken with a meal. In some embodiments a suitable dosage of alisertib is taken while fasting.

[0086] Suitable weekly dosages of paclitaxel can generally range, in single or divided or multiple doses, from about 40 mg/m² to about 80 mg/m² per week. Other suitable weekly dosages of paclitaxel can generally range, in single or divided or multiple doses, from about 50 mg/m² to about 75 mg/m² per week. Other suitable weekly dosages of paclitaxel can generally range, in single or divided or multiple doses, from about 50 mg/m² to about 70 mg/m² per week, or from about 60 mg/m² to about 70 mg/m² per week. In other embodiments, suitable weekly

dosages are about 40 mg/m², about 45 mg/m², about 50 mg/m², about 55 mg/m², about 60 mg/m², about 65 mg/m², about 70 mg/m², or about 75 mg/m² per week.

[0087] Additionally, it will be appreciated that the frequency with which any of these therapeutic agents can be administered can be once or more than once over a period of about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 20 days, about 28 days, about a week, about 2 weeks, about 3 weeks, about 4 weeks, about a month, about every 2 months, about every 3 months, about every 4 months, about every 5 months, about every 6 months, about every 7 months, about every 8 months, about every 9 months, about every 10 months, about every 11 months, about every year, about every 2 years, about every 3 years, about every 4 years, or about every 5 years.

[0088] For example, an agent may be administered daily, weekly, biweekly, or monthly for a particular period of time. In some embodiments, a certain amount of alisertib can be administered on a daily basis over a period of three days. Alternatively, an agent may be administered daily, weekly, biweekly, or monthly for a particular period of time followed by a particular period of non-treatment. In some embodiments, a certain amount of alisertib can be administered daily for three days followed by four days of no administration, followed by administration daily for three days followed by four more days of no administration, followed by administration daily for three days followed by four more days of no administration. In some embodiments, a certain amount of a taxane can be administered weekly over a three week period.

[0089] In some embodiments, alisertib and the taxane are cyclically administered to a patient. Cycling therapy involves the administration of a first agent (e.g., a first prophylactic or therapeutic agents) for a period of time, followed by the administration of a second agent and/or third agent (e.g., a second and/or third prophylactic or therapeutic agents) for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improve the efficacy of the treatment.

[0090] In one embodiment, alisertib and the taxane are administered for at least 1 to 12 cycles. In one embodiment, alisertib and the taxane are administered for at least 1 to 6 cycles. In one embodiment, alisertib and the taxane are administered for at least 1 cycle. In one embodiment, alisertib and the taxane are administered for at least 1, 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 11, or at least 12 cycles. In one embodiment, alisertib and the taxane are administered for at least 1 cycle. In one embodiment, alisertib and the taxane are administered for at least 2 cycles. In one embodiment, alisertib and the taxane are administered for at least 3 cycles. In one embodiment, alisertib and the taxane are administered for at least 4 cycles. In one embodiment, alisertib and the taxane are administered for at least 5 cycles. In one embodiment, alisertib and the taxane are administered for at least 6 cycles.

[0091] In some embodiments, the treatment period during which an agent is administered is then followed by a non-treatment period of a particular time duration, during which the therapeutic agents are not administered to the patient. This non-treatment period can then be followed by a series of subsequent treatment and non-treatment periods of the same or different frequencies for the same or different lengths of time. In some embodiments, the treatment and non-treatment periods are alternated. It will be understood that the period of treatment in cycling therapy may continue until the patient has achieved a complete response or a partial response, at which point the treatment may be stopped. Alternatively, the period of treatment in cycling therapy may continue until the patient has achieved a complete response or a partial response, at which point the period of treatment may continue for a particular number of cycles. In some embodiments, the length of the period of treatment may be a particular number of cycles, regardless of patient response. In some other embodiments, the length of the period of treatment may continue until the patient relapses.

[0092] For example, a certain amount of alisertib can be administered twice daily for 3 days followed by 11 days of non-treatment followed by 3 days of twice daily administration. In some embodiments, the treatment and non-treatment periods are alternated. In other embodiments, a

first treatment period in which a first amount of alisertib is administered can be followed by another treatment period in which a same or different amount of the same alisertib is administered. The second treatment period can be followed by other treatment periods. During the treatment and non-treatment periods, one or more additional therapeutic agents can be administered to the patient.

[0093] In one embodiment, the administration is on a 21-day dose schedule in which alisertib is administered twice-daily in a schedule of 7 days on followed by 14 days off. In some embodiments, a first treatment period in which a first amount of alisertib is administered can be followed by another treatment period in which a same or different amount of the same alisertib is administered. The second treatment period can be followed by other treatment periods. During the treatment and non-treatment periods, one or more additional therapeutic agents can be administered to the patient.

[0094] In one embodiment, the administration is on a 28-day dose schedule in which alisertib is administered twice-daily in a schedule of 3 days on followed by 4 days off. In one such embodiment, alisertib is administered twice-daily in a schedule of 3 days on followed by 4 days off repeated weekly. In one such embodiment, alisertib is administered twice-daily in a schedule of 3 days on followed by 4 days off repeated weekly for 1, 2, or 3 weeks. In one embodiment, alisertib is administered twice-daily in a schedule of 3 days on followed by 4 days off repeated weekly for 1 week. In one embodiment, alisertib is administered twice-daily in a schedule of 3 days on followed by 4 days off repeated weekly for 2 weeks. In one such embodiment, alisertib is administered twice-daily in a schedule of 3 days on followed by 4 days off repeated weekly for 3 weeks.

[0095] In one embodiment, the administration is on a 28-day dose schedule in which alisertib is administered twice-daily in a schedule of 3 days on followed by 4 days off, repeated weekly for three weeks concomitantly with the first dose of once-weekly paclitaxel, repeated weekly for 3 weeks (the twice-daily alisertib is given on days 1, 2, 3, 8, 9, 10, 15, 16, and 17 (*i.e.*; 1-3, 8-10, and 15-17); and the weekly paclitaxel is given on days 1, 8, and 15 of the 28-day schedule.

[0096] In another embodiment, the administration is on a 28-day dose schedule in which alisertib is administered twice-daily in a schedule of 2 days on followed by 5 days off, repeated weekly for three weeks concomitantly with the first dose of once-weekly paclitaxel, repeated weekly for 3 weeks (the twice-daily alisertib is given on days 1, 2, 8, 9, 15, and 16; and the weekly paclitaxel is given on days 1, 8, and 15 of the 28-day schedule).

[0097] In one embodiment, the administration is on a 28-day dose schedule in which alisertib is administered twice-daily in a schedule of 3 days on followed by 4 days off, repeated weekly for two weeks concomitantly with the first dose of once-weekly paclitaxel, repeated weekly for 3 weeks (the twice-daily alisertib is given on days 1, 2, 3, 8, 9, and 10; and the weekly paclitaxel is given on days 1, 8, and 15 of the 28-day schedule).

[0098] In another embodiment, the administration is on a 28-day dose schedule in which alisertib is administered twice-daily in a schedule of 3 days on followed by 11 days off, repeated once, concomitantly with the first and third dose of once-weekly paclitaxel, repeated weekly for 3 weeks (the twice-daily alisertib is given on days 1, 2, 3, 15, 16, and 17; and the weekly paclitaxel is given on days 1, 8, and 15 of the 28-day schedule).

[0099] In one embodiment, a compound disclosed herein is administered at an initial dose. In one embodiment, a compound disclosed herein is administered at an escalated dose from the initial dose. In one embodiment, a compound disclosed herein is administered at a reduced dose from the initial dose. In one embodiment, alisertib is administered at an escalated dose from the initial dose. In one embodiment, alisertib is administered at an initial dose of 20 mg per day and escalated to 120 mg per day. In one embodiment, alisertib is administered at an initial dose of 50 mg twice daily and reduced to 40 mg twice daily. In one embodiment, alisertib is administered at an initial dose of 40 mg twice daily and reduced to 20 mg twice daily. In one embodiment, alisertib is administered at an initial dose of 20 mg twice daily and reduced to 10 mg twice daily.

[00100] In one embodiment, a compound disclosed herein is administered at an initial dose. In one embodiment, a compound disclosed herein is administered at an escalated dose from the initial dose. In one embodiment, a compound disclosed herein is administered at a reduced dose

from the initial dose. In one embodiment, paclitaxel is administered at an initial dose of 60 mg/m² per day. In one embodiment, paclitaxel is administered at a reduced dose of about 50 mg/m² per day from the initial dose. In one embodiment, paclitaxel is administered at a reduced dose of about 40 mg/m² per day from the initial dose. In one embodiment, paclitaxel is administered at a reduced dose of about 20% from the initial dose. In one embodiment, paclitaxel is administered at a reduced dose of about 20% from the initial dose of 60 mg/m².

[00101] In one embodiment, alisertib is administered at an escalated dose from the initial dose. In one embodiment, paclitaxel is administered at a reduced dose from the initial dose. In one embodiment, alisertib is administered at an initial dose of 20 mg per day and escalated to 120 mg per day. In one such embodiment, paclitaxel is administered at an initial dose of 60 mg/m² per day. In one such embodiment, paclitaxel is administered at a reduced dose of about 50 mg/m² per day from the initial dose. In one embodiment, paclitaxel is administered at a reduced dose of about 40 mg/m² per day from the initial dose. In one embodiment, paclitaxel is administered at a reduced dose of about 20% from the initial dose. In one embodiment, paclitaxel is administered at a reduced dose of about 20% from the initial dose of 60 mg/m². In one embodiment, alisertib is administered at an initial dose of 20 mg per day and escalated to 120 mg per day and paclitaxel is administered at an initial dose of 60 mg/m² per day. In one embodiment, alisertib is administered at an initial dose of 20 mg per day and escalated to 120 mg per day and paclitaxel is administered at a reduced dose of about 50 mg/m² per day from the initial dose. In one embodiment, alisertib is administered at an initial dose of 20 mg per day and escalated to 120 mg per day and paclitaxel is administered at a reduced dose of about 40 mg/m² per day from the initial dose. In one embodiment, alisertib is administered at an initial dose of 20 mg per day and escalated to 120 mg per day and paclitaxel is administered at a reduced dose of about 20% from the initial dose of 60 mg/m².

[00102] In one embodiment, alisertib is administered at an initial dose of 50 mg twice daily and reduced to 40 mg twice daily. In one such embodiment, paclitaxel is administered at an initial dose of 60 mg/m² per day. In one embodiment, alisertib is administered at an initial dose

of 40 mg twice daily and reduced to 20 mg twice daily. In one such embodiment, paclitaxel is administered at an initial dose of 60 mg/m² per day. In one embodiment, alisertib is administered at an initial dose of 20 mg twice daily and reduced to 10 mg twice daily. In one such embodiment, paclitaxel is administered at an initial dose of 60 mg/m² per day.

[00103] In one embodiment, alisertib is administered at an initial dose of 50 mg twice daily and reduced to 40 mg twice daily and paclitaxel is administered at a reduced dose of about 50 mg/m² per day from the initial dose. In one embodiment, alisertib is administered at an initial dose of 40 mg twice daily and reduced to 20 mg twice daily and paclitaxel is administered at a reduced dose of about 50 mg/m² per day from the initial dose. In one embodiment, alisertib is administered at an initial dose of 20 mg twice daily and reduced to 10 mg twice daily and paclitaxel is administered at a reduced dose of about 50 mg/m² per day from the initial dose. In one embodiment, alisertib is administered at an initial dose of 50 mg twice daily and reduced to 40 mg twice daily and paclitaxel is administered at a reduced dose of about 40 mg/m² per day from the initial dose. In one embodiment, alisertib is administered at an initial dose of 40 mg twice daily and reduced to 20 mg twice daily and paclitaxel is administered at a reduced dose of about 40 mg/m² per day from the initial dose. In one embodiment, alisertib is administered at an initial dose of 20 mg twice daily and reduced to 10 mg twice daily and paclitaxel is administered at a reduced dose of about 40 mg/m² per day from the initial dose. In one embodiment, alisertib is administered at an initial dose of 50 mg twice daily and reduced to 40 mg twice daily and paclitaxel is administered at a reduced dose of about 20% from the initial dose. In one embodiment, alisertib is administered at an initial dose of 40 mg twice daily and reduced to 20 mg twice daily and paclitaxel is administered at a reduced dose of about 20% from the initial dose. In one embodiment, alisertib is administered at an initial dose of 20 mg twice daily and reduced to 10 mg twice daily and paclitaxel is administered at a reduced dose of about 20% from the initial dose.

[00104] Alisertib can be administered by any method known to one skilled in the art. For example, alisertib can be administered in the form of a composition, in one embodiment a

pharmaceutical composition of alisertib and a pharmaceutically acceptable carrier, such as those described herein. Preferably, the pharmaceutical composition is suitable for oral administration. In some embodiments, the pharmaceutical composition is a tablet for oral administration, such as an enteric coated tablet. Such tablets are described in US Publication No. 2010/0310651, which is hereby incorporated by reference in its entirety. In some other embodiments, the pharmaceutical composition is a liquid dosage form for oral administration. Such liquid dosage forms are described in US Publication No. 2011/0039826, hereby incorporated by reference. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[00105] The taxane (e.g., paclitaxel, nab-paclitaxel, or docetaxel) can be administered by any method known to one skilled in the art. For example, the taxane can be administered in the form of a composition, in one embodiment a pharmaceutical composition of a taxane and a pharmaceutically acceptable carrier, such as those described herein. In some embodiments, the pharmaceutical composition is a liquid dosage form, which can be administered via an intravenous route, such as intravenous injection or intravenous infusion. In one embodiment, paclitaxel is administered via intravenous injection. In another embodiment ABRAXANE® is administered via intravenous injection. Such pharmaceutical compositions are described in US Patent No. 6,096,331 and US Patent No. 6,506,405.

[00106] The term “pharmaceutically acceptable carrier” is used herein to refer to a material that is compatible with a recipient subject, preferably a mammal, more preferably a human, and is suitable for delivering an active agent to the target site without terminating the activity of the agent. The toxicity or adverse effects, if any, associated with the carrier preferably are commensurate with a reasonable risk/benefit ratio for the intended use of the active agent.

[00107] The terms “carrier”, “adjuvant”, or “vehicle” are used interchangeably herein, and include any and all solvents, diluents, and other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. *Remington: The*

Science and Practice of Pharmacy, 20th Ed., ed. A. Gennaro, Lippincott Williams & Wilkins, 2000 discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds described herein, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as disodium hydrogen phosphate, potassium hydrogen phosphate, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium hydroxide and aluminum hydroxide, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, pyrogen-free water, salts or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, and zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose, sucrose, starches such as corn starch and potato starch, cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate, powdered tragacanth; malt, gelatin, talc, excipients such as cocoa butter and suppository waxes, oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil, glycols such as propylene glycol and polyethylene glycol, esters such as ethyl oleate and ethyl laurate, agar, alginic acid, isotonic saline, Ringer's solution, alcohols such as ethanol, isopropyl alcohol, hexadecyl alcohol, and glycerol, cyclodextrins, lubricants such as sodium lauryl sulfate and magnesium stearate, petroleum hydrocarbons such as mineral oil and petrolatum. Coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00108] The pharmaceutical compositions can be manufactured by methods well known in the art such as conventional granulating, mixing, dissolving, encapsulating, lyophilizing, or emulsifying processes, among others. Compositions may be produced in various forms, including granules, precipitates, or particulates, powders, including freeze dried, rotary dried or spray dried powders, amorphous powders, tablets, capsules, syrup, suppositories, injections, emulsions, elixirs, suspensions or solutions. Formulations may optionally contain solvents, diluents, and other liquid vehicles, dispersion or suspension aids, surface active agents, pH modifiers, isotonic agents, thickening or emulsifying agents, stabilizers and preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired.

[00109] According to a preferred embodiment, the compositions disclosed herein are formulated for pharmaceutical administration to a mammal, preferably a human being.

[00110] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents such as phosphates or carbonates.

[00111] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules,

pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00112] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00113] Compositions for use in the method of the invention may be formulated in unit dosage form for ease of administration and uniformity of dosage. The expression “unit dosage form” as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. A unit dosage form for parenteral administration may be in ampoules or in multi-dose containers.

[00114] Kits and other articles of manufacture for treating proliferative diseases are also provided herein. In one embodiment, a kit is provided that comprises alisertib, as described herein; a taxane, or a pharmaceutically acceptable salt thereof, as described herein; and instructions. The kit may optionally further include the one or more additional therapeutic agents, as described herein. The instructions may indicate the disease state for which the kit is to be used, storage information, dosing information and/or instructions regarding how to administer alisertib, the taxane, and/or additional therapeutic agent or agents. The kit may also comprise packaging materials. The packaging material may comprise a container for housing the contents of the kit. The kit may also optionally comprise additional components, such as syringes for administration of the contents of the kit. The kit may comprise alisertib, the taxane, and/or additional therapeutic agent or agents in single or multiple dose forms.

[00115] In another embodiment, an article of manufacture is provided that comprises alisertib, as described herein; taxane, or a pharmaceutically acceptable salt thereof; and packaging materials. The article of manufacture may optionally further include the one or more additional therapeutic agents. The packaging material may comprise a container for housing the contents of the article of manufacture. The container may optionally comprise a label indicating the disease state for which the article is to be used, storage information, dosing information and/or instructions regarding how to administer alisertib, taxane, and/or additional therapeutic agent or agents. The article may also optionally comprise additional components, such as syringes for administration of the composition. The article may comprise alisertib, taxane, and/or additional therapeutic agent or agents in single or multiple dose forms.

[00116] A wide variety of therapeutic agents may have a therapeutically relevant added benefit in combination with alisertib and a taxane of the present disclosure. Combination therapies that comprise alisertib and a taxane disclosed herein with one or more other therapeutic agents can be used, for example, to: 1) enhance the therapeutic effect(s) of the methods disclosed herein and/or the one or more other therapeutic agents; 2) reduce the side effects exhibited by the methods disclosed herein and/or the one or more other therapeutic agents; and/or 3) reduce the

effective dose of alisertib and/or the taxane of the present disclosure and/or the one or more other therapeutic agents.

[00117] In some embodiments, the method disclosed herein comprises administration of alisertib and a taxane and an additional therapeutic agent, wherein the amounts of each agent are therapeutically effective when used in combination.

[00118] In certain embodiments, alisertib and a taxane are administered with the concomitant or sequential administration of cisplatin or doxorubicin. It will be appreciated that the therapy includes administration of the therapeutic agents concurrently or sequentially. Alternatively, the therapeutic agents can be combined into one composition which is administered to the patient.

[00119] Examples of therapeutic agents that may be used in combination with alisertib and a taxane of the present disclosure include, but are not limited to, anti-proliferative agents, anticancer agents, alkylating agents, antibiotic agents, antimetabolic agents, hormonal agents, plant-derived agents, and biologic agents. Examples of some of the above classes of additional therapeutic agents are listed below for purposes of illustration and not for purposes of limitation, as these examples are not all-inclusive. Many of the examples below could be listed in multiple classes of anti-cancer agents and are not restricted in any way to the class in which they are listed.

[00120] Alkylating agents are polyfunctional compounds that have the ability to substitute alkyl groups for hydrogen ions. Examples of alkylating agents include, but are not limited to, bischloroethylamines (nitrogen mustards, e.g. chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, uracil mustard), aziridines (e.g. thiotepa), alkyl alkane sulfonates (e.g. busulfan), nitrosoureas (e.g. carmustine, lomustine, streptozocin), nonclassic alkylating agents (altretamine, dacarbazine, and procarbazine), platinum compounds (carboplatin and cisplatin). These compounds react with phosphate, amino, hydroxyl, sulfhydryl, carboxyl, and imidazole groups. Under physiological conditions, these drugs ionize and produce positively charged ion that attach to susceptible nucleic acids and proteins, leading to cell cycle arrest and/or cell death. Combination therapy including a compound of the present disclosure and an

alkylating agent may have therapeutic synergistic effects on cancer and reduce side effects associated with these chemotherapeutic agents.

[00121] Antibiotic agents are a group of drugs that produced in a manner similar to antibiotics as a modification of natural products. Examples of antibiotic agents include, but are not limited to, anthracyclines (e.g. doxorubicin, daunorubicin, epirubicin, idarubicin and anthracenedione), mitomycin C, bleomycin, dactinomycin, plicatamycin. These antibiotic agents interfere with cell growth by targeting different cellular components. For example, anthracyclines are generally believed to interfere with the action of DNA topoisomerase II in the regions of transcriptionally active DNA, which leads to DNA strand scissions. Bleomycin is generally believed to chelate iron and forms an activated complex, which then binds to bases of DNA, causing strand scissions and cell death. Combination therapy including a compound of the present disclosure and an antibiotic agent may have therapeutic synergistic effects on cancer and reduce side effects associated with these chemotherapeutic agents.

[00122] Antimetabolic agents are a group of drugs that interfere with metabolic processes vital to the physiology and proliferation of cancer cells. Actively proliferating cancer cells require continuous synthesis of large quantities of nucleic acids, proteins, lipids, and other vital cellular constituents. Many of the antimetabolites inhibit the synthesis of purine or pyrimidine nucleosides or inhibit the enzymes of DNA replication. Some antimetabolites also interfere with the synthesis of ribonucleosides and RNA and/or amino acid metabolism and protein synthesis as well. By interfering with the synthesis of vital cellular constituents, antimetabolites can delay or arrest the growth of cancer cells. Examples of antimetabolic agents include, but are not limited to, fluorouracil (5-FU), floxuridine (5-FUdR), methotrexate, leucovorin, hydroxyurea, thioguanine (6-TG), mercaptopurine (6-MP), cytarabine, pentostatin, fludarabine phosphate, cladribine (2-CDA), asparaginase, and gemcitabine. Combination therapy including a compound of the present disclosure and an antimetabolic agent may have therapeutic synergistic effects on cancer and reduce side effects associated with these chemotherapeutic agents.

[00123] Hormonal agents are a group of drug that regulate the growth and development of their target organs. Most of the hormonal agents are sex steroids and their derivatives and analogs thereof, such as estrogens, androgens, and progestins. These hormonal agents may serve as antagonists of receptors for the sex steroids to down regulate receptor expression and transcription of vital genes. Examples of such hormonal agents are synthetic estrogens (e.g. diethylstilbestrol), antiestrogens (e.g. tamoxifen, toremifene, fluoxymesterol and raloxifene), antiandrogens (bicalutamide, nilutamide, and flutamide), aromatase inhibitors (e.g., aminoglutethimide, anastrozole and tetrazole), ketoconazole, goserelin acetate, leuprolide, megestrol acetate and mifepristone. Combination therapy including a compound of the present disclosure and a hormonal agent may have therapeutic synergistic effects on cancer and reduce sides effects associated with these chemotherapeutic agents.

[00124] Plant-derived agents are a group of drugs that are derived from plants or modified based on the molecular structure of the agents. Examples of plant-derived agents include, but are not limited to, vinca alkaloids (e.g., vincristine, vinblastine, vindesine, vinzolidine and vinorelbine), and podophyllotoxins (e.g., etoposide (VP-16) and teniposide (VM-26)). These plant-derived agents generally act as antimitotic agents that bind to tubulin and inhibit mitosis. Podophyllotoxins such as etoposide are believed to interfere with DNA synthesis by interacting with topoisomerase II, leading to DNA strand scission. Combination therapy including a compound of the present disclosure and a plant-derived agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[00125] Biologic agents are a group of biomolecules that elicit cancer/tumor regression when used alone or in combination with chemotherapy and/or radiotherapy. Examples of biologic agents include, but are not limited to, immuno-modulating proteins such as cytokines, monoclonal antibodies against tumor antigens, tumor suppressor genes, and cancer vaccines. Combination therapy including a compound of the present disclosure and a biologic agent may have therapeutic synergistic effects on cancer, enhance the patient's immune responses to

tumorigenic signals, and reduce potential side effects associated with this chemotherapeutic agent.

[00126] Cytokines possess profound immunomodulatory activity. Some cytokines such as interleukin-2 (IL-2, aldesleukin) and interferon have demonstrated antitumor activity and have been approved for the treatment of patients with metastatic renal cell carcinoma and metastatic malignant melanoma. IL-2 is a T-cell growth factor that is central to T-cell-mediated immune responses. The selective antitumor effects of IL-2 on some patients are believed to be the result of a cell-mediated immune response that discriminates between self and nonself. Examples of interleukins that may be used in conjunction with the compounds disclosed herein include, but are not limited to, interleukin 2 (IL-2), and interleukin 4 (IL-4), interleukin 12 (IL-12).

[00127] Interferons include more than 23 related subtypes with overlapping activities, all of the IFN subtypes are within the scope of the present disclosure. IFN has demonstrated activity against many solid and hematologic malignancies, the later appearing to be particularly sensitive.

[00128] Other cytokines that may be used in conjunction with the compounds disclosed herein include those cytokines that exert profound effects on hematopoiesis and immune functions. Examples of such cytokines include, but are not limited to erythropoietin, granulocyte-CSF (G-CSF, filgrastim or Neupogen®), and granulocyte, macrophage-CSF (sargramostim). These cytokines may be used in conjunction with a compound disclosed herein to reduce chemotherapy-induced myelopoietic toxicity.

[00129] Other immuno-modulating agents other than cytokines may also be used in conjunction with the compounds disclosed herein to inhibit abnormal cell growth. Examples of such immuno-modulating agents include, but are not limited to bacillus Calmette-Guerin, levamisole, and octreotide, a long-acting octapeptide that mimics the effects of the naturally occurring hormone somatostatin.

[00130] Tumor suppressor genes are genes that function to inhibit the cell growth and division cycles, thus preventing the development of neoplasia. Mutations in tumor suppressor genes cause the cell to ignore one or more of the components of the network of inhibitory signals,

overcoming the cell cycle check points and resulting in a higher rate of controlled cell growth—cancer. Examples of the tumor suppressor genes include, but are not limited to, DPC-4, NF-1, NF-2, RB, p53, WT1, BRCA1, and BRCA2.

[00131] RB codes for the pRB protein, a nuclear protein that is a major inhibitor of cell cycle. RB is involved in retinoblastoma as well as bone, bladder, small cell lung and breast cancer. P53 codes for p53 protein that regulates cell division and can induce apoptosis. Mutation and/or inactivation of p53 is found in a wide ranges of cancers, including SCLC. The tumor suppressor gene can be transferred into the tumor cells where it exerts its tumor suppressing functions. Combination therapy including a compound disclosed herein and a tumor suppressor may have therapeutic synergistic effects on patients suffering from SCLC.

[00132] Cancer vaccines are a group of agents that induce the body's specific immune response to tumors. Most of cancer vaccines under research and development and clinical trials are tumor-associated antigens (TAAs). TAA are structures (i.e. proteins, enzymes or carbohydrates) which are present on tumor cells and relatively absent or diminished on normal cells. By virtue of being fairly unique to the tumor cell, TAAs provide targets for the immune system to recognize and cause their destruction. Example of TAAs include, but are not limited to gangliosides (GM2), prostate specific antigen (PSA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) (produced by colon cancers and other adenocarcinomas, e.g. breast, lung, gastric, and pancreas cancer s), melanoma associated antigens (MART-1, gp100, MAGE 1,3 tyrosinase), papillomavirus E6 and E7 fragments, whole cells or portions/lysates of antologous tumor cells and allogeneic tumor cells.

[00133] An adjuvant may be used to augment the immune response to TAAs. Examples of adjuvants include, but are not limited to, bacillus Calmette-Guerin (BCG), endotoxin lipopolysaccharides, keyhole limpet hemocyanin (GKLH), interleukin-2 (IL-2), granulocyte-macrophage colony-stimulating factor (GM-CSF) and cytoxan, a chemotherapeutic agent which is believe to reduce tumor-induced suppression when given in low doses.

[00134] In certain embodiments, the one or more additional treatments is selected from radiation, chemotherapy, immunotherapy, or other targeted anticancer therapy.

[00135] *C. Treatment of SCLC with Alisertib and/or Combinations Thereof*

[00136] In one embodiment, provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib to a patient having SCLC, wherein the SCLC is c-Myc positive and/or has a retinoblastoma 1 gene (RB1) mutation, and/or has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is platinum sensitive SCLC. In one embodiment, the SCLC is platinum resistant or refractory SCLC. In one embodiment, the patient has limited stage SCLC. In one embodiment, the patient has extensive stage SCLC.

[00137] In one embodiment, provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and a taxane to a patient having SCLC, wherein the SCLC is c-Myc positive and/or has a retinoblastoma 1 gene (RB1) mutation, and/or has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is platinum sensitive SCLC. In one embodiment, the SCLC is platinum resistant or refractory SCLC. In one embodiment, the patient has limited stage SCLC. In one embodiment, the patient has extensive stage SCLC. In some such embodiments, the taxane is paclitaxel or nab-paclitaxel.

[00138] In one embodiment, provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and/or has a retinoblastoma 1 gene (RB1) mutation, and/or has a tumor protein p53 gene (TP53) mutation. In one embodiment, provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation. In one embodiment, the SCLC is platinum sensitive SCLC. In one embodiment, the SCLC is platinum resistant or refractory SCLC. In one embodiment, the patient has limited stage SCLC. In one embodiment, the patient has extensive stage SCLC. In some such embodiments, paclitaxel is nab-paclitaxel.

[00139] In one embodiment, provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is platinum sensitive SCLC. In one embodiment, the SCLC is platinum resistant or refractory SCLC. In one embodiment, the patient has limited stage SCLC. In one embodiment, the patient has extensive stage SCLC. In some such embodiments, paclitaxel is nab-paclitaxel.

[00140] In one embodiment, provided herein is method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC has a retinoblastoma 1 gene (RB1) mutation and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is platinum sensitive SCLC. In one embodiment, the SCLC is platinum resistant or refractory SCLC. In one embodiment, the patient has limited stage SCLC. In one embodiment, the patient has extensive stage SCLC. In some such embodiments, paclitaxel is nab-paclitaxel.

[00141] In one embodiment, provided herein is a method of treating small cell lung cancer (SCLC) comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation, and has a tumor protein p53 gene (TP53) mutation. In one embodiment, the SCLC is platinum sensitive SCLC. In one embodiment, the SCLC is platinum resistant or refractory SCLC. In one embodiment, the patient has limited stage SCLC. In one embodiment, the patient has extensive stage SCLC. In some such embodiments, paclitaxel is nab-paclitaxel.

[00142] In one embodiment, the RB1 mutation is any mutation selected from Table 2 or any combination thereof. In one embodiment, a patient has SCLC wherein the SCLC has one or more mutations selected from Table 2.

[00143] In one embodiment, the TP53 mutation is any mutation selected from Table 3 or any combination thereof. In one embodiment, a patient has SCLC wherein the SCLC has one or more mutations selected from Table 3. In one embodiment, the patient has SCLC wherein the

SCLC has one or more mutations selected from Table 2 and/or Table 3. In one embodiment, the patient has SCLC wherein the SCLC is c-Myc positive and/or has one or more mutations selected from Table 2. In one embodiment, the patient has SCLC wherein the SCLC is c-Myc positive and/or has one or more mutations selected from Table 3. In one embodiment, the patient has SCLC wherein the SCLC is c-Myc positive and/or has one or more mutations selected from Table 2 and/or Table 3.

[00144] In one embodiment, the c-Myc amplification or overexpression is determined by immunohistochemical analysis. In one embodiment, the c-Myc alteration is determined by immunohistochemical analysis.

[00145] In one embodiment, the RB1 mutation and/or TP53 mutation is determined by next-generation sequencing (NGS) analysis. Methods for determining c-Myc amplification or overexpression and/or the mutational analyses as described herein can be determined by any method known to one skilled in the art.

[00146] *D. Examples*

[00147] A retrospective analysis was conducted to evaluate the benefit of alisertib and paclitaxel over placebo and paclitaxel in patients with resistant or refractory SCLC and having SCLC that is c-Myc positive and/or has RB1 mutation and/or has TP53 mutation or a combination thereof.

[00148] *i. Study Design:*

[00149] A multicenter, randomized, double-blind, placebo controlled phase II trial enrolled patients across sites in the United States, Canada, and Europe. Patients were randomized 1:1 to receive either alisertib (40 mg by mouth twice daily for 3 weeks on days 1–3, 8–10, and 15–17) plus paclitaxel (60 mg/m² intravenously on days 1, 8, and 15) or placebo (by mouth twice daily as per alisertib) plus paclitaxel (80 mg/m² intravenously on days 1, 8, and 15) in 28-day cycles. The study enrolled patients at least 18 years old with a pathologically (histologically or cytologically) confirmed diagnosis of SCLC. Patients were required to have progressed within 180 days of last platinum dose, after receiving a standard platinum-based chemotherapy regimen

as first-line treatment, and to have measurable disease per the Response Evaluation Criteria in Solid Tumors version 1.1 within 2 weeks before randomization.

[00150] ii. *Key Inclusion/Exclusion Criteria*

[00151] Patients with mixed or combined small cell and non-small cell histology were eligible, as were those with treated brain metastases, provided that the lesions had been stable for ≥ 2 weeks (i.e., off steroids or on a stable dose of steroids) and patients were without neurologic dysfunction that would confound the evaluation of treatment-emergent neurologic and/or other adverse events. Key inclusion criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1, absolute neutrophil count $\geq 1500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, hemoglobin ≥ 9 g/dL, total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (ULN), serum alanine aminotransferase or aspartate aminotransferase $\leq 2.5 \times$ the institutional ULN ($< 5 \times$ if liver function test elevations were due to liver metastases), serum albumin $\geq$ the lower limit of normal, and creatinine $< 1.5 \times$ the institutional ULN or estimated creatinine clearance (using the Cockcroft–Gault formula) ≥ 30 mL/min for patients with creatinine levels above institutional limits. Patients could not previously have received any prior second-line therapy for relapsed or progressive small-cell lung cancer including retreatment with their original front-line regimen. No prior treatment with an Aurora A kinase inhibitor, pan-Aurora-targeted agent, paclitaxel, or any other taxane was permitted; prior treatment with any other investigational agent for relapsed disease was also not allowed. No previous irradiation to a site of measurable or evaluable disease was permitted, unless there was evidence of progression. Patients who had not fully recovered from surgery within 3 weeks (2 weeks for minor surgery), or radiation therapy within 2 weeks, of enrolment could not be included in the study.

[00152] Other key exclusion criteria included: prior history of grade ≥ 2 neurotoxicity that was not resolved to grade ≤ 1 ; symptomatic and/or progressive brain metastases or carcinomatous meningitis; treatment with clinically significant enzyme inducers within 14 days of the first dose of study drug or requirement for treatment with a proton pump inhibitor, H2 antagonist, or pancreatic enzymes; prior history of malignancy (within 3 years of the first dose of study drug or

with any residual disease); or any other severe acute or chronic medical or psychiatric condition that would make the patient unsuitable for the study (including uncontrolled diabetes or cardiovascular disease).

[00153] *iii. Assessment of c-Myc Expression*

[00154] c-Myc expression was assessed in archival tumor tissue samples (obtained prior to treatment), if available, by immunohistochemical analysis of formalin-fixed, paraffin-embedded tissue blocks. The c-Myc immunohistochemistry assay was a clinically validated test from PhenoPath (Seattle, WA, USA). Slides were incubated with the primary antibody (c-Myc Y69, Abcam, ab32072) and 3,3'-diaminobenzidine was used as the detection chromogen. Whole slide scans were scored by a trained pathologist for percent positive tumor cells and modal intensity (0, 1+, 2+, 3+).

[00155] *iv. Next-Generation Sequencing of Circulating Tumor DNA*

[00156] Baseline plasma samples were requested from all patients enrolled on the study. Plasma samples were collected and processed for next-generation sequencing (NGS) analysis of circulating tumor DNA (ctDNA). Patient samples were sequenced successfully, and mutations were called in and used for the correlative analysis. A custom PlasmaSelect-R™ (Personal Genome Diagnostics, Inc., Baltimore, MD, USA) targeted gene NGS panel was designed to evaluate 80 genes selected based on recurrent dysregulation in the small-cell lung cancer (SCLC) literature (Table 1). Genes involved in cell cycle regulation, NOTCH and phosphoinositide 3-kinase (PI3K) signaling, and histone modification, along with other known oncogenic activating mutations, were selected. Full coding regions were analyzed in all 80 genes, with copy number variations specifically analyzed for AURKA and MYC. Although CRIPAK was included on the gene panel, these results were excluded from the correlative analyses due to its status as a potential pseudogene. (Abascal F, *et al. Nucleic Acids Res.* 2018;46:7070-7084.) The assay targets a read coverage of 20,000× with sensitivity >0.1% for single nucleotide variants and >0.2% for amplifications.

[00157] *v. Statistical Methods*

[00158] Assuming a median PFS of 3 months for the placebo/paclitaxel arm, and that alisertib/paclitaxel could improve median PFS to 5 months (a 40% reduction of hazard), a minimum of 138 PFS events were required for the primary analysis (two-sided alpha: 0.05; power 85%). Patient enrollment was estimated based on 16 months of accrual (at 6–13 patients per month), 6 months of PFS follow-up, a dropout rate of about 15%, and 1:1 randomization to treatment.

[00159] PFS was tested using a two-sided stratified (by randomization stratification factors) log-rank test to compare treatment arms (alpha: 0.05). Hazard ratios (HRs) and 95% confidence intervals (CI) were estimated using a stratified Cox proportional hazard regression model, with treatment as the explanatory variable. Kaplan–Meier survival curves were provided for each arm. OS and other time-to-event endpoints were analyzed using similar methods. Death events were to be obtained from approximately 80% of patients in the ITT population or at 14 months after the last patient was randomized. Duration of response was summarized descriptively for responders only.

[00160] Stratified Cochran–Mantel–Haenszel tests were used to compare responses (overall response rate [complete response or partial response] and disease control rate) between arms, with logistic regression models used to estimate treatment effect.

[00161] Assessment of c-Myc expression by immunohistochemistry was analyzed in two ways: percentage of positive cells or a dichotomized readout converted to a binary variable (positive/negative) based on the modal intensity. For both methods, a Cox proportional hazard model was used to analyze PFS, with treatment and c-Myc expression as the main effects; their interaction was also assessed.

[00162] Interactions between genetic alterations and treatments (alisertib versus placebo) were tested with a Cox proportional hazards model for PFS and OS. The genetic alterations tested included: single gene mutations (mutant allele frequency [MAF] ≥ 0.01), pathway gene mutations, and mutation load. Pathway gene mutations were categorized based on the 876 MetaCore™ molecular signaling pathways and the status of pathway-level mutation was defined

by: 1) counting the number of mutated member genes in a given pathway, and 2) converting the count of mutated genes into a binary variable with ‘mutant’ and ‘wild-type’ variants (i.e., if the count was ≥ 1 , it was ‘mutant’; otherwise, it was ‘wild type’).

[00163] **Table 1.** PlasmaSELECT-R™ Custom Panel Designed for Small-Cell Lung Cancer

<i>PlasmaSELECT-R™ custom panel designed for SCLC</i>			
<i>ABL1</i>	<i>DIP2C</i>	<i>HNFI1A</i>	<i>RASSF8</i>
<i>ADCY1</i>	<i>DNMT3A</i>	<i>IDH1</i>	<i>RB1</i>
<i>ALK</i>	<i>EGFR</i>	<i>KDR</i>	<i>RBL1</i>
<i>APC</i>	<i>ELAVL2</i>	<i>KHSRP</i>	<i>RBL2</i>
<i>AR</i>	<i>EP300</i>	<i>KIAA1211</i>	<i>RGS7</i>
<i>ARID2</i>	<i>EPHA3</i>	<i>KIF21A</i>	<i>RIMS2</i>
<i>ATM</i>	<i>EPHA7</i>	<i>KIT</i>	<i>RUNX1T1</i>
<i>ATRAX</i>	<i>ERBB4</i>	<i>KMT2A</i>	<i>SATB2</i>
<i>AURKA*</i>	<i>ERICH3</i>	<i>KRAS</i>	<i>SMAD4</i>
<i>BCLAF1</i>	<i>FANCA</i>	<i>MET</i>	<i>SMARCB1</i>
<i>BRAF</i>	<i>FBN2</i>	<i>MYC*</i>	<i>SPHKAP</i>
<i>CDK6</i>	<i>FBXW7</i>	<i>NOTCH1</i>	<i>STK11</i>
<i>CNTNAP2</i>	<i>FGFR2</i>	<i>NOTCH2</i>	<i>SYNE1</i>
<i>COL11A1</i>	<i>FGFR3</i>	<i>NOTCH3</i>	<i>TMEM132D</i>
<i>COL22A1</i>	<i>FMN2</i>	<i>NOTCH4</i>	<i>TP53</i>
<i>COL4A2</i>	<i>FOXE1</i>	<i>NPM1</i>	<i>TP73</i>
<i>CREBBP</i>	<i>GNA11</i>	<i>PIK3CA</i>	<i>VHL</i>
<i>CRIPAK</i>	<i>GNAQ</i>	<i>PLSCR4</i>	<i>ZDBF2</i>
<i>CTNNA1</i>	<i>GRIK3</i>	<i>PTEN</i>	<i>ZNF217</i>
<i>CTNNB1</i>	<i>GRM8</i>	<i>RAD50</i>	<i>ZNF521</i>

Targeted gene panel designed to analyze genomic profiles of SCLC patients from ctDNA. An 80-gene panel was designed to cover major genes and key biological pathways previously implicated in SCLC, as well as additional genes included for discovery and correlative analyses (*denotes genes also analyzed for amplification events).

ctDNA, circulating tumor DNA; SCLC, small cell lung cancer.

[00164] *vi. Results*

[00165] *a. Correlative Analysis of Genetic Alterations in Relation to Clinical Efficacy*

[00166] The association between genetic alterations in ctDNA and clinical outcomes (PFS and OS) during treatment with alisertib/paclitaxel was assessed. The correlative analysis of clinical outcomes (PFS and OS) was assessed in relation to individual gene mutations, biological pathway gene mutations, and overall mutation load. PFS and OS were compared between the two treatment arms (alisertib/paclitaxel versus paclitaxel/placebo) with patients categorized based on the presence of mutations termed “mutant.” The mutations identified in a post-hoc analysis are listed in Table 2 and Table 3.

[00167] In patients with SCLC with c-Myc positive and RB1 mutations and in the patients with c-Myc positive and TP53 mutations, the combination of alisertib and paclitaxel gave a very strong statistically significant benefit in PFS and OS and the magnitude of the benefit is much larger than in patients with c-Myc positive alone.

[00168] Patients with c-Myc positive SCLC had median PFS = 4.63 versus 2.27 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.35 [95% CI: 0.16–0.78], $p = 0.006$. (FIG. 1A). In the same population, median OS = 7.20 versus 4.44 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.27 [95% CI: 0.11–0.70], $p = 0.004$. (FIG. 1B).

[00169] Patients with RB1 mutant SCLC had median PFS = 3.68 versus 1.84 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.41 [95% CI: 0.25–0.69], $p \leq 0.001$. (FIG. 2A). In the same population, median OS = 7.20 versus 4.47 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.47 [95% CI: 0.28–0.77], $p = 0.002$. (FIG. 2B).

[00170] Patients with c-Myc positive and RB1 mutant SCLC had median PFS = 5.54 versus 1.99 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.17 [95% CI: 0.05–0.64], $p = 0.003$. (FIG. 3A). In the same population, median OS = 9.56 versus

2.92 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.12 [95% CI: 0.03–0.55], $p = 0.002$. (**FIG. 3B**).

[00171] Patients with TP53 mutant SCLC had median PFS = 3.32 versus 2.17 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.60 [95% CI: 0.40–0.89], $p = 0.009$. (**FIG. 4A**). In the same population, median OS = 5.98 versus 5.13 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.74 [95% CI: 0.49–1.11], $p = 0.139$. (**FIG. 4B**).

[00172] Patients with c-Myc positive and TP53 mutant SCLC had median PFS = 4.63 versus 1.99 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.37 [95% CI: 0.14–0.94], $p = 0.027$. (**FIG. 5A**). In the same population, median OS = 9.56 versus 4.21 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.24 [95% CI: 0.08–0.76], $p = 0.009$. (**FIG. 5B**).

[00173] Patients with RB1 mutant and TP53 mutant SCLC had median PFS = 3.58 versus 2.10 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.43 [95% CI: 0.25–0.72], $p = 0.001$. (**FIG. 6A**). In the same population, median OS = 7.20 versus 4.44 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.48 [95% CI: 0.28–0.80], $p = 0.004$. (**FIG. 6B**).

[00174] Patients with RB1 mutant, TP53 mutant and c-Myc positive SCLC had median PFS = 5.54 versus 1.99 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.17 [95% CI: 0.05–0.64], $p = 0.003$. (**FIG. 7A**). In the same population, median OS = 9.56 versus 2.92 months in the alisertib/paclitaxel and placebo/paclitaxel arms, respectively (HR = 0.12 [95% CI: 0.03–0.55], $p = 0.002$. (**FIG. 7B**).

[00175] The data showed that SCLC patients with c-Myc positive, and/or RB1 mutant, and/or TP53 mutant SCLC showed a benefit from the treatment with alisertib and paclitaxel as compared to placebo/paclitaxel.

[00176] **Table 2.** List of RB1 mutations identified from patients in a post-hoc analysis.

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	RB1	chr13_49027160-49027160_C_G	576S>X	Substitution	Nonsense
SCLC	RB1	chr13_48939102-48939102_C_	P312Qfs*20	Deletion	Frameshift
SCLC	RB1	chr13_49033835-49033865_GCCTATCTC CGGCTAAATACACTTT GTGAAC_	Y659Ffs*8	Deletion	Frameshift
SCLC	RB1	chr13_48881532-48881538_ATGGAGT_	G86Wfs*23	Deletion	Frameshift
SCLC	RB1	chr13_49039497-49039505_AGATCAAGG _	827PRSR>P	Deletion	In-frame deletion
SCLC	RB1	chr13_49033916-49033916_C_T	685Q>X	Substitution	Nonsense
SCLC	RB1	chr13_48947603-48947603_C_G	397S>X	Substitution	Nonsense
SCLC	RB1	chr13_48955535-48955535_G_T	551E>X	Substitution	Nonsense
SCLC	RB1	chr13_49030438-49030438_C_	Q639Rfs*4	Deletion	Frameshift
SCLC	RB1	chr13_49027197-49027197_T_	A589Lfs*22	Deletion	Frameshift
SCLC	RB1	chr13_48951100-48951100_A_	D421Vfs*2	Deletion	Frameshift
SCLC	RB1	chr13_48919227-48919246_TCTTTAACTT ACTAAAAGAA_	F131Yfs*2	Deletion	Frameshift
SCLC	RB1	chr13_48916852-48916852_T_C	380+2T>C	Substitution	Splice site donor
SCLC	RB1	chr13_49037911-49037912_AG_	D718Pfs*2	Deletion	Frameshift
SCLC	RB1	chr13_49037866-49037866_G_C	2107-1G>C	Substitution	Splice site acceptor

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	RB1	chr13_48923130-48923130_T_C	193V>A	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_48916851-48916851_G_T	380+1G>T	Substitution	Splice site donor
SCLC	RB1	chr13_48954300-48954300_G_T	1422-1G>T	Substitution	Splice site acceptor
SCLC	RB1	chr13_49039451-49039464_ATATAAAAT TTCAG_	Y813Rfs*20	Deletion	Frameshift
SCLC	RB1	chr13_48919214-48919214_A_G	381-2A>G	Substitution	Splice site acceptor
SCLC	RB1	chr13_48941638-48941641_TCTT_	S318Nfs*13	Deletion	Frameshift
SCLC	RB1	chr13_49039455-49039455_A_T	814K>X	Substitution	Nonsense
SCLC	RB1	chr13_48953785-48953785_C_A	463S>X	Substitution	Nonsense
SCLC	RB1	chr13_48955471-48955471_C_G	529Y>X	Substitution	Nonsense
SCLC	RB1	chr13_48955562-48955562_T_C	560S>P	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_48916759-48916759_G_T	97E>X	Substitution	Nonsense
SCLC	RB1	chr13_49030387-49030387_G_	R621Lfs*2	Deletion	Frameshift
SCLC	RB1	chr13_48954198-48954198_C_T	467R>X	Substitution	Nonsense
SCLC	RB1	chr13_48951054-48951054_A_G	406N>D	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_48878161-48878161_G_A	38G>D	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_49030434-49030434_C_T	637Q>X	Substitution	Nonsense
SCLC	RB1	chr13_49027128-49027128_G_C	1696-1G>C	Substitution	Splice site acceptor

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	RB1	chr13_48951141-48951141_G_T	435G>X	Substitution	Nonsense
SCLC	RB1	chr13_48955447-48955459_TAATTTAAAAGCC_	N522Lfs*6	Deletion	Frameshift
SCLC	RB1	chr13_48951144-48951144_C_A	436Q>K	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_49027192-49027192_G_T	587E>X	Substitution	Nonsense
SCLC	RB1	chr13_49039348-49039348_C_A	778T>N	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_48951086-48951086_GAAAAGAGTGAAGGATATAGGA	Y424Efs*11	Insertion	Frameshift
SCLC	RB1	chr13_49030416-49030416_C	Q631Pfs*22	Insertion	Frameshift
SCLC	RB1	chr13_48951087-48951087_A_T	417K>X	Substitution	Nonsense
SCLC	RB1	chr13_48934171-48934171_A_G	209E>G	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_48947615-48947615_T_	S402Pfs*8	Deletion	Frameshift
SCLC	RB1	chr13_48951169-48951169_A_T	444Q>L	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_48954372-48954378_ATAGCAG_	1493_1498+1 delATAGCAG	Deletion	Frameshift
SCLC	RB1	chr13_48955381-48955381_A_T	1499-2A>T	Substitution	Splice site acceptor
SCLC	RB1	chr13_49039238-49039249_TTCCACCAGGGT_	2316_2325+2 delTTCCACCAGGGT	Deletion	Frameshift
SCLC	RB1	chr13_48955573-48955573_G_T	563W>C	Substitution	Nonsynonymous coding

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	RB1	chr13_49033905-49033905_G_A	681W>X	Substitution	Nonsense
SCLC	RB1	chr13_49030362-49030378_CCAAAGAAA AAAGGTTC_	P613Nfs*34	Deletion	Frameshift
SCLC	RB1	chr13_48934155-48934155_G_T	204E>X	Substitution	Nonsense
SCLC	RB1	chr13_49047527-49047527_G_A	2520+1G>A	Substitution	Splice site donor
SCLC	RB1	chr13_48951172-48951172_T_A	1332+2T>A	Substitution	Splice site donor
SCLC	RB1	chr13_48954299-48954299_A_G	1422-2A>G	Substitution	Splice site acceptor
SCLC	RB1	chr13_48939025-48939048_TTCAGGTGA AAAATGTTTATTCA_	288EVKNVY F>-	Deletion	In-frame deletion
SCLC	RB1	chr13_48937001-48937005_CAGAA_	N258Efs*11	Deletion	Frameshift
SCLC	RB1	chr13_48953760-48953760_C_T	455R>X	Substitution	Nonsense
SCLC	RB1	chr13_49033940-49033940_G_T	693E>X	Substitution	Nonsense
SCLC	RB1	chr13_49033932-49033932_A_G	690N>S	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_48934157-48934157__AGTAAACT CTCACCTCCCATGTTG CTCAAAGAACCATAT	204E>EVNS HLPCCSKN HI	Insertion	In-frame insertion
SCLC	RB1	chr13_48934159-48934159__TAAACTCTC ACCTCCCATGTTGCTC AAAGAACCA	L206Nfs*17	Insertion	Frameshift
SCLC	RB1	chr13_48936963-48936963_T_C	244I>T	Substitution	Nonsynonymous coding

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	RB1	chr13_49027156-49027159_CAA_T_	S576Rfs*34	Deletion	Frameshift
SCLC	RB1	chr13_48951166-48951166_C_G	443S>X	Substitution	Nonsense
SCLC	RB1	chr13_48937019-48937019_A_	I263*	Deletion	Frameshift
SCLC	RB1	chr13_48916799-48916799_T_C	110L>P	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_48916803-48916803_T_G	111D>E	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_48916836-48916836_A_C	122K>N	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_48937031-48937031_C_A	267L>I	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_49047494-49047494_A_G	2490-2A>G	Substitution	Splice site acceptor
SCLC	RB1	chr13_49039339-49039339_A_T	2326-2A>T	Substitution	Splice site acceptor
SCLC	RB1	chr13_48881525-48881526_TC_	S83Cfs*26	Deletion	Frameshift
SCLC	RB1	chr13_48881528-48881528_G_T	84V>L	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_49039206-49039206_C_T	762Q>X	Substitution	Nonsense
SCLC	RB1	chr13_49039161-49039161_G_T	747E>X	Substitution	Nonsense
SCLC	RB1	chr13_48878085-48878093_GCCGCCGCT_	I3AAA>-	Deletion	In-frame deletion
SCLC	RB1	chr13_48878091-48878091_G_A	15A>T	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_49027171-49027171_G_T	580E>X	Substitution	Nonsense
SCLC	RB1	chr13_49027183-49027183_G_	D584Ifs*27	Deletion	Frameshift

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	RB1	chr13_48955572-48955572_G_A	563W>X	Substitution	Nonsense
SCLC	RB1	chr13_48934194-48934194_C_T	217Q>X	Substitution	Nonsense
SCLC	RB1	chr13_49027162-49027162_A_T	577K>X	Substitution	Nonsense
SCLC	RB1	chr13_49039340-49039340_G_T	2326-1G>T	Substitution	Splice site acceptor
SCLC	RB1	chr13_48955394-48955394_C_T	504Q>X	Substitution	Nonsense
SCLC	RB1	chr13_48955538-48955538_C_T	552R>X	Substitution	Nonsense
SCLC	RB1	chr13_49027244-49027244_A_G	604D>G	Substitution	Nonsynonymous coding
SCLC	RB1	chr13_49027248-49027248_G_T	1814+1G>T	Substitution	Splice site donor
SCLC	RB1	chr13_48951156-48951156_G_T	440E>X	Substitution	Nonsense
SCLC	RB1	chr13_49039443-49039443_A_T	810K>X	Substitution	Nonsense
SCLC	RB1	chr13_49030473-49030474_TT_	F650Lfs*2	Deletion	Frameshift
SCLC	RB1	chr13_48934169-48934169_G_	E209Kfs*5	Deletion	Frameshift
SCLC	RB1	chr13_48878146-48878150_CAGAG_	E34Gfs*13	Deletion	Frameshift
SCLC	RB1	chr13_49039501-49039501_C_G	829S>X	Substitution	Nonsense
SCLC	RB1	chr13_48878162-48878162__C	E40Gfs*9	Insertion	Frameshift
SCLC	RB1	chr13_48934197-48934224_TTAATGCTA TGTGTCCTTGACTATT TTA_	M219Nfs*36	Deletion	Frameshift

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	RB1	chr13_48934200-48934200__AACTCTCACCTCCCATGTTGCTC	M219Nfs*53	Insertion	Frameshift
SCLC	RB1	chr13_48951105-48951105_G_T	423G>X	Substitution	Nonsense
SCLC	RB1	chr13_48919275-48919275_C_	A147Vfs*6	Deletion	Frameshift

[00177] Note: "X" is outdated HGVS nomenclature for "*" which references the introduction of a stop codon. For example, in patient with RB1 mutation 576S>X is outdated HGVS nomenclature that translates to current nomenclature as S576*.

[00178] **Table 3.** List of TP53 mutations identified from patients in a post-hoc analysis.

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	TP53	chr17_7578556-7578566_TGTAGGAAGAG_	376-12_376-2delCTCTTCCTACA	Deletion	Splice site acceptor
SCLC	TP53	chr17_7578394-7578394_T_C	179H>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577100-7577100_T_C	280R>G	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577058-7577058_C_A	294E>X	Substitution	Nonsense
SCLC	TP53	chr17_7578461-7578461_C_A	157V>F	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578266-7578266_T_A	195I>F	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577556-7577556_C_G	242C>S	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577142-7577142_C_T	266G>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577559-7577559_G_A	241S>F	Substitution	Nonsynonymous coding

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	TP53	chr17_7577099-7577099_C_G	280R>T	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578208-7578208_T_C	214H>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7576851-7576851_A_T	993+2T>A	Substitution	Splice site donor
SCLC	TP53	chr17_7578467-7578467_T_G	155T>P	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579350-7579367_AGCCCAGACGGAAACCGT_	107YGFR LGF>Y	Deletion	In-frame deletion
SCLC	TP53	chr17_7577566-7577566_T_C	239N>D	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578455-7578455_C_G	159A>P	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578466-7578466_G_T	155T>N	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578517-7578520_GCCA_	L137Pfs*32	Deletion	Frameshift
SCLC	TP53	chr17_7577130-7577146_AGCTGTTCCGTCCCAGT_	L265*	Deletion	Frameshift
SCLC	TP53	chr17_7578457-7578457_C_A	158R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577082-7577082_C_T	286E>K	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578190-7578190_T_C	220Y>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577556-7577556_C_A	242C>F	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577536-7577536_T_	R249Gfs*96	Deletion	Frameshift
SCLC	TP53	chr17_7578486-7578487_AT_	D148Vfs*32	Deletion	Frameshift

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	TP53	chr17_7577511-7577511_A_G	257L>P	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577108-7577108_C_T	277C>Y	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577095-7577095_G_T	281D>E	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577547-7577547_C_A	245G>V	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577114-7577114_C_T	275C>Y	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577142-7577142_C_T	266G>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577117-7577117_A_T	274V>D	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578394-7578394_T_A	179H>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579349-7579349_A_C	113F>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577082-7577082_C_A	286E>X	Substitution	Nonsense
SCLC	TP53	chr17_7577548-7577548_C_A	245G>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577120-7577120_C_T	273R>H	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7574003-7574003_G_	R342Efs*3	Deletion	Frameshift
SCLC	TP53	chr17_7578222-7578223_TC_	R209Kfs*6	Deletion	Frameshift
SCLC	TP53	chr17_7578530-7578530_A_C	134F>V	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578555-7578555_C_T	376-1G>A	Substitution	Splice site acceptor
SCLC	TP53	chr17_7578271-7578271_T_A	193H>L	Substitution	Nonsynonymous coding

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	TP53	chr17_7578208-7578208_T_C	214H>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577120-7577120_C_A	273R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578551-7578581_AGTACTG TAGGAAGAGGAA GGAGACAGAGTT_	376-27_379delAACTC TGTCTCCTTCC TCTTCCTACAG TACT	Deletion	Frameshift
SCLC	TP53	chr17_7578550-7578550_GGAAAG TCAGGGCACAAGT	P128Lfs*4	Insertion	Frameshift
SCLC	TP53	chr17_7577120-7577120_C_A	273R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577144-7577144_A_C	265L>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577085-7577085_C_A	285E>X	Substitution	Nonsense
SCLC	TP53	chr17_7578253-7578253_C_A	199G>V	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578479-7578479_G_A	151P>S	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579529-7579529_C_T	53W>X	Substitution	Nonsense
SCLC	TP53	chr17_7576928-7576928_T_C	920-2A>G	Substitution	Splice site acceptor
SCLC	TP53	chr17_7574009-7574009_T_	M340Cfs*5	Deletion	Frameshift
SCLC	TP53	chr17_7577574-7577574_T_C	236Y>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577082-7577082_C_A	286E>X	Substitution	Nonsense
SCLC	TP53	chr17_7577106-7577106_G_A	278P>S	Substitution	Nonsynonymous coding

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	TP53	chr17_7574035-7574035_T_C	994-2A>G	Substitution	Splice site acceptor
SCLC	TP53	chr17_7577141-7577141_C_T	266G>E	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579373-7579373_C_A	105G>V	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579395-7579395_G_A	98P>S	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577121-7577121_G_A	273R>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578463-7578463_C_G	156R>P	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577151-7577151_T_A	263N>Y	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577156-7577156__AAAACC AGGCTCCAT	783- 1_783insATGGA GCCTGGTTTT	Insertion	Splice site acceptor
SCLC	TP53	chr17_7578469-7578469_C_A	154G>V	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579455-7579455_C_A	78A>S	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7576890-7576890_T_	K319Rfs*26	Deletion	Frameshift
SCLC	TP53	chr17_7577609-7577609_C_A	673-1G>T	Substitution	Splice site acceptor
SCLC	TP53	chr17_7577535-7577535_C_A	249R>M	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578176-7578176_C_G	672+1G>C	Substitution	Splice site donor
SCLC	TP53	chr17_7578373-7578373_T_G	186D>A	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578369-7578382_ACCATCG CTATCTG_	548_559+2delCA GATAGCGATGG T	Deletion	Frameshift

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	TP53	chr17_7578370-7578370_C_G	559+1G>C	Substitution	Splice site donor
SCLC	TP53	chr17_7577535-7577535_C_A	249R>M	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578442-7578442_T_C	163Y>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577018-7577018_C_A	919+1G>T	Substitution	Splice site donor
SCLC	TP53	chr17_7577532-7577532_G_A	250P>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577046-7577046_C_A	298E>X	Substitution	Nonsense
SCLC	TP53	chr17_7574017-7574017_C_A	337R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7576918-7576918_TGGG	N310Tfs*28	Insertion	Frameshift
SCLC	TP53	chr17_7579375-7579375_C_A	104Q>H	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579374-7579374_C_A	105G>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578253-7578253_C_A	199G>V	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577538-7577538_C_A	248R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578461-7578461_C_A	157V>F	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578555-7578555_C_A	376-1G>T	Substitution	Splice site acceptor
SCLC	TP53	chr17_7577090-7577090_C_G	283R>P	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577108-7577108_C_T	277C>Y	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578555-7578555_C_T	376-1G>A	Substitution	Splice site acceptor

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	TP53	chr17_7578220-7578220_T_	N210Tfs*37	Deletion	Frameshift
SCLC	TP53	chr17_7577022-7577022_G_A	306R>X	Substitution	Nonsense
SCLC	TP53	chr17_7579310-7579310_A_T	375+2T>A	Substitution	Splice site donor
SCLC	TP53	chr17_7578534-7578534_C_G	132K>N	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577574-7577574_T_C	236Y>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578370-7578370_C_T	559+1G>A	Substitution	Splice site donor
SCLC	TP53	chr17_7578455-7578455_C_G	159A>P	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577534-7577534_C_A	249R>S	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577547-7577547_C_A	245G>V	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577106-7577106_G_A	278P>S	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579395-7579395_G_C	98P>A	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577538-7577538_C_A	248R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578268-7578268_A_C	194L>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578236-7578236_A_C	205Y>D	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578190-7578190_T_C	220Y>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578479-7578479_G_C	151P>A	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578443-7578443_A_G	163Y>H	Substitution	Nonsynonymous coding

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	TP53	chr17_7578235-7578235_T_C	205Y>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577058-7577058_C_A	294E>X	Substitution	Nonsense
SCLC	TP53	chr17_7577120-7577120_C_A	273R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578406-7578406_C_T	175R>H	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578273-7578273_C_A	192Q>H	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577548-7577548_C_A	245G>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578268-7578268_A_C	194L>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578407-7578407_G_A	175R>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578406-7578406_C_A	175R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578394-7578394_T_C	179H>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578555-7578555_C_A	376-1G>T	Substitution	Splice site acceptor
SCLC	TP53	chr17_7577538-7577538_C_T	248R>Q	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578394-7578394_T_C	179H>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578380-7578380_C_A	184D>Y	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578265-7578265_A_G	195I>T	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577114-7577114_C_T	275C>Y	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578190-7578190_T_G	220Y>S	Substitution	Nonsynonymous coding

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	TP53	chr17_7579355-7579356_AG_	L111Gfs*37	Deletion	Frameshift
SCLC	TP53	chr17_7578431-7578431_G_A	167Q>X	Substitution	Nonsense
SCLC	TP53	chr17_7577058-7577058_C_A	294E>X	Substitution	Nonsense
SCLC	TP53	chr17_7578394-7578394_T_C	179H>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577539-7577539_G_C	248R>G	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577538-7577538_C_T	248R>Q	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578271-7578271_T_C	193H>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578190-7578190_T_C	220Y>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579575-7579575_G_A	38Q>X	Substitution	Nonsense
SCLC	TP53	chr17_7577565-7577565_T_C	239N>S	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578503-7578503_C_T	143V>M	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578461-7578461_C_A	157V>F	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577120-7577120_C_T	273R>H	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7574017-7574017_C_A	337R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577120-7577120_C_A	273R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579836-7579836_C_A	74+3G>T	Substitution	Splice site donor
SCLC	TP53	chr17_7577142-7577142_C_G	266G>R	Substitution	Nonsynonymous coding

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	TP53	chr17_7578406-7578406_C_T	175R>H	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578212-7578212_G_A	213R>X	Substitution	Nonsense
SCLC	TP53	chr17_7578412-7578412_A_T	173V>E	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577082-7577082_C_T	286E>K	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7574029-7574029_C_A	333R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578290-7578290_C_A	560-1G>T	Substitution	Splice site acceptor
SCLC	TP53	chr17_7577036-7577036_G_A	301P>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577035-7577035_T_	S303Afs*42	Deletion	Frameshift
SCLC	TP53	chr17_7579358-7579358_C_A	110R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578371-7578371_C_T	187G>S	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577580-7577580_T_C	234Y>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577568-7577568_C_T	238C>Y	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577114-7577114_C_T	275C>Y	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578265-7578265_A_G	195I>T	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578203-7578203_C_A	216V>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577120-7577120_C_A	273R>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578413-7578413_C_A	173V>L	Substitution	Nonsynonymous coding

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	TP53	chr17_7578271-7578271_T_C	193H>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578203-7578203_C_A	216V>L	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577580-7577580_T_C	234Y>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578224-7578224_T_A	209R>X	Substitution	Nonsense
SCLC	TP53	chr17_7578200-7578200_C_	V217Wfs*30	Deletion	Frameshift
SCLC	TP53	chr17_7577536-7577536_T_C	249R>G	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577105-7577105_G_C	278P>R	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577097-7577097_C_T	281D>N	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579437-7579440_CCGC_	A83Pfs*39	Deletion	Frameshift
SCLC	TP53	chr17_7579485-7579485_C_A	68E>X	Substitution	Nonsense
SCLC	TP53	chr17_7578455-7578455_C_G	159A>P	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577120-7577120_C_T	273R>H	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578392-7578392_C_A	180E>X	Substitution	Nonsense
SCLC	TP53	chr17_7578246-7578246_C_A	201L>F	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7573988-7573988_C_A	347A>S	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579414-7579414_C_A	91W>C	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578469-7578469_C_A	154G>V	Substitution	Nonsynonymous coding

Tumor Type	Gene Symbol	Nucleotide Position (Genomic hg19)	Amino Acid (Protein)	Mutation Type	Consequence
SCLC	TP53	chr17_7574003-7574003_G_A	342R>X	Substitution	Nonsense
SCLC	TP53	chr17_7578290-7578290_C_T	560-1G>A	Substitution	Splice site acceptor
SCLC	TP53	chr17_7577539-7577539_G_A	248R>W	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577120-7577120_C_T	273R>H	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7579467-7579467_C_A	74A>S	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578407-7578407_G_C	175R>G	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578453-7578453_G_	M160Wfs*10	Deletion	Frameshift
SCLC	TP53	chr17_7578454-7578454_G_A	159A>V	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577094-7577094_G_A	282R>W	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577120-7577120_C_G	273R>P	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577018-7577018_C_A	919+1G>T	Substitution	Splice site donor
SCLC	TP53	chr17_7577120-7577120_C_T	273R>H	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577497-7577497_A_T	782+2T>A	Substitution	Splice site donor
SCLC	TP53	chr17_7574002-7574002_C_G	342R>P	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7578503-7578503_C_T	143V>M	Substitution	Nonsynonymous coding
SCLC	TP53	chr17_7577142-7577142_C_G	266G>R	Substitution	Nonsynonymous coding

[00179] Note: "X" is outdated HGVS nomenclature for "*" which references the introduction of a stop codon. For example, in patient with RB1 mutation 576S>X is outdated HGVS nomenclature that translates to current nomenclature as S576*.

[00180] The examples set forth above are provided to give those of ordinary skill in the art with a complete disclosure and description of how to make and use the claimed embodiments, and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference.

CLAIMS:

1. A method of treating small cell lung cancer (SCLC), comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and has a retinoblastoma 1 gene (RB1) mutation.
2. A method of treating small cell lung cancer (SCLC), comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive and has a tumor protein p53 gene (TP53) mutation.
3. A method of treating small cell lung cancer (SCLC), comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC has a retinoblastoma 1 gene (RB1) mutation and has a tumor protein p53 gene (TP53) mutation.
4. A method of treating small cell lung cancer (SCLC), comprising administering alisertib and paclitaxel to a patient having SCLC, wherein the SCLC is c-Myc positive, has a retinoblastoma 1 gene (RB1) mutation and has a tumor protein p53 gene (TP53) mutation.
5. The method of any one of claims 1 to 4, wherein the SCLC is platinum resistant or refractory SCLC.
6. The method of any one of claims 1 to 4, wherein the SCLC is platinum sensitive SCLC.
7. The method of any one of claims 1 to 6, wherein the c-Myc positive is determined by immunohistochemical analysis.
8. The method of any one of claims 1 to 6, wherein the RB1 mutation and/or TP53 mutation is determined by next-generation sequencing (NGS) analysis.
9. The method of any one of claims 1 to 8, wherein the alisertib is administered before administration of the paclitaxel.

10. The method of any one of claims 1 to 8, wherein the alisertib is administered during administration of the paclitaxel.
11. The method of any one of claims 1 to 8, wherein the alisertib is administered after administration of the paclitaxel.
12. The method of any one of claims 1 to 8, wherein the paclitaxel is administered before administration of the alisertib.
13. The method of any one of claims 1 to 8, wherein the paclitaxel is administered during administration of the alisertib.
14. The method of any one of claims 1 to 8, wherein the paclitaxel is administered after administration of the alisertib.
15. The method of any one of claims 1 to 14, wherein the alisertib is administered orally at a dose of about 20 mg to about 40 mg.
16. The method of claim 15, wherein the alisertib is administered orally at a dose of about 20 mg.
17. The method of claim 15, wherein the alisertib is administered orally at a dose of about 30 mg.
18. The method of claim 15, wherein the alisertib is administered orally at a dose of about 40 mg.
19. The method of any one of claims 1 to 18, wherein the paclitaxel is administered at a dose of about 60 mg/m² intravenously.
20. The method of any one of claims 1 to 19, wherein the alisertib is administered on days 1-3, 8-10, and 15-17 of a 28-day treatment cycle.

21. The method of claim 20, wherein the alisertib is administered twice daily.
22. The method of claim 20, wherein the alisertib is administered twice daily for three weeks as a part of a 28 day treatment cycle.
23. The method of any one of claims 1 to 22, wherein the paclitaxel is administered on days 1, 8, and 15 of a 28-day treatment cycle.
24. The method of any one of claims 1 to 23, wherein the alisertib and paclitaxel are administered for at least 1 to 12 cycles.
25. The method of any one of claims 1 to 24, wherein the alisertib and paclitaxel are administered for at least 2 cycles.
26. The method of any one of claims 1 to 25, wherein the alisertib and paclitaxel are administered for at least 6 cycles.
27. The method of any one of claims 1 to 26, wherein the paclitaxel is nab-paclitaxel.
28. The method of any one of claims 1 to 27, comprising administering a prophylactically effective amount of Granulocyte-Colony-Stimulating Factor (G-CSF).