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| **Official Title:** | A PHASE I/II STUDY OF BOMEDEMSTAT COMBINED WITH MAINTENANCE IMMUNOTHERAPY FOR PATIENTS WITH NEWLY DIAGNOSED EXTENSIVE STAGE SMALL CELL LUNG CANCER (ES-SCLC) |
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# A PHASE I/II STUDY OF BOMEDEMSTAT COMBINED WITH MAINTENANCE IMMUNOTHERAPY FOR PATIENTS WITH NEWLY DIAGNOSED EXTENSIVE STAGE SMALL CELL LUNG CANCER (ES-SCLC)

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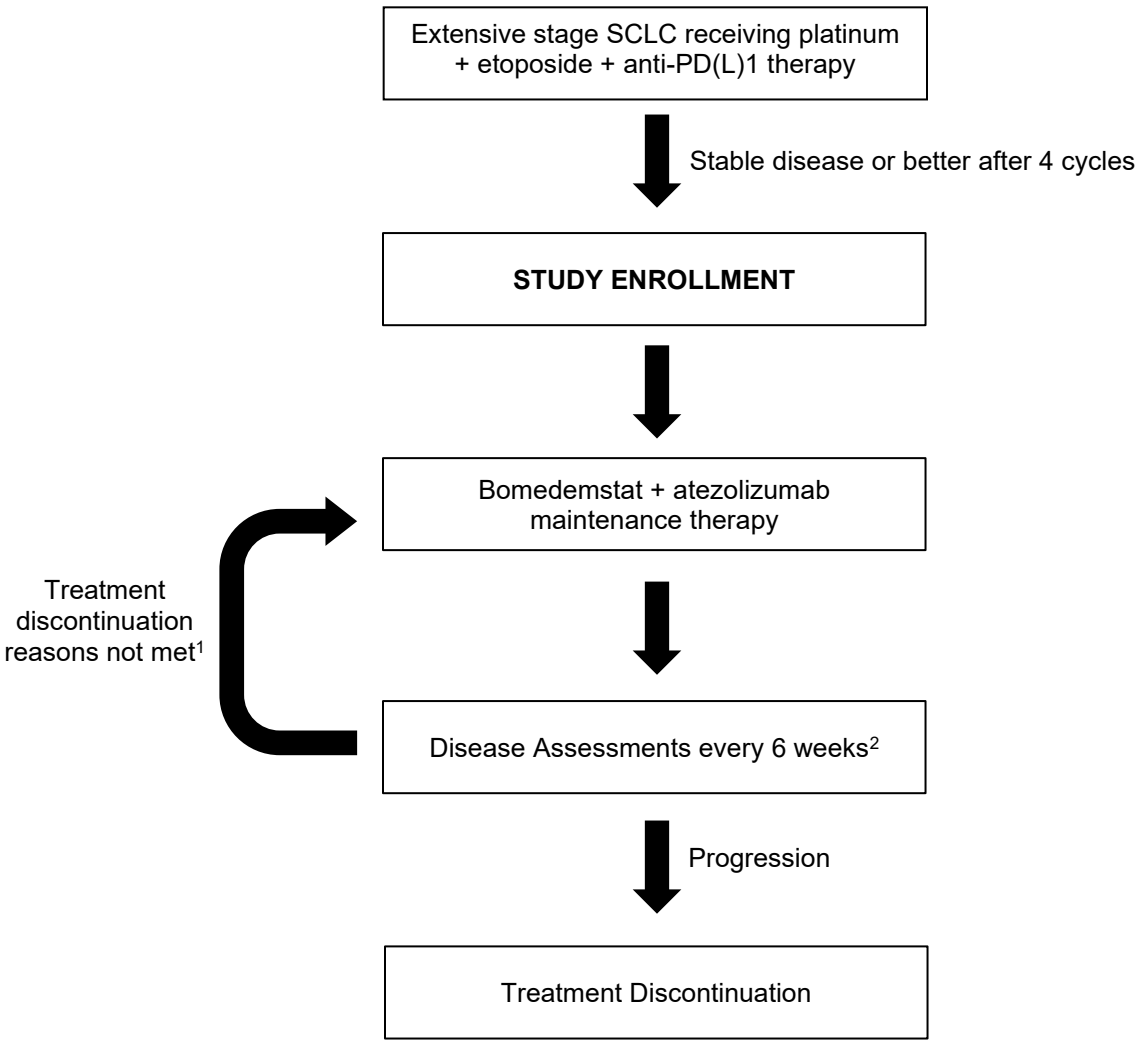
**SCHEMA**




1. Patients should receive study treatment until one of the treatment discontinuation reasons is met. Treatment discontinuation reasons are listed in Section 6.6.

2. Disease assessments can be made within 7 days of the actual specified interval (e.g. 6 weeks +/- 7 days). After 24 weeks of study treatment, disease assessments can be collected every 9 weeks +/- 7 days at the discretion of the investigator.

## 1.0 OBJECTIVES

To evaluate the addition of bomedemstat to standard of care (SOC) maintenance atezolizumab following first line platinum-etoposide and immune checkpoint inhibitor therapy.

### 1.1 Primary Objectives

1. Evaluate the percentage of patients alive and progression-free six months after initiating maintenance therapy with bomedemstat and atezolizumab.

2. Evaluate the safety and tolerability of maintenance therapy with bomedemstat and atezolizumab.

### 1.2 Secondary Objectives

1. Evaluate overall survival (OS).

### 1.3 Additional Objectives

1. Evaluate the objective response rate in patients with measurable disease at the time of study enrollment.

2. Collect blood and tumor tissue for correlative studies.

## 2.0 BACKGROUND

### 2.1 Newly Diagnosed Extensive Stage Small Cell Lung Cancer (ES-SCLC)

Small cell lung cancer is an aggressive and highly lethal neuroendocrine neoplasm that represents approximately 15% of all lung cancer in the United States[1]. SCLC is usually metastatic at initial presentation and while induction chemotherapy leads to radiographic response in most patients, disease progression is often rapid and eventually occurs in virtually all patients. Following the onset of disease progression, treatment options are limited and outcomes are poor.

Based on the remarkable activity in other tumor types and the high mutation burden in SCLC due to tobacco exposure, immune checkpoint inhibitors (ICIs) have been enthusiastically tested in clinical trials at various points in the natural history of SCLC[2]. However, in contrast to non-small cell lung cancer (NSCLC) and other tumor types with high mutation burden, results in SCLC have been modest at best. The Phase III trials IMpower133[3] and CASPIAN[4] reported a median overall survival (OS) benefit of approximately two months with the addition of ICI to first line chemotherapy. Atezolizumab and durvalumab both received FDA approval for this indication, changing the SOC for newly diagnosed ES-SCLC patients. Despite this, the median overall survival of patients with ES-SCLC remains extremely poor at 12-13 months. This had led to several recent studies attempting to improve both the response to ICI as well as second line therapy options. The addition of an anti-CTLA4 antibody to an anti-PD1-containing regimen did not lead to improved outcomes in either first[5] or later[6] lines of therapy. Lurbinectedin received accelerated approval in 2020 based on an uncontrolled Phase II study demonstrating a response rate of 35% in the second line, but persistently low OS at 9.3 months[7]. There remains an unmet need to identify novel therapeutics with activity in SCLC, as well as a need to elucidate rational biomarkers of patient subgroups with elevated probability of benefit[8].

### 2.2 LSD1 Demethylase

LSD1, also known as KDM1A, is an enzyme that plays a critical role in the regulation of gene expression via both its enzymatic activity and through interaction with partner proteins. Enzymatically, LSD1 removes

mono- and dimethyl groups from histone (H) H3 at critical lysines (K), K4 and K9[9]. Methylation of histone H3K4 and H3K9 are post-translational modifications associated with changes in the confirmation of chromatin, the highly ordered complex of genomic DNA and associated proteins[10,11]. Changes in chromatin structure influence the accessibility of template DNA to the core transcriptional machinery, namely the RNA polymerase complex and key transcription factors (TFs), thereby influencing rates of gene transcription and subsequent protein synthesis[10,11].

LSD1 can also influence the local chromatin state through its interaction with partner proteins. Many TFs, both activators such as V-Myb Avian Myeloblastosis Viral Oncogene Homolog (MYB) and steroid hormone receptors, as well as repressors such as growth factor independence 1 transcription repressor (GFI1) and RE-1 silencing transcription factor (REST), recruit LSD1 to specific genomic locations[12-14]. LSD1 is part of a larger protein complex, also containing Co-RE-1 silencing transcription factor (CoREST) or nucleosome remodeling and histone deacetylase (NuRD), which dictates the cell- and site-specific chromatin remodeling[15,16]. These complexes may also include DNA methyltransferase 1 (DNMT1) and histone deacetylases 1, 2 or 3 (HDAC1, 2, or 3), all of which contribute to maintaining or modifying the epigenetic state at that genomic site[17,18]. Thus, an important property of LSD1 beyond its own enzymatic activity is its function as a scaffold for other proteins and epigenetic enzymes that are co-recruited to genomic sites. Likewise, LSD1 bound to specific sites precludes the binding of other factors that may influence transcription. LSD1 thereby regulates the epigenetic state of the cell by influencing the local state of chromatin at key lineage-defining genes via both enzymatic and non-enzymatic mechanisms.

### 2.3 Rationale for LSD1 Inhibition in SCLC

SCLC does not harbor frequent mutations in “druggable” oncogenic drivers or tumor suppressors[19-21]. Instead, this neuroendocrine tumor type co-opts the same transcriptional programs necessary for normal lung neuroendocrine cell development to sustain tumor cell growth. Achaete-scute homolog 1 (ASCL1) is a transcription factor that promotes neuroendocrine transcriptional programs[22,23], and the deletion of *ASCL1* strongly suppresses tumorigenesis in a genetically engineered mouse model of SCLC[22]. During lung development, NOTCH signaling negatively regulates ASCL1[23], and the activation of NOTCH family members also potently suppresses SCLC in mouse models[19]. Knowledge of these genetic dependencies has not had a clinical impact on the treatment of SCLC given the challenges of activating NOTCH or suppressing ASCL1 using conventional pharmacological approaches.

SCLC also exhibits frequent mutations in chromatin-regulating genes[19-21], leading to efforts to target the altered epigenetic landscapes of SCLC for therapeutic vulnerabilities. LSD1 is very highly expressed in SCLC tumors and cell lines. In a screen of >150 cancer cell lines across a variety of tumor types, the LSD1 inhibitor GSK2879552 (GlaxoSmithKline) led to inhibition of proliferation in cell lines from two cancer types: acute myelogenous leukemia (AML) and SCLC[24]. In AML, LSD1 inhibition has been associated with pro-differentiation phenotypes[25] and LSD1 inhibitors are being tested in AML clinical trials[26,27]. LSD1 is also a potential therapeutic target for solid tumors, especially SCLC and other neuroendocrine tumors, and LSD1 inhibitors have been moved into Phase 1 trials that include SCLC patients (e.g., Clinical Trial IDs NCT02712905, NCT02875223, and NCT02034123)[28].

Despite multiple studies identifying LSD1 inhibitors as potently growth suppressive to SCLC pre-clinical models, the mechanism of action had not been elucidated until recently, when variable sensitivity to LSD1 inhibition in a panel of PDX models was exploited by scientists in the MacPherson lab at the Fred Hutchinson Cancer Center[29]. In brief, the LSD1 inhibitor ORY1001 showed heterogeneous tumor inhibitory effects in a panel of seven PDX models of SCLC, with one model (FHSC04, which was derived from a patient with chemo-resistant disease) exhibiting complete tumor regression with LSD1 inhibitor monotherapy. Molecular analyses of FHSC04 tumors that had been exposed to a short duration of LSD1 inhibitor therapy showed strong upregulation of the NOTCH pathway, including NOTCH1, NOTCH2, and target genes *HES1*, *HEY1* and *REST*[29]. While NOTCH acts as an oncogene in some cancer types, expression of active NOTCH1 suppressed SCLC in mouse models[19] and NOTCH1 is the target of inactivating mutations in SCLC[19], suggesting that NOTCH1 may be a SCLC tumor suppressor. NOTCH1

activation also results in suppression of the pivotal SCLC transcription factor ASCL1[30,31]. ORY1001 treatment induced a sharp reduction in ASCL1 protein levels in the FHSC04 model[29]. Activation of NOTCH causing suppression of ASCL1 could explain rapid tumor regression, as ASCL1 is critical for SCLC oncogenesis, with deletion of ASCL1 strongly suppressing SCLC in mouse models[22]. These mechanistic studies established robust activation of the NOTCH pathway and striking suppression of the transcription factor ASCL1 in response to pharmacologic inhibition of LSD1[29]. Although these changes were greatest in the PDX model that was most sensitive to the LSD1 inhibitor, some level of activation of NOTCH signaling and ASCL1 suppression in response to LSD1 inhibition was commonly seen in the tested models[29], suggesting that LSD1 inhibition alone could exert meaningful anti-tumor activity in a considerable fraction of patients with SCLC.

### 2.4 Existing Clinical Data on LSD1 Inhibition in SCLC

A clinical trial describing monotherapy with the LSD1 inhibitor GSK2879552 in patients with relapsed or refractory SCLC was recently reported[28]. In this multicenter single-arm Phase I dose-escalation/-expansion trial, 29 patients were assigned to one of nine dose cohorts. As expected, thrombocytopenia was the most common dose-limiting toxicity, with Grade 3 or higher thrombocytopenia occurring in 10 patients (35%). Other recurrent Grade 3 or higher toxicities were anemia (1 patient), neutropenia (2 patients), asthenia (2 patients), and encephalopathy (3 patients, one of which was grade 5). Eight patients underwent dose reduction due to thrombocytopenia and seven of those eight were receiving a dose of 2 mg daily or higher. Ten of the 29 patients on study received a dose of less than 2 mg daily. The disease control rate at week 16 was 14% (4 of 29 patients). Of the 4 patients experiencing disease control at 16 weeks, three were receiving a dose of 2 mg daily or higher.

Four patients on the study experienced encephalopathy: one at grade 2, two at grade 3, and one at grade 5. Encephalopathy was not associated with distinctive imaging findings or a specific pathophysiology. In total, six drug-related serious adverse events were deemed to have occurred, of which four were encephalopathy. After three study holds due to encephalopathy adverse events, the decision was made to halt the study due to unfavorable risk-benefit profile.

LSD1 is known to play a key role in neuronal differentiation and gene expression regulation[32], and preclinical investigation revealed that GSK2879552 does cross the blood-brain barrier, suggesting a possible mechanistic explanation for the encephalopathy observed. Clinical studies of other LSD1 inhibitors that are not known to penetrate the central nervous system (CNS), such as ORY-1001[33] and bomedemstat, have not identified encephalopathy as a drug-related adverse event. It is therefore likely that a lack of CNS penetration is a necessary attribute of a clinically tractable LSD1 inhibitor. Furthermore, it is not possible to appreciate the anti-tumor efficacy of LSD1 inhibitor therapy in SCLC based on the described experience with GSK2879552 because a limited number of patients were treated at higher dose levels before the study was halted.

### 2.5 Possible Synergy Between LSD1 Inhibition and Immune Checkpoint Inhibition

LSD1 expression is found in many tumor types and it has been proposed that LSD1 activity may be oncogenic through a variety of mechanisms, including direct repression of canonical tumor suppressor genes as well as establishment of a more “plastic” (permissive) epigenetic state that permits adaptive activation of various tumorigenic pathways including stemness and pro-proliferative gene expression programs[34]. More recently, it has become clear that LSD1 is involved in regulating the immune tumor microenvironment, and multiple lines of evidence now suggest that LSD1 inhibition could meaningfully potentiate the activity of immune checkpoint inhibitors in multiple tumor types, including (and, perhaps, especially) SCLC.

Although not focused on SCLC, studies in multiple immunocompetent pre-clinical model systems have established a role for LSD1 in regulating tumor cell inflammatory gene expression and have suggested that

LSD1 inhibition can potentiate immune checkpoint inhibitor therapy[35,36]. Tumors in mice treated with anti-PD-1 antibody alone grew unabated whereas the addition of pharmacologic[36] or genetic[35] inhibition of LSD1 was associated with dramatic suppression of tumor growth. Mechanistic studies revealed several lines of evidence in support of this phenotype. LSD1 inhibition led to de-repression of silenced retroviral elements in the cellular genome and suppression of several RNA-induced silencing complex (RISC) components[35]. The net result of these changes was markedly increased accumulation of double-stranded RNA (dsRNA) in the cytoplasm, which was sensed by intracellular pattern recognition receptors and activated a pro-immunogenic interferon signaling cascade[35]. LSD1 inhibition therefore led to increased expression of pro-immunogenic and T cell-attracting chemokines such as CXCL9 and CXCL10[35]. Methylation patterns at the promoters of these key immunogenic genes were also altered, suggesting that LSD1 might also directly target these genes to maintain an immunosuppressive state in the unperturbed cancer cell[35]. These studies were carried out in tumor models that were poorly immunogenic at baseline, highlighting the potential for LSD1 inhibition to improve the efficacy of immunotherapy in contexts where it has not historically provided substantial benefit. Gene expression profiling in patient tumors also revealed a negative correlation between LSD1 expression and levels of pro-inflammatory gene transcripts, further supporting an immunosuppressive role for LSD1[35,36]. LSD1 inhibition is therefore an appealing strategy to boost anti-tumor immunity and response to immune checkpoint inhibition in patients, but this has not yet been tested in clinical trials.

More recently, additional evidence has emerged to support the potentially immunogenic role of LSD1 inhibition in SCLC. It was first observed almost forty years ago that SCLC cell lines exhibited defects in antigen presentation[37], and this phenomenon has been proposed as a potential explanation for the modest and heterogeneous efficacy of immunotherapy in patients with SCLC. Still, it was not clear whether antigen presentation machinery (APM) defects were correlated with other genetic or epigenetic features of SCLC. Multiple recent studies of SCLC patients and model systems have linked reduced expression of canonical neuroendocrine (NE) genes (such as ASCL1) and increased expression of the NOTCH pathway to increased intra-tumoral inflammatory gene expression signatures and, critically, improved outcomes after exposure to immune checkpoint inhibitors[38-42]. Indeed, increased NOTCH pathway activity is associated with recovery of APM expression and function, and overexpression of a NOTCH pathway member induced recovery of APM expression in a SCLC model[42]. As discussed above, the MacPherson lab has shown that LSD1 inhibition consistently leads to downregulation of NE genes and upregulation of NOTCH signaling in a spectrum of SCLC models. LSD1 is therefore a promising candidate therapeutic target to potentiate the activity of immunotherapy in SCLC. Indeed, in unpublished data, the MacPherson lab has shown that LSD1 inhibition synergizes with immune checkpoint blockade in an immunocompetent murine model.

### 2.6 Bomedemstat

Bomedemstat (formerly IMG-7289) is an orally available, irreversible inhibitor of LSD1 which demonstrates activity against LSD1 in human AML cells at concentrations of less than 5 nM. Irreversible inhibitors of LSD1 include tranylcypromine (TCP) which has been used for the treatment of depression for decades. The targets of TCP therapy, however, include all FAD-dependent monoamine oxidases (MAOs) in addition to LSD1. TCP inactivates LSD1 in a manner identical to its action on MAO-A and MAO-B because these three enzymes share a similar oxidative chemistry. Bomedemstat, however, inhibits MAO-A with an $IC_{50}$ of ~27 uM and MAO-B with an $IC_{50}$ of ~34 uM, thereby exhibiting a high degree (>4000-fold) of selectivity for LSD1. Pharmacokinetic studies in mouse, rat and dog and pharmacokinetic modeling in human systems suggest that once-daily dosing in humans would achieve therapeutic exposures without significant drug accumulation. In the treatment of more than 160 patients in completed or ongoing Phase 2 studies, a single case of encephalopathy has occurred; no other major safety signals have been observed[43,44].

### 2.7 Bomedemstat Dose Justification

LSD1 plays a key role in hematopoietic stem/progenitor cell proliferation and differentiation[45] and lineage-specific myelosuppression is therefore an expected mechanism-based outcome of LSD1 inhibition[28]. LSD1

inhibition has its greatest effects on thrombopoiesis, granulopoiesis, and lastly erythropoiesis with monopoiesis being unaffected[28]. These effects are dose-dependent and fully reversible upon withdrawal of treatment.

Chronic toxicity studies in rat (26-week) and dog (39-week) were conducted in which bomedemstat was administered once-daily at doses up to 6 and 1.5 mg/k/d, respectively. These studies concluded the toxicity observed was due to exaggerated pharmacological effect on specific lineages of myeloid hematopoiesis. Animals showed a dose-dependent decrease in platelets and, to a lesser extent in red cell number and neutrophil counts, with an increase in monocytes and no effect on the number of circulating lymphocytes. There was no evidence that inhibition of LSD1 affected the function of any terminally differentiated circulating cells. In the 26-week rat toxicity study, the no-observed-adverse-effect level (NOAEL) was 2 mg/kg/d; in the 39-week dog toxicology study, the NOAEL was 1 mg/kg/d.

In the CTP-101 study, bomedemstat was administered to patients with high-risk AML and MDS; the therapeutic thesis was to completely inhibit LSD1 in all hematopoietic cells, targeting both leukemic stem cells and blasts, recognizing that patients would need clinical support for cytopenias. The starting dose was 0.75 mg/kg/d and the optimal dose, at which no safety signals have been observed, was deemed to be 6.0 mg/kg/d. Patients at all dose levels of bomedemstat required platelet transfusions, although the sensitivity of thrombopoiesis to LSD1 inhibition in high-risk AML/MDS patients likely reflects the generally compromised nature of the bone marrow, including the reduction of megakaryocytes, in that disease.

Subsequently, bomedemstat is being tested in ongoing Phase 2 studies for the treatment of myelofibrosis[43] and essential thrombocythemia[44]. In these studies, bomedemstat dosing is titrated to a target platelet count, and a starting dose of 0.6 mg/kg/d was eventually selected for both studies as optimal to efficiently achieve a therapeutic exposure in individual patients (the RP2D)[43]. In the myelofibrosis study, which has fully enrolled with 89 patients, there have been fourteen serious adverse events (SAEs) attributed to bomedemstat, all of which were grade 3 or lower with the exception of one Grade 4 thrombocytopenia in which a dosing error may have contributed[43]. In the essential thrombocythemia study, albeit with lower patient accrual (n=30), four SAEs have been observed, both deemed unrelated to bomedemstat by Investigators[44]. No dose-limiting toxicities, safety signals, or deaths due to study drug were observed in either study.

We therefore hypothesize that a starting dose of 0.5 mg/kg/d for all patients with a platelet count ≥100x10$^3$/mcL, and 0.4 mg/kg/d for patients with a platelet count of 75-99x10$^3$/mcL, of bomedemstat free base (to account for recent receipt of myelosuppressive chemotherapy) will be well-tolerated and will achieve therapeutically relevant levels in patients with extensive stage SCLC completing induction chemoimmunotherapy and transitioning to maintenance treatment.

## 3.0 DRUG INFORMATION

### 3.1 Bomedemstat

Bomedemstat is an investigational drug that will be supplied by the Imago Biosciences. Details regarding bomedemstat formulation, storage, dispensing, dosage, administration, etc., are described in an accompanying pharmacy manual.

#### *3.1.1 Formulation*

The drug product is bomedemstat, a bis-tosylate salt. The free base of bomedemstat is the active moiety. Bomedemstat will be supplied in capsules of multiple strengths. These strengths, based on bomedemstat free base, i.e. the active substance, may include: 5 mg, 10 mg, 25 mg, and 50 mg. Additional strengths may be added over the duration of the study. Such details will be included via updates to the Pharmacy Manual. Details on capsules, including strengths, colors, and sizes, can be found in the pharmacy manual.

### *3.1.2 Storage*

The recommended long-term storage conditions for bomedemstat are for the storage temperature not to exceed 25°C. Bomedemstat must be stored in a secure area with access limited to the Investigator and authorized staff and under the physical conditions that are consistent with bomedemstat-specific requirements. Bomedemstat supplies will be stored securely under the appropriate conditions according to the federal, state and local laws. Procedures for bomedemstat storage and accountability are detailed in a pharmacy manual.

### *3.1.3 Dispensing*

All material supplied is for use only in this clinical study and should not be used for any other purpose. Only patients enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized site staff may dispense study drug.

The Investigator is responsible for bomedemstat accountability, reconciliation and record maintenance per Site Standard Operating Procedure.

### *3.1.4 Dosage*

All patients will be treated daily until disease progression that meets criteria to discontinue treatment, or unacceptable toxicity (see Section 6.6). Dosing will begin on Day 1 at the starting dose ($D_s$), which is 0.5 mg/kg/d bomedemstat free base for all patients with a platelet count ≥100x$10^3$/mcL, and 0.4 mg/kg/d for patients with a platelet count of 75-99x$10^3$/mcL. The calculated dose will be rounded to the nearest 5 mg increment for dispensation and administration. Details on the selection of and rationale for the starting dose and dosing schedule can be found in Section 2.7.

Using dose titration, all patients will be dosed to the bomedemstat $D_{pi}$ (platelet inhibitory dose), which reflects the on-target activity of the drug. The $D_{pi}$, is anticipated to be ≤2 mg/kg/d; however, this is not the upper limit for titration purposes as the dose needed to achieve a therapeutic effect will vary among patients and may change over time. The platelet titration target expected to be associated with a clinically significant therapeutic effect is a platelet count of *approximately* ≥50x$10^3$/mcL to ≤99x$10^3$/mcL. Titration and re-challenge rules based on evaluation of platelet, ANC, and Hgb counts are described in Section 6.2. The maximum dose is 6 mg/kg/d.

Bomedemstat dosing will be based on the patient's weight on the first day of study treatment. If during the study the patient's weight differs from Day 1 by more than 10%, the amount of bomedemstat dispensed should be updated to the current weight. The source data must clearly document the weight used.

In the event of uncertainty regarding dose modification of bomedemstat for adverse events, or uncertainty regarding management of clinically significant changes in platelets, neutrophil counts, or other hematologic parameters, the PI should be consulted.

### *3.1.5 Administration*

Appropriately trained personnel of the study site will provide instruction pertaining to bomedemstat administration. All bomedemstat doses will be self-administered by the patient off-site.

Patients should be instructed to:

1. Take their bomedemstat once daily, at night before bed at approximately the same time (suggest that patient select their dosing time with consideration given to fasting requirements).

2. Swallow their bomedemstat capsules whole, with a glass of water.

3. Take bomedemstat on an empty stomach (fast for 1 hour prior to and 30 minutes after dose). Patients may have clear liquids prior to their dose and following study drug administration. Patients may take other medications at the same time as bomedemstat.

*3.1.6 Missed Doses*

Patients who do not take their bomedemstat dose at the usual required time should take it immediately upon noting that it was not taken; however, the patient should not take the dose more than 12 hours after the usual dosing time. If a patient misses a dose, they should not take two doses the following day, but should notify their study coordinator and continue with their normal daily dose the following day.

For a dosing hiatus due to a serious adverse event (SAE), please consult the Principal Investigator for guidance on dosing re-start. Patients who miss an extended number of bomedemstat doses or exhibit serial non-compliance with treatment may be removed from the study at the discretion of the Principal Investigator.

*3.1.7 Dose Modifications for Toxicity*

See Section 6.2 and 6.3 as appropriate to the specific toxicity.

## 3.2 Atezolizumab

Please see the current Package Insert provided by the manufacturer for detailed information regarding atezolizumab[46]. Atezolizumab (Tencentriq®, Genentech) is a commercially available programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of multiple solid tumors including SCLC and its safety and efficacy are well-characterized.

*3.2.1 Formulation*

Atezolizumab injection for intravenous use is a sterile, preservative-free, colorless to slightly yellow solution in single-dose vials. Each 20 mL vial contains 1200 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg), and sucrose (821.6 mg), with a pH of 5.8.

*3.2.2 Storage*

Atezolizumab injection is a sterile, preservative-free, and colorless to slightly yellow solution for intravenous infusion supplied as a carton containing one 1,200 mg/20 mL single-dose vial (NDC 50242-917-01).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

*3.2.3 Dispensing*

3.2.3.1 Preparation

Visually inspect drug product for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if the solution is cloudy, discolored, or visible particles are observed. Do not shake the vial. Prepare the solution for infusion as follows. Withdraw the required volume of atezolizumab from the vial(s) using sterile needle and syringe. Dilute to a final concentration between 3.2 mg/mL and 16.8 mg/mL in a polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP. Dilute with only 0.9% Sodium Chloride Injection, USP. Mix diluted solution by gentle inversion. Do not shake. Discard used or empty vials of atezolizumab.

3.2.3.2 Storage of Infusion Solution

This product does not contain a preservative. Administer immediately once prepared. If diluted atezolizumab infusion solution is not used immediately, store solution either:

1. At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration of the infusion, or
2. Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from time of preparation.

Do not freeze. Do not shake.

*3.2.4 Dosage*

Administer atezolizumab as 1200 mg every 3 weeks.

*3.2.5 Administration*

Please see the manufacturer's package insert for administration instructions.

*3.2.6 Missed Doses*

Patients who do not receive an intended atezolizumab infusion should have the infusion administered as soon as possible. If an intended infusion is delayed by more than 48 hours, the Principal Investigator should be consulted to guide dosing re-start. Patients who miss an extended number of bomedemstat doses or exhibit serial non-compliance with treatment may be removed from the study at the discretion of the Principal Investigator.

*3.2.7 Dose Modifications for Toxicity*

Please see the manufacturer's package insert for detailed information regarding dosage modification for toxicities of atezolizumab.

## 4.0 STAGING CRITERIA

Limited stage (LS) and extensive stage (ES) disease are defined as follows:

1. Limited stage disease: Tumor and any metastases to regional lymph nodes (hilar, mediastinal, or ipsilateral supraclavicular) are confined to one hemithorax and can be encompassed in a single radiation port.
2. Extensive stage disease: Extension of disease beyond the areas defined for limited disease.

   *Note*: A cytologically confirmed malignant pleural effusion constitutes extensive stage disease. Patients who have progressed following treatment for limited stage small cell lung cancer are considered to have extensive stage disease.

See Section 15.1 for VALG staging details.

## 5.0 ELIGIBILITY CRITERIA

Subjects must meet all the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator.

### 5.1 Inclusion Criteria

Patients must meet all of the following applicable criteria to be eligible for enrollment:

1. Adult aged 18 years or older and willing and able to provide written informed consent.

2. Histologically confirmed diagnosis of extensive stage small-cell lung cancer (ES-SCLC).

   *Note*: Previously treated limited stage SCLC (LS-SCLC) patients are eligible if disease progression had occurred following completion of definitive treatment for LS-SCLC. Determination of disease progression after prior therapy for LS-SCLC is at the discretion of the investigator.

3. Having received four cycles of platinum-etoposide concurrent with three or four cycles of immune checkpoint inhibitor as induction systemic therapy for ES-SCLC immediately prior to study enrollment (see below for definitions). Note that immune checkpoint inhibitor may have been omitted from the first cycle only.

   Platinum is defined as cisplatin or carboplatin. Immune checkpoint inhibitor is defined as atezolizumab, durvalumab, or other anti-PDL1 or anti-PD1 monoclonal antibody that is approved by the US Food and Drug Administration for first-line treatment of ES-SCLC in combination with platinum and etoposide at the time of treatment receipt. Immediately prior is defined as receipt of Cycle 1 Day 1 of platinum-etoposide +/- immune checkpoint inhibitor no more than 112 days prior to Cycle 1 Day 1 of study treatment, and administration of fourth cycle of platinum-etoposide and immune checkpoint inhibitor no more than 30 days prior to Cycle 1 Day 1 of study treatment.

4. Eligible to receive maintenance atezolizumab, as defined by stable disease or better, following induction platinum-etoposide and immune checkpoint inhibitor. Determination of response to induction therapy is at the discretion of the investigator. Investigators should contact the PI if clarification is needed.

5. ECOG performance status of ≤ 2.

6. Minimum life expectancy of ≥ 12 weeks.

7. Satisfactory laboratory parameters:

   a. Absolute neutrophil count (ANC) ≥ 1000/mcL

      *Note*: myeloid growth factor use within 14 days of study treatment initiation is not permitted. Growth factor may have been previously administered during induction chemoimmunotherapy.

   b. Platelet count (Plt) ≥ $75x10^3$/mcL (without transfusion)

   c. Hemoglobin (Hgb) ≥ 8.0 g/dL (transfusion is permitted)

   d. Calculated glomerular filtration rate (GFR; using the Cockcroft-Gault equation) ≥ 40 mL/min or serum creatinine ≤ 1.5x upper limit of normal

   e. Serum total bilirubin ≤ 1.5x upper limit of normal (ULN) or ≤ 3x ULN for subjects with Gilbert's disease

   f. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5x ULN (≤ 5x ULN if evidence of hepatic involvement by malignant disease)

g. The following coagulation parameters must be met only in patients not receiving anticoagulant agents at baseline.

   i. international normalized ratio (INR) < 1.5x upper limit of normal

   ii. activated partial thromboplastin time (aPTT) < 1.5x the local upper limit of normal

   *Note*: there is no INR or aPTT threshold for patients who are receiving anticoagulant agents at baseline, but patients must be on a stable dose of anticoagulant, and discontinuation of all anticoagulation while the platelet count is below $50x10^3$/mcL must be deemed appropriate for the patient by the investigator prior to enrollment (see Section 5.2).

8. Able to swallow capsules.

9. Amenable to peripheral blood sampling during the study.

10. Female subjects of childbearing potential should be willing to use 2 methods of birth control or abstain from heterosexual activity for the course of the study through 28 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year.

11. Male subjects who are sexually active with female partner(s) of childbearing potential should be willing to use an adequate method of contraception starting with the first dose of study therapy through 28 days after the last dose of study therapy.

### 5.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible for study participation:

1. Prior receipt of systemic therapy for ES-SCLC other than four cycles of induction platinum-etoposide and immune checkpoint inhibitor (see Section 5.1 for definitions of these terms).

2. Diagnosis of LS-SCLC that has not been previously treated.

3. Receipt of radiation therapy for symptomatic deterioration and/or radiographic disease progression that was administered after initiation of induction platinum-etoposide and immune checkpoint inhibitor.

   *Note:* the presence of untreated asymptomatic brain metastasis, or a history of receipt of radiation to brain metastasis that was not initiated in response to symptomatic deterioration and/or radiographic disease progression following initiation of induction systemic therapy, does not preclude study participation. Investigators should contact the PI if clarification is needed.

4. Anticipated use of prophylactic cranial irradiation or consolidative thoracic radiation therapy during study participation.

   *Note*: Palliative radiation to the CNS for new CNS disease that develops during study participation is allowed (Section 8.2.7.1).

5. History of prior immune-related adverse event or other toxicity associated with immune checkpoint inhibitor that precludes safe administration of maintenance atezolizumab, in the opinion of the investigator.

6. Current or prior use of immunosuppressive medication within 14 days prior to the first dose of study treatment. The following are exceptions to this criterion:

    a. Intranasal, inhaled, topical steroids or local steroid injections (e.g., intra-articular injection).

    b. Systemic corticosteroids at doses not to exceed 10 mg/d of prednisone or equivalent.

    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

7. Active autoimmune disease requiring systemic immunosuppression or history of autoimmune disease requiring systemic immunosuppression within the last 2 years.

    *Note*: Systemic immunosuppression should be interpreted as systemic glucocorticoids at a dose of greater than 10 mg/day of prednisone or equivalent, systemic biologic agents including monoclonal antibodies against inflammatory mediators, or small molecule agents. Investigators should contact the PI if clarification is needed.

8. Active pneumonitis or interstitial lung disease (ILD), or a history of pneumonitis/ILD, which required systemic immunosuppression (e.g. corticosteroids).

9. Known bleeding disorder (e.g., dysfibrinogenaemia, factor IX deficiency, hemophilia, Von Willebrand's disease, Disseminated Intravascular Coagulation [DIC], fibrinogen deficiency, or other clotting factor deficiency), at the discretion of the investigator.

10. History of severe thrombocytopenia or platelet dysfunction, including: immune thrombocytopenic purpura; thrombotic microangiopathy including thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, complement-mediated thrombotic microangiopathy, or drug-induced thrombotic microangiopathy; inherited platelet function disorders, including Bernard-Soulier Syndrome, gray platelet syndrome, Wiskott-Aldrich Syndrome, Glanzmann Thrombasthenia, or Chediak-Higashi Syndrome. Investigators should contact the PI if a patient has a history of severe thrombocytopenia due to a cause not listed here or if any other clarification is needed.

11. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to bomedemstat or LSD1 inhibitors (i.e., monoamine oxidase inhibitors; MAOIs) that contraindicates their participation.

12. Any hypersensitivity to PD-1/PD-L1 targeting agents.

13. Current use of monoamine oxidase A and B inhibitors (MAOIs).

14. Current use of a prohibited medication (e.g. romiplostim) or expected to require any of these medications during treatment with the investigational drug.

15. Current or anticipated use of an antiplatelet (e.g. clopidogrel), anticoagulant (e.g. warfarin or apixaban), or NSAID with antiplatelet activity (e.g. aspirin, ibuprofen), that, in the opinion of the investigator, could NOT be safely discontinued when the subject's platelet count decreases below $50x10^3$/mcL.

16. Has undergone major surgery within 4 weeks prior to starting study drug and/or has not recovered from side effects of such surgery. *Note*: Major surgery and recovery are defined at the discretion of the investigator.

17. Receipt of a live vaccine within 30 days of first dose of study therapy.

18. Uncontrolled active infection.

19. Any concomitant active malignancy considered clinically significant by the investigator.

20. Known human immunodeficiency virus (HIV) infection or known active Hepatitis B or Hepatitis C virus infection (testing will not be conducted as part of Screening procedures).

21. History of any illness/impairment of gastrointestinal (GI) function that might interfere with drug absorption (e.g. chronic diarrhea), confound the study results or pose an additional risk to the patient by participation in the study.

22. Use of an investigational agent within 28 days, or the equivalent of at least 7 half-lives of that agent, whichever is the shorter, prior to the study Day 1.

23. Females who are pregnant or breastfeeding or plan to become pregnant or breastfeed at any time during the study.

## 6.0 TREATMENT PLAN

### 6.1 Study Overview

This is an open label, single arm, single institution Phase 1-2 study testing the activity and tolerability of the LSD1 inhibitor bomedemstat in combination with maintenance immune checkpoint inhibitor (ICI) in patients with newly diagnosed extensive stage SCLC treated with first-line induction platinum-etoposide and ICI. Bomedemstat dosing will be titrated to platelet count suppression (an on-target toxicity). Consideration of bomedemstat dose escalation will occur on an every three week schedule. As such, for convenience, all patients will receive the ICI atezolizumab in combination with bomedemstat, including patients who received a different ICI as part of induction with platinum-etoposide.

The starting dose of bomedemstat will be determined according to the screening platelet count as follows. For patients with a platelet count of ≥100x$10^3$/mcL, the starting dose will be 0.5 mg/kg/d. For patients with a platelet count of 75-99x$10^3$/mcL, the starting dose will be 0.4 mg/kg/d. See Sections 2.7 and 3.1.4 for bomedemstat starting dose selection rationale. A safety evaluation will be performed as described in Section 10.2 and the starting dose will be modified accordingly, if necessary.

Bomedemstat will be administered orally, once daily, for a 21-day cycle. Bomedemstat should be taken on an empty stomach. See Section 3.1.5 for detailed administration instructions. Because bomedemstat exhibits on-target toxicity of lineage-specific myelosuppression that preferentially affects platelet production, bomedemstat dosing will be titrated to a target platelet count of 50-99x$10^3$/mcL as described in Section 6.2. Detailed guidance regarding bomedemstat dose modification for toxicities (including myelosuppression) is described in Section 6.3.

Atezolizumab will be administered via IV infusion at a flat dose of 1,200 mg every 3 weeks in keeping with the medication's prescribing information regarding standard of care use[46].

Subjects who at any time experience severe toxicity meeting criteria for treatment discontinuation (see Section 6.6.2) will not be eligible for further study treatment and will be converted to Off Treatment status.

Radiographic disease response assessments will occur every 6 weeks +/- 7 days (after completion of 24 weeks of study treatment, the interval can be extended to every 9 weeks +/- 7 days at the discretion of the investigator) for the duration of study participation with disposition based on the results as follows:

1. Subjects who experience disease response (CR or PR) or stable disease without evidence of clinical deterioration will continue bomedemstat and atezolizumab maintenance therapy. Absence of clinical deterioration is determined by the treating physician and is defined as follows:

a. Absence of signs and symptoms of disease progression.

b. Absence of rapid disease progression.

c. Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention.

2. Subjects who experience disease progression that is isolated to the CNS are eligible to continue study treatment following definitive therapy to the CNS disease, provided that ongoing study treatment is likely to provide additional benefit to the patient, at the discretion of the investigator and after appropriate discussion with the patient. See Section 8.2.7.1 for further details.

3. Subjects who experience confirmed disease progression by RECIST 1.1 (other than isolated CNS progression) and/or clinical deterioration should discontinue study treatment (see Section 6.6.1).

   *Note:* Subjects with unconfirmed disease progression by RECIST 1.1 who do not have evidence of clinical deterioration may continue to receive study treatment, at the discretion of the investigator and after appropriate discussion with the patient. Subjects should be monitored closely and a follow-up scan should be performed after 28 days, or sooner if clinical deterioration occurs. If the follow-up scan confirms disease progression, the subject should discontinue study treatment. See Section 8.2.7.2 for further details.

Subjects will be followed closely until disease progression per RECIST 1.1 or initiation of new anticancer treatment, whichever occurs first; and will afterwards be followed for survival until death or study termination, whichever occurs first. Blood samples for biomarker assessments will be collected at protocol-defined timepoints to support study endpoints.

## 6.2 Bomedemstat Dose Titration to Platelet Count

Bomedemstat dose titration to platelet count will be performed according to the titration and re-challenge rules described in Table 6.1 and Table 6.2 as follows. Dose titration rules use the absolute platelet count and the relative change from the most recent scheduled assessment. Prior to cycle 2 day 1, dose increases are not permitted, and dose titration should be performed according to Table 6.1. Starting on Day 1 of cycle 2, dose increases are permitted, and dose titration should be performed according to Table 6.2. The maximum allowed dose is 6 mg/kg/d. Dose increases require adequate neutrophil and erythrocyte indices, and dose increases are not permitted within 21 days of a previous dose change, where change is inclusive of dose increase or dose reduction. After a dose hold, when platelets have returned to >50x$10^3$/mcL, the subject should be re-challenged with bomedemstat at 50% of the previous dose. Dose reductions for safety reasons are permitted at any time.

**Table 6.1. Bomedemstat titration to goal platelet count and re-challenge rules for cycle 1, days 8 and 15.**

| **Platelet Assessment** | | **Rules** | | |
|---|---|---|---|---|
| **Platelet count (x $10^3$/mcL)** | **Change in Platelet Count Relative to Previous Scheduled Assessment** | **Titrate Dose?** | **Titration Rule** | **Re-challenge Rule** |
| ≥100 | Any, including same count | Maintain | N/A | N/A |
| 50-99 | Any increase *or* same count | Maintain | N/A | N/A |

| | | | | |
|---|---|---|---|---|
| 50-99 | <50% decrease[1] | Down-titrate[1] | **Decrease** current dose by **0.1** mg/kg[1] | N/A |
| 50-99 | ≥50% decrease[1] | Down-titrate[1] | **Decrease** current dose by **0.2** mg/kg if starting dose was 0.5 mg/kg or by **0.1** mg/kg if starting dose was 0.4 mg/kg[1] | N/A |
| <50 | Any change[1] | **HOLD DOSE[1]** | **HOLD DOSE[1]** | Resume at **50%** of previous dose when platelets return to >50x$10^3$/mcL.[2] |

1. If pseudothrombocytopenia due to blood sample coagulation or platelet clumping is suspected, the CBC should be repeated. If the second blood draw confirms that the first draw yielded a falsely low platelet count, the result of the first draw should be ignored and the dose of bomedemstat calculated based on the result of the second draw.
2. ANC ≥ 1.0 x $10^3$/mcL (1.0 x $10^9$/L) and Hgb ≥ 8 g/dL (80 g/L) are needed for or re-challenge.

**Table 6.2. Bomedemstat titration to goal platelet count and re-challenge rules for all days with CBC evaluation in *cycle 2* and beyond.**

| Platelet Assessment | | Rules | | |
|---|---|---|---|---|
| **Platelet count (x $10^3$/mcL)** | **Change in Platelet Count Relative to Previous Scheduled Assessment** | **Titrate Dose?** | **Titration Rule** | **Re-challenge Rule** |
| ≥200 | Any, including same count | Up-titrate[1,2,3] | **Increase** current dose by **0.15** mg/kg | N/A |
| 100-199 | <75% decrease[4] *or* same count *or* any increase | Up-titrate[1,2,3] | **Increase** current dose by **0.1** mg/kg | N/A |
| 100-199 | ≥75% decrease[4] | Maintain[4] | N/A | N/A |
| 50-99 | <50% decrease[4] *or* same count *or* any increase | Maintain[4] | N/A | N/A |
| 50-99 | ≥50% decrease[4] | Down-titrate[4] | **Decrease** current dose by **0.1** mg/kg or **25%**, whichever results in a lower dose | N/A |
| <50 | Any change[4] | **HOLD DOSE[4]** | **HOLD DOSE[5]** | Resume at **50%** of previous dose when platelets return to > 50x$10^3$/mcL.[1] |

1. ANC ≥ 1.0 x $10^3$/mcL (1.0 x $10^9$/L) and Hgb ≥ 8 g/dL (80 g/L) are needed for up-titration or re-challenge.
2. Dose up-titration is not permitted if any dose change (including up- or down-titration) has occurred within the previous 21 days.
3. The maximum allowed dose of bomedemstat is 6 mg/kg/d.
4. If pseudothrombocytopenia due to blood sample coagulation or platelet clumping is suspected, the CBC should be repeated. If the second blood draw confirms that the first draw yielded a falsely low platelet count, the result of the first draw should be ignored and the dose of bomedemstat calculated based on the result of the second draw.
5. Prophylactic platelet transfusion is at the discretion of the treating investigator. Prophylactic platelet transfusion is strongly encouraged for platelet count < 10x$10^3$/mcL.

## 6.3 Dose Modification for Toxicity

Toxicity will be graded using Common Terminology Criteria for Adverse Events (CTCAE version 5.03). Dose modification of bomedemstat for hematologic toxicities is listed in Table 6.3. Please note that use of hematopoietic growth factors is prohibited during study participation (see Section 6.4.3). Dose modification of bomedemstat for other toxicities potentially related to bomedemstat is listed in Table 6.4. If multiple toxicities suggesting conflicting dose modifications are present simultaneously, the rule that results in the lowest bomedemstat dose should be followed.

Dose modification, interruption, or discontinuation of atezolizumab for toxicity should be performed according to the prescribing information[46].

Subjects that require more than three down-titrations or dose holds of bomedemstat will render the subject ineligible for further treatment in the study and the subject will be converted to Off Treatment status.

Furthermore, encephalopathy of any grade is always considered a serious adverse event as well as an unacceptable toxicity and should result in immediate treatment discontinuation (see Sections 8.6.1 and 10.2.1).

**Table 6.3. Dose modification of bomedemstat related to hematologic toxicities.**

| Toxicity | Grade | Management[1] |
|---|---|---|
| Neutropenia | 3 (ANC 0.5-1x$10^3$/mcL) | Continue bomedemstat dosing and maintain dose level. |
| | 4 (ANC <0.5x$10^3$/mcL) | **Hold** bomedemstat dosing until ANC recovery to ≥1.0x$10^3$/mcL. Reduce dose by **0.1** mg/kg/d upon reinitiating. |
| Febrile Neutropenia | ≥3 | **Hold** bomedemstat dosing for at least 7 days and until ANC recovery to ≥1.0x$10^3$/mcL. Reduce dose by **0.1** mg/kg/d upon reinitiating. |
| Anemia | 3 (Hgb <8 g/dL) | Continue bomedemstat dosing and maintain dose level. Transfusion of red blood cells is at the discretion of the treating physician and does not require bomedemstat dose modification. |
| | 4 (Life-threatening consequences; urgent intervention indicated) | **Hold** bomedemstat dosing until Hgb recovery to ≥8 g/dL. Reduce dose by **0.1** mg/kg/d upon reinitiating. |
| Thrombocytopenia | See Table 6.1 and Table 6.2. | |
| Lymphopenia | Any | Dose interruption or study discontinuation is not required for lymphopenia of any grade. |

1. Use of hematopoietic growth factors is prohibited during study participation (see Section 6.4.3).

**Table 6.4. Dose modification of bomedemstat related to non-hematologic toxicities.**

| | | Management | | | |
|---|---|---|---|---|---|
| **Type** | **Grade** | **Hold treatment?** | **Timing for restarting treatment** | **Dose/schedule for restarting/treatment** | **Discontinue subject?** (After consultation with PI) |
| Non-laboratory | 1 | No | N/A | N/A | N/A |
| | 2 | Consider withholding for persistent symptoms | Toxicity resolves to Grade 0-1 or baseline | **Reduce** dose by **0.1** mg/kg/d upon reinitiating. | Toxicity does not resolve to Grade ≤1 or baseline |

| | | | | | |
|---|---|---|---|---|---|
| | 3, lasting >3 days despite optimal supportive care | **Yes** | | | within 4 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event.* |
| | 4 | **Yes** | | | |
| Laboratory, non-hematologic or hematologic *not* listed in Table 7-4 | 1-2 | Consider withholding for clinically significant abnormalities following consultation with study PI | N/A | N/A | N/A |
| | 3-4, if medical intervention is required or abnormality leads to hospitalization | **Yes** | Toxicity resolves to Grade 0-1 or baseline | **Reduce** dose by **0.1** mg/kg/d upon reinitiating. | Toxicity does not resolve to Grade ≤1 within 4 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event.* |

In case clinically significant non-hematologic toxicity does not resolve to Grade 0-1 or baseline within 4 weeks after last dose of any study treatment, investigational treatment with bomedemstat should be permanently discontinued, and the subject should be converted to Off Treatment status. Clinical significance is at the discretion of the investigator. With investigator and sponsor agreement, subjects with a non-hematologic laboratory adverse event still at Grade 2 after 4 weeks may continue treatment in the study and retain On Treatment status only if asymptomatic and controlled.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater following re-challenge of bomedemstat are not eligible for further study treatment and should be converted to Off Treatment status.

## 6.4 Prior and Concomitant Therapy

Prior therapies include systemic therapies, radiation, and surgeries.

Any concomitant therapy given for a study protocol related AE should be recorded from Cycle 1 Day 1 of study treatment through the Safety Follow-Up Visit.

### *6.4.1 Required Prior or Concomitant Therapy*

Subjects must have received four cycles of platinum-etoposide and three or four cycles of ICI immediately prior to study enrollment (for details, see Section 5.0).

### *6.4.2 Allowed Concomitant Therapy*

Standard supportive care measures for symptom control or drug related toxicity are allowed, such as analgesics, antiemetics, electrolyte replacement, and hydration. Other prescribed medications for non-neoplastic conditions are allowed, as well as vitamins and nutritional or herbal supplements, which must be recorded in the medication list.

Concomitant corticosteroids (prednisone or equivalent) may be used at a dose of ≤10 mg/day. The use of intermittent high dose corticosteroid treatment to prevent or manage hypersensitivity reactions or other noncancer-related symptoms is allowed (including premedication for known hypersensitivity reactions to contrast material for imaging scans).

Routine prophylaxis with vaccines is permitted, excluding those containing live microorganisms.

If the subject is taking chronic suppressive anti-infectives (e.g., antiviral, antifungal, or antibacterial), appropriate evaluation must be completed prior to registration, and documentation must exclude active infection. The subject should continue suppressive anti-infectives for the duration of study participation.

Birth control or contraceptive measures are allowed.

### *6.4.3 Prohibited Concomitant Therapy*

Subjects are prohibited from receiving the following therapies during trial participation:

1. Any other systemic anti-cancer therapy, including chemotherapy, immunotherapy, or biologic therapy not specified in this protocol.

2. Any investigational agents not specified in this protocol.

3. Monoamine oxidase A and B inhibitors (MAOIs).

4. All hematopoietic growth factors: romiplostim, eltrombopag, granulocyte and granulocyte-macrophage colony stimulating factor (G-CSF and GM-CSF) and erythropoietin (EPO).

5. Systemic corticosteroids at a dose of >10 mg/d (prednisone equivalent).

   *Note*: The use of intermittent high dose corticosteroid treatment to prevent or manage hypersensitivity reactions or other symptoms not related to cancer is allowed (including premedication for known hypersensitivity reactions to contrast material for imaging scans).

6. Radiation therapy, including prophylactic cranial irradiation and consolidative thoracic radiation therapy. Note that radiation therapy for isolated CNS progression is allowed, during which time bomedemstat should be held (see Section 8.2.7.1).

7. Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live-attenuated vaccines and are not allowed.

8. Subjects are specifically prohibited from receiving the following therapies while the platelet count is < $50x10^3$/mcL:

   a. Non-steroidal anti-inflammatory medications with COX-1 inhibitory/antiplatelet activity (e.g. aspirin, ibuprofen, naproxen, etc.).

b. Antiplatelet agents, e.g. clopidogrel, prasugrel, ticagrelor, ticlopidine.

c. Anticoagulation with warfarin, Factor Xa inhibitors (e.g. apixaban, edoxaban, rivaroxaban), direct thrombin inhibitors (e.g. dabigatran), or low molecular weight heparins (enoxaparin, dalteparin).

## 6.5 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

1. Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

2. Immune-related adverse events: Immune-related adverse events should be managed in keeping with institutional and national guidelines[47].

3. Infusion reactions while receiving atezolizumab: Acute infusion reactions should be managed according to institutional guidelines.

4. Transfusions: transfusions of red blood cells and platelets are at the discretion of the investigator and should be performed in accordance with institutional guidelines. Prophylactic transfusion of platelets when the platelet count is < $10x10^3$/mcL is strongly encouraged.

## 6.6 Discontinuation of Study Treatment and/or Withdrawal from Study for Individual Subjects

Specific criteria for discontinuation of study treatment and/or withdrawal from study are listed in Sections 6.6.1 (disease progression) and 6.6.2 (other reasons).

Subjects may withdraw consent at any time for any reason or be withdrawn from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

Subjects who meet criteria to discontinue study treatment will be converted to Off Treatment status and will be followed per the Study Calendar (Section 7.0) via the End of Treatment Visit and Survival Follow-up assessments (see Section 8.5.3), including the collection of any protocol-specified blood specimens, unless consent is withdrawn, or the subject is lost to follow-up or enrolled in another clinical study.

Subjects who discontinue study treatment for a reason other than disease progression and have not initiated other anti-cancer therapy will be followed with Monitoring assessments (Section 8.5.3.3).

All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

### *6.6.1 Disease progression*

Confirmed radiographic disease progression per RECIST 1.1 (Section 9.2.4) renders a subject ineligible for further study treatment, except that isolated CNS progression does not require permanent study treatment discontinuation (see Section 8.2.7.1 for further detail).

In the event of unconfirmed disease progression, study treatment can be continued until disease progression is confirmed (see Section 8.2.7.2 for further detail).

### *6.6.2 Other criteria for discontinuation of study treatment and/or withdrawal*

An individual subject will not receive any further study treatment and will proceed to Off Treatment monitoring if any of the following occur in the subject in question:

1. The subject withdraws consent.
2. Unacceptable adverse events as defined in Section 6.3.

   Note that encephalopathy of any grade is always considered an unacceptable adverse event (see Section 10.2.1).
3. Adverse event that, in the opinion of the investigator, contraindicates further dosing.
4. Subject noncompliance that, in the opinion of the investigator, warrants withdrawal, e.g., refusal to adhere to scheduled visits.
5. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
6. Intercurrent illness that prevents further administration of treatment.
7. Investigator's decision to withdraw the subject.
8. The subject has a confirmed positive serum pregnancy test.
9. Noncompliance with trial treatment or procedure requirements.
10. The subject is lost to follow-up.
11. Grade ≥ 3 infusion reaction.

## 7.0 STUDY CALENDAR

| *Title/Cycle* | Screening | On Treatment 21 Day Cycles | | | | Off Treatment | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Every Treatment Cycle** | | | | **End of Treatment** | **Monitoring** | **Safety Follow-Up** | **Survival Follow-Up** |
| *Timing* | *Day -28 to 1* | *Day 1* | *Day 8* | *Day 15* | *Within 7 days of Day 1 of next cycle* | *Time of discontin.* | *~Q8w* | *30d after discontinuation of study treatment* | *~Q12w* |
| *Window (days)* | - | *+/- 2 (subseq. cycles)* | *+/- 2* | *+/- 2* | | *+ 7* | *+/- 7* | | *+/- 14* |
| Informed Consent | X | | | | | | | | |
| Inclusion / Exclusion Criteria | X | | | | | | | | |
| Demographics / Medical History / Prior and Concomitant Medication Review | X | | | | | | | | |
| Bomedemstat Administration[1] | | Daily | → | → | → | | | | |
| Atezolizumab Administration[2] | | X | | | | | | | |
| Survival Status | | | | | | | | | X |
| Adverse Event / Concomitant Medication Review[3] | | X[3] | | | | X | X | X | |
| Full Physical Examination | X | | | | | | | | |
| Directed Physical Examination[3] | | X[3] | | | | X | X | X | |
| Vital Signs and Weight | X | X | | | | X | X | X | |
| ECOG Performance Status | X | X | | | | X | X | X | |
| Pregnancy Test | X | | | | | | | | |
| Complete Blood Count with Differential (CBC w/ Diff)[4] | X | X | X[4] | X[4] | | X | X | X | |
| Comprehensive Serum Chemistry Panel | X | X | | | | X | X | X | |
| PT/INR and aPTT | X | | | | | | | | |
| Serum cortisol, FT4, TSH | | X | | | | | | | |
| Archival tissue collection | X | | | | | | | | |
| Blood for correlative research | X | X | | | | X | X | | |
| Disease/response assessment[5] | X[5] | | | | X[5] | | X[5] | | |

1. Bomedemstat is taken daily. All doses are self-administered by the patient off-site.
2. Atezolizumab is administered in the clinic as an IV infusion. There are no specific restrictions regarding timing relative to the patient's bomedemstat dose.
3. Note that, during On Treatment status, provider visits (to facilitate AE/concomitant medication review and physical examination) are only required on Day 1 of each treatment cycle. Visits on other cycle days, including Day 8 and Day 15, can be performed if clinically necessary but are not mandated.
4. Weekly CBC w/ diff required throughout Cycle 1. After Cycle 1, CBC w/ diff should be performed weekly until the patient has not required a bomedemstat dose modification or hold for at least 28 days, at which point CBC w/ diff can be spaced out to no less frequently than every 14+/-2 days. If a dose modification is subsequently required, weekly CBC w/ diff should resume until at least 28 days have elapsed without need for a dose modification or hold, at which point CBC w/ diff can again be spaced out to no less frequently than every 14+/-2 days.

5. Disease/response assessment during the screening period may have been performed up to 14 days prior to initiation of study treatment. Disease response assessments will occur every 6 weeks. After completion of 24 weeks of study treatment, the intervals can be extended to up to 9 weeks +/- 7 days. CT scans should encompass at least the chest and abdomen. CT pelvis should be included according to usual clinical practice. For patients who are known to have CNS disease at the time of study enrollment, monitoring of the CNS should proceed according to usual clinical practice.

## 8.0 STUDY PROCEDURES AND ASSESSMENTS

The Study Calendar (Section 7.0) summarizes the study procedures to be performed at each visit. Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

### 8.1 Subject Enrollment

#### *8.1.1 Informed Consent*

The Investigator must obtain documented consent from each potential subject prior to participating in the study.

Consent must be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial per Institutional Standards.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

#### *8.1.2 Inclusion/Exclusion Criteria*

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

#### *8.1.3 Medical History*

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that is considered clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

#### *8.1.4 Prior and Concomitant Medications Review*

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement.

#### *8.1.5 Disease Details*

The investigator or qualified designee will obtain prior and current details regarding disease status.

#### *8.1.6 Prior Treatment Details*

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation, and surgeries.

### *8.1.7 Assignment of Patient Number*

Patients will be assigned a Patient Number upon consent.

## 8.2 Clinical Procedures/Assessments

The following clinical assessments should be performed in accordance with the Study Calendar (Section 7.0).

### *8.2.1 Adverse Event (AE) Monitoring*

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs. Adverse experiences will be graded and recorded throughout the study according to NCI CTCAE Version 5.03. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken regarding investigational treatment.

Please refer to Section 8.6 for detailed information regarding the assessment and recording of AEs. AE monitoring may occur more frequently than required as clinically indicated.

### *8.2.2 Concomitant Medications Review*

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement.

### *8.2.3 Full Physical Exam*

The investigator or qualified designee will perform a complete physical exam. Clinically significant abnormal findings should be recorded as medical history.

### *8.2.4 Directed Physical Exam*

For timepoints that do not require a full physical exam, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study treatment administration.

### *8.2.5 Vital Signs*

The investigator or qualified designee will measure and record vital signs, including temperature, pulse, respiratory rate, weight, and blood pressure.

### *8.2.6 ECOG Performance Status*

The investigator or qualified designee will assess ECOG Performance Status (see Section 9.4).

### *8.2.7 Radiographic Disease/Response Assessment*

Radiographic assessments of measurable disease will be performed using CT imaging with IV contrast. CT scans should encompass at least the chest and abdomen. CT pelvis should be included according to usual clinical practice. RECIST 1.1 criteria will be used to assess response to therapy. Radiographic imaging will be performed every 6 weeks (42 +/- 7 days). After completion of 24 weeks of study treatment, the interval between radiographic evaluations can be extended to up to 9 weeks +/- 7 days, according to the discretion of the investigator. For patients who are known to have CNS disease at the time of enrollment, CNS imaging should be performed during study participation according to usual clinical practice.

8.2.7.1 Isolated Central Nervous System Progression

Isolated CNS progression does not require discontinuation of study treatment. Bomedemstat should be held for seven days prior to until seven days following the administration of CNS-directed therapy (e.g. a standard course of whole brain radiotherapy or stereotactic radiosurgery, in accordance with institutional practice). The subject may then resume study therapy when clinically appropriate. If more than 4 weeks have elapsed since the previous dose of study drug, the subject should undergo a radiographic disease assessment before restarting study treatment.

8.2.7.2 Treatment Beyond Initial Determination of Progression

If a subject has unconfirmed PD (Section 9.2.4) and is clinically stable and without symptomatic deterioration (Section 9.2.6), it is at the discretion of the Investigator to continue study treatment per protocol until PD is confirmed (Section 9.2.4). For subjects with new lesions, the diameters of the new lesions will be recorded.

Clinically stable is defined as:

1. Absence of symptoms and signs indicating clinically significant PD (including worsening of laboratory values).

2. Absence of rapid progression of disease or progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

Upon confirmation of PD (Section 9.2.4) or onset of symptomatic deterioration / loss of clinical stability, study treatment should be discontinued. Administration of study treatment beyond confirmed progression is not permitted.

*8.2.8 Tumor Tissue Collection and Correlative Studies Blood Sampling*

Archival tumor tissue (defined as 10-15 serial sections, each 4 microns thick, mounted onto positively charged glass slides, or a block) will be requested as part of study participation. However, adequate archival tissue is not a requirement for study participation. Archival tissue samples will be tested for immunohistochemical expression studies of key markers which may include PD-L1, ASCL1, ATOH1, NEUROD1, POU2F3, REST, and YAP1.

Peripheral blood samples for correlative research studies should be collected in two to three 10 mL lavender top (EDTA) or Streck cfDNA tubes (~20-30 mL per collection). Research blood collections will be performed for correlative research studies at the following timepoints: during screening, at every radiographic assessment, and at end of treatment visit, regardless of whether radiographic assessment was performed. If radiographic assessment intervals are extended due to durable clinical benefit, research blood collection intervals will be extended to match.

Correlative studies will be performed in the MacPherson lab at the Fred Hutchinson Cancer Center in Seattle, WA. Correlative studies will include isolation of circulating tumor cells for multi-omic analysis (e.g. measurements of DNA alterations, mRNA transcript levels, and protein abundance) and the generation of patient-derived xenograft models, to isolate circulating free DNA (cfDNA) for multidimensional analysis (e.g. DNA alterations, fragmentation patterns), and to isolate genomic DNA from peripheral blood mononuclear cells for more accurate identification of somatic mutations. The goal of correlative studies is to identify predictors of clinical benefit from bomedemstat in combination with atezolizumab.

## 8.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below.

### *8.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)*

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 8.1. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to initiation of the next cycle of study treatment.

**Table 8.1. Laboratory tests.**

| CBC w/ Diff | Complete serum chemistry panel | Other |
|---|---|---|
| Hematocrit | Alanine aminotransferase (ALT) | Activated partial thromboplastin time (aPTT) |
| Hemoglobin | Albumin | Cortisol, serum |
| Platelet count | Alkaline phosphatase | Prothrombin time (PT/INR) |
| White blood cell count (total) | Aspartate aminotransferase (AST) | Serum beta-human chorionic gonadotropin ( $\beta$ -hCG) (*required if urine test is inconclusive*) |
| Red blood cell count | Bilirubin, Total | Thyroid stimulating hormone (TSH) |
| Absolute neutrophil count | Blood Urea Nitrogen | Thyroxine, free (FT4) |
| | Carbon dioxide (CO2 or Bicarbonate) | Urine pregnancy test (*only for women of childbearing potential*) |
| | Chloride | Blood for correlative studies |
| | Creatinine | |
| | Glucose | |
| | Potassium | |
| | Protein, Total | |
| | Sodium | |

## 8.4 Other Procedures

### *8.4.1 Treatment Discontinuation or Subject Withdrawal*

When a subject discontinues study treatment permanently or withdraws prior to trial completion, all applicable activities should be performed at the time of discontinuation (Section 7.0). Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.6. An End of Treatment visit (Section 8.5.3.1) should be performed within 7 days. If the subject has not experienced disease progression (see Section 8.2.7) and has not withdrawn from the study, the subject should undergo regular Monitoring visits (Section 8.5.3.3) for disease assessment according to the Study Calendar (Section 7.0).

## 8.5 Visit Requirements

Visit requirements are outlined in the Study Calendar (Section 7.0). Specific procedure-related details are provided above in Clinical Procedures/Assessments (Section 8.2).

### *8.5.1 Screening Period*

The following assessments will be performed up to 14 days prior to Cycle 1 Day 1:

1. Full Physical Examination
2. Vital Signs and weight
3. ECOG Performance Status
4. Pregnancy test or Serum $\beta$-HCG in females of childbearing potential
5. CBC w/ Diff
6. PT/INR and aPTT
7. Comprehensive serum chemistry panel
8. Archival tissue collection, if available
9. Radiographic disease assessment (see Section 8.2.7).
    a. CT with IV contrast of the chest and abdomen. CT pelvis should be included according to usual clinical practice. For patients known to have CNS disease, CNS imaging should be performed according to usual clinical practice.
10. Blood for correlative studies

### *8.5.2 On Treatment Period*

The following assessments will be performed at On Treatment Period visits as identified in the Study Calendar (Section 7.0). Specific procedure-related details are provided above in Clinical Procedures/Assessments (Section 8.2).

1. Adverse event review
2. Concomitant medication review
3. Directed physical examination
4. Vital signs and weight
5. ECOG performance status
6. CBC with differential
7. Comprehensive serum chemistry panel
8. TSH, FT4, and random serum cortisol
9. Radiographic disease/response assessment (see Section 8.2.7)

10. Blood for correlative studies (see Section 8.2.8)

*8.5.3 Off Treatment Visits*

8.5.3.1 End of Treatment Visit

The mandatory End of Treatment visit should be conducted at the time of permanent study treatment discontinuation, or within 7 days thereafter, unless the patient is unable to participate in the visit.

8.5.3.2 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after cessation of study treatment, or before the initiation of a new anti-cancer treatment outside the confines of this study, whichever comes first, unless the patient is unable to participate in the visit. All AEs that occur prior to the Safety Follow-Up Visit should be recorded.

8.5.3.3 Monitoring

Subjects who discontinue study treatment for a reason other than disease progression or withdrawal from study move into the monitoring phase and should be assessed radiographically every 8 weeks (56 ± 7 days) as in Section 8.2.7 to monitor disease status. Every effort will be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

8.5.3.4 Survival Follow-up

Once a subject is no longer eligible for study treatment due to disease progression or starts a new anti-cancer therapy outside the confines of this study, the subject moves into the survival follow-up phase. Survival status of the subject will be ascertained every 12 weeks, via medical records or by directly contacting the patient, until death, withdrawal of consent, or the end of the study, whichever occurs first. Three attempts to contact a subject should be made before the subject is considered lost to follow up.

## 8.6 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, regardless of whether the event is considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with receipt of study therapy, is also an adverse event.

Adverse events may occur during study therapy or within the follow-up period specified by the protocol, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Only adverse events that meet the following definition will be recorded:

1. All grade 3 and higher adverse events

2. Grade 1-2 adverse events that require medical intervention, i.e. initiation of a new medication, or are otherwise clinically significant at the discretion of the investigator

3. Any adverse event that requires a dose reduction or dose delay of either bomedemstat or atezolizumab

Adverse events will be recorded from Cycle 1 Day 1 until the Safety Monitoring visit performed according to the Study Calendar (Section 7.0), using the Adverse Event case report forms/worksheets. For subjects who discontinue study therapy for a reason other than disease progression and are being followed with Monitoring visits (Section 8.5.3.3), adverse events should continue to be monitored. Adverse events related to either bomedemstat or atezolizumab will be followed until resolution or stabilization of the AE or until the beginning of a new anti-neoplastic therapy, whichever occurs first. The reporting timeframe for adverse events meeting any serious criteria is described below.

*8.6.1 Serious Adverse Events*

SAEs will be reported promptly, using the SAE Report Form, once the Investigator determines that the event meets the protocol definition of an SAE. The Investigator or designee will report the SAE within 24 hours of his/her becoming aware of these events regardless of relationship of the SAE to the use of study drug, in accordance with the instructions in the SAE Report Form Completion Guidelines. The Investigator will always provide an assessment of relatedness at the time of the initial report. The SAE Report will always be completed as thoroughly as possible with all available details of the event within the designated time frames. Copies of relevant patient records, autopsy reports, and other documents may be requested.

A detailed SAE reporting procedure and contact information will be included in the SAE Report Form Completion Guidelines which will be finalized before any patients are consented. If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before reporting the SAE. The SAE Report will be updated when additional information is received within 24 hours of receipt of such information.

The Institutional Review Board (IRB) must be notified in writing of any SAEs that require expedited reporting to Regulatory Authorities. All SAEs meeting expedited reporting requirements will be reported to FDA in accordance with reporting requirements.

A Serious Adverse Event (SAE), which must be reported to the Principal Investigator within 24 hours of awareness via pager, is any adverse event that meets any of the following criteria:

1. Fatal (i.e., the adverse event directly causes or leads to death)
2. Life-threatening (i.e., the adverse event, in the view of the Investigator, places the subject at immediate risk of death). Note: this does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death
3. Requires or prolongs inpatient hospitalization
4. Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the subject’s ability to conduct normal life functions)
5. Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
6. Significant medical event in the Investigator's judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)
7. Encephalopathy of any grade (see Section 10.2.1)

Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.

### *8.6.2 Overdose*

An overdose for bomedemstat will be defined as any dose of study drug(s) that is 10% or more over the prescribed dose per cycle as described in the study protocol. The investigator must notify the Principal Investigator of this event via pager within 24 hours of awareness (although not considered an SAE).

No specific information is available on the treatment of overdose of bomedemstat. There is no specific antidote for bomedemstat overdose. In clinical studies, the highest total daily dose tested was 6 mg/kg/d. Aside from expected hematologic toxicities, no recurrent adverse events were noted up to the 6 mg/kg/d dose. The pharmacological effects may be prolonged after serum levels of active bomedemstat are no longer present. It is not known if bomedemstat is dialyzable. In the event of overdose, bomedemstat should be held and the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided as clinically indicated.

### *8.6.3 Pregnancy*

#### 8.6.3.1 Maternal exposure

If a patient becomes pregnant during study participation, bomedemstat will be discontinued immediately and permanently and the subject will be ineligible for further receipt of treatment in the study.

Pregnancy itself is not regarded as an AE unless there is a suspicion that bomedemstat and/or atezolizumab may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the Principal Investigator within 1 day, *i.e*. immediately, but no later than 24 hours of when he or she becomes aware of it.

The designated study representative will work with the Investigator to ensure that all relevant information is provided to the sponsor approved Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

#### 8.6.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 30 days after the last dose of bomedemstat and 90 days after the last dose of atezolizumab, whichever is longer.

Pregnancy of the patient’s partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose of study treatment, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient’s partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

## 9.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

### 9.1 Measurability of Lesions

#### *9.1.1 Measurable disease*

Note that measurable disease is defined differently for malignant lymph nodes vs other disease as follows.

Lesions other than malignant lymph nodes that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. It is strongly recommended that CT slice of 0.5 cm be used. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in short axis (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

#### *9.1.2 Non-measurable disease*

All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to <1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as are previously radiated lesions that have not progressed.

#### *9.1.3 Notes on measurability*

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. It is no longer necessary to distinguish between spiral and conventional CT.

2. Body scans should be performed with breath-hold scanning techniques, if possible.

3. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with stand-alone CT. The slice thickness of 0.5 cm or less is highly recommended. If CT scans have slice thickness > 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

4. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

5. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

6. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is still present, a default measurement of 0.5 cm should be applied.

7. If the radiologist believes the lesion is no longer discernible, a default measurement of 0.0 cm should be recorded.

## 9.2 Objective Status at Radiographic Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, all potential sites of metastases should be evaluated at each time point rather than following only sites of disease identified at baseline. It is acceptable to image only the areas of the body most likely to be involved with metastatic disease for the tumor type (chest, abdomen, pelvis, and/or bone scan are typical), with the addition of any areas with suspected involvement based upon clinical symptoms. For study-specific imaging requirements, see the Study Calendar in Section 7.0.

### *9.2.1 Complete Response (CR)*

Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

### *9.2.2 Partial Response (PR)*

Applies only to participants with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

### *9.2.3 Stable Disease*

Does not qualify for CR, PR, PD or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

### *9.2.4 Progressive Disease / Disease Progression (PD)*

One or more of the following must occur:

1. 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm.

2. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided).

3. Appearance of any new lesion/site (see Section 9.2.4.2 for details).

4. Death due to disease without prior documentation of progression and without symptomatic deterioration.

9.2.4.1 Confirmation of PD

Unconfirmed disease progression is defined as a single disease assessment showing disease progression as defined above. Confirmed disease progression is defined as a second determination of progression at least 4 weeks after the initial report of progression.

If the second assessment documents an absence of progression, the participant's disease is deemed not to have progressed and the initial report of progression is coded as a pseudo-progression. If there are no additional disease assessments at least 4 weeks after the initial assessment documenting absence of progression (either due to inadequate or missing assessment) then the initial assessment will be coded as a progression. Any indication of progression (per the definition above) reported after the determination of pseudo-progression will be coded a progression and will not require a second assessment to confirm progression.

9.2.4.2 Notes on new lesions

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Regarding new lesions, FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

*9.2.5 Relapse/Progression, Following Surgery*

Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration.

*9.2.6 Symptomatic Deterioration*

Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

*9.2.7 Assessment inadequate, objective status unknown*

Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

*9.2.8 Objective status notes*

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent; a participant who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the participant could alter the size of the effusion.

### 9.3 Best Response (RECIST 1.1 criteria)

This is calculated from the sequence of objective statuses.

1. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

2. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

3. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

4. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

5. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after Registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

6. Increasing disease: Objective status of progression within 12 weeks of Registration, not qualifying as anything else above.

7. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of Registration, not qualifying as anything else above.

8. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after Registration and no other response category applies.

### 9.4 Performance Status

Participants will be graded according to the ECOG Performance Status Scale.

| POINT | DESCRIPTION |
|---|---|

| | |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. |
| 2 | Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours. |
| 3 | Capable of limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled; cannot carry on any self-care; totally confined to bed or chair. |

### 9.5 Dose-limiting Toxicity (DLT) Definition

DLT to bomedemstat combined with atezolizumab is defined as the occurrence of any of the following toxicities by CTCAE 5.03 determined to be possibly, probably, or likely related to bomedemstat or atezolizumab occurring within 21 days of initiation of treatment. The specific events are:

1. Grade 4 non-hematologic toxicity (not laboratory).
2. Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care.
3. Any Grade 3 or Grade 4 non-hematologic laboratory value if:
    a. Medical intervention is required to treat the patient, or
    b. The abnormality leads to hospitalization
4. Thrombocytopenia leading to clinically significant sequelae (i.e., a clinically significant bleeding event or the need for prophylactic transfusions).

    *Note*: Thrombocytopenia is defined for this purpose as a platelet count < $100x10^3$/mcL. A clinically significant bleeding event is defined as an event that is life-threatening, cannot be controlled, and/or results in hemodynamic instability. Prophylactic transfusion is defined as platelet transfusion in the setting of a platelet count of < $10x10^3$/mcL.
5. Febrile neutropenia.
6. Grade 5 toxicity.

### 9.6 Progression-Free Survival (PFS)

From the date of registration to the date of first document of PD or symptomatic deterioration (as defined above), or death due to any cause. PFS for participants last known to be alive without report of progression, symptomatic deterioration, or death is censored at date of last contact.

### 9.7 Overall Survival (OS)

Measured from the date of registration until death from any cause. OS for participants last known to be alive is censored at the date of last contact.

### 9.8 Treatment Discontinuation Reasons (See Section 6.6)

See Section 6.6.

## 10.0 STATISTICAL CONSIDERATIONS

### 10.1 Overview

This study will be conducted as a single institution, single arm study as described in Section 6.1. Patients with newly diagnosed ES-SCLC undergoing induction therapy with platinum-etoposide and ICI will be treated with bomedemstat maintenance therapy in combination with standard of care maintenance atezolizumab until disease progression, unacceptable toxicity, or other treatment discontinuation reason.

The primary objectives of this study are to evaluate the safety of bomedemstat in combination with maintenance atezolizumab and to evaluate the percentage of patients who are alive and free from disease progression at 6 months following the initiation of bomedemstat with atezolizumab.

### 10.2 Safety Evaluation

The DLT assessment period is 21 days from initiation of treatment. The first 6 eligible patients who receive at least one dose of bomedemstat and atezolizumab with at least 21 days of follow-up (safety analysis population) will be closely monitored for toxicities. If more than 2 patients experience DLTs (see Section 9.5), then the starting dose of bomedemstat for a given platelet count will be reduced by 0.1 mg. Otherwise, accrual will proceed as described in Section 10.3. If the dose is reduced, following 6 additional patients meeting the criteria to be assessed for DLTs, the same rules will apply (continue at dose if <3 patients with DLT and dose reduce by 0.1 mg if >2 with DLT).

#### *10.2.1 Stopping Rule for Encephalopathy*

Due to the previous association of LSD1 inhibitors with encephalopathy[28], the occurrence of encephalopathy of any grade at any point during study participation will result in immediate study discontinuation and cessation of study treatment for all subjects.

#### *10.2.2 Stopping Rule for Recurrent Toxicity*

If four or more patients experience unacceptable toxicity requiring permanent cessation of study treatment, the study will be immediately discontinued, and study treatment will cease for all subjects.

### 10.3 Sample Size Justification and Analysis Plans

The total accrual goal to this study is 34 eligible patients. Based on the IMPOWER133 study, we estimate that 35% of patients with ES-SCLC are alive and free from disease progression at 6 months after initiation of maintenance anti-PD(L)1 therapy. With 34 patients, this study design has 90% power to detect a 25% improvement in 6-month PFS rates (from 35 to 60%) using a 1-sided binomial test at the 5% level. The observation of 17 patients progression-free (i.e. alive without PD or symptomatic deterioration) at 6 months (a 50% rate) would be considered evidence to rule out a 35% 6-month PFS rate. With 34 patients, proportions can be estimated to within 17% with 95% confidence and any toxicity with at least 10% prevalence is likely to be observed with 97% confidence.

Additional analyses will evaluate proportions (such as toxicity or response rates within subgroups) accompanied by 95% confidence intervals. Distributions for time-to-event outcomes (PFS, OS) will be evaluated using the method of Kaplan-Meier. For point estimates at landmark times, the associated 95%

confidence interval (CI) will be calculated using Greenwood's formula and based on a log-log transformation applied on the survival function.

### 10.4 Study Duration

Based on prior accrual to SCLC clinical trials at the Fred Hutchinson Cancer Center (previously Seattle Cancer Care Alliance), it is estimated that 34 patients can be accrued over 24 months.

### 10.5 Data and Safety Monitoring

See Section 11.1.

## 11.0 STUDY MANAGEMENT

All investigators on the protocol will receive formal training in the ethical conduct of human research. Institutional support of trial monitoring is provided in accordance with the Fred Hutchinson Cancer Center/University of Washington Cancer Consortium's data and safety monitoring plan.

### 11.1 Monitoring of the study

Institutional support of trial monitoring will be in accordance with the Fred Hutch/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, Fred Hutch Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or Fred Hutch employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed as needed by the Consortium Data and Safety Monitoring Committee (DSMC), Fred Hutch Scientific Review Committee (SRC) and the Fred Hutch/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study. The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state, and federal guidelines.

### 11.2 Data Management

The Principal Investigator, or her/his designees, will prepare and maintain adequate and accurate participant case histories with observations and other data pertinent to the study. Original source documents should be transcribed to Case Report Forms (CRFs) and used to analyze the study data. Source documents include hospital records, clinical charts, laboratory and pharmacy records, and recorded electronic data.

All data required by the trial will be entered onto paper and electronic case report forms. Any required corrections to data on paper case report forms must be made in such a way that the original entry is not obscured. Only designated study staff will enter data for study participants after study visits. Case report forms will be checked against source document data by study staff. Patient records will be kept in a secure location at the Fred Hutchinson Cancer Center accessible only to research authorized personnel. The patient identity will be kept as confidential as possible as required by law. Except as required by law, the patient will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Study subjects will be assigned an ID code. Information about the code will be kept in a secure location and access limited to research study personnel. The results of this research study

may be presented at scientific or medical meetings or published in scientific journals. However, the patient identity will not be disclosed. The patient's personal data which may be included in the investigator's database shall be treated in compliance with all applicable laws and regulations.

## 12.0 ETHICAL CONSIDERATIONS

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

The protocol will be approved and reviewed by the Cancer Consortium Scientific Review Committee (SRC) and the Institutional Review Board (IRB). Once activated, the protocol will be reviewed at least annually by both institutional entities.

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the Cancer Consortium IRB and SRC. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation.

Trial oversight will be carried out by the Principal Investigator, Dr. Rafael Santana-Davila, and his research staff, who will be qualified by education, training and experience to perform their respective tasks. Services of personnel for whom sanctions have been invoked for scientific misconduct or fraud will not be used. They will meet weekly to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above.

## 13.0 ABBREVIATIONS

| Abbreviation | Full term |
|---|---|
| CR | Complete response |
| DLT | Dose-limiting toxicity |
| DSMP | Date safety monitoring plan |
| ES | Extensive stage disease |
| ICI | Immune checkpoint inhibitor, i.e. monoclonal antibody targeting the PD-1/PD-L1 signaling axis |
| KDM1A | Lysine-specific demethylase 1A (preferred gene symbol for the gene LSD1) |
| LS | Limited stage disease |
| LSD1 | Lysine-specific demethylase 1 |
| PD | Progressive disease (also referred to as "disease progression") |
| PFS | Progression-free survival |
| PR | Partial response |
| SCLC | Small cell lung cancer |
| SD | Stable disease |

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## 15.0 APPENDIX

### 15.1 VALG Staging Details

Participants must have Extensive Stage (ES) SCLC as defined in the Veterans Administration Lung Study Group (VALG) staging system as follows:

| Stage | Characteristics |
|---|---|
| **Limited** | 7. Disease confined to one hemithorax, although local extensions may be present; and<br>8. No extrathoracic metastases except for possible ipsilateral,<br>9. supraclavicular nodes if they can be included in the same portal as the primary tumor; and<br>10. Primary tumor and regional nodes that can be adequately treated and totally encompassed in every portal |
| **Extensive** | 11. Inoperable patients who cannot be classified as having limited disease<br>12. NOTE: limited stage patients who develop |

| | |
|---|---|
| | disease progression during or following completion of definitive chemoradiation are considered to have extensive stage disease |