Phase II Trial of Platinum-Etoposide Chemotherapy and Durvalumab (MEDI4736) with Sub-Ablative Radiation in Patients with Newly Diagnosed Stage IV Small Cell Lung Cancer

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Statement of Compliance

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

Weill Cornell Medicine

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Institution Name

Ashish Saxena

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Principal Investigator's Name	**Principal Investigator's Signature**	**Date**

List of Abbreviations

3D-CRT	3D Conformal Radiation Therapy
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
CBC	Complete Blood Count
CI	Confidence Interval
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed Tomography
CTLA-4	Cytotoxic T-Lymphocyte-Associated protein 4
CTC	Circulating Tumor Cell
CTSC	Clinical Translational Science Center
D	Day
dL	Deciliter
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
EIPM	Englander Institute for Precision Medicine
EOT	End of Treatment
EpCAM	Epithelial Cell Adhesion Molecule
ES-SCLC	Extensive-Stage Small Cell Lung Cancer
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
HBV	Hepatitis B virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICB	Immune Checkpoint Blockade
ICF	Informed Consent Form
ImAE	Immune-Mediated Adverse Event
IMRT	Intensity Modulated Radiation Therapy

IO	Immunotherapy
IRB	Institutional Review Board
kg	Kilogram
mAb	Monoclonal Antibody
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PCI	Prophylactic Cranial Irradiation
PD-1	Programmed Cell Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PDTO	Patient Derived Tumor Organoids
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PS	Performance Status
RANKL	Receptor Activator of Nuclear Factor-κB Ligand
RECIST	Response Evaluation Criteria in Solid Tumors.
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiotherapy
SCLC	Small Cell Lung Cancer
SRS	Stereotactic Radiosurgery
TfR	Transferrin Receptor
TNM	Tumor, Node, Metastasis
TRT	Thoracic Radiotherapy
uL	Microliter
ULN	Upper Limit of Normal
VALCSG	Veterans Administration Lung Cancer Study Group
WBRT	Whole Brain Radiation Therapy

WCM	Weill Cornell Medicine
WES	Whole-Exome Sequencing

1. Protocol Summary

Full Title:	Phase II Trial of Platinum-Etoposide Chemotherapy and Durvalumab (MEDI4736) with Sub-Ablative Radiation in Patients with Newly Diagnosed Stage IV Small Cell Lung Cancer
Short Title:	Chemo-IO + RT in SCLC
Clinical Phase:	II
Principal Investigators:	Ashish Saxena, MD, PhD and Encouse Golden MD, PhD
Study Description:	This is a non-randomized, open-label, single-arm pilot phase II study of non-ablative radiotherapy in combination with standard-of-care chemo-immunotherapy in patients with untreated, extensive-stage (Stage IV) small cell lung cancer. Subjects will be treated with etoposide plus platinum (carboplatin or cisplatin) chemotherapy together with the PD-L1 checkpoint inhibitor durvalumab, which is a standard of care in this disease setting. Subjects will also receive a total of 6 Gy of radiotherapy X 5 fractions via 3D-CRT, IMRT, or SBRT and targeting multiple sites of intrathoracic disease when feasible and/or any site required for palliation of symptoms. Radiation will start prior to the completion of the second cycle of chemo-immunotherapy but will ideally begin on the first day of the first cycle; no further radiation will be planned after this. The hypothesis of this study is that the addition of sub-ablative doses of radiation to combination chemotherapy and immunotherapy will be safe and feasible and result in improved outcomes for patients with treatment-naive, extensive-stage small cell lung cancer.
Sample Size:	N= 42
Enrollment:	This study will plan to enroll 42 subjects to allow for 34 to be evaluable for the primary endpoints.
Study Population:	Adults aged 18 or older with untreated, extensive-stage small cell lung cancer.
Enrollment Period:	40 Months
Study Design:	This is a prospective, non-randomized, open-label, single-arm pilot phase II study of non-ablative radiotherapy in combination with standard-of-care chemo-immunotherapy in patients with untreated, extensive-stage (Stage IV) small cell lung cancer. This study will plan to enroll 42 subjects to allow for 34 to be evaluable for the primary

	endpoints. All subjects will be treated with etoposide plus platinum (carboplatin or cisplatin) chemotherapy together with the PD-L1 checkpoint inhibitor durvalumab, which is a standard of care in this disease setting. All subjects will also receive a total of 6 Gy of radiotherapy X 5 fractions via 3D-CRT, IMRT, or SBRT and targeting multiple sites of intrathoracic disease when feasible and/or any site required for palliation of symptoms. Radiation will start prior to the completion of the second cycle of chemo-immunotherapy but will ideally begin on the first day of the first cycle; no further radiation will be planned after this. There will be a safety run-in period involving the first 10 subjects enrolled wherein if there is a 30% or greater incidence of grade 3 or higher toxicities with the proposed treatment regimen - specifically from radiation therapy (with focus on pneumonitis, pericarditis, esophagitis, rib fracture, or hemoptysis) or immune-mediated adverse events (other than thyroid dysfunction) - then the radiation regimen will subsequently be switched to 5 Gy radiation per day for 5 fractions. Systemic therapy will be given as follows: - Carboplatin at AUC = 5-6 mg/mL per min or Cisplatin at 75-80mg/m2 on Day 1 of each 21-day cycle, for 4 cycles - Etoposide at 80-100mg/m2 on Day 1, Day 2, and Day 3 of each 21-day cycle, for 4 cycles - Durvalumab at 1500mg on Day 1 of each 21-day cycle, for 4 cycles; following this, subjects will receive 1500mg Durvalumab once every 4 weeks until disease progression. Prophylactic Cranial Irradiation (PCI) and consolidative Thoracic Radiotherapy (TRT) will not be given.
Description of Sites/ Facilities Enrolling Participants:	This study will enroll subjects at NewYork Presbyterian Hospital-Weill Cornell Medicine. All sites are in the United States and within New York City.
Study Duration:	48 Months
Participant Duration:	12 months
Study Agent/Device Name Intervention Description:	- Carboplatin AUC = 5-6 mg/mL per min IV or Cisplatin 75-80mg/m2 IV on Day 1 of each 21-day cycle, for 4 cycles - Etoposide 80-100mg/m2 IV on Day 1, Day 2, and Day 3 of each 21-day cycle, for 4 cycles

- Durvalumab 1500mg IV on Day 1 of each 21-day cycle, for 4 cycles; following this, subjects will receive 1500mg Durvalumab IV once every 4 weeks until disease progression
- A total dose of 6 Gy radiation per day for 5 fractions via 3D-CRT, IMRT, or SBRT and targeting multiple sites of intrathoracic disease when feasible and/or any site required for palliation of symptoms. Radiation will start prior to the completion of the second cycle of chemo-immunotherapy but will ideally begin on the first day of the first cycle

Primary Objective:

To examine the safety and efficacy of adding multi-site, non-ablative radiation to standard systemic therapy with carboplatin or cisplatin and etoposide plus durvalumab for patients with extensive-stage small cell lung cancer.

Exploratory Objectives:

- To examine the tumor-immune microenvironment and the circulating immune cell and inflammatory protein composition in responders vs non-responders.
- To grow tumor organoids from tissue samples collected
- To isolate and characterize circulating tumor cells (CTCs) from peripheral blood

Specifically, will examine:

1. Cytokine levels, including type I interferon (IFN-I)
2. Frequencies of immune cells among peripheral blood mononuclear cells (PBMCs): $CD4^+$ T cells, $CD8^+$ T cells, natural killer (NK) cells, myeloid-derived suppressor cells (MDSCs), T regulatory cells (Tregs), macrophages, dendritic cells (DCs)
3. Frequencies of tumor-infiltrating lymphocytes (TILs) in tumor samples
4. T cell receptor (TCR) repertoire of $CD8^+$ T cells from PBMCs and TILs
5. RNA sequencing profiles of tumors, tumor organoids, and CTCs
6. Mechanisms of resistance using tumor organoids

Endpoints:

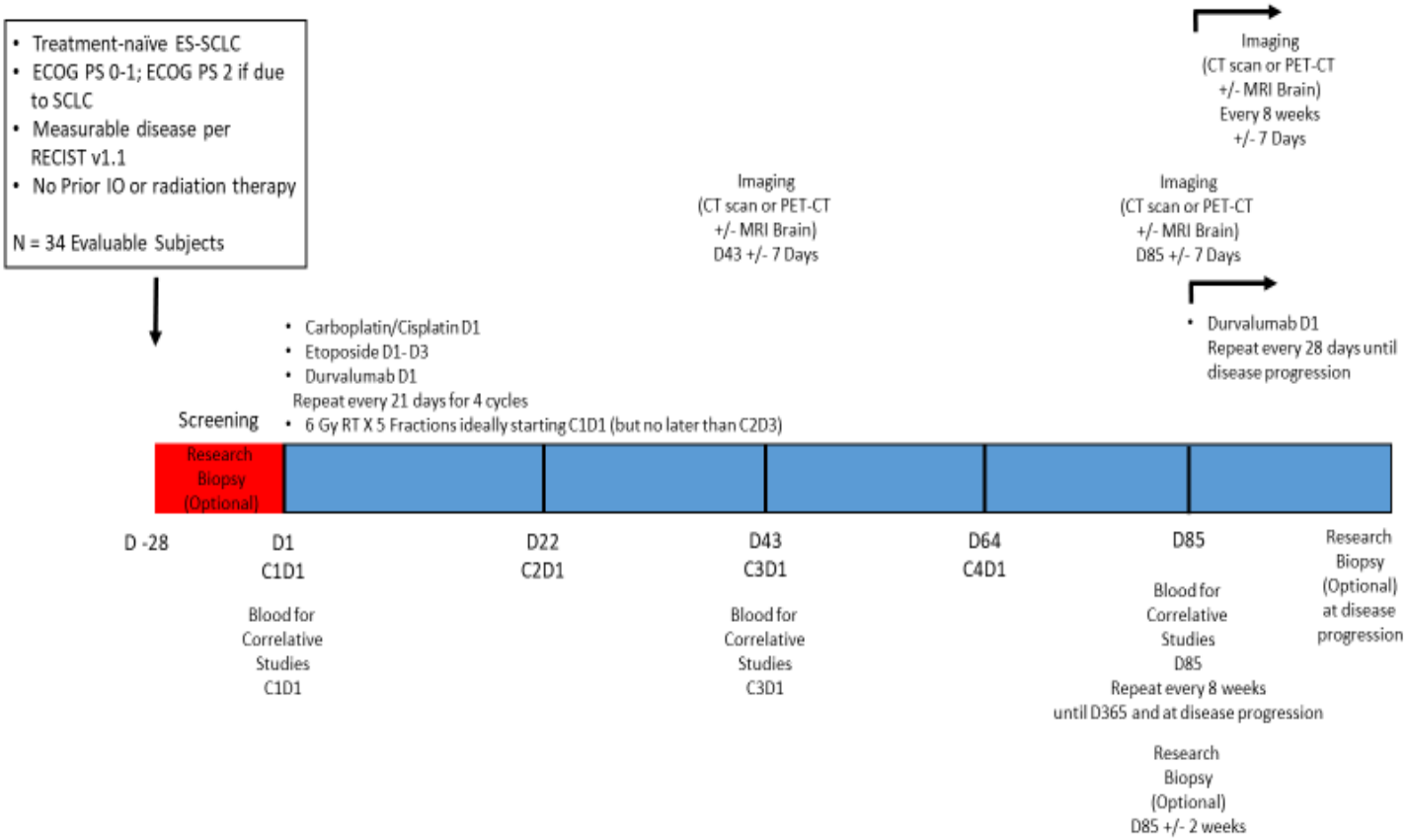
Co-Primary Endpoints:

- 12-month Progression-Free Survival
- Safety in terms of Incidence of ≥ Grade 3 Toxicities related to therapy given

Secondary Endpoints:

- 12-month Overall Survival
- Response Rate
- Median Progression-Free Survival
- Median Overall Survival
- Pattern of Disease Progression

1.1 Schema



1.2 Study Objectives

1.2.1 Primary Objective

To examine the safety and efficacy of adding multi-site, non-ablative radiation to standard systemic therapy with carboplatin or cisplatin and etoposide plus durvalumab for patients with extensive-stage small cell lung cancer.

Co-Primary Endpoints:

- 12-month Progression-Free Survival
- Safety in terms of Incidence of ≥ Grade 3 Toxicities related to therapy given

Secondary Endpoints:

- 12-month Overall Survival
- Response Rate
- Median Progression-Free Survival
- Median Overall Survival
- Pattern of Disease Progression

1.2.2 Exploratory Objectives

- To examine the tumor-immune microenvironment and the circulating immune cell and inflammatory protein composition in responding and resistant individuals.
- To isolate and characterize circulating tumor cells (CTCs) from peripheral blood
- To grow tumor organoids from tissue samples collected

Specifically will examine:

1. Cytokine levels, including type I interferon (IFN-I)
2. Frequencies of immune cells among peripheral blood mononuclear cells (PBMCs): CD4+ T cells, CD8+ T cells, natural killer (NK) cells, myeloid-derived suppressor cells (MDSCs), T regulatory cells (Tregs), macrophages, dendritic cells (DCs)
3. Frequencies of tumor-infiltrating lymphocytes (TILs) in tumor samples
4. T cell receptor (TCR) repertoire of CD8+ T cells from PBMCs and TILs
5. RNA sequencing profiles of CTCs
6. Mechanisms of resistance using tumor organoids

2. Background

2.1 Small Cell Lung Cancer

Lung Cancer is the leading cause of cancer death in the United States and is expected to account for roughly one-fourth of cancer deaths in this country in 2020[1]. It has traditionally been divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), based on tumor histology. SCLC represents approximately 10-15% of new lung carcinoma diagnoses, and this disease is characterized by a rapid doubling time and early development of lymph node and distant metastases, often already present at the time of diagnosis. The VALCSG system is the most commonly used staging system in clinical practice and divides small cell lung cancer into limited-stage and extensive-stage disease. Limited-stage small cell lung cancer is defined as disease confined to one side of the chest as evidence by imaging and/or the ability of a radiation oncologist to encompass the disease in a “tolerable radiation field”. Patients with limited-stage disease are typically treated with curative intent using concurrent chemotherapy and radiation therapy, with 5-

year survival rates between 13% and 38%. Rarely, in cases of very limited disease, patients may undergo surgical resection followed by adjuvant chemotherapy and possibly adjuvant radiation. Patients who demonstrate SCLC beyond the limited-stage are classified as having extensive-stage SCLC (ES-SCLC). This includes those with malignant pleural effusion, contralateral lung nodules on both sides of the chest, distant metastases, and/or an overall disease burden that cannot be safely radiated within a "tolerable radiation field"[2,3]. ES-SCLC generally corresponds to Stage IV disease according to the TNM staging system[4].

About two-thirds of patients present with ES-SCLC, and although it is initially highly sensitive to chemotherapy with high response rates, most responses are not durable and the disease quickly progresses and becomes refractory to chemotherapy treatment. The median survival with standard platinum-etoposide chemotherapy is about 10 months, and this was the standard-of-care treatment for ES-SCLC for decades[2,3]. More recently, however, there have been multiple attempts to improve systemic therapy with the addition of immunotherapy. Among these efforts, IMPower133 was the first positive study, demonstrating that the addition of the anti-PD-L1 monoclonal antibody (mAb) atezolizumab to carboplatin and etoposide significantly improved progression-free survival (PFS) and overall survival (OS) compared to chemotherapy alone (median PFS = 5.2 months vs 4.3 months with hazard ratio for disease progression or death = 0.77 [95% Confidence Interval (CI) = 0.62 to 0.96 with p = 0.02]; median OS = 12.3 months vs 10.3 months with hazard ratio for death = 0.70 [95% CI = 0.54 to 0.91 w/ p = 0.007] [5]. The positive findings from IMPower133 established the combination of chemotherapy plus immune checkpoint blockade (ICB) as the new standard-of-care approach for ES-SCLC. However, despite achieving statistical significance, the absolute improvement in median PFS or OS with the addition of atezolizumab was only 1-2 months beyond chemotherapy alone. Recently, planned interim analysis results from CASPIAN, a phase 3 trial using the anti-PD-L1 mAb durvalumab +/- the anti-CTLA-4 mAb tremelimumab in combination with platinum-etoposide chemotherapy for patients with ES-SCLC showed that the addition of durvalumab to chemotherapy also improved median OS compared to chemotherapy alone (median OS = 13.0 months vs 10.3 months with hazard ratio of 0.73 [95% CI = 0.59 – 0.91 with p = 0.0047]). However the absolute improvement in median OS with the addition of durvalumab was again less than 3 months and the 12-month PFS rate with combination chemotherapy-durvalumab was only 18%[6].

In light of the above, there remains a significant opportunity and an unmet need for novel therapeutic approaches for ES-SCLC to enhance the effectiveness of the combination of chemotherapy and ICB. Interestingly, consolidative thoracic radiotherapy was not permitted in either IMPower133 or CASPIAN. However, the CREST trial, which did not utilize any ICB therapy, showed a 10% 2-year survival rate benefit for patients with ES-SCLC receiving consolidative thoracic radiotherapy after any response to 4-6 cycles of standard platinum-based chemotherapy (13% 2-year OS in the thoracic radiation group [CI = 9%–19%], *vs* 3% in the control group [CI = 2%–8%]; p=0·004)[7]. This has given rise to the speculation that radiotherapy may be contributing to more than local control within the irradiated field, including immune-mediated distant control of disease, and that radiation could be a formidable partner with immune checkpoint blockade[8].

2.2 Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca for use in the treatment of cancer. The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro*

studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ[9]. *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism[9]. Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.
The non-clinical and clinical experience with Durvalumab is fully described in the most current version of the durvalumab Investigator's Brochure. To date durvalumab has been given to more than 8000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents.

2.3 Radiation Therapy and Tumor Immunity

Radiation therapy has generally had a limited role for the upfront management of ES-SCLC. Historically, this was based on the prevailing belief that radiation therapy, functioning primarily as a local modality, would have a very modest role once a cancer has metastasized. This was due to the expectation that radiation would have a limited effect on clinically meaningful endpoints in the setting of metastatic disease. However, this view of radiation therapy has gradually been superseded by a more nuanced perspective: The observation that radiation may occasionally induce anti-tumor effects on non-targeted lesions, termed the abscopal effect, has led to investigations that established the critical interplay between radiation therapy and tumor immunity[10]. Mechanistically, radiation therapy promotes immunogenic cell death in tumor cells, thereby recruiting elements of the innate and adaptive immune response and effectively converting an immunosuppressive tumor microenvironment into one that can generate and support tumor immunity. Multiple preclinical studies have demonstrated that the primary mediators of radiation-induced immunity are CD8+ T cells[11]. In early-phase trials of patients with metastatic NSCLC, local sub-ablative stereotactic body radiation therapy (SBRT) to a metastatic lesion, in combination with immunotherapy (e.g., the anti-CTLA-4 mAb ipilimumab), has been shown to generate clinically significant tumor immunity, leading to a robust systemic response that appears to be an important contributor to the tumor response[12]. Additionally, in patients with non-resectable Stage III NSCLC, the robust overall survival benefit without undue toxicity reported with the addition of durvalumab in the PACIFIC trial was preceded by comprehensive concurrent chemoradiation targeting the primary tumor and loco-regional nodal metastases[13]. Thus, reduction in tumor burden and relief of immune suppression afforded by concurrent chemoradiation may potentially augment immunogenicity.

Several lines of clinical evidence have recently suggested that local consolidation with radiotherapy in select subsets of patients with low metastatic disease burden can meaningfully extend survival[14-16]. While confirmatory phase III studies are pending, the overall survival signal with multi-site SBRT observed in the SABR-COMET study of stereotactic ablative radiotherapy vs standard of care palliative treatment in patients with oligometastatic cancers is compelling and suggests that this approach is feasible and associated with an improved quality-of-life – although caution should be applied as treatment-related mortality did occur in the SBRT arm[16,17]. Gomez et al. found a median OS benefit for local consolidative radiotherapy (41.2 months [95% CI = 18.9 months to not reached]) versus maintenance therapy or observation (17.0 months [95% CI = 10.1 to 39.8 months] with p = .017 in NSCLC patients with oligometastatic disease (~2/3^{rds} had only a single metastatic site). In addition, no additional grade 3 or greater toxicities were observed in the radiotherapy arm[15]. Given the early clinical promise of multi-site radiation, it is a rational extension to evaluate multi-site radiation in the context of immunotherapy. Luke et al. conducted a phase I trial of multi-site SBRT

followed by pembrolizumab. While response rates were modest in a heterogeneous, heavily pre-treated population, these investigators did observe upregulation of an IFN-ɣ-related RNA signature in non-irradiated lesions (prior to receipt of immunotherapy) providing evidence of systemic immunomodulation in response to multi-site SBRT[18].

The clinical benefit associated with multi-site radiation may simply be a reflection of improved outcomes due to cytoreduction and direct tumor cell kill. However, a reduction in systemic disease burden may also facilitate anti-tumor immunity. It is known that persistent antigenic stimulation, as occurs in the context of established tumors (that have escaped immune surveillance) and chronic viral infection, may lead to impaired cytotoxic T-cell function and an exhausted T-cell phenotype[19]. As such, a high tumor burden state may be conceptualized as a state of immune dysfunction due to excessive and persistent antigen. Huang et al. eloquently demonstrated that pre-treatment tumor burden is a major determinant of outcome among melanoma patients treated with anti-PD-1 immunotherapy and provided mechanistic evidence that CD8+ T-cell reinvigoration (Ki-67+ PD-1+) alone may not be sufficient to yield a clinical response in the context of high tumor burden[20]. Indeed, an elevated "reinvigoration-to-tumor burden" ratio was positively associated with objective response rate and overall survival. As such, a reduction in tumor burden and consequently antigen load may in part explain how cytoreductive therapies such as multi-site SBRT can facilitate responses to immunotherapy. In support of this concept, preclinical models have demonstrated that the cytoreductive effects of cisplatin can further augment abscopal responses in mice treated with radiation and anti-PD-1 therapy. The addition of cisplatin to the radio-immunotherapy doublet led to enhanced T-cell trafficking and antigen-specific T-cell infiltration into non-irradiated tumors, which extended survival relative to any other combination regimen[21].

The aforementioned translational studies and proof-of-principle trials have paved the way for ongoing studies combining radiation with ICB in metastatic NSCLC. However, there are a paucity of similar studies in ES-SCLC, particularly in the front-line setting. A small (17 subject) randomized phase II study of tremelimumab and durvalumab with or without SBRT (at 9Gy X 3 fractions to one selected tumor site) for patients with relapsed ES-SCLC who had received 1-2 lines of prior therapy failed to show sufficient signals for efficacy with ICB therapy with or without SBRT, though there was a trend toward improved PFS and OS with the addition of radiation[22].

2.4 Rationale

As detailed above, survival for patients with ES-SCLC is generally poor, with median overall survival only around 12-13 months even with initial treatment involving combination chemotherapy and immunotherapy[5,6]. Subsequent treatments for this study population usually involve single-agent chemotherapies, which then show median survivals of only 3-6 months[3]. Thus, new strategies are still needed to improve outcomes in this patient population. The addition of sub-ablative and possibly multi-site intrathoracic radiation to standard chemo-immunotherapy may enhance the tumor immune response and lead to better survival outcomes for this patient population.

2.5 Risk/Benefit Assessment

2.5.1 Known Potential Risks

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism,

and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis, and endocrinopathies including hypo- and hyper-thyroidism.

Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/interstitial lung disease (ILD), endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus (which may present with diabetic ketoacidosis), and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion related reactions, hypersensitivity reactions, pancreatitis, encephalitis, serious infections, subcutaneous injection site reaction, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis)

For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.

The potential adverse effects (AEs) of the systemic therapy regimen of cisplatin or carboplatin plus etoposide together with durvalumab were reported in the results of the CASPIAN study (see Appendix A). Specifically, AEs of any cause and grade occurred in 98% of subjects treated with durvalumab plus platinum-etoposide, while 62% of those in this study arm developed any grade 3 or 4 AE, the most common of which were neutropenia and anemia. Only 9% of subjects developed an AE that lead to discontinuation of therapy, however. Deaths due to AE of any cause occurred in 5% of subjects, similar to that in the standard platinum-etoposide group. Immune-mediated AEs (ImAEs) occurred in 20% of subjects treated with durvalumab plus platinum-etoposide, with only 5% being grade 3 or 4. The most common ImAEs were hypo- and hyperthyroidism. Death due to ImAE occurred in <1% of subjects (1 subject – due to hepatotoxicity)[6].

A primary objective of this study is to evaluate the risks of adding non-ablative radiation to the above treatment regimen. Potential risks which the study will focus on will be an increase in ImAEs (other than thyroid dysfunction, which is generally easily managed), and an increase in radiation-related AEs, specifically pneumonitis, pericarditis, esophagitis, rib fracture, and hemoptysis. The reported rates of pneumonitis after SBRT requiring intervention range from 0-29%, with an uncommon occurrence of severe (≥ grade 3) pneumonitis[23-26]. Reported cardiac events associated with SBRT occur in 0-7.9% of treated patients[23,27-29]. Chest wall related toxicities after SBRT include skin toxicity (1.2-14%)[30,31], rib fracture (5%) and chronic chest wall pain (5-25%) and are usually associated with peripherally located lung tumors[32,33]. Esophageal injury ranging from mild esophagitis to stricture, perforation, and/or fistula formation has been reported to occur in 12% of patients treated with SBRT[34,35]. Finally, with standard fractionation schemes fatal hemoptysis secondary to aortic damage, rupture, aneurysm, or aortic dissection may occur in up to 5.7% of patients, particular for those that receive a maximum composite dose to 1cm^3 of the aorta ≥ 120Gy (25% rate of grade 5 toxicity) versus < 120Gy (0% rate of grade 5 toxicity)[36]. Similar cases have been reported with

SBRT[37]. Currently, 50Gy delivered over five fractions has been a widely adopted SBRT regimen for treatment of centrally located tumors and tumors close to the chest wall[38,39]. Less intensive SBRT fractionation schemes or risk-adapted approaches further limits toxicities and provides for a safer approach[26,40-42]. For this study, we have chosen a conservative regimen of 25-30Gy delivered over five fractions (less than the commonly used 50Gy delivered over five fractions regimen). While this radiation will be delivered via SBRT whenever feasible, radiation via 3D-CRT and IMRT will also be permitted..

2.5.2 Known Potential Benefits

The potential benefit of the systemic therapy regimen of cisplatin or carboplatin plus etoposide together with durvalumab were reported in the results of the CASPIAN study and are outlined in the background section of this protocol.[6] We hypothesize that the addition of radiation to one or more sites of disease will enhance the efficacy of systemic chemotherapy plus immunotherapy, improving 12-month progression free survival and possibly also response rates and median progression-free and overall survival. This hypothesis is based on data outlined in the background section which have shown that radiation in dosages similar to those used in this protocol can augment checkpoint-inhibitor-induced, immune-mediated killing of non-small cell lung cancer. This includes unpublished preliminary data from our clinical trial of neoadjuvant durvalumab with or without non-ablative SBRT for the pre-operative treatment of stage I, II, and IIIA NSCLC (https://clinicaltrials.gov/ct2/show/NCT02904954) and our clinical trial of ipilimumab plus nivolumab with non-ablative SBRT for stage IV NSCLC (https://clinicaltrials.gov/ct2/show/NCT03168464).

2.5.3 Assessment of Potential Risks and Benefits

Given known safety profiles of systemic therapy with platinum-etoposide plus durvalumab systemic therapy, as well as those of non-ablative radiation, we believe that the combination of these two approaches will be safe and feasible in this study population of patients with treatment-naïve ES-SCLC. As safety will be a primary objective of this study, the subjects will be monitored closely for adverse events, which will be a primary endpoint of the trial. The study includes a safety run-in period involving the first 10 subjects enrolled wherein if there is a 30% or greater incidence of grade 3 or higher toxicities with the radiation regimen of 6 Gy per day for 5 fractions - specifically from radiation therapy or ImAEs (other than thyroid dysfunction) - then the radiation regimen will subsequently be switched to 5 Gy radiation per day for 5 fractions. If there is still a 30% or greater incidence of grade 3 or higher toxicities from radiation therapy or ImAEs adverse events among the subsequent 10 subjects, then the study will be terminated.

We therefore believe that the potential value of the information gained from this trial and the potential for improvement in outcomes will likely outweigh the possible increased risk to participants.

2.6 Correlative Studies Background

2.6.1 Tumor-Immune Microenvironment and Circulating Immune Cells/Inflammatory Proteins

An anti-tumor immune response is dependent on the appropriate balance of activities

from effector cells and suppressor cells in the tumor-immune microenvironment[43]. ICB therapies can alter the compositions of circulating and tumor-infiltrating immune cells and these compositions can correlate with treatment response[44-46]. Additionally, radiation therapy to tumors causes accumulation of DNA in the cytoplasm of irradiated cells which in turn leads to the activation of the cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) pathway, with the resultant production of type 1 interferon (IFN) and other pro-inflammatory cytokines. These cytokines also play a role in tumor-immune response.[47] Other cytokines and soluble factors that can be increased by radiation therapy may be associated with immune suppression (e.g., soluble MICA/B, soluble CD73)[48].

We therefore will plan to examine the tumor-immune microenvironment and the circulating immune cell and inflammatory protein composition in the study subjects, as correlative studies. Specifically, we will isolate peripheral blood mononuclear cells (PBMCs) and examine them for frequencies of CD4+ T cells, CD8+ T cells, natural killer (NK) cells, myeloid-derived suppressor cells (MDSCs), T regulatory cells (Tregs), macrophages, and dendritic cells (DCs). We will specifically examine $Ki67^{+}PD\text{-}1^{+}$ CD8 T cells with an effector-like phenotype ($HLA\text{-}DR^{+}CD38^{+}Bcl\text{-}1^{low}$) since they have been shown to be predictive of response In lung cancer patients treated with anti-PD-1 when increased within 4 weeks of treatment start from baseline by two to seven-fold [49]. We will also quantify cytokine levels in the peripheral blood of subjects, particularly type-1 IFN. Additionally, if we are able to obtain sufficient tissue from biopsy samples, we will examine the frequencies of tumor-infiltrating lymphocytes (TILs) in these samples, as well as the T cell receptor (TCR) repertoire of the CD8+ T cells from the TILs and the PBMCs. These studies may provide insight into the mechanisms of immune response and resistance to the treatment modalities used in this study.

2.6.2 Tumor Organoids

As part of the Englander Institute for Precision (EIPM) at Weill Cornell Medicine, the Tumor Organoid Platform is an active program focused on development of 3D patient derived tumor organoids (PDTO) from metastatic and primary anatomic sites, obtained through biopsies, surgical resections and rapid autopsy procedures. The fresh tissue is obtained through our IRB-approved precision medicine clinical trial where full patient consent is obtained for both organoid and xenograft development. Standard operation procedures are in place for all aspects of tissue processing and culture maintenance. In this setting, we are able to extend our personalized medicine program to include high throughput and/or targeted drug screening which can be validated through histologic examination and genomic sequencing, and both *in vivo* and *in vitro* models. To date, we have established in our biobank, more than a 100 3D PDTOs, spanning a range of 13 primary tumor types that can be used for a variety of experiments and co-clinical trials (Figure 1).

In our recent publications, PDTO samples have demonstrated high purity as well as ploidy and genomic burden profiles that matched patient tumor data. Allele-specific copy-number analysis of 1,062 putative cancer genes showed a median of 86% concordance when comparing PDTOs to the native tumor tissues. Minor differences observed are either due to subclonality in the native tumor (subclones not represented in the PDTO) or due to the progression of the PDTO/PDX. Similarly, SNV analysis showed excellent concordance between native tumors and matching PDTOs. We have demonstrated that

these specimens can be successfully thawed and reestablished in culture for use in scientific research. Organoid technologies are developed in a dedicated space which is comprised of 3 four-foot biosafety cabinets, 6 Panasonic incubators, a Beckman Coulter centrifuge, an Olympus inverted microscope (CKX53), Olympus DP73 camera and Cell Sense Imaging Software, VWR water bath and a Thermo Scientific, MaxQ 4450 incubated shaker.

The EIPM's new high throughput drug screening platform is an integrative robotics system that connects some of the most coveted laboratory equipment on the market into a fully modular, HEPA filtered unit. With capabilities such as high content imaging, endpoint reads using a variety of PMT channels, in house static and dynamic incubator systems, a centrifuge and a state of the art liquid handler connected by two robotic arms and a powerful scheduling software, fully customized experiments can be run in their entirety in a sterile environment. Instrument software is scheduled to be 21CFR.11 compliant by the end of 2021 and it is our goal to develop our platform into a CLIA certified testing facility.

The Operetta CLS high content imaging system enables live cell experiments, 3D imaging, and high resolution and fast read times. Associated with Harmony software which is specifically designed for 3D cell models, the Operetta is capable of sensitive and quantitative measurements that can be used as a stand-alone reader or incorporated into our high throughput automation system. Spinning disk confocal optics and synchronized LED illumination provide stable excitation and minimize phototoxicity and bleaching for meaningful live-cell assays. A large format sCMOS camera with water-immersion objectives provides high resolution, while the software addresses the imaging and analysis challenges presented by complex cellular models.

Over the last few months we have been optimizing and validating image-based cell viability measurements using our previously biobanked organoids. The validation was done against an endpoint metabolic measure of ATP production. For this, one of our established colorectal lines, PM1230, which was shown to have a mutation in KRAS was treated with the MEK inhibitor Trametinib. A dose response curve starting at 3µM with an 8-point dilution of 1:3 was compared to an untreated control (DMSO). Duplicate experiments were run in parallel; one for the purpose of imaging and the other for cell titer glo measurement of cell metabolism. After 4 days of treatment, NucBlue and Cell Mask were added to the plates slotted for image analysis, after which they were incubated for 1 hour at 37°C. A pre-scan analysis was performed at a magnification of 5X (air) to pre-select an unbiased population of organoids utilizing instrument based software features. Selected organoids were then re-scanned at 63X (water-immersion), using z-stack analysis tools in order to perform 3D image analysis. As shown in Figure 2, both methods exhibit the same drug response. Although further optimization is required to reach the full potential of this platform, these results are a promising use of high content imaging as a complement to the indirect measure of viability using Cell Titer Glo.

As proof-of-concept, we have already generated and banked 15 lung PDTOs from treatment naïve Non-Small Cell Lung Cancer patients. Targeted sequencing of the initial lung PDTOs lines showed they contain cancer driver mutations (KRAS, EGFR and P53), confirming that our growth conditions are optimized for lung cancer organoids (Figure 3). In this study we will focus on growing organoids from Small Cell Lung Cancer patients.

3.

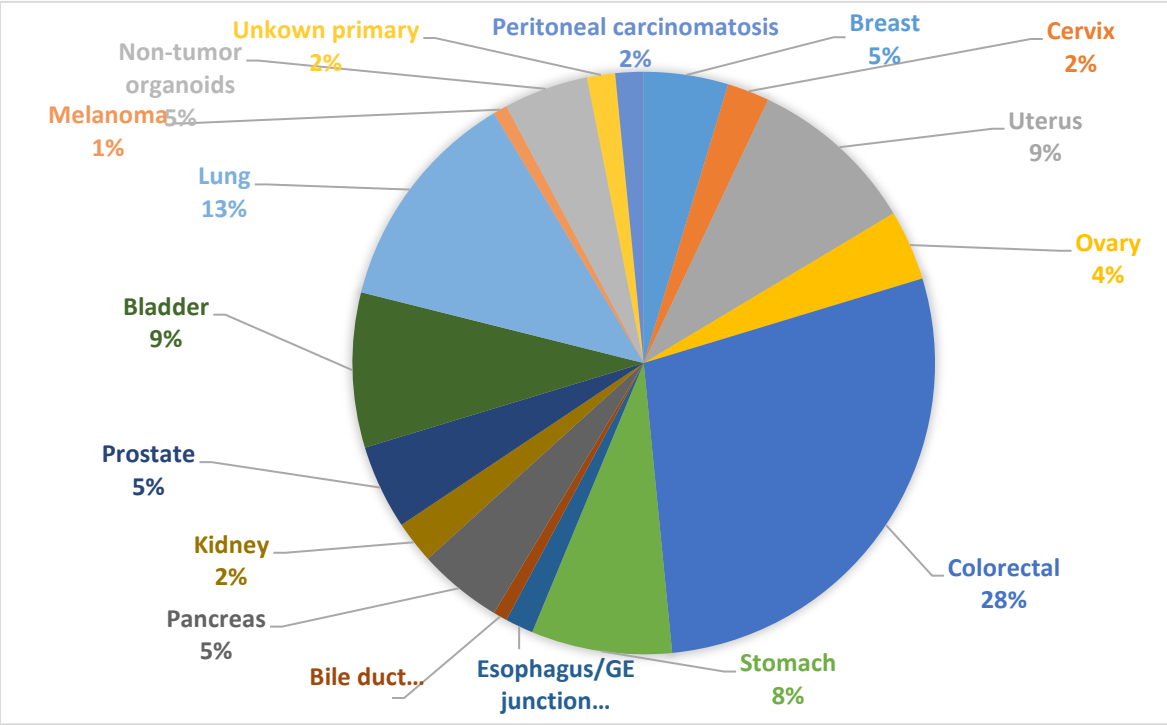


Figure 1. Patient-derived tumor organoid biobank at Englander Institute for Precision Medicine

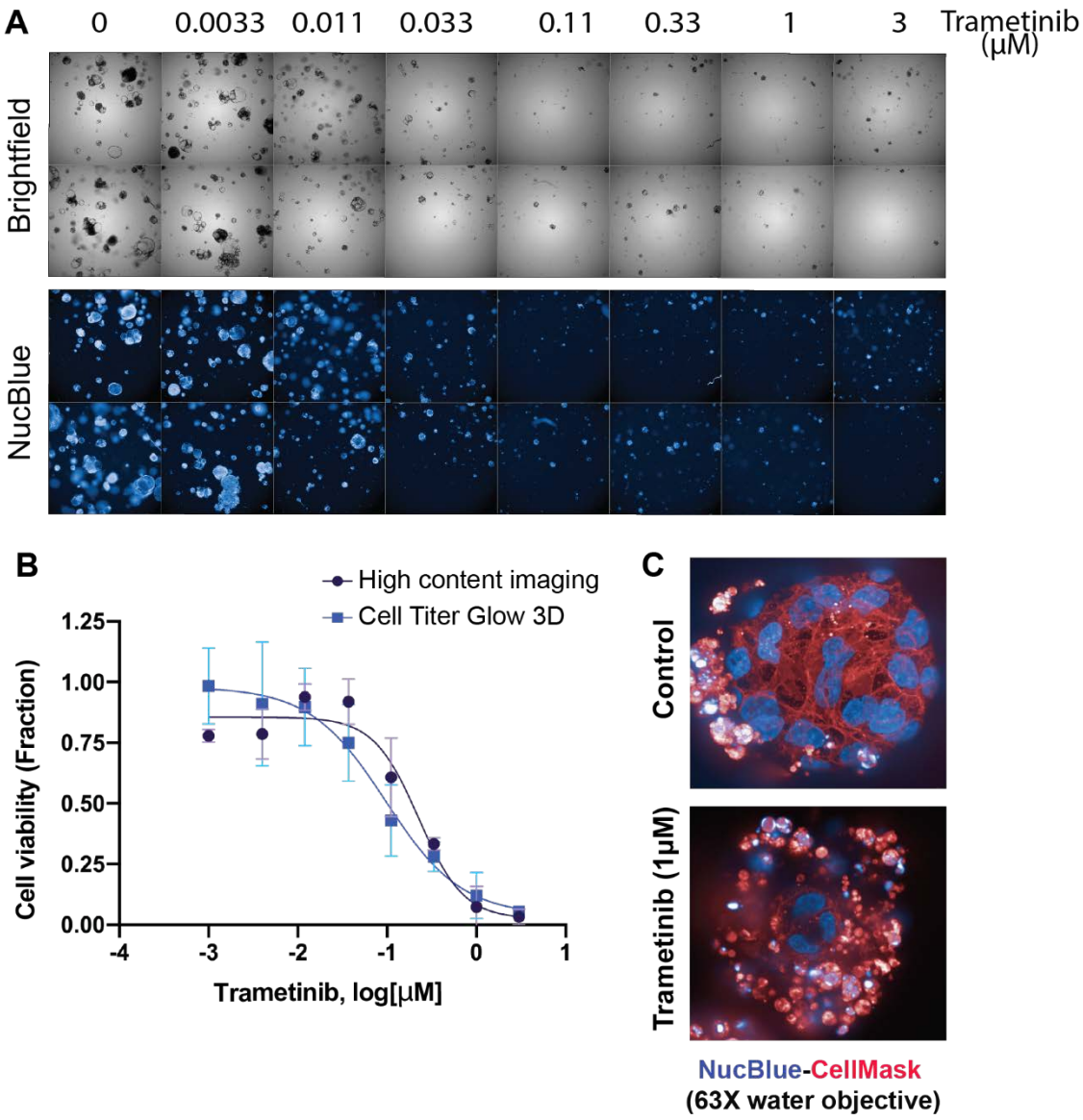


Figure 2. Optimization of the high throughput imaging platform. (A) Representative brightfield (upper panel) and NucBlue (lower panel) pictures of a colorectal organoid line (PM1230) treated with a dose response of Trametinib, a K-Ras inhibitor (starting at 3µM with a 3-dilution factor). The pictures were taken with a 5X air objective (B) Quantification of organoid volume (μm^3) using our high content system Operetta in combination with Harmony Software based on 3D imagining of NucBlue. (C) Viability measurement of organoid line PM1230 in a parallel experiment to (A) using Cell Titer Glo 3D, which measures ATP production. Data was normalized to control (untreated) and represents meanSEM. (D) Representative pictures of PM1230 colorectal organoids at 63X magnification stained with NUcBlue (Blue) and CellMask (Red).

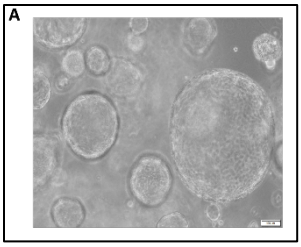


Figure 3 Representative brightfield picture of Non-Small Cell Lung tumor organoids cultured in matrigel.

2.6.3 Circulating Tumor Cells

A technical limitation of studies aimed to understand molecular determinants of therapeutic response in cancer cells is the availability of tumor tissue. First, the invasive nature of biopsies often prevents longitudinal analysis of the dynamic response of cancer and immune cells to the treatment. Second, tissue derived from the biopsy of a single tumor site may not recapitulate the entire tumor biology. This lack of tumor material, together with the inability to perform serial tumor biopsies, limits extensive and longitudinal investigation of the molecular determinants of tumor response to treatment and disease progression.

To overcome these limitations, we will utilize circulating tumor cells (CTCs) as a source of tumor material to investigate the molecular response of tumor cells to the proposed treatment. To date, most CTC enrichment methodologies (including the only FDA-cleared method, CellSearch), utilize the Epithelial Cell Adhesion Molecule (EpCAM) as a positive selection CTC marker. Several studies reported that CellSearch successfully identifies CTCs in SCLC patients and that EpCAM-based CTC enumeration yields prognostic significance[50]. $EpCAM^{+}$-CTCs have been previously utilized to interrogate the molecular characteristics of SCLC as they can recapitulate clinical response to chemotherapy in patients[51]. However, EpCAM expression is significantly reduced or even lost during the epithelial-mesenchymal transition (EMT), a key process in cancer progression during which metastatic capability is acquired[52]. Therefore, the population of $EpCAM^{+}$-CTCs represents only a subpopulation of CTCs, limiting their biological relevance and clinical use. To help overcome this limitation in NSCLC patients, Dr. Paraskevi Giannakakou's lab identified Transferrin Receptor (TfR) as an alternative cell-surface antigen that can be used to capture CTCs across the EMT gradient. TfR is a cell surface protein that mediates intracellular iron uptake by binding to the iron carrier transferrin. This protein is expressed at low levels in many normal tissues but it is significantly over-expressed in cancer cells, including NSCLC cells[53]. However, it is unclear if this protein is overexpressed in SCLC tumors and CTCs, though we are currently assessing this in the lab.

As a correlative study of this trial, we will prospectively and longitudinally isolate and molecularly analyze CTCs and matching peripheral blood mononuclear cells (PBMCs) from subjects receiving the combination of chemo-immunotherapy and non-ablative radiation. The goal of our analysis is to identify genes/pathways associated with clinical response/resistance to this treatment by performing untargeted RNA sequencing of patient-derived-CTCs (tumor compartment) with matching PBMCs (immune compartment).

To overcome the limitations intrinsic to an EpCAM-based positive selection, we will enrich CTCs by using the antigen-agnostic RosetteSep™ Circulating Epithelial Tumor Cells

enrichment assay (STEMCELL™ Technologies); this approach utilizes anti-CD45/antiglycophorin A antibody complexes that crosslinks red blood cells (glycophorin A+) and white blood cells (CD45+), which are subsequently eliminated by gradient-based separation. Such antigen agnostic approach allows the enrichment of a pool of heterogeneous subpopulation of CTCs compared to traditional approaches that rely on positive selection of epithelial markers (i.e. EpCAM). Additionally, if work in the lab shows that SCLC CTCs express TfR (as NSCLC CTCs do), then we will also attempt to use this marker to help isolate CTCs from the subjects in this study.

Gene set enrichment analysis of differentially expressed genes between baseline, on-treatment, and relapse CTCs will be performed to identify pathways associated with onset of resistance to the treatment. To assess immune cell activation induced by treatment, matched PBMCs will be isolated from the above and gene expression analysis will be performed. Gene set enrichment analysis of differentially expressed genes between baseline and on treatment will reveal immune signatures characterizing host immune activation as a consequence of the treatment and will identify immune components that discriminate responders from non-responder patients.

3. Study Design

3.1 Overall Design

This is a prospective, non-randomized, open-label, single-arm pilot phase II study of non-ablative radiation in combination with standard-of-care chemo-immunotherapy in patients with untreated, extensive-stage small cell lung cancer. The hypothesis of this study is that the addition of sub-ablative doses of radiation to combination chemotherapy and immunotherapy will be safe and feasible and result in improved outcomes for patients with treatment-naive, extensive-stage small cell lung cancer.

The study will plan to enroll 42 subjects across 3 sites to allow for 34 subjects to be evaluable for the primary endpoints. All subjects will be treated with etoposide plus platinum (carboplatin or cisplatin) chemotherapy together with the PD-L1 checkpoint inhibitor durvalumab, which is a standard of care in this disease setting. All subjects will also receive a total of 6 Gy of radiotherapy per day for 5 fractions. Radiation will start prior to the completion of the second cycle of chemo-immunotherapy but will ideally begin on the first day of the first cycle; no further radiation will be planned after this.

There will be a safety run-in period involving the first 10 subjects enrolled wherein if there is a 30% or greater incidence of grade 3 or higher toxicities with the proposed treatment regimen - specifically from radiation therapy (with focus on pneumonitis, pericarditis, esophagitis, rib fracture, or hemoptysis) or immune-mediated adverse events (other than thyroid dysfunction) - then the radiation regimen will subsequently be switched to 5 Gy radiation per day for 5 fractions. If there is still a 30% or greater incidence of grade 3 or higher toxicities from radiation therapy or immune-mediated adverse events among the subsequent 10 subjects, then the study will be terminated. If this does not occur, then accrual will continue until 34 total subjects are evaluable.
Systemic therapy will be given as follows:

- Carboplatin at AUC = 5-6 mg/mL per min or Cisplatin at 75-80mg/m2 on Day 1 of each 21-day cycle, for 4 cycles

- Etoposide at 80-100mg/m2 on Day 1, Day 2, and Day 3 of each 21-day cycle, for 4 cycles
- Durvalumab at 1500mg on Day 1 of each 21-day cycle, for 4 cycles; following this, subjects will receive 1500mg Durvalumab once every 4 weeks until disease progression.

Treatment will continue until disease progression, intolerability due to toxicity, or withdrawal of consent. Prophylactic Cranial Irradiation (PCI) and consolidative Thoracic Radiotherapy (TRT) will not be given.

This study will enroll subjects at NewYork Presbyterian Hospital-Weill Cornell Medicine.

3.2 Scientific Rationale for Study Design

This is a pilot study to examine the feasibility and preliminary safety and efficacy results of combining chemotherapy and IO therapy with non-ablative radiation in ES-SCLC patients. Given the incidence of SCLC encountered at the involved study sites, a single-arm trial was determined to be more feasible in terms of accrual needed to achieve a statistically significant outcome. The goal of the current trial is to show proof of concept for the therapeutic approach of combining chemotherapy and IO therapy with non-ablative radiation and to provide data that would support a larger, randomized-controlled trial.

As chemotherapy plus IO therapy is already the standard of care treatment for ES-SCLC, the addition of radiation to this approach will be the variable being tested. We will use the results of the CASPIAN study[6] as a historical control for comparison. As such, the study interventions in this trial were chosen to mirror those of the experimental arm (platinum + etoposide + durvalumab) of the CASPIAN trial. As in that trial, PCI and TRT will not be given following completion of chemotherapy and immunotherapy. The endpoints being evaluated in this trial have also been reported for the experimental arm of the CASPIAN study.

3.3 Justification for Dose

Carboplatin, Cisplatin, Etoposide, and Durvalumab will be given at their FDA-approved dosages and in concordance with the treatment regimen administered in the CASPIAN study.

Durvalumab will be given at a fixed dose in this trial, as was done in the CASPIAN study. A population PK model was developed for durvalumab using monotherapy data from a Phase I study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.
Similar findings have been reported by others[54-57]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies[55]. In addition, they investigated 18 therapeutic proteins and

peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters[56].
A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

Non-ablative radiation will be given at a dose of 6 Gy X 5 fractions, ideally starting on the first day of the first cycle of the systemic therapy regimen. We have previously shown that this dose and fractionation scheme is safe to deliver, while inducing responses to the immune checkpoint inhibitor Ipilimumab in non-small cell lung cancer patients[12,58]. We will allow subjects in this current trial to start radiation after the first cycle of systemic therapy, but not after the second cycle.

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Assessments (SoA), Section 6.1. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial.

4. Subject Selection

4.1 Study Population

Subjects with a diagnosis of untreated extensive-stage small cell lung cancer who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.2 Inclusion Criteria

1. Adults ≥ 18 years old
2. Written informed consent from subject or from Health Care Proxy prior to performing any protocol-related procedures, including screening evaluations.
3. Pathological diagnosis of SCLC from biopsy (core biopsy or fine needle aspiration); mixed-histology (NSCLC and SCLC) allowed
4. ES-SCLC (American Joint Committee on Cancer, 8th edition, stage IV [T any, N any, M1a or M1b], or T3–4 due to multiple lung nodules that are too extensive or tumor or nodal volume that is too large to be encompassed in a tolerable radiation plan)
5. Brain metastases allowed, but must be asymptomatic without the need for systemic steroids at doses more than 10 mg/day of prednisone or its equivalent, or treated with Whole Brain Radiation Therapy (WBRT) or Stereotactic Radiosurgery (SRS)
6. Body weight > 30kg
7. ECOG Performance Status (PS) 0-1 at enrollment. ECOG PS 2 allowed if PS decline considered by treating study investigator to be secondary to SCLC
8. At least 1 lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥15 mm) with CT, PET-CT, or MRI and that is

suitable for accurate repeated measurements as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines.

9. No prior exposure to IO therapy including, but not limited to, anti-CTLA-4, anti-PD-1, antiPD-L1, and anti-PD-L2 antibodies
10. No prior radiation therapy in the past 3 years prior to study enrollment. Radiation treatment of brain metastases from small cell lung cancer will be permitted, as per inclusion criteria 5 above. Other specific radiotherapy treatments occurring within the past 3 years, such as electron beam therapy for skin cancers, pterygium irradiation with Sr-90 or SRS for non-malignant disease, or prior I-131 for hyperthyroidism, may not be an absolute contraindication, and will be considered on a case by case basis.
11. Life expectancy of at least 12 weeks from the start of therapy
12. Adequate baseline organ functions as defined below
    a. Hemoglobin ≥8.0 g/dL.
    b. Absolute neutrophil count ≥1.5 × 10^3/uL (use of granulocyte colony-stimulating factor is not permitted at screening).
    c. Platelet count ≥75 × 10^3/uL.
    d. Serum bilirubin ≤1.5 × the ULN. This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.
    e. In patients without hepatic metastasis: ALT and AST ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST ≤5 × ULN.
    f. Measured or calculated creatinine clearance: >60 mL/min for patients on cisplatin and >45 mL/min for patients on carboplatin, as determined by Cockcroft–Gault (using actual body weight).
        i. Males:
        Creatinine clearance (mL/min) = [Weight (kg) × (140 − Age)]/[72 × serum creatinine (mg/dL)]
        ii. Females:
        Creatinine clearance (mL/min) = [Weight (kg) × (140 − Age)]/ [72 × serum creatinine (mg/dL)] × 0.85
13. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    a. Women <50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    b. Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

4.3 Exclusion Criteria

1. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
    a. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
    b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.
2. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.
3. Participation in another clinical study with a therapeutic investigational product during the last 4 weeks.
4. Contraindications to platinum-based chemotherapy
5. Contraindications to radiation therapy
6. Prior radiation therapy to same site as proposed sub-ablative radiation site
7. Cannot tolerate radiation treatment position or immobilization
8. Any concurrent chemotherapy, investigational product, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable, as is use of bisphosphonate or RANKL inhibitor therapy for prevention of skeletal-related events from bone metastases.
9. History of another primary malignancy except for:
    a. Malignancy treated with curative intent and with no known active disease ≥3 years before the first dose of the investigational product and of low potential risk for recurrence.
    b. Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease.
    c. Adequately treated carcinoma in situ without evidence of disease (e.g., cervical cancer in situ).
10. History Limited-Stage SCLC treated with concurrent chemo-radiation
11. History of allogenic organ transplantation.
12. Major surgical procedure (as defined by the investigator) within 28 days prior to Cycle 1 Day 1 of systemic therapy. Local surgery of isolated lesions for palliative intent is acceptable.
13. Paraneoplastic syndrome of autoimmune nature, requiring systemic treatment (systemic steroids or immunosuppressive agents)
14. Documented, active, and uncontrolled autoimmune or inflammatory disorders (including inflammatory bowel disease, diverticulitis with the exception of diverticulosis, systemic lupus erythematosus, sarcoidosis syndrome, Wegener syndrome (granulomatosis with polyangiitis), Graves' disease, rheumatoid arthritis, hypophysitis, and uveitis, etc.). The following are exceptions to this criterion:
    a. Patients with vitiligo or alopecia.
    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement

c. Any chronic skin condition that does not require systemic therapy.
d. Patients with celiac disease controlled by diet alone.
e. Patients without active disease in the last 5 years may be included but only after consultation with the medical monitor and with appropriate subspecialty consultation (e.g. with endocrinology, gastroenterology, rheumatology, etc.)
f. Patients whose autoimmune or inflammatory disorder is controlled with medication may be included but only after consultation with the medical monitor and with appropriate subspecialty consultation (e.g. with endocrinology, gastroenterology, rheumatology, etc.)

15. Uncontrolled intercurrent illness, including but not limited to, uncontrolled ongoing or active infection, interstitial lung disease, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring adverse events, or compromise the ability of the patient to give written informed consent.
16. Active infection, including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), HBV (known positive HBV surface antigen result), HCV, or HIV (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of HBV core antibody and absence of HBV surface antigen) are eligible, as are patients with HBV infection controlled by antiviral medication (defined as undetectable viral load). Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid.
17. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. 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 physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication). Premedication with steroids for chemotherapy is acceptable.
18. History of active primary immunodeficiency.
19. Receipt of live, attenuated vaccine within 30 days prior to the first dose of durvalumab
20. Female patients who are pregnant or breast-feeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy.
21. Known allergy or hypersensitivity to durvalumab, etoposide, carboplatin, cisplatin, or any of their excipients.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of absence of a measurable lesion, ECOG performance status, life expectancy, laboratory parameters, being on systemic corticosteroid therapy, inability to tolerate radiation treatment position or immobilization, or uncontrolled intercurrent illness or active infection may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

4.5 Strategies for Recruitment and Retention

To increase recruitment for this study, we will receive referrals from 4 sites within the NewYork-Presbyterian hospital system – NewYork Presbyterian Hospital-Weill Cornell Medicine, NewYork Presbyterian Lower Manhattan Hospital, NewYork-Presbyterian Brooklyn Methodist, and NewYork-Presbyterian Queens. Not only will this help recruitment in terms of number of subjects but, due to the differing patient demographics in the areas served by each site, we should also be able to enroll subjects of different races and ethnicities. In the near future we hope to open this study at the Brooklyn and Queens affiliate sites, once the logistics of transporting study drug have been resolved.

This study will plan to enroll 42 subjects to allow for 34 to be evaluable for the primary endpoints. We anticipate accruing roughly 1 subject per month.
Subjects will be identified and approached by treating medical oncologists or radiation oncologists in the outpatient clinics of any of the sites involved in the trial. The trial may also be discussed with patients who are admitted to the hospital at any of the enrolling sites.

The trial will be listed on the Joint Clinical Trials Office (JCTO) public website and will also be discussed at local professional meetings such as the NY Lung Cancer Learning Center conferences, in order to help generate referrals.

Subjects will not be compensated for taking part in this trial.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

6. Study Procedures

6.1 Schedule of Assessments

Table 1. Schedule of trial events

	Screening D -28 to D-1	Cycle 1					Cycles 2 - 4			C5D1+ (D85+)	EOT
		D1	D2	D3	D4	D5	D1	D2	D3		
Carboplatin/Cisplatin		X					X				
Etoposide		X	X	X			X	X	X		
Durvalumab		X					X			X[a]	
Radiation[b]		X	X	X	X	X					
Informed consent	X										
Inclusion/Exclusion criteria review	X										
Radiation Simulation	X										
Medical history	X	X					X			X[a]	X
Physical exam	X	X					X			X[a]	X
Concurrent Medications	X	X					X			X[a]	X
Vital signs including Height and Weight	X	X					X			X[a]	X
CT or PET-CT[c]	X						X[d]			X[d,e]	
MRI Brain[f]	X						X[d,g]			X[d,e,g]	
CBC w/diff	X	X					X			X[a]	X
Serum chemistry with LFTs	X	X					X			X[a]	X
Amylase and/or Lipase	X	X					X			X[a]	X
Thyroid Function Panel	X	X					X			X[a]	X
Hepatitis A, B, C Profile	X										
Beta-hCG[h]	X	X					X			X	X
Adverse event Capture	Continuous Assessment										
Blood for correlative studies		X					X			X[i]	X
Research biopsy (Optional)	X									X[j]	X

[a] After D85, repeat every 28 days (+/- 7 days) until disease progression
[b] Exact radiation schedule to be determined by treating Radiation Oncologist; all five fractions of radiation should be completed within 2 weeks of first radiation dose (>3 weeks is an acceptable variation); SBRT is preferred but 3D-CRT and IMRT are permitted.
[c] CT scans of the Chest and Abdomen/Pelvis with or without Contrast; PET-CT Skull Base to Thigh
[d] Imaging can be done +/- 7 days
[e] After D85, repeat every 8 weeks +/- 7 days until disease progression
[f] MRI Brain with and without Contrast
[g] MRI Brain only needs to be done at this time point if subject was found to have brain metastases at baseline assessment; otherwise MRI Brain can be done as clinically indicated
[h] For pre-menopausal females of childbearing potential
[i] After D85, repeat every 8 weeks (+/- 7 days) until D365
[j] Optional Research Biopsy can be done +/- 21 days

Abbreviations: C = Cycle; D = Day; diff = differential; LFTs = Liver Function Tests; EOT = End of Treatment

6.1.1 Screening Visit (-28 to -1 Days before start of treatment)

- Informed consent
- Inclusion/Exclusion Criteria Review
- Medical History
- Medication History/Concurrent Medications
- Vital signs including Height and Weight
- Physical Exam
- Labwork: CBC with differential; Serum Chemistry with Liver Function Tests; Amylase and/or Lipase; Thyroid Function Panel; Hepatitis A, B, and C profile; Beta-hCG (for pre-menopausal females)
- CT Chest and Abdomen/Pelvis with or without Contrast or PET-CT Skull Base to Thigh
- MRI Brain with and without Contrast
- Optional Research Biopsy
- Radiation Simulation and Treatment Planning

6.1.2 Treatment Phase

6.1.2.1 Cycle 1 Day 1 (Day 1)

- Interval Medical History
- Concurrent Medications
- Vital signs including Height and Weight
- Physical Exam
- Labwork: CBC with differential; Serum Chemistry with Liver Function Tests; Amylase and/or Lipase; Thyroid Function Panel; beta-hCG (for pre-menopausal females)
- Blood for Correlative Studies
- Fraction 1 (6 Gy) of radiation (when feasible) – repeat 6 Gy for total of 5 fractions; fractions do not need to be given on consecutive days but all

attempts should be made to do so. When feasible, radiation should be given before chemo-immunotherapy on any given day. Radiation may start after Cycle 1 Day 1 but not after Cycle 2 Day 3

- Carboplatin AUC = 5-6 mg/mL per min IV or Cisplatin 75-80mg/m2 IV on D1
- Etoposide 80-100mg/m2 IV on D1, D2, and D3
- Durvalumab 1500mg IV on D1

6.1.2.2 Cycle 2 Day 1 (Day 22) (± 7 days)

- Interval Medical History
- Concurrent Medications
- Vital signs including Height and Weight
- Physical Exam
- Labwork: CBC with differential; Serum Chemistry with Liver Function Tests; Amylase and/or Lipase; Thyroid Function Panel; beta-hCG (for pre-menopausal females)
- Adverse Event Evaluation
- Carboplatin AUC = 5-6 mg/mL per min IV or Cisplatin 75-80mg/m2 IV on D22
- Etoposide 80-100mg/m2 IV on D22, D23, and D24
- Durvalumab 1500mg IV on D22

6.1.2.3 Cycle 3 Day 1 (Day 43) (± 7 days)

- CT Chest and Abdomen/Pelvis with or without Contrast or PET-CT Skull Base to Thigh – should ideally be done with results obtained prior to D43
- MRI Brain with and without Contrast if indicated – should ideally be done with results obtained prior to D43
- Interval Medical History
- Concurrent Medications
- Vital signs including Height and Weight
- Physical Exam
- Labwork: CBC with differential; Serum Chemistry with Liver Function Tests; Amylase and/or Lipase; Thyroid Function Panel; beta-hCG (for pre-menopausal females)
- Adverse Event Evaluation
- Blood for Correlative Studies
- Carboplatin AUC = 5-6 mg/mL per min IV or Cisplatin 75-80mg/m2 IV on D43
- Etoposide 80-100mg/m2 IV on D43, D44, and D45
- Durvalumab 1500mg IV on D43

6.1.2.4 Cycle 4 Day 1 (Day 64) (± 7 days)

- Interval Medical History
- Concurrent Medications
- Vital signs including Height and Weight
- Physical Exam
- Labwork: CBC with differential; Serum Chemistry with Liver Function Tests; Amylase and/or Lipase; Thyroid Function Panel; beta-hCG (for pre-menopausal females)
- Adverse Event Evaluation
- Carboplatin AUC = 5-6 mg/mL per min IV or Cisplatin 75-80mg/m2 IV on D64
- Etoposide 80-100mg/m2 IV on D64, D65, and D66
- Durvalumab 1500mg IV on D64

6.1.2.5 Cycle 5 Day 1 (Day 85) (± 7 days) and Beyond until Disease Progression

- CT Chest and Abdomen/Pelvis with or without Contrast or PET-CT Skull Base to Thigh – should ideally be done with results obtained prior to D85
    - Repeat every 8 weeks (± 7 days) until disease progression
- MRI Brain with and without Contrast if indicated – should ideally be done with results obtained prior to D85
    - Repeat every 8 weeks (± 7 days) if indicated until disease progression
- Interval Medical History
    - Repeat every 28 days (± 7 days) until disease progression
- Concurrent Medications
    - Repeat every 28 days (± 7 days) until disease progression
- Vital signs including Height and Weight
    - Repeat every 28 days (± 7 days) until disease progression
- Physical Exam
    - Repeat every 28 days (± 7 days) until disease progression
- Labwork: CBC with differential; Serum Chemistry with Liver Function Tests; Amylase and/or Lipase; Thyroid Function Panel; beta-hCG (for pre-menopausal females)
    - Repeat every 28 days (± 7 days) until disease progression
- Adverse Event Evaluation
    - Repeat every 28 days (± 7 days) until disease progression
- Blood for Correlative Studies
    - Repeat every 8 weeks (± 7 days) until D365
- Durvalumab 1500mg IV on D85
    - Repeat every 28 days (± 7 days) until disease progression
- Optional Research Biopsy (± 21 days)

6.1.2.6 End of Treatment Visit – To Occur at Radiographic or Clinical Disease Progression (± 28 days)

- Interval Medical History
- Concurrent Medications
- Vital signs including Height and Weight
- Physical Exam
- Labwork: CBC with differential; Serum Chemistry with Liver Function Tests; Amylase and/or Lipase; Thyroid Function Panel; beta-hCG (for pre-menopausal females)
- Adverse Event Evaluation
- Blood for Correlative Studies
- Optional Research Biopsy

6.1.3 Follow-up Phase: From Time of Progression to Withdrawal from Study or Death

- Interval Medical History
    - Every 28 days (± 7 days) for the first 84 days; then every 84 days (± 7 days)
- Concurrent Medications
    - Every 28 days (± 7 days) for the first 84 days; then every 84 days (± 7 days)
- Vital signs including Height and Weight
    - Every 28 days (± 7 days) for 84 days
- Physical Exam
    - Every 28 days (± 7 days) for 84 days
- Labwork: CBC with differential; Serum Chemistry with Liver Function Tests; Thyroid Function Panel
    - Every 28 days (± 7 days) for 84 days
- Adverse Event Evaluation
    - Every 28 days (± 7 days) for the first 84 days; then every 84 days (± 7 days)

7. Study Intervention

7.1 Chemotherapy

Carboplatin, Cisplatin, and Etoposide will be used in the FDA-approved manner for ES-SCLC and infused via IV using standard institutional guidelines. Carboplatin will be given at an area under the curve (AUC) of 5-6 mg/mL per min; alternatively, Cisplatin will be given at 75-80mg/m2 on Day 1 of a 21-day cycle. The choice of Carboplatin vs Cisplatin and the exact dosing of each drug will be

determined by the treating medical oncologist. Switching from Cisplatin-based to Carboplatin-based therapy will be permitted if this is done due to adverse effects from Cisplatin or to otherwise improve tolerability of the chemotherapy regimen. In general, Carboplatin will be infused over 1 hour and Cisplatin over 2 hours.

Etoposide will be given at 80-100mg/m2 on Day 1, Day 2, and Day 3 of a 21-day cycle, with the exact dosage again determined by the treating medical oncologist. In general, Etoposide will be infused over 1 hour.

Pre-medications given to prevent and treat chemotherapy-induced nausea and vomiting as well as chemotherapy-induced infusion reactions will be given as per institutional guidelines and at the discretion of the treating medical oncologist.

7.2 Immunotherapy

7.2.1 Supply of Durvalumab

Durvalumab will be supplied by AstraZeneca as a 500 mg vial concentrate for solution for infusion. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal volume is 10 mL.

Durvalumab is a sterile, clear to opalescent, colorless to slightly yellow solution, free from visible particles.

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Investigational product must be kept in original packaging until use to prevent prolonged light exposure.

7.2.2 Preparation and Administration of Durvalumab Doses with an IV Bag

During the first 4 cycles of treatment, durvalumab will be administered prior to chemotherapy drugs.

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature
  If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hrs.

A dose of 1500 mg (for patients >30 kg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30 mL (i.e. 1500 mg) of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If patient weight falls to ≤30 kg, weight-based dosing at 20 mg/kg will be administered using an IV

bag size selected such that the final concentration is within 1 to 15 mg/mL.

Standard infusion time is 1 hour, however if there are interruptions, the total allowed time must not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

7.2.3 Monitoring of Dose Administration

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion related reaction is Grade 3 or higher in severity, study drug will be discontinued. Standard infusion time is one hour, however if there are interruptions, the total allowed time must not exceed 8 hours at room temperature (otherwise requires new infusion preparation). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in Appendix B.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

7.3 Radiation Therapy

7.3.1 Localization, Simulation, and Immobilization

Simulation for multi-site radiation requires the presence of the following: the treating physician (or a designee with knowledge of the patient and multi-site radiation procedures), a physicist dedicated to doing multi-site radiation, and the simulation therapists trained in the setup of patients undergoing multi-site radiation. Radiation will be performed by SBRT whenever feasible, though 3D-CRT and IMRT are also permitted. The simulation will be scheduled in ARIA (or an alternate scheduling system such as MOSAIQ) and assigned to the appropriate staff. The team will discuss all treatment sites during the “time-out” procedure and prior to performing the simulation. **Every effort should be made to have the treating physician present at the simulation and on the first day of treatment.**

Patients will be positioned in a stable pose conducive to allowing accurate reproducibility of the target position throughout treatment. All patients will undergo CT-based treatment planning in custom made immobilization devices. An adequate immobilization device for radiation is required. **At WCM-New York Presbyterian the FREEDOMX™ SBRT module by CDR systems will be used for patient immobilization whenever possible.** Respiratory motion management is required for SBRT. **The FREEDOM™ pneumatic abdominal compression belt or the abdominal compression paddle (used in conjunction with the FREEDOMX™ SBRT module) is preferred for managing respiratory and tumor motion while maintaining maximum patient comfort.** The patient will be coached into the shallow breathing technique prior to and during the time of simulation and for each SBRT session. The compression belt (if used) will be tested for leaks before simulation and treatment and the pressure will be monitored throughout (≤ 3-4 mmHg variation is allowed). **The simulation therapists will document localization setup on the CDR setup sheet and upload into ARIA.** CT scan range must allow simultaneous view of the patient's anatomy adequately to ensure contouring of all targeted lesions, as well as necessary organs at risk (OAR). High resolution CT scans should be obtained with uniform slice thickness of ≤ 3 mm (≤ 2mm slice thickness through the area of interest is preferred) throughout.

7.3.2 Use of Contrast Agents

The use of IV contrast is recommended **(not required for peripheral lung lesions)**. A complete metabolic panel to acquire an estimated glomerular filtration rate (eGFR) should be obtained ≤ 30 days prior to the date of CT simulation. If recent labs are not available, new labs are recommended to be drawn at the time of consultation or ≥ 24hrs prior to the date of CT simulation to allow adequate time for acquisition of final laboratory results. A questionnaire of allergies (including IV/oral contrast) will be filled out by the patient and reviewed by the nurse and physician prior to simulation. **If the patient requires steroids due to a history of an allergic reaction to IV/oral contrast, CT simulation without contrast should be given due consideration. Every attempt should be made to have the treating MD present at the time of CT simulation. For additional information, see the NYP-Weill Cornell Radiation Oncology Department Policy and Procedure for IV contrast administration for CT-Simulation (T127) and the Department of Radiology Protocols at http://radiqal.nyp.org/pronto/login_web.**

7.3.3 Respiratory Motion Assessment and Management

Lesions with potential for respiratory motion **(for example thoracic targets)** should be evaluated by appropriate means including 4D CT scan, implanted fiducial marker, or fluoroscopy at the time of simulation. Respiratory motion management including abdominal compression, active breathing control, breath hold, end expiratory gating, or fiducial marker tracking is recommended for any lesion to be treated with expected motion > 5mm; therefore, thoracic lesions should be planned with some sort of respiratory control. A recommended approach would be to use an ITV technique for motion < 1cm, but for motion > 1cm (typically too large for a free breathing ITV) motion management including but not limited to abdominal compression, active-breathing control (ABC), gating, breath hold, etc. should be used. **The FREEDOM™ pneumatic abdominal compression belt (used in conjunction with the FREEDOMX™ SBRT module) or the abdominal compression paddle are preferred for managing respiratory and tumor motion while maintaining maximum patient comfort.** For patients that will be treated on the MRIdian LINAC, the breath hold and automated beam-gating technique will be used.

7.3.4 Localization Using Daily IGRT

This study requires the use of image guided radiation treatment (IGRT). IGRT as defined by NRG Oncology is a computer assisted process that uses imaging devices that generate a series of coordinates for shifting the patient support system in three orthogonal directions (sometimes also including rotational changes) to position the treatment beams relative to target regions. The allowed technologies are as follows: cone-beam CT (CBCT) using either a specially mounted kV imaging head or the MV treatment beam with an opposed electronic imaging panel, dual fixed-position in-room kV imaging systems that are orthogonal or near orthogonal, an in-room standard diagnostic CT scanner that is geometrically linked to the treatment unit, and the Tomotherapy® approach. Simple portal imaging approaches that do not use computer assistance are not considered suitable for this study.

7.3.5 IGRT requirements

The minimum IGRT requirement for thoracic lesions is listed below. Volumetric imaging refers to 3D modalities (e.g. kV cone-beam, MV cone-beam, CT on rails), while orthogonal imaging refers to 2D modalities (e.g., kV OBI, ExacTrac). When fiducials are used a CBCT needs to be used to document not only the accuracy of the target but also the relationship of the target with the OAR – this cannot be adequately assessed with orthogonal films alone.

Table 2

Location	**Minimum IGRT Requirement**	
	No Fiducials	**With Fiducials**
Lung	Volumetric (3D)	Volumetric (3D) + Orthogonal kV (2D)
Mediastinal/Cervical LN	Volumetric (3D)	N/A

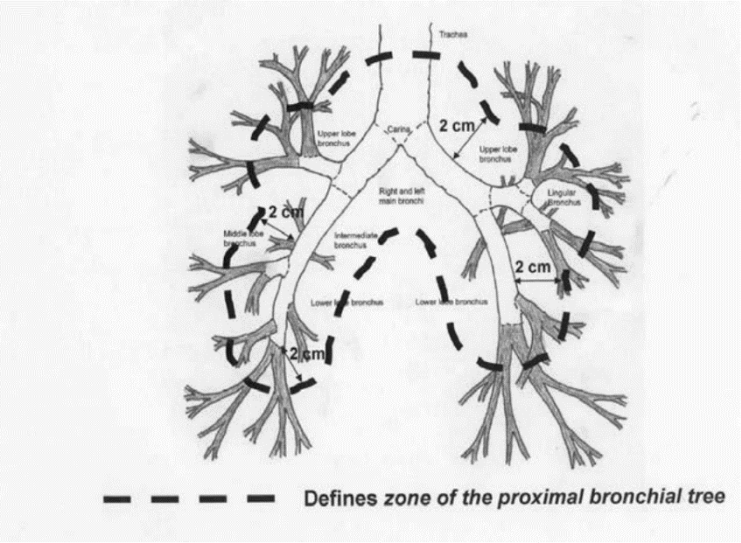
7.3.6 Target Volumes

7.3.6.1 Thoracic lesions

Thoracic lesions to be treated will be dictated by the ability to meet pre-specified dose constraints for adjacent organs at risk (OARs).

Lung Central: GTV within 2 cm of proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi) as described in RTOG 0813/0915. Tumors that are immediately

adjacent to mediastinal or pericardial pleura (PTV touching the pleura) also are considered central tumors.



Lung Peripheral: lesions within the lung parenchyma with GTV outside of the proximal bronchial tree.

Mediastinal/Cervical LN: Mediastinal: GTV arising within the anatomic space between the lungs, above the diaphragm, and below the thoracic inlet at the level of the top of the sternal notch. Cervical Lymph Nodes: GTV occurring within cervical lymph nodes Levels I-VI and/or retropharyngeal spaces.

7.3.7 Target Volume Definition Based on Location

Specific radiation planning parameters depend on the location of the treated lesion as well as mechanism used for motion management/evaluation. The table below defines appropriate planning CT window/leveling, recommended additional modality scans to be fused, as well as how to define the GTV, ITV, CTV, and PTV for intrathoracic disease. Only rigid registration will be permitted for multi-modality fusion. In general, the GTV is defined as the entirety of the lesion as seen on planning CT scan aided by additional diagnostic imaging studies (i.e., PET/CT or MRI). Use of additional diagnostic studies is left to the discretion of the treating physician. The CTV = GTV; there is no margin added for microscopic extension. In general, either a helical CT or 4DCT will be used for defining the GTV/ITV depending upon the tumor motion encountered, although both scans may be acquired at the time of simulation. Typically, the ITV is generated using either expiratory/inspiratory phase scans or from reconstructed maximum intensity projection (MIP) scans. Maximum/minimum intensity projections (MIP/MinIP) should be used with caution because the MIP reconstruction for lung or MinIP reconstruction for liver may erroneously define an ITV in cases of significant irregular breathing or when tumors abut soft tissue structures (e.g., the diaphragm for MIP) or fat (for the MinIP).

The approach for target volume delineation for extrathoracic sites of disease will follow the example of intrathoracic disease as outlined in section 7.3. For any site of disease, the constraints for the organs at risk per the modified TG101 constraints in section 7.3 will be maintained.

Table 3

Planning Parameter	Location		
	Lung Central	**Lung Peripheral**	**Mediastinal/Cervical LNs**
CT window/level	Pulmonary/Mediastinal	Pulmonary/Mediastinal	Pulmonary/Mediastinal
Additional Studies	PET/CT	PET/CT	PET/CT
GTV definition	Lesion	Lesion	Lesion
CTV definition	GTV/ITV	GTV/ITV	GTIV/ITV
PTV expansion	CTV + 3-5mm	CTV + 3-5mm	CTV + 3-5mm

Note: A GTV to ITV expansion of greater than 1cm in any one direction is strongly discouraged and alternative respiratory management technique is suggested. Mediastinal lymph nodes should undergo motion assessment and an ITV should be generated to account for motion.

7.3.8 Treatment Planning

General Considerations: A variety of planning techniques can be used to deliver radiation. General guidelines include the following:

- Multiple coplanar or non-coplanar beam arrangements are acceptable.
- Typically, 7-13 static radiation beams with equal weighting are used. It is recommended that at least 10 beams be used when possible.
- A minimum field dimension of 3 cm should be observed while treating small lesions with 3D-CRT.
- Dynamic conformal arcs are acceptable. It is recommended that arcs span a total for all beams of 340 degrees.
- For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3 cm when treating small lesions.
- The prescription isodose line covering 95% the PTV will generally be 80-90% but may range from 60-90% where the maximum dose is 100%. As a result, a "hotspot" will exist within the PTV that is equal to the prescription dose divided by the prescription isodose line (i.e., 45 Gy/0.6 = 75 Gy when 45 Gy is prescribed to the 60% isodose).
- Doses higher than the prescription isodose (i.e., hotspots) should be manipulated to occur within the target.
- For 3D conformal plans, the goal of covering 95% of the PTV with the prescription isodose line will be maintained with the hotspots inside of the target. Organ at risk dose constraints will need to be maintained and take precedent to minimize risk of toxicities.
- Hotspot location should be reviewed by the treating radiation oncologist. Every effort should be made to plan for the hotspots to be within the target while the constraints for the organs at risk are maintained for both 3D and IMRT. The DMax for 3D plans should be no more than 115% of the prescription dose.

Dose calculations: All dose distributions shall include corrections for heterogeneities. All doses should be reported in terms of dose-to-water and not in terms of dose-to-medium. Successful treatment planning will require accomplishment of all the following criteria:

1. Normalization: The treatment plan should be initially normalized such that 100% corresponds to the maximum dose within the PTV (MAXPTV). While this point will typically correspond to the PTV center of mass, it can be located elsewhere within the PTV.
2. Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface. Doses less than 95% of the prescription dose are restricted to the outside edges of the PTV. The prescription isodose surface selected MUST be ≥ 60% and ≤ 90% of the dose maximum within the PTV (MAXPTV). The MAXPTV corresponds to the normalization point (100%) of the plan as noted in number 1 above.
3. Target Dose Heterogeneity: Rather than prioritizing target dose homogeneity, SBRT treatment planning prioritizes adequate minimum target coverage and rapid dose fall-off gradients outside of the target. Hot spots within targets are generally accepted without consequence since targets are mostly tumor. The only exception is when the hotspot within the PTV also intersects an OAR.
4. Critical Organ Doses: Respect all critical organ dose-volume limits.
5. High-Dose Spillage:

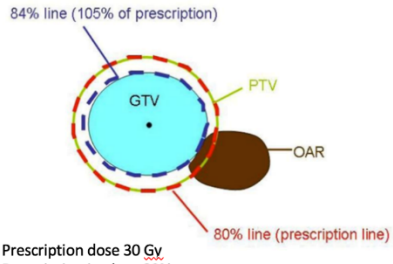
a. Location: Any dose > 105% of the prescription dose should occur within the PTV and not within the normal tissues outside the PTV.
b. Volume: Acceptable isodose distributions should be as conformal as possible. To this end, the ratio of prescription isodose volume to PTV should be as small as possible.
   i. The ratio of the prescription isodose volume to the PTV volume should be < 1.2. Acceptable variations include a ratio of 1.2-1.5. Ratios above 1.5 will be considered unacceptable variations. The prescription line for each lesion will be contoured for calculation of this ratio. The prescription line will be labelled as V_5000 with the 5000 changing to reflect the prescription dose in cGy.
   ii. Guidelines for the ratio of the 50% prescription isodose volume to the PTV volume (R50%) and for the maximum dose at 2cm (D2cm) from the PTV are given in table below.
   iii. Given that conformal tumor coverage is often more difficult to achieve in lung than in more homogeneous organs, these ratios should serve as a guide for liver, abdominal-pelvic, mediastinal/cervical lesions as well.
   iv. Elliptically shaped lesions as well as extremity lesions may not meet these guidelines. This is acceptable if normal tissue constraints are respected. These criteria will not be required in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3 cm results in the inability to meet a conformity ratio of 1:5.

Table 4

PTV Volume (cc)	Ratio of 50% Prescription Isodose Volume to PTV Volume, R50%	Maximum Dose at 2cm (D2cm) from PTV in any direction as % of Prescribed Dose
1.8	< 7.5	< 57
3.8	< 6.5	< 57
7.4	< 6	< 58
13.2	< 5.8	< 58
22	< 5.5	< 63
34	< 5.3	< 68
50	< 5	< 77
70	< 4.8	< 86
95	< 4.4	< 89
126	< 4	< 91
163	< 3.7	< 94

Note: For values of PTV dimension or volume not specified, linear interpolation between table entries is required. For tumors within 2 cm of the skin, it may be difficult to meet the values for D2cm and R50%. In these cases, these criteria will not be used.

7.3.9 Planning Priorities



1. Prescription dose 30 Gy
2. Prescription isodose 80%
3. 105% of prescription dose 31.5 Gy (corresponds to 84% isodose line
4. Maximum dose (normalization) at isocenter is 37.5 Gy

Every attempt should be made to successfully satisfy all of the planning goals and OAR criteria. In some circumstances, it may not be possible to meet all the ideal criteria, leading to plans in the Variation Acceptable range. Thus, suggested priority of planning goals in order of importance is as follows:

1. Respect spinal cord, cauda equina, sacral plexus and brachial plexus dose constraints.
2. Meet dose "compactness" constraints including the prescription isodose surface coverage, high-dose spillage (location and volume), and intermediate dose spillage (D2cm, and R50%) as these define the aim in using SBRT. Dose compactness should be assessed for plans based on treatment dose for a single lesion at a time.
3. Meet critical structure constraints other than those listed in 1. OAR dose constraints should be met based on composite dose planning. Unacceptable deviations should be avoided in all cases.
4. In cases where PTV coverage cannot be achieved while avoiding unacceptable deviations to OAR, coverage of a section of PTV including or immediately adjacent to the OAR may be as low as 70% of the prescription dose ONLY in this situation.

7.3.10 Critical structures

The following table outlines the naming of the various normal and critical structures. If multiple lesions named PTV_5000 exist, each should be labelled according to numerical order of the anatomical sites listed below (e.g., "PTV_5000_1" is a peripheral lung lesion while "PTV_5000_4" is a liver lesion). If multiple lesions exist within a single anatomical site, each lesion can be distinguished by adding a letter to the end of the PTV name ("PTV_5000_1a" and "PTV_5000_1b").

Table 5

Standard Name	Description
Group 1: Lung – Peripheral	
PTV_3000_1	For peripheral lung tumors
GTV_3000_1	For peripheral lung tumors
PTV_20_1	PTV with 2cm expansion
NonPTV_1	External minus PTV
NonPTV_20_1	External minus PTV_20 (PTV with a 2 cm expansion)
Spinal Cord	Spinal Cord
Brachial Plexus	Brachial Plexus
BrachialPlexus_L	Left Brachial Plexus
BrachialPlexus_R	Right Brachial Plexus
BronchialTree	carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi

Esophagus	Esophagus
GreatVessels	Great Vessels
BronchTree_20	Proximal bronchial tree expanded by 2cm
Larynx	Larynx
ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should be contoured
Heart	Heart
External	Body surface
SkinOAR	Skin will be defined as the outer 0.5 cm of the body surface
Lungs	Combined Left and Right Lungs - GTV
Lung_R	Right Lung- GTV
Lung_L	LEFT Lung- GTV
Trachea	Trachea
Stomach	Stomach
Liver	Liver
BileDuct	Bile duct
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Group 2: Lung – Central	***Description***
PTV_3000_2	For central lung tumors
GTV_3000_2	For central lung tumors
PTV_20_2	PTV with 2cm expansion
NonPTV_2	External minus PTV
NonPTV_20_2	External minus PTV_20 (PTV with a 2 cm expansion)
SpinalCord	Spinal Cord
BrachialPlexus	Brachial Plexus
BrachialPlexus_L	Left Brachial Plexus
BrachialPlexus_R	Right Brachial Plexus
BronchialTree	carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi
Esophagus	Esophagus
GreatVessels	Great Vessels
BronchTree_20	Proximal bronchial tree expanded by 2cm
Larynx	Larynx
ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should be contoured
Heart	Heart
External	Body surface
SkinOAR	Skin will be defined as the outer 0.5 cm of

	the body surface
Lungs	Combined Left and Right Lungs
Lung_R	Right Lung - GTV
Lung_L	Left lung - GTV
Trachea	Trachea
Stomach	Stomach
Liver	Liver
BileDuct	Bile duct
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Esoph_NonAdj	Esophagus (Non-adjacent wall)
Trachea_NonAdj	Trachea (Non-adjacent wall)
GrVess_NonAdj	Great vessels (Non-adjacent wall)
Group 3 Mediastinal/Cervical Lymph Node	***Description***
PTV_3000_3	For central lung tumors
GTV_3000_3	For central lung tumors
PTV_20_3	PTV with 2cm expansion
NonPTV_3	External minus PTV
NonPTV_20_3	External minus PTV_20 (PTV with a 2 cm expansion)
SpinalCord	Spinal Cord
BrachialPlexus	Brachial Plexus
BrachialPlexus_L	Left Brachial Plexus
BrachialPlexus_R	Right Brachial Plexus
BronchialTree	carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi
Esophagus	Esophagus
GreatVessels	Great Vessels
BronchTree_20	Proximal bronchial tree expanded by 2cm
Larynx	Larynx
ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should be contoured
Heart	Heart
External	Body surface
SkinOAR	Skin will be defined as the outer 0.5 cm of the body surface
Lungs	Combined Left and Right Lungs
Lung_R	Right Lung
Lung_L	Left lung
Trachea	Trachea
Stomach	Stomach
Liver	Liver

BileDuct	Bile duct
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Esoph_NonAdj	Esophagus (Non-adjacent wall)
Trachea_NonAdj	Trachea (Non-adjacent wall)
GrVess_NonAdj	Great vessels (Non-adjacent wall)

7.3.11 Organs at risk

All lesion-specific organs at risk (OAR) must be contoured. The specific OAR to be contoured will depend on the location of lesion to be treated. The contour of structures that have a lumen (bronchus, trachea, esophagus, etc.) will include both the “wall” and the “lumen” to result in a cylindrical structure. In general, OAR within 5 cm of any lesion should be contoured. To identify these OARs, all PTVs will be expanded by 5 cm and any OAR that overlaps with PTV + 5 cm must be contoured.

7.3.12 Critical Organ Dose-Volume Limits

Dose distributions of organs at risk are critical to understand toxicity following SBRT. To facilitate planning, dose should be calculated on a single CT scan simultaneously with in-plane resolution of at least 2 x 2 x 3mm. Dose-volume histograms will be generated to evaluate dose to critical organs at risk.

7.3.13 Planning priorities for Organs at Risk

The spinal cord doses are absolute limits. Some OARs (i.e., the esophagus, trachea, bronchi and heart within the lung) may be situated adjacent to the treated GTV/PTV. As such, there is no specified limit as tumors that are immediately adjacent to that organ will not be able to be treated to the prescription doses without irradiating a small volume of that organ to the prescribed dose. In such a case, the planning must be accomplished so that there is no hot spot within that organ, even if that organ is part of the GTV/PTV, i.e., that no part of any serial OAR receives more than 105% of the prescribed dose. In addition, the volume of the OAR in question needs to be minimized, both in length and in the width (i.e., circumference), with efforts made to reduce the dose to the contralateral wall of the organ. For parallel OAR, exceeding the doses by more than 110% of the prescribed dose will be considered unacceptable. For non-spinal cord OAR with known sensitivity to high doses of radiation (including the bowel, esophagus, and stomach) included within a PTV or immediately adjacent to PTVs, a prescription dose at the lower end of acceptable variation should be used. Additionally, every effort should be made to cover the GTV with the prescription dose while ensuring rapid fall off to the organ at risk. Coverage of a section of PTV including or immediately adjacent to the OAR may be as low as 70% of the prescription dose ONLY in this situation. Every effort should be made to cover 100% of the GTV by the prescription dose at the lower end of acceptable variation. For tumors that are not immediately adjacent to any OAR, centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures; we expect that the OAR doses will be as low as achievable (ideally, < 6 Gy/fraction).

Table 6: Modified AAPM Task Group 101 dose constraints for 5 fractions[59]

Serial Organ	Volume	Volume Dose (Gy)	Avoidance Endpoint (≥ Grade 3)
Spinal Cord	0.03 cc	30	Myelitis
	0.35 cc	23	
	1.2 cc	14.5	
Ipsilateral Brachial Plexus	0.03 cc	30.5	Brachial Plexopathy
	3 cc	27	
Cauda Equina	0.03 cc	32	Neuritis
	5 cc	30	
Sacral Plexus	0.03 cc	32	Neuropathy
	5 cc	30	Neuritis
Trachea and Ipsilateral Bronchus	0.03 cc	40	Stenosis/Fistula
	4 cc	16.5	
Esophagus	0.03 cc	35	Stenosis/Fistula
	5 cc	19.5	
Heart/Pericardium	0.03 cc	38	Pericarditis
	15 cc	32	
Great vessels	0.03 cc	53	Aneurysm
	10 cc	47	
Skin	0.03cc	39.5	Ulceration
	10 cc	36.5	
Stomach	0.03 cc	32	Ulceration/Fistula
	10 cc	18	
Duodenum	0.03 cc	32	Ulceration
	5 cc	18	
	10 cc	12.5	
Jejunum/Ileum	0.03 cc	35	Enteritis/obstruction
	5 cc	19.5	
Colon	0.03 cc	38	Colitis/Fistula
	20 cc	25	
Rectum	0.03 cc	38	Proctitis/Fistula
	20	25	
Bladder	0.03 cc	38	Cystitis/Fistula
	15 cc	18.3	
Ureter	0.03 cc	45	Stenosis
Femoral head	10 cc	30	Necrosis
Bile Duct	0.03 cc	41	Stenosis
Renal hilum/Vascular Trunk	< 2/3 volume	23	Malignant Hypertension
Chest Wall	1 cc	45	Pain/Necrosis
	5 cc	40	
Rib	0.03 cc	43	Pain or Fracture
	1 cc	35	

Parallel Organ*	Volume	Volume Dose (Gy)	Avoidance Endpoint
Lung (total)	< 37% lung volume	13.5	Pneumonitis
	<1500 cc	12.5	Basic Lung Function
	<1000 cc	13.5	Pneumonitis
Renal cortex	< 200 cc	17.5	Basic Renal Function
Liver	<700 cc	15	Basic Liver Function

Note: Every effort should be made to avoid circumferential irradiation. Doses to serial OAR up to and including 105% of the dose prescribed to the PTV will be an acceptable variation. Doses to parallel OAR up to 110% of the values listed in the table will be an acceptable variation.
*ClearCheck: **For parallel organs dose constraints shall include the Minimal Volume Spared (MVS); for example, MVS1350cGy ≥ 1000cc for Lung (total).**

7.3.14 Documentation requirements

In general, treatment interruptions should be avoided by preventative medical measures and supportive therapies. Treatment breaks, including indications, must be clearly documented in the treatment record.

7.3.15 Compliance Criteria

7.3.15.1 Treatment Duration

Treatment duration will be defined per lesion. Per Protocol, all five fractions of radiation should be completed within 2-3 weeks of first radiation dose (>3 weeks is an unacceptable variation).

7.3.15.2 PTV Dosimetry Compliance

Acceptable variations in the protocol prescription dose (dose covering 95% of the PTV) should be evaluated for each lesion. Prescription doses outside of the variation acceptable range will be scored as Deviation Unacceptable. Scoring of PTV coverage will be: acceptable if ≥ 95%, variation acceptable if 70-95%, deviation unacceptable if < 70%.

7.3.15.3 Organ at Risk Dosimetry Compliance

Critical structure doses should be based on composite dose distribution when more than one met is treated. Respect spinal cord, cauda equina, sacral plexus and brachial plexus dose constraints. Any dose to spinal cord, cauda equina, sacral plexus above that listed in the above Tables will be considered an unacceptable deviation. For all other OAR, when OAR dose criteria cannot be accomplished by following planning priorities, doses to serial OAR of more than 105% of the dose prescribed to the PTV will be Unacceptable Deviations. Doses to parallel OAR exceeding 110% of the dose prescribed to the PTV will be scored as unacceptable deviations. Doses in the range between the numbers in the tables and unacceptable deviation will be considered acceptable variations.

7.4 Availability

As the systemic chemotherapy agents (Carboplatin, Cisplatin, and Etoposide) employed in this study will be used according to their FDA-approved indications, they will be obtained through the various institutions taking part in this trial and billed to the subjects' insurance. Durvalumab will be supplied

by AstraZeneca. Radiation treatment will be delivered at the appropriate facilities within each participating institution.

7.5 Dosing Delays/Dose Modifications

Dose-reductions up to Carboplatin AUC = 2.5, Cisplatin = 35mg/m2, and/or Etoposide = 50mg/m2 will be permitted during treatment at the discretion of the treating medical oncologist. There will be no dose-reductions for Durvalumab. Infusion times for chemotherapy and Durvalumab may be adjusted to improve tolerability, as per the treating medical oncologist.

Each 21-day cycle of Carboplatin/Cisplatin + Etoposide + Durvalumab may be delayed up to 4 weeks. Each 28-day cycle of single-agent Durvalumab may be delayed up to 6 weeks.

Every effort should be made to limit dose-reductions and delays in chemotherapy and immunotherapy.

All five fractions of radiation should be completed within 2-3 weeks of first radiation dose. Greater than 3 weeks is an unacceptable variation.

7.6 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications will be recorded and/or updated on subject medication log throughout the course of the study and saved in subject binder, if applicable.

7.6.1 Prohibited Medications

- Any investigational anticancer therapy other than those under investigation in this study.
- Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study.
- EGFR TKIs
- Live attenuated vaccines
- Herbal and natural remedies which may have immune-modulating effects
- Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers

<u>The following are allowed exceptions</u>:

- Use of immunosuppressive medications for the management of IP-related AEs,
- Short-term premedication for patients receiving chemotherapy where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions
- Use in patients with contrast allergies.
- In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.

In addition, a temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).

7.6.2 Contraception

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

1. Female patient of child-bearing potential

Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (Table 7) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Non-sterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

2. Male patients with a female partner of childbearing potential

Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 7).

Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 7. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/ desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

7.6.3 Blood Donation

Patients should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab.

Table 7: Highly Effective Methods of Contraception (<1% Failure Rate)

• Barrier/Intrauterine methods	• Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based

[a] This is also considered a hormonal method

7.7 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays, chemotherapy plus Durvalumab will continue for 4 cycles with subsequent single-agent Durvalumab continuing indefinitely, or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

Subjects may continue on single-agent Durvalumab after disease progression by RECIST criteria if this is felt to be beneficial by the treating medical oncologist. RECIST progression should be confirmed on 2 imaging scans at least 4 weeks apart, though this is not required.

7.8 Duration of Follow Up

Subjects will be followed for 2 years after removal from study or until death, whichever occurs first. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.9 Study Intervention/Follow-up Compliance

The study will be conducted as described in the final IRB-approved protocol. Adherence to the protocol will be assessed and verified by the research study team, the DSMB, and, if needed, by the medical monitor. Repeated attempts will be made to get subjects to return for study follow-up appointments; however, after 3 months subjects will be considered “lost to follow-up” and no longer participating in the study.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

An individual subject who is discontinued from the study will not receive any further investigational product. An investigator may discontinue a participant from the study for the following reasons:

1. If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

2. Disease progression which requires discontinuation of the study intervention

3. If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation because continuing investigational therapy might constitute a safety risk

4. Participant unable to receive radiation, chemotherapy, or ICB therapy for 12 weeks.

5. Withdrawal of consent or p*articipant lost to follow-up after several attempts to contact subject to schedule study visit.*

6. Adverse event related to radiation or chemotherapy that, in the opinion of the investigator or the sponsor, contraindicates further treatment with these modalities

7. Pregnancy or intent to become pregnant

8. Adverse event related to durvalumab that is Grade ≥ 3, with the exception of toxicities that do not meet criteria for discontinuation as per guidelines in Appendix B or per NCCN Clinical Practice Guidelines in Oncology Management of Immunotherapy-Related Toxicities[60].

9. Grade ≥ 3 infusion reaction

10. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants discontinuation, such as refusal to adhere to scheduled visits or initiation of alternative anticancer therapy including another investigational agent

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to, changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Interval Medical History
- Concurrent Medications
- Vital signs including Height and Weight
- Physical Exam
- Labwork: CBC with differential; Serum Chemistry with Liver Function Tests; Thyroid Function Panel
- Adverse Event Evaluation

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits for 3 months and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 14 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Correlative/Special Studies

9.1 Tumor-immune microenvironment and the T-cell response

These studies will be done in the laboratory of Dr. Sandra DeMaria, MD at WCM.

A comprehensive approach is proposed to analyze immunological changes that reflect both local and systemic responses, and general immune activation as well as tumor antigen-specific T cell responses. To this end, serial blood samples (50-ml) will be collected for serum and peripheral blood mononuclear cells (PBMC): at baseline, day 43, day 85 (at response evaluation) and thereafter every 8 weeks and at progression. Small aliquots of PBMC will be used ex vivo for preparation of DNA and RNA, and the remainder preserved frozen until evaluation by flow cytometry and/or by functional assays. Tumor tissue will be obtained at baseline, at day 85 and at progression from patients who consent to optional biopsies. Three 18G cores will be allocated for the following: DNA and RNA isolation (snap frozen), histology and multiplex imaging (fixed in formalin), and for generation of organoids by the EIPM Ex-vivo Lab (see section 9.2.1).

Flow cytometry analysis of circulating PBMC: Cryo-preserved PBMC isolated from serially collected blood following standardized SOPs, will be analyzed by multi-parameter flow cytometry. Specifically, levels of regulatory T cells (Tregs), will be monitored, and T cells (CD3+CD4+ and CD3+CD8+) analyzed for markers of naïve, effector and central memory phenotype (CD45RA/CCR7), proliferation (Ki67), and activation/exhaustion (CD25, CD137, PD-1, Tim-3, CTLA-4, and LAG3). Myeloid cells will be investigated for the expression of granulocytic and monocytic MDSC markers, and for the expression levels of MHC-I and MHC-II molecules, costimulatory and co-inhibitory molecules, including PD-L1. We will measure $Ki67^{+}PD\text{-}1^{+}$ CD8 T cells with an effector-like phenotype ($HLA\text{-}DR^{+}CD38^{+}Bcl\text{-}1^{low}$) since they have been shown to be predictive of response In lung cancer patients treated with anti-PD-1 when increased within 4 weeks of treatment start from baseline by two to seven-fold [49].

Soluble markers: Serum/plasma levels of multiple chemokines and cytokines reflecting inflammatory and immune responses (IL-6, IL-10, IL-2, IFN-γ, CXCL10/11, TNFα, CCL2, CCL5, etc.) will be measured using the human cytokine array (R&D Systems). We will also use a sensitive ELISA assay (Cat 41415-1, PBL assay Science) to measure the levels of serum IFNb since this cytokine is mechanistically relevant to the immunogenicity of SBRT [12]. In addition, other cytokines and soluble factors that can be increased by RT may be associated with immune suppression (e.g., soluble MICA/B, soluble CD73) [48].

Whole Exome Sequencing (WES) and Neoantigen prediction will be performed as we have previously described [12]. Briefly, DNA isolated from tumor and from PBMC (normal tissue control) will

be used for WES performed by the genomics core at WCM. Baseline tumor and PBMC WES data will be used in VarScan2 to detect somatic variants. Variants with somatic p-value (SPV) < 0.05 are considered statistically significant. Optitype algorithm will be used for HLA genotyping [61]. The VCF files containing somatic mutations will be subjected to standard VEP, Downstream, and Wildtype annotations, and filtered for frameshift and missense mutations [62]. Additionally, variant allele frequency (VAF) data will be generated using bamreadcount. The NetMHC and NetMHCpan algorithms will be used to predict patient-specific MHC-I binding for all possible 8-11 amino-acid long variant and corresponding wildtype peptide chains spanning the mutation using the pVAC-seq pipeline [63-65]. Candidate neoepitopes will be synthesized and tested in vitro for recognition by the patients' T cells isolated from blood in ELISPOT assays.

TCRB CDR3 sequencing and repertoire analysis. Amplification and sequencing of TCRB CDR3 regions will be performed using the Adaptive Biotechnologies ImmunoSEQ platform [66]. We have experience using this platform to analyze the expansion of TCR repertoire induced by treatment with RT and anti-CTLA-4 in mice [67] and in patients [12].

Multiplex imaging by mass cytometry using the Hyperion Imaging System: The Hyperion™ Imaging System brings together imaging capability with proven CyTOF® technology to facilitate Imaging Mass Cytometry™ applications. This allows highly multiplexed IHC enabling the simultaneous analysis of up to 37 protein markers [68]. Over 60 metal-labeled antibodies are currently commercially available (Fluidigm) and have been optimized to detect markers in immuno-oncology pathways and cancer. Fluidigm also provides metal-labeling kits to prepare additional custom antibodies. We will use the Maxpar® Complete Human T Cell Immuno-oncology Panel Set to characterize infiltrating T cells. This panel has been validated and provides information about naïve, central memory, effector memory and effector CD4 and CD8 T cells, naïve and memory Tregs, Th1 and Th2 T cells, activation and homing status, and checkpoint expression. Additional panels will be used to characterize myeloid populations [69], and B cells, depending on the initial findings. Data deconvolution will be performed by Dr. Elemento, a co-investigator in this protocol.

9.2 Organoids from SCLC Tissue

Tissue from standard of care or research biopsies will be brought to the EIPM via standard operating procedures in place here at WCM. Organoid specimens are biobanked when the culture has demonstrated that it can be successfully expanded beyond its initial plating. We define successful establishment of PDTO cultures as when they contain viable cells that form spheroid-like structures and can be propagated after the initial processing for at least five passages. Tumor verification assays involve histologic examination to ensure that the tissue initially submitted is tumor[70], and that the growing organoids are tumoral as well[71]. The specimens are then characterized, stored in our living biobank, and used for functional studies. Once they are considered successfully established, they are subjected to Whole-Exome Sequencing (WES) to test concordance at base-pair resolution with the native tumor[72,73]. We evaluate tumor purity and ploidy using the CLONET computational framework (CLONality Estimate in Tumors)[74].

Our plan is to optimize and use the Operetta system (see background section 2.5.3) to run the high throughput drug screening planned in the current study. Drug screenings performed in our high throughput platform would have two readouts: a primary readout of organoid growth/death as determined by imaging over time and a secondary endpoint readout of cell metabolism as an indirect measure of cell viability. 3D analysis includes parameters such as intensity, position, morphology (such as solid vs. hollow sphere, cell shape, etc.) and texture. Following 3D analysis, a final endpoint luminescence measurement using Cell titer Glo will be taken to measure cell viability on our high

throughput drug screening robot's Biotek Synergy Neo plate reader. Each compound will be tested in a dose-response manner and hits will be determined based on two primary criteria, efficacy of each compound relative to the rest of the compounds in the screen (AUC), and impact of each compound on that specific organoid relative to the rest of the organoids that have been tested (Z-score).

9.3 Circulating Tumor Cells

These studies will be done in the laboratory of Dr. Paraskevi Giannakakou, PhD at WCM.

All subjects in this study will get blood samples drawn for circulating tumor cell (CTC) enrichment. CTCs and PBMCs will be collected before the initiation of therapy (baseline), during the course of the treatment (on-treatment) and at the moment of disease progression (relapse).

Twenty mL of peripheral whole blood will be collected at each time point in two 10 mL EDTA tubes (purple top) by standard venous phlebotomy. Gently invert the tubes 8-10 times after blood collection. Tubes will be stored at ambient temperature until brought to the Giannakakou lab at Weill Cornell Medicine. Do not freeze the tubes. The tubes must be received by the Giannakakou lab within 24 hours of collection. Ensure that the EDTA tubes are transported at ambient temperature. If collected samples cannot be transported on the same day of collection (e.g. Friday-Saturday or Holiday collections), please contact the Giannakakou lab at 212 746-0293 for further instruction at least 24 hours prior to anticipated collection.

CTC enrichment will be performed at the Giannakakou lab and CTCs will be analyzed for transcriptomic studies. Briefly, CTCs will be enriched by negative depletion using the RosetteSep Human CD45 depletion cocktail (STEMCELL technologies). If SCLC CTCs are found to express TfR, then this protein will also be used as a positive selection marker. At each time point, 1 mL of the blood collected will be used to isolate peripheral blood mononuclear cells (PBMCs), using density centrifugation (Ficoll).

RNA will be extracted from CTCs and PBMCs and gene expression will be analyzed by RNA-sequencing. Differentially expressed genes in the enriched CTCs and matching PBMCs between C1D1 and subsequent time points will be identified, and gene set enrichment analysis of differentially expressed genes between C1D1 and the on-treatment and relapse time points will be performed to identify specific pathways and biological functions associated with sensitivity or resistance to the treatment.

10. Measurement of Effect

10.1 Progression-Free Survival

PFS will be defined as the time from first study treatment to the point of either radiographic progression of malignancy by RECIST 1.1 criteria or death. Death will be considered clinical progression if the cause of death is felt to be due to the underlying malignancy (vs due to toxicity or a non-malignancy related cause such as accident). Median PFS will be estimated using the Kaplan-Meier method.
The proportion of subjects without progression (as defined above) at 12-months after start of study treatment will constitute the 12-month PFS rate, which is the primary endpoint of this study.

10.2 Overall Survival

OS will be defined as the time from first study treatment to the time of death from any cause. Median OS will be estimated using the Kaplan-Meier method.
The proportion of subjects still alive at 12-months after start of study treatment will constitute the 12-month OS rate.

10.3 Response Criteria

Response will be assessed based on imaging as per RECIST 1.1 criteria. The Overall Response Rate (ORR) will be calculated by the proportion of subjects achieving a RECISTv1.1 complete or partial response.

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject

to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints

One primary aim of this study is to demonstrate that the addition of radiation to chemotherapy and immunotherapy is associated with an improvement in 12-month PFS from 18% historical control to approximately 38% with the addition of radiation. With a sample size of 34 patients receiving chemotherapy/immunotherapy plus radiation, a one-group chi-square test will have 80% power to detect the difference between a null hypothesis 12-month PFS proportion of 18% (i.e., historical control) and an alternative hypothesis 12-month PFS proportion of 38% (i.e., chemotherapy + immunotherapy + radiation), with a 0.05 two-sided significance level. As well, a sample size of 34 patients will allow a two-sided 95% confidence interval for the expected 12-month PFS proportion (38%) to be constructed to be within ± 16.3% of the observed 12-month PFS proportion.

The second primary aim of this study is to evaluate the safety of combining carboplatin + etoposide chemotherapy, durvalumab immunotherapy, and non-ablative radiation to one or more sites of disease. Due to this, we propose a safety run-in for the first 10 subjects. If there is a 30% or greater incidence of grade 3 or higher toxicities with the proposed treatment regimen, specifically from radiation therapy (with focus on pneumonitis, pericarditis, esophagitis, rib fracture, or hemoptysis) or immune-mediated adverse events (other than thyroid dysfunction), then the radiation regimen will be switched to 5 Gy radiation per day for 5 days. If there is still a 30% or greater incidence of grade 3 or higher toxicities from radiation therapy or immune-mediated adverse events among the subsequent 10 subjects, then the study will be terminated. If this does not occur, then accrual will continue until 34 total subjects are evaluable.

12.2 Sample Size/Accrual Rate

This study will plan to enroll 42 subjects to allow for 34 to be evaluable for the primary endpoints.
We plan to accrue roughly 1 subject per month.

12.3 Stratification Factors

As this is a pilot study with a relatively small number of patients, no stratification is planned. However, sub-group analysis of patients with ECOG PS 2 vs PS 0-1 will be performed for the primary endpoint of the study.

12.4 Analysis of Endpoints

All analyses will be performed in SAS Version 9.4 (SAS Institute, Inc., Cary, North Carolina).

12.4.1 Analysis of Primary Endpoints

The primary endpoint of the 12-month PFS proportion will be calculated and a 95% confidence interval will be estimated via binomial proportions. A one-group chi-square test will be used to compare the 12-month PFS proportion with a historical 12-month PFS proportion of 18%. PFS will also be estimated using the Kaplan-Meier method, and 95% confidence intervals for PFS estimates (including median PFS) will be calculated using Greenwood's formula.

The primary endpoint of safety will be described by the incidence of ≥ Grade 3 toxicities definitely or probably related to the treatments given (i.e. radiation, immunotherapy, and/or chemotherapy), as reported and graded by NCI CTCAE version 5.0.
Full descriptive analysis of safety will also be conducted (e.g. AEs considered causally related to treatment regimen, serious AEs, AEs leading to discontinuation).

12.4.2 Analysis of Secondary Endpoints

Secondary endpoints of the objective response proportion and 12-month overall survival (OS) will be calculated and 95% confidence intervals will be estimated via binomial proportions.

OS will also be estimated using the Kaplan-Meier method, and 95% confidence intervals for OS estimates (including median OS) will be calculated using Greenwood's formula.

Pattern of disease progression will focus on the rates of progression in the radiated lesions vs non-radiated lesions and rates of new lesions.

12.5 Interim Analysis

No interim analysis for efficacy is planned. Interim analyses for safety will be performed as outlined in Section 12.1.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with carboplatin or cisplatin with etoposide and durvalumab or their first radiation fraction.

Hy's Law
Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix B, the Toxicity Management Guidelines, for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

12.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they have received at least 1 cycle of platinum plus etoposide chemotherapy with durvalumab and completed radiation.

13. Adverse Event Reporting Requirements

13.1 Reporting

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1.1 Reporting of Deaths to AstraZeneca

All deaths must be recorded and reported as outlined in Section 13.2.2 and 13.4.3. In addition, all SAEs resulting in death or death of unknown cause must be reported to AstraZeneca via AEMailboxClinicalTrialTCS@astrazeneca.com within 7 calendar days of awareness or sooner when required

13.1.2 Overdose

An overdose is defined as a patient receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol. Any overdose of a study patient with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor. The sponsor must report these to AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 13.4.3 for contact information) within 7 calendar days or sooner when required. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section 13.4.3). There is currently no specific treatment in the event of an overdose of durvalumab.

13.1.3 Hepatic Function Abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law

case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the sponsor. The Sponsor must report these events to AstraZeneca Patient Safety using the designated Safety e-mailbox (see Section 13.4.3 for contact information) within 7 calendar days or sooner when required, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study patient will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca/MedImmune.

13.1.4 Pregnancy

Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study 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 sponsor within 1 day, i.e., immediately, but no later than 24 hours of when he or she becomes aware of it.

The sponsor will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days. The Sponsor must report to AstraZeneca Patient Safety using the designated Safety e-mailbox (see Section 13.4.3 for contact information) within 7 calendar days or sooner when required for pregnancies with SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

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 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period should, 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.

13.2 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.2.1 Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

13.2.2 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported and documented in the CRF, in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported.
- The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the CRF.

13.2.3 Investigational Agent or Device Risks (Expected Adverse Events)

As the combination of platinum + etoposide chemotherapy and Durvalumab immunotherapy is now FDA-approved for patients with ES-SCLC, the "investigational

agent" in this study will be the sub-ablative radiation. Mild to moderate (grade <3) adverse events from thoracic radiation include the following: esophagitis, dermatitis, radiation recall reaction, pleural effusion, pericardial effusion, pleuritic pain, non-cardiac chest pain, chest wall pain, pneumonitis, atelectasis, cough, dyspnea, pulmonary fibrosis, generalized muscle weakness, fatigue, photosensitivity, telangiectasias, FEV decrease, WBC decrease, lymphocyte count decrease, and neutrophil count decrease. Severe adverse events (grade ≥3) from radiation may also include the above mentioned plus those listed in Table 6.

13.2.4 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

13.2.5 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.2.6 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.3 Definition of Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious.

If the Investigator has any questions in regards to an event being an ImAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis / transaminase increases

- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
    - Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Intestinal Perforations

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to:

- Pericarditis
- Sarcoidosis
- Uveitis
- Other events involving the eye and skin
- Hematological events
- Rheumatological events
- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis.

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix B). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

13.4 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition. Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this latter situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

Adverse Events (AEs) for malignant tumors reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.
The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is not the tumor for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

13.4.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.4.2 Reporting of SAE to FDA

SAEs will be reported to the FDA as per FDA reporting guidelines by the IND application sponsor. IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected. Unexpected fatal or life-threatening suspected adverse reactions

represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information. SA

i. death,
ii. a life-threatening adverse event,
iii. in-patient hospitalization or prolongation of existing hospitalization,
iv. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
v. a congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious.

CDER INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Biological Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

13.4.3 Reporting of SAE to AstraZeneca

Institution will send AstraZeneca copies of any and all serious adverse event reports filed with the FDA or other applicable regulatory authorities, as well as copies of any correspondence with the FDA or other applicable regulatory authorities, regarding any and all serious adverse events, irrespective of association with the Study Drug(s) in the course of the Clinical Trial. SAE reports (individual case reports and line listings) and accompanying cover page will be sent to AstraZeneca via Email: AEmailboxclinicaltrialTCS@astrazeneca.com

13.5 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

13.6 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event

description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study team will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 90 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.]

14. Data and Safety Monitoring Plan (DSMP)

This study will utilize the Weill Cornell Medicine (WCM) Institutional Data Safety Monitoring Board (DSMB) and follow its policies and procedures for monitoring the study for safety concerns. The WCM DSMB is comprised of medical specialists and advisors on human rights issues in human subjects research. The WCM DSMB will review the IRB approved protocol, the data and safety monitoring plan, and any stopping guidelines during protocol initiation. During the course of the study, the DSMB will review cumulative study data at a specified interval to evaluate safety, risk-benefit ratio, study conduct, and scientific validity and integrity of the trial. The WCM DSMB may also convene as needed if stopping criteria are met or other safety issues arise that the Principal Investigator and/or IRB would like the WCM DSMB to address. Ultimately, the DSMB validates the continuation of the trial or determines if a study needs modification or termination. After each evaluation, the DSMB will provide the principle investigator with recommendations for protocol modification, continuation, or termination.

For this study, a report will be submitted to the DSMB every 6 months. A report will also be submitted if it is determined that the radiation fractionation schedule needs to be adjusted as per the study protocol. If the study stopping rule below is met, then a report will also be submitted to the DSMB at that time.

14.1 Stopping Rule

If there is a 30% or greater incidence of grade 3 or higher toxicities with the proposed treatment regimen in the first 10 subjects, specifically from radiation therapy (with focus on pneumonitis, pericarditis, esophagitis, rib fracture, or hemoptysis) or immune-mediated adverse events (other than thyroid dysfunction), then the radiation regimen will be switched to 5 Gy radiation per day for 5 days. If there is still a 30% or greater incidence of grade 3 or higher toxicities from radiation therapy or immune-mediated

adverse events among the subsequent 10 subjects, then the study will be terminated. If this does not occur, then accrual will continue until 34 total subjects are evaluable.

If safety concerns arise, the DSMB will identify these concerns and recommend modification or termination of the clinical trial.

14.2 Study Monitoring

The study will be monitored by the WCM DSMB as described in the DSMP.

The study team (consisting of the PI, Research Nurse, and Data Manager at a minimum) will review monthly AE reports to ensure there are no unexpected or unacceptable safety concerns.

Dr. Ana Molina, M.D. will serve in the capacity of Independent Medical Monitor.

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Appendix A

Adverse Events Reported in CASPIAN Trial of Platinum-Etoposide vs Durvalumab plus Platinum - Etoposide. Tables 4 and S5-S8 from Publication of Trial[6]

	Durvalumab plus platinum–etoposide (n=265)		Platinum–etoposide (n=266)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any event	260 (98%)	163 (62%)	258 (97%)	166 (62%)
Any serious event	82 (31%)	57 (22%)	96 (36%)	70 (26%)
Any event leading to discontinuation*	25 (9%)	7 (3%)	25 (9%)	7 (3%)
Any event leading to death†	13 (5%)	--	15 (6%)	--
Adverse events with an incidence of at least 10% in any grade category or events of grade 3 or 4 with an incidence of at least 2% in either group‡				
Neutropenia	111 (42%)	64 (24%)	124 (47%)	88 (33%)
Anaemia	102 (38%)	24 (9%)	125 (47%)	48 (18%)
Nausea	89 (34%)	1 (<1%)	89 (33%)	5 (2%)
Alopecia	83 (31%)	3 (1%)	91 (34%)	2 (1%)
Constipation	44 (17%)	2 (1%)	51 (19%)	0
Decreased appetite	48 (18%)	2 (1%)	46 (17%)	2 (1%)
Thrombocytopenia	41 (15%)	15 (6%)	53 (20%)	25 (9%)
Fatigue	48 (18%)	4 (2%)	45 (17%)	3 (1%)
Vomiting	39 (15%)	0	44 (17%)	3 (1%)
Asthenia	40 (15%)	5 (2%)	40 (15%)	3 (1%)
Leucopenia	40 (15%)	17 (6%)	32 (12%)	14 (5%)
Dyspnoea	31 (12%)	5 (2%)	28 (11%)	3 (1%)
Neutrophil count decreased	26 (10%)	17 (6%)	31 (12%)	17 (6%)
Diarrhoea	26 (10%)	3 (1%)	30 (11%)	3 (1%)
Cough	33 (12%)	2 (1%)	18 (7%)	0
Hyponatraemia	26 (10%)	10 (4%)	12 (5%)	7 (3%)
Febrile neutropenia	17 (6%)	14 (5%)	17 (6%)	17 (6%)
White blood cell count decreased	14 (5%)	4 (2%)	17 (6%)	6 (2%)
Platelet count decreased	16 (6%)	4 (2%)	14 (5%)	6 (2%)
Pneumonia	11 (4%)	5 (2%)	18 (7%)	9 (3%)
Hypertension	15 (6%)	8 (3%)	7 (3%)	1 (<1%)
Lipase increased	12 (5%)	9 (3%)	7 (3%)	4 (2%)
Amylase increased	11 (4%)	6 (2%)	2 (1%)	1 (<1%)

Data cutoff was March 11, 2019. Listed are all adverse events that occurred during the treatment period and up to 90 days after the last dose of durvalumab or platinum–etoposide or up to the start of any subsequent therapy (whichever occurred first). Platinum–etoposide=etoposide plus either cisplatin or carboplatin. *Includes patients who permanently discontinued at least one study drug. †Adverse events of any cause leading to death in the durvalumab plus platinum–etoposide group were sudden death in two patients, and acute respiratory failure, aspiration, cardiac arrest, dehydration, hepatotoxicity, hypoxia, pancytopenia, pulmonary artery thrombosis, pulmonary embolism, sepsis, and septic shock in one patient each; adverse events of any cause leading to death in the platinum–etoposide group were pneumonitis and death in two patients each, and acute cardiac failure, acute respiratory failure, cardiac arrest, cardiopulmonary failure, cerebrovascular accident, haematotoxicity, pancytopenia, pneumonia, sudden cardiac death, sudden death, and thrombocytopenia and haemorrhage (in the same patient) in one patient each. ‡The events are listed in descending order of frequency across both treatment groups.

***Table 4*: Adverse events of any cause (safety population)**

Table S5: **Treatment-related adverse events as assessed per the investigator (safety population)**

	Durvalumab + EP (n=265)		EP (n=266)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any treatment-related event, n (%)	237 (89%)	121 (46%)	240 (90%)	138 (52%)
Any treatment-related serious event, n (%)	35 (13%)	25 (9%)	50 (19%)	45 (17%)
Any treatment-related event leading to discontinuation, n (%)*	15 (6%)	3 (1%)	13 (5%)	4 (2%)
Any treatment-related event leading to death, n (%)†	5 (2%)	–	2 (1%)	–
Treatment-related adverse events with an incidence of ≥5% in any grade category or events of grade 3 or 4 with an incidence of ≥2% in either arm, n (%)‡				
Neutropenia	104 (39%)	61 (23%)	116 (44%)	86 (32%)
Anaemia	85 (32%)	21 (8%)	103 (39%)	38 (14%)
Alopecia	74 (28%)	3 (1%)	85 (32%)	2 (1%)
Nausea	74 (28%)	0	75 (28%)	5 (2%)
Thrombocytopenia	37 (14%)	14 (5%)	48 (18%)	24 (9%)
Vomiting	32 (12%)	0	38 (14%)	2 (1%)
Decreased appetite	33 (12%)	1 (<1%)	35 (13%)	1 (<1%)
Leucopenia	36 (14%)	15 (6%)	32 (12%)	14 (5%)
Fatigue	30 (11%)	2 (1%)	36 (14%)	3 (1%)
Asthenia	27 (10%)	2 (1%)	31 (12%)	2 (1%)

	Durvalumab + EP (n=265)		EP (n=266)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutrophil count decreased	24 (9%)	16 (6%)	28 (11%)	17 (6%)
Constipation	23 (9%)	0	24 (9%)	0
Diarrhoea	17 (6%)	2 (1%)	15 (6%)	2 (1%)
Febrile neutropenia	15 (6%)	13 (5%)	17 (6%)	17 (6%)
White blood cell count decreased	12 (5%)	4 (2%)	17 (6%)	6 (2%)
Platelet count decreased	14 (5%)	4 (2%)	13 (5%)	6 (2%)
Paraesthesia	14 (5%)	0	11 (4%)	0
Hypothyroidism	23 (9%)	0	0	0
Hyperthyroidism	22 (8%)	0	0	0
Lipase increased	10 (4%)	8 (3%)	2 (1%)	1 (<1%)

Data cutoff date: March 11, 2019. Listed are all adverse events assessed by the investigator as possibly related to any study treatment that occurred during the treatment period and up to 90 days after the last dose of durvalumab or EP or up to the start of any subsequent therapy (whichever occurred first). *Includes patients who permanently discontinued at least one study drug. †Treatment-related adverse events leading to death in the durvalumab plus EP arm were cardiac arrest, dehydration, hepatotoxicity, pancytopenia, and sepsis in one patient each. Treatment-related adverse events leading to death in the EP arm were pancytopenia and thrombocytopenia/haemorrhage in one patient each. ‡The events are listed in descending order of frequency across both treatment arms. EP=platinum-etoposide.

Table S6: **Serious adverse events occurring in ≥2 patients in any treatment arm (safety population)**

	Durvalumab + EP (n=265)	**EP (n=266)**
Any serious event, n (%)*	82 (31%)	96 (36%)
Febrile neutropenia	12 (5%)	12 (5%)
Anaemia	5 (2%)	12 (5%)
Pneumonia	6 (2%)	9 (3%)
Thrombocytopenia	1 (<1%)	9 (3%)
Neutropenia	2 (1%)	7 (3%)
Pancytopenia	4 (2%)	3 (1%)
Hyponatraemia	2 (1%)	4 (2%)
Pneumonitis	3 (1%)	3 (1%)
Diarrhoea	1 (<1%)	4 (2%)
Acute kidney injury	2 (1%)	2 (1%)
Chronic obstructive pulmonary disease	3 (1%)	1 (<1%)
Pleural effusion	2 (1%)	2 (1%)
Cerebrovascular accident	0	3 (1%)
General physical health deterioration	2 (1%)	1 (<1%)
Hypokalaemia	0	3 (1%)
Respiratory tract infection	2 (1%)	1 (<1%)
Sepsis	2 (1%)	1 (<1%)
Sudden death	2 (1%)	1 (<1%)
Syncope	1 (<1%)	2 (1%)
Transient ischaemic attack	2 (1%)	1 (<1%)
Upper respiratory tract infection	2 (1%)	1 (<1%)
Vomiting	0	3 (1%)
Acute myocardial infarction	0	2 (1%)
Atrial fibrillation	2 (1%)	0
Constipation	2 (1%)	0

	Durvalumab + EP (n=265)	EP (n=266)
Death	0	2 (1%)
Deep vein thrombosis	2 (1%)	0
Dyspnoea	0	2 (1%)
Lung infection	0	2 (1%)
Nausea	0	2 (1%)
Pyrexia	0	2 (1%)
Septic shock	2 (1%)	0
Type 1 diabetes mellitus	2 (1%)	0

Data cutoff date: March 11, 2019. Listed are all serious adverse events that occurred during the treatment period and up to 90 days after the last dose of durvalumab or EP or up to the start of any subsequent therapy (whichever occurred first). *The events are listed in descending order of frequency across both treatment arms. EP=platinum-etoposide.

Table S7: **Adverse events leading to treatment discontinuation (safety population)**

	Durvalumab + EP (n=265)	**EP (n=266)**
Any event leading to discontinuation, n (%)*,†	25 (9%)	25 (9%)
Acute kidney injury	3 (1%)	4 (2%)
Neutropenia	1 (<1%)	2 (1%)
Sudden death	2 (1%)	1 (<1%)
Thrombocytopenia	0	3 (1%)
Cardiac arrest	1 (<1%)	1 (<1%)
Deafness	0	2 (1%)
Pancytopenia	1 (<1%)	1 (<1%)
Acute cardiac failure	0	1 (<1%)
Acute respiratory failure	0	1 (<1%)
Anaemia	1 (<1%)	0
Aspiration	1 (<1%)	0
Asthenia	1 (<1%)	0
Atrial fibrillation	0	1 (<1%)
Bacterial urinary tract infection	1 (<1%)	0
Cardiopulmonary failure	0	1 (<1%)
Cerebrovascular accident	0	1 (<1%)
Death	0	1 (<1%)
Diabetic ketoacidosis	1 (<1%)	0
Diarrhoea	1 (<1%)	0
Haematotoxicity	0	1 (<1%)
Haemorrhage	0	1 (<1%)
Hepatic failure	1 (<1%)	0
Hepatitis C	1 (<1%)	0
Hepatotoxicity	1 (<1%)	0
Infectious pleural effusion	0	1 (<1%)

	Durvalumab + EP (n=265)	EP (n=266)
Ischaemic stroke	0	1 (<1%)
Lung disorder	1 (<1%)	0
Multiple organ dysfunction syndrome	0	1 (<1%)
Muscular weakness	1 (<1%)	0
Nephropathy	1 (<1%)	0
Neurotoxicity	1 (<1%)	0
Pneumonia	0	1 (<1%)
Pneumonitis	1 (<1%)	0
Pulmonary artery thrombosis	1 (<1%)	0
Pulmonary embolism	1 (<1%)	0
Renal failure	0	1 (<1%)
Seizure	0	1 (<1%)
Sepsis	1 (<1%)	0
Sudden cardiac death	0	1 (<1%)
Tinnitus	1 (<1%)	0
Tumour lysis syndrome	0	1 (<1%)

Data cutoff date: March 11, 2019. Listed are all adverse events leading to discontinuation that occurred during the treatment period and up to 90 days after the last dose of durvalumab or EP or up to the start of any subsequent therapy (whichever occurred first). *Includes patients who permanently discontinued at least one study drug. †The events are listed in descending order of frequency across both treatment arms. EP=platinum-etoposide.

Table S8: **Immune-mediated adverse events (grouped terms) (safety population)**

	Durvalumab + EP (n=265)		EP (n=266)	
	Any grade*	**Grade 3 or 4**	**Any grade***	**Grade 3 or 4**
Any immune-mediated adverse event (grouped term), n (%)[†,‡]	52 (20%)	12 (5%)	7 (3%)	1 (<1%)
Hypothyroid events	24 (9%)	0	2 (1%)	0
Hyperthyroid events	14 (5%)	0	0	0
Pneumonitis	7 (3%)	2 (1%)	2 (1%)	1 (<1%)
Hepatic events	7 (3%)	5 (2%)	0	0
Dermatitis/rash	4 (2%)	0	2 (1%)	0
Diarrhoea/colitis	4 (2%)	1 (<1%)	1 (<1%)	0
Thyroiditis	4 (2%)	0	0	0
Type 1 diabetes mellitus	4 (2%)	4 (2%)	0	0
Adrenal insufficiency	1 (<1%)	0	0	0
Pancreatic events	1 (<1%)	1 (<1%)	0	0
Other rare/miscellaneous[§]	2 (1%)	0	0	0

Data cutoff date: 11 March 2019. Listed are all immune-mediated adverse events that occurred during the treatment period and up to 90 days after the last dose of durvalumab or EP or up to the start of any subsequent therapy (whichever occurred first). *Grade 5 immune-mediated adverse events occurred in one patient receiving durvalumab plus EP (hepatotoxicity) and one patient receiving EP (pneumonitis). †An immune-mediated adverse event is defined as an event that is associated with drug exposure and 21 consistent with an immune-mediated mechanism of action, where there is no clear alternate etiology and the event required treatment with systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy. ‡The events are listed in descending order of frequency across both treatment arms. §The events in the 'other rare/miscellaneous' category were both arthritis.
EP=platinum-etoposide.

Appendix B

Toxicity Management Guidelines (TMGs)

Drug Substance	Durvalumab and Tremelimumab
TMG Version	28 October 2021

ANNEX TO PROTOCOL

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy

Note: Annex is to be used in any clinical trial protocol within which patients are treated with
Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy

Table of Contents

1. VERSION HISTORY

28 October 2021

The Toxicity Management Guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors durvalumab [MEDI4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either drug is used alone or both drugs are used in combination and, also, other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) are administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

Dosing modification and toxicity management for immune-mediated, infusion-related, and nonimmune–mediated reactions associated with the use of a checkpoint inhibitor or checkpoint inhibitors in this protocol – whether that is durvalumab alone, tremelimumab alone, or durvalumab + tremelimumab in combination, or durvalumab +/- tremelimumab in combination with other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) administered concurrently or sequentially – should therefore be performed in accordance with this Annex to Protocol, which for the purposes of submission and approval of substantial updates is maintained as a standalone document. TMG updates are iterated by date, and should be used in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version specified in the clinical study protocol.

Although the TMG versioning is independent of the protocol, the TMG Annex to Protocol should be read in conjunction with the Clinical Study Protocol, where if applicable additional references for the management of toxicities observed with other anti-cancer treatment are included in the specific section of the Clinical Study Protocol.

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy – 28 October 2021

1.1. General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO)) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.

Early identification and management of imAEs is essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying imAEs. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, durvalumab and/or tremelimumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With longterm steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis, gastrointestinal protection, and glucose monitoring. Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

1.2. Relevant Society Guidelines for Management of imAEs

These society guidelines are provided as references to serve in support of best clinical practice and the TMGs. Please note, these were the current versions of these guidelines at the time of updating TMGs. Please refer to the most up to date version of these guidelines.

1. Brahmer JR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021;9:e002435
2. Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36(17):1714-1768.
3. Haanen JBAG, et al. Management of toxicities for immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up. Annals Oncol 2017;28(Suppl4):i119-i1142.
4. Sangro B, et al. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol 2020;72(2):320-341.
5. Thompson JA, et al. National Comprehensive Cancer Network Guidelines: Management of immunotherapy-related toxicities version 3.2021. Published May 14, 2021.

Pediatric Considerations Regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTCAE grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks of** initiating corticosteroids.	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for steroid dosing (i.e., mg/kg/day) provided for adult patients should also be used for pediatric patients. The recommendations for intravenous immunoglobulin (IVIG) and plasmapheresis use provided for adult patients may be considered for pediatric patients. – The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric

patients ≥ 6 years old. For subsequent dosing and dosing in children < 6 years old, consult a pediatric specialist.

- For pediatric dosing of mycophenolate mofetil, consult a pediatric specialist.
- With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. infection, progressive disease) - Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. - Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as described below. - Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high-

		resolution computed tomography (CT) scan. – Consider Pulmonary and Infectious Diseases consults.
Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory workup, and then as clinically indicated.
Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. □ If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper (≤10 mg prednisone or equivalent).	**For Grade 2** Monitor symptoms daily and consider hospitalization. – Obtain Pulmonary and Infectious Diseases Consults; – consider discussing withClinical Study Lead, as needed.
		– Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider chest CT with contrast

		and repeat in 3-4 weeks. – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy. such as tumor necrosis factor (TNF) inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Consider, as necessary, discussing with Clinical Study Lead.
Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4**

		– Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 2 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution:
Diarrhea/Colitis		rule out sepsis and refer to infliximab label for general guidance before using infliximab.

Any Grade	General Guidance	For Any Grade
(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)		Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for *Clostridium difficile* toxin, etc. – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** – **PERMANENTLY DISCONTINUE STUDY**

		DRUG FOR ANY GRADE OF INTESTINAL PERFORATION. – Steroids should be considered in the absence of clear alternative etiology, even for lowgrade events, in order to prevent potential progression to higher grade events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1	No dose modifications.	**For Grade 1** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2

Grade 2		below. If negative and no infection, continue Grade 1 management.
	□ d study drug/study regimen until resolution to de ≤1 If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper (<10 mg prednisone, or equivalent).	– **For Grade 2** Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consult a gastrointestinal (GI) specialist for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation.

		– If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start additional immunosuppressant agent such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.** – Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤1 in 3 to 4 days.
Grade 3 or 4		
	Grade 3 □ For patients treated with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration.

	after completion of steroid taper (≤10 mg prednisone per day, or equivalent). For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study investigator, in discussion with AstraZeneca Clinical Study Lead. For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy, Permanently discontinue study drug for 1) Grade 3 diarrhea colitis or 2) Any grade of intestinal perforation in any patient treated with immune checkpoint inhibitor (ICI). **Grade 4** Permanently discontinue study drug/study regimen.	– Urgent GI consult and imaging and/or colonoscopy as appropriate. If still no improvement within 2 days, continue steroids and promptly add further immunosuppressants. (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**

Hepatitis (elevated liver function tests (LFTs))	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications). – Monitor and evaluate LFTs: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin (T. bili.).
	Grade 1	□ No d ɔse modifications. □ If it ʌorsens, then consider holding therapy.	**For Grade 1** – Continue LFT monitoring per protocol.
	Grade 2	□ Hold study drug/study regimen dose until Grade 2 resol ıtion to Grade ≤1. □ If tox icity improves to Grade ≤1 or baseline and there were ɨlevations in bilirubin, resume study g/study	**For Grade 2** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until LFT elevations improve or resolve.

Infliximab should not be used for management of immune-related

regimen after completion of steroid taper (<10 mg ≤1 in 1 to 2 days, prednisone or equivalent).

– If no resolution to Grade ≤1 in 1 to 2 days, prednisone or equivalent). consider discussing with Clinical Study Lead, as needed.

□Permanently discontinue study drug/study regimen for any

– If event is persistent (>2 to 3 days) or case meeting Hy's law criteria (AST and/or ALT ≥3 × worsens, promptly start prednisone 1 to

equivalent. **hepatitis.**	ULN + bilirubin ≥2 × ULN without initial findings of cholestasis (i.e., elevatedALP) and in the absence of any alternative cause.	2 mg/kg/day PO or IV

PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma (HCC) patients

1.2.1. Grade 3 or 4 For Grade 3

- Hold study drug/study regimen For

Grade ≤1 or baselineResume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline after elevations in transaminases ≤8 × ULN (and no elevations in bilirubin), or elevations in bilirubin ≤5 × ULN until resolution to

completion of steroid taper (<10 mg prednisone, or equivalent).

- If in combination with tremelimumab, do not restart tremelimumab.

Permanently discontinue study drug/study regimen for elevations in transaminases >8 × ULN or any elevations in bilirubin >5 × ULN

1.2.2. For Grade 4

Permanently discontinue study drug/study regimen.

1.2.3. For Grade 3 or 4

- Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent.

- If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available.

  Infliximab should NOT be used.
- Perform Hepatology Consult, abdominal workup, and imaging as appropriate.

Hepatitis (elevated LFTs) **Infliximab should not be used for management of THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients immune-related hepatitis.** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time)	**Any Elevations of AST, ALT, or T. Bili as Described Below**	**General Guidance**	**For Any Elevations Described** Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – Monitor and evaluate liver function test: AST, ALT, ALP, and T. Bili. – For hepatitis B (HBV) + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg). – For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-

occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**		fold. For HCV+ with Hepatitis B core antibody (HBcAb) +: Evaluate for both HBV and HCV as above.

Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline	□ No dose modifications. □ If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. □ For all transaminase elevations , see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	

	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline	Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN . If toxicity worsens, then treat as described for elevations in the rows below.If toxicity improves to AST or ALT ≤5.0×ULN , resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead. – If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting additional immunosuppressants. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in

			consultation with hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline	□ Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN Resume study drug/study regimen if elevations downgrade □ to AST or ALT ≤5.0×ULN and after completion of steroid taper (<10 mg prednisone, or equivalent). Permanently discontinue study drug/study	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); – obtain abdominal ultrasound, including Doppler assessment of – liver perfusion; and consider liver

	Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if	regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days	biopsy. Consider discussing with Clinical Study Lead, as needed. If investigator suspects toxicity to be immune-mediated, promptly initiate empiric
	elevated >ULN at baseline		IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. − If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an additional immunosuppressant. (e.g.,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines). Discuss with Stucy Clinical Lead if mycophenolate is not available. **Infliximab should NOT be used.**

	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen. **Same as above (except recommend obtaining liver biopsy early)**	
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise** - **For example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)** - **For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**			
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	– **For Any Grade** Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). Consult a nephrologist. Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and

		creatinine, decreased creatinine clearance, electrolyte imbalance, decreased urine output, or proteinuria). – Consider using steroids in the absence of a clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade events.
Grade 1	No dose modifications.	**For Grade 1** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4.
Grade 2		– Consider symptomatic treatment, including hydration, electrolyte replacement, and

		diuretics.
	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. □ If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2** Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup.When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4	Permanently discontinue study drug/study	**For Grade 3 or 4**

		regimen.	
			– Carefully monitor serum creatinine daily. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant in consultation with a nephrologist.
Rash or Dermatitis (Including Pemphigoid)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade	**General Guidance**	– **For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Monitor for signs and symptoms of dermatitis (rash and pruritus). **HOLD STUDY DRUG IF STEVENSJOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), OR**

depending on type of skin rash)		**OTHER SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED.** – **PERMANENTLY DISCONTINUE STUDY DRUG IF SJS, TEN, OR SCAR IS CONFIRMED.**
Grade 1	No dose modifications.	**For Grade 1** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emolient, lotion, or institutional standard).
Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. □ If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg	**For Grade 2** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy

	prednisone, or equivalent).	
		– Consider moderate-strength topical steroid.
		– If no improvement of rash/skin lesions occurs within 3 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event persists for >1 week or recurs.

	Grade 3 or 4	**For Grade 3** □ Hold study drug/study regimen until resolution to Grade ≤1 or baseline. □ If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4** Permanently discontinue study drug/study regimen.	– **For Grade 3 or 4** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. Consider skin biopsy (preferably more than 1) as clinically feasible. Consider, as necessary, discussing with Clinical Study Lead.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	– **For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Consider consulting an endocrinologist for endocrine events. Consider discussing with Clinical Study Lead, as needed. Monitor patients for signs and symptoms of endocrinopathies. (Non-specific symptoms include

		headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits,
		polydipsia, polyuria, hypotension, and weakness.) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c)).If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the

		investigator should send a blood sample for appropriate autoimmune antibody testing. – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
Grade 1	No dose modifications.	**For Grade 1** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide assessment of early-morning adrenocorticotropin hormone (ACTH), cortisol, TSH and free T4; also consider gonadotropins, sex

		hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2, 3, or 4	□ For Grade 2-4 endocrinopathies <u>other than hypothyroidism and type 1 diabetes mellitus (T1DM)</u>,	**For Grade 2, 3, or 4** Consult endocrinologist to guide evaluation of endocrine function – and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan.

consider holding study drug/study regimen dose until acute symptoms resolve.

- Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent).
- Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.

- For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or T1DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement.
- Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.
- Isolated T1DM may be treated with appropriate diabetic therapy, and without corticosteroids. **Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis**.
- For patients with normal endocrine workup (laboratory assessment or magnetic resonance imaging (MRI) scans), repeat laboratory

			assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	1.2.4. For Any Grade – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, viral infection, concomitant medications, substance abuse). – For modest asymptomatic elevations in serum amylase and
	Grade 1	No dose	

		lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. - Assess for signs/symptoms of pancreatitis - Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT)
1.2.5. Grade 2, 3, or 4	For Grade 2, 3, or 4 In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
		- If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase - If evidence of pancreatitis, manage according to pancreatitis recommendations

Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Consider Gastroenterology referral
	Grade 2, 3, or 4	**For Grade 2 or 3** Hold study drug/study regimen dose until resolution to Grade ≤1. If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4** Permanently discontinue study drug/study regimen.	– **For Grade 2, 3, or 4** Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. IV hydration
Neurotoxicity (to include but not limited to non-infectious meningitis, non-infectious encephalitis,	**Any Grade** (Depending on the type of neurotoxicity, refer to NCI CTCAE applicable version in study	**General Guidance**	**For Any Grade** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or

and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	protocol for defining the CTCAE grade/severity)		weakness). Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.
			– **FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.**
	Grade 1 **Grade 2** **Grade 3 or**	No dose modifications.	**For Grade 1** – See “Any Grade” recommendations above.

4	• For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. • For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days.	**For Grade 2** – Consider, as necessary, discussing with the Clinical Study Lead. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE).
	For Grade 3 or 4 Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider, as necessary, discussing with Clinical Study Lead. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2

			mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE).
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	– **For Any Grade** Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and

accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult.

- The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability.

		– Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – **It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.**
Grade 1	No dose modifications.	**For Grade 1** – Consider discussing with the Clinical Study Lead, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. –Consult a neurologist.
Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1.	Permanently discontinue

study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.

1.2.6. For Grade 2

- Consult a neurologist.
- Consider discussing with the Clinical Study Lead, as needed.
- Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above.
- Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).

MYASTHENIA GRAVIS:

- Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist.
- **Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG**. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient.
- If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, **Grade 3 or 4**

For Grade 3 or 4

Permanently discontinue study drug/study regimen.

if successful, can also serve to reinforce the diagnosis.

- Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers, calcium channel blockers, muscle relaxants).

GUILLAIN-BARRE:

- It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.

	○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.	neurotoxicity present, consider starting AChE
	1.2.7. For Grade 3 or 4 – Consider discussing with Clinical Study Lead, as needed. –Recommend hospitalization. – Monitor symptoms and consult a neurologist. *MYASTHENIA GRAVIS:* ○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like	inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.
		○ Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers, calcium channel blockers, muscle relaxants). *GUILLAIN-BARRE:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not

			typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
1.2.8. Myocarditis	Any Grade	General Guidance (Refer to NCI CTCAE biopsy-proven immune-mediated myocarditis.	Discontinue drug permanently if applicable version in study protocol for defining the CTCAE grade/severity)
1.2.9. For Any Grade			– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function.

		– Consider discussing with the Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (ECG), echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated.

		Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
Grade 2, 3 or 4 □	If Grade 2-4, permanently discontinue study drug/study regimen.	**For Grade 2-4** Monitor symptoms daily, – hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating

provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**

1.2.10. Myositis/ Polymyositis Any Grade General Guidance

(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)

1.2.11. For Any Grade

- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
- Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble
swallowing can occur and

progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be newonset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up.

- If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation.
- Consider, as necessary, discussing with the Clinical Study Lead.
- Initial work-up should include clinical evaluation, creatine kinase, aldolase, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) level, urine myoglobin, and additional

		laboratory workup as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.
Grade 1	No dose modifications.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. –Consider Neurology consult.

Grade 2 □ Hold study drug/study regimen dose until resolution to Grade ≤1.

□ Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.

- Consider, as necessary, discussing with the Clinical Study Lead.

For Grade 2

- Monitor symptoms daily and consider hospitalization.
- Obtain Neurology consult, and initiate evaluation.
- Consider, as necessary, discussing with the

Clinical Study Lead.

- If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant
- If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day
- If after start of IV methylprednisolone at 2 to mg/kg/day there is no improvement within to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using**

1.2.12. Grade 3 or 4	For Grade 3 • Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.		**infliximab.** **For Grade 3 or 4** – Monitor symptoms closely; recommend hospitalization.
1.2.13. For Grade 4	– Consider whether patient may require IV IG, plasmapheresis.		– Obtain Neurology consult – Consider discussing with the Clinical Study Lead, as needed.

• Permanently discontinue study drug/study regimen.
– Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant.

– If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – The Clinical Study Lead may be contacted for immunemediated reactions not listed in the "specific immunemediated reactions" section – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	□ Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	• If toxicity worsens, then treat as Grade 3 or Grade 4.

- Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper.
- Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper

Grade 3 Hold study drug/study regimen

Grade 4 Permanently discontinue study drug/study regimen

1.2.14. For Grade 2, 3, or 4

Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines. (See page 4).

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Managen
Any Grade	General Guidance	**For Any Grade** – Manage per institutional standa discretion of investigator. – Monitor patients for signs and s infusion-related reactions (e.g., shaking chills, flushing and/or it in heart rate and blood pressur chest discomfort, or skin rashes (e.g., generalized urticaria, angi wheezing, hypotension, or tach
Grade 1 or 2	**For Grade 1** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2** • The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. • Subsequent infusions may be given at 50% of the initial infusion rate.	– **For Grade 1 or** – Acetaminophen and/or antihist administered per institutional s discretion of the investigator. – Consider premedication per ins or study protocol prior to subse Steroids should not be used for premedication of Grade ≤2 infu

Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** Manage severe infusion-related institutional standard, appropri – practice guidelines, and society
	Non-Immune-Mediated Reactions	
Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**Dose Modifications**	**Toxicity Manager**
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institut
Grade 1	No dose modifications.	Treat accordingly, as per institut
	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institut
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institut
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institut

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

1.3. List of Abbreviations

AChE	Acetylcholinesterase	ILD	Interstitial lung disease
ACTH	Adrenocorticotropic hormone	imAE(s)	Immune-mediated adverse event
ALT	Alanine aminotransferase	INR	International normalized ratio

ASCO	American Society of Clinical Oncology	IU	International units
AST	Aspartate aminotransferase	IV	Intravenous
(T) Bili	(Total) Bilirubin	IVIG	Intravenous immunoglobulin
BNP	B-type natriuretic peptide	LDH	Lactate dehydrogenase
BUN	Blood urea nitrogen	LFTs	Liver function tests
CRP	C-reactive protein	LLN	Lower limit of normal
CT	Computed tomography	MRCP	Magnetic resonance cholangiopancreatography
CTCAE	Common Terminology Criteria for Adverse Events	MRI	Magnetic resonance imaging
CTLA-4	Cytotoxic T-lymphocyte antigen-4	NCCN	National Comprehensive Cancer N
DILI	Drug-induced liver injury	NCI	National Cancer Institute
ECG	Electrocardiogram	PD-L1	Programmed cell death ligand-1
ECHO	Echocardiogram	PJP	Pneumocystis jerovicii pneumonia
ESMO	European Society of Medical Oncology	PO	By mouth
GI	Gastrointestinal	SCAR	Severe cutaenous adverse reactio
HBcAb	Hepatitis B core antibody	SITC	Society for Immunotherapy of Ca
HBeAg	Hepatitis B envelope antigen	SJS	Stephen Johnson Syndrome
HBsAg	Hepatitis B surface antigen	T1DM	Type 1 diabetes mellitus
HBV	Hepatitis B virus	T3	Triiodothyronine
HCC	Hepatocellular cancer	T4	Thyroxine
HCV	Hepatitis C virus	TEN	Toxic Epidermal Necrolysis
HgA1c	Hemoglobin A1C	TMG(s)	Toxicity management guideline(s)
ICI(s)	Immune checkpoint inhibitor(s)	TSH	Thyroid stimulating hormone
		ULN	Upper limit of normal