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ADMIRAL Trial: Adaptive-Dose to Mediastinum with Immunotherapy (Durvalumab MEDI4736) and Radiation in Locally-advanced non-small cell lung cancer

PROTOCOL SYNOPSIS

Clinical Protocol

Study Title: ADMIRAL Trial: Adaptive-Dose to Mediastinum with Immunotherapy (Durvalumab MEDI4736) and Radiation in Locally-advanced non-small cell lung cancer
Protocol Number: 10459
Clinical Phase: Phase II
Study Duration: 2 years
Investigational Product(s) and Reference Therapy: The study will enroll patients with unresectable stage III NSCLC, who are typically treated with concurrent chemoradiation per standard of care, plus 1-year of adjuvant durvalumab (MEDI4736) based on results of the PACIFIC trial, showing a survival benefit to adding 1-year of adjuvant durvalumab after concurrent chemoradiation for unresectable NSCLC. The two investigation components of this study are: 1) giving durvalumab for 2 years starting with concurrent chemoradiation, which is being tested in a large randomized trial PACIFIC-2; and 2) instead of radiating all visible lung cancer to 60 Gy in 30 daily fractions over 6 weeks per standard of care, only the primary lung tumor will initially receive treatment with hypofractionated radiation therapy (60 Gy in 15 fractions given over 3 weeks). Mediastinal nodal disease will only receive radiation if there is persistent disease after initial induction therapy (chemo-immunotherapy plus radiation to the primary lung tumor). Durvalumab will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for infusion after dilution.
Research Hypothesis Adaptive radiation therapy to the mediastinum with hypofractionated radiation to the primary tumor (concurrent with chemo-immunotherapy), will improve progression-free survival (PFS) due to better local control of the primary lung tumor, as well as decrease toxicity when compared to historical controls (PACIFIC-2, randomized trial comparing chemoradiation versus chemoradiation plus concurrent durvalumab, and adjuvant durvalumab), in patients with unresectable locally advanced NSCLC.
Objectives: **Primary Objectives:** The study will enroll patients with stage III NSCLC. The primary objective is to compare the 1-year PFS rate in patients treated with concurrent chemotherapy, durvalumab and hypofractionated radiation

therapy to the primary lung tumor followed by response adaptive mediastinal radiation and durvalumab relative to expected data on durvalumab maintenance therapy (PACIFIC-2 trial).

Secondary Objective(s):

A key secondary objective will be an evaluation of the frequency and severity of pneumonitis.

Additional secondary objectives include:

- To evaluate overall survival;
- To evaluate the pathologic response rate of the mediastinum to chemo-immunotherapy plus primary lung tumor radiation
- To evaluate the frequency and severity of toxicities graded with CTCAE, version 5

Exploratory Objective(s):

Immune profile on peripheral blood and tumor.

Study Design:

All patients will undergo standard of care staging with PET/CT, MRI/CT head, and mediastinal evaluation with EBUS or mediastinoscopy.

Induction therapy will include:

1a) Squamous cell carcinoma: cisplatin/etoposide every 4 weeks for 2 cycles (weeks 1 to 8, cisplatin 50 mg/m2 on days 1, 8, 29, and 36; etoposide 50 mg/m2 on days 1-5, and 29-33);

OR

1b) Non-squamous cell carcinoma: cisplatin/pemetrexed every 3 weeks for 3 cycles (weeks 1 to 8, cisplatin 75 mg/m2 and pemetrexed 500 mg/m2 on days 1, 22, and 43);

AND

2) durvalumab 1,500 mg q4 weeks

AND

3) hypofractionated radiation to the primary lung tumor (60 Gy in 15 fractions from weeks 1 to 3, or 60 Gy in 8 fractions from weeks 1-2, radiation fractionation depends on tumor anatomy).

Compared to standard of care chemoradiation for stage III NSCLC, this regimen gives similar chemotherapy, adds durvalumab, removes mediastinal radiation, and gives a higher biological radiation dose to the primary tumor (60 Gy in 8-15 fractions instead of 30 fractions).

At week 9, patients will be restaged with CT c/a/p, and those with pathologically enlarged mediastinal nodes will undergo repeat EBUS/mediastinoscopy. If pathologically positive lymph nodes are found, radiation will be given to the mediastinum (2 Gy/fraction to 60 Gy) starting week 12.

Durvalumab will continue be given every 4 weeks for 2 years from the start of concurrent chemoradiotherapy (as tested in PACIFIC-2 trial).

Number of Centers: 3

Number of Patients: 40

Study Population: Unresectable stage III NSCLC

Inclusion Criteria:

- Histologically or cytologically documented NSCLC
- Stage III NSCLC according to AJCC staging v8
- At least one mediastinal site of disease that is discontiguous from all other visible sites of disease and can be excluded from primary tumor site radiation (i.e. at least 10 mm separation between tumors)
- A maximum of 20 patients with bulky mediastinal disease will be allowed on this trial, defined as at least one contiguous mediastinal mass with minimum diameter >2 cm, that is not contiguous with the primary tumor (and therefore would not be irradiated during radiation to the primary tumor)
- No surgery for lung cancer for at least 3 years (from consent)
- Age 18 years or older
- ECOG 0-1
- No other malignancies for at least 3 years, excluding low grade or non-invasive malignancies such as skin cancers, prostate cancers, and DCIS
- Women cannot be pregnant and must be willing to use contraception if premenopausal
- Adequate organ function as defined by: ANC>1500/mm3, platelets>100k/mm3, hemoglobin >9.0 g/dL, creatinine CL>40 mL/min, serum bilirubin <1.5x ULN, AST and ALT <2.5x ULN
- Weight >30 kg
- See section 4.1 for more durvalumab-specific requirements

Exclusion Criteria:

- Prior anti-PD-1 or PD-L1 antibodies, including durvalumab
- Prior chemotherapy in the past 3 years
- Prior thoracic radiation that would preclude curative-intent radiation dose as outlined in this study
- Active or previous autoimmune disease (within the past 2 years) or a history of primary immunodeficiency;

- Evidence of uncontrolled, concurrent illness or ongoing or active infections
- See Section 4.2 for more durvalumab-specific requirements

Investigational Product(s), Dose and Mode of Administration:

Patients will receive 1500 mg durvalumab via IV infusion Q4W, starting with chemoradiation, for up to a maximum of 2 months (up to 24 doses/cycles), until confirmed disease progression, or unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Radiation treatment planning in this study will try to eliminate mediastinal radiation in patients who achieve a complete response to induction therapy. For patients whose primary lung tumor is physically separate from the involved mediastinal nodes, it will not be difficult to safety deliver radiation to mediastinal nodes (in patients who did not have a complete response to induction therapy) after radiation to the primary tumor (given during induction therapy). For patients where the primary lung tumor is contiguous with hilar or mediastinal nodal disease, the contiguous volume will be treated with hypofractionated radiation during weeks 1-3, but all other involved (but non-contiguous) mediastinal nodes will not be treated, allowing response assessment at week 9. This will allow for additional radiation to the previously untreated mediastinal nodes without exceeding normal tissue constraints. At the time of initial treatment planning, all patients will be planned for two radiation courses: 1) initial radiation to the primary+contiguous nodes if present, and 2) radiation to previously untreated mediastinal nodes if residual disease found on week 9 EBUS/mediastinoscopy; this ensures that normal tissue dose constraints will be met even if the second course of radiation is required. All patients not able to meet normal tissue dose constraints, will not be enrolled on the trial.

Study Assessments and Criteria for Evaluation:

Safety Assessments:

Toxicity per CTCAE v5

Efficacy Assessments:

- The primary endpoint is 1-year progression-free survival (PFS): PFS is defined as the duration from study registration to progression, symptomatic deterioration, or death due to any cause, whichever comes first. PFS for patients last known to be alive and progression-free, will be censored at the date of last contact.
- Overall survival (OS): OS is defined as the duration from study registration to death due to any cause. OS for patients last known to be alive will be censored at the date of last contact.
- Pathologic response (CR, PR) to mediastinum
- Objective response (CR or PR) rate

Statistical Methods and Data Analysis:

This study will compare the 1-year PFS rate in patients treated with concurrent chemotherapy, durvalumab and hypofractionated radiation therapy to the primary lung tumor followed by response adaptive mediastinal radiation and durvalumab relative to historical data on durvalumab maintenance therapy (PACIFIC data used for sample size calculations as data from PACIFIC-2 is not yet available).

Sample Size Determination:

The 1-year PFS rate in the PACIFIC trial was 56%, but the PACIFIC trial study population is different from this trial in that it enrolled only patients who completed chemoradiation, did not have progression of disease, and recovered from excess toxicity, before enrolling to receive adjuvant durvalumab. This study will enroll patients at initial diagnosis, prior to starting chemoradiation. This study's patient population is analogous to SWOG S0023, in which 75% of stage III patients were able to receive consolidation chemotherapy following induction chemoradiotherapy. We assume that all patients who were unable to receive consolidation therapy progressed prior to one year (or had significant long term toxicity which leads to worse outcomes). Therefore, our estimate of the historical 1-year PFS rate with maintenance durvalumab following induction chemotherapy is 42% (75% x 56%). This number may be updated as more information from the trials become available. A design with 40 patients has 90% power to rule out a 1-year PFS rate of 42% at the 1-sided 5% level, if the true 1-year is 65%. The observation of at least 22 patients (55%) alive and progression free at 1 year would be considered evidence to rule out a 1-year PFS rate of 42%. Sample size calculations were performed using https://stattools.crab.org/Calculators/oneArmBinomialColored.html.

With 40 patients, binary proportions (response, toxicity) can be estimated within 16% with 95% confidence. Survival distributions will be estimated using the method of Kaplan-Meier. Confidence interval for median times will be estimated using the method of Brookmeyer-Crowley.

The incidence of grade 3 or worse pneumonitis attributable to treatment will be evaluated and compared against the PACIFIC trial results.

SCHEDULE OF STUDY ASSESSMENTS

	Pre-treatment [a]	Week1-4	Week5-8	Week 9-11	Week 12-18	C6 to C24 or PD
Informed Consent						
Informed consent	X					
Demography, including baseline characteristics and tobacco use	X					
Eligibility criteria	X					
Study procedures						
Treatment Visits (vitals, PE, ECOG, meds, AE assessment) [b]	X	X	X	X	X	X
Cisplatin/etoposide [c]		X	X			
Durvalumab Q4 weeks [d]		X	X	X	X	X
Radiation [e]		X			X(if applicable)	
EBUS/Mediastinoscopy [f]	X			X		
Study blood draw [g]	X		X	X	X	X (every 4 months)
Repeat biopsy of primary lung tumor (optional) [h]				X		
Laboratory Assessments						

	Pre-treatment [a]	**Week1-4**	**Week5-8**	**Week 9-11**	**Week 12-18**	**C6 to C24 or PD**
Labs [i]	X	X	X	X	X	X
Hepatitis B and C and HIV	X					
Pregnancy test [j]	X					
Efficacy evaluations						
Tumor evaluation (CT) [k]	X[m]			X[m]	Q12w ± 3w for the first 52 weeks (relative to the date of consent), and then standard of care	

Please see section 7 for more detailed explanation of study procedures. All patients will be followed per standard clinical care after completion of cycle 24 of durvalumab: at least every 6 months until 3 years from diagnosis, and yearly until 5 years from diagnosis.

[a] All pre-treatment procedures must be performed up to 45 days before Day 1, except for histology which has no time restriction.

[b] Treatment visits will be per standard of care, which is typically at least every 4 weeks during chemotherapy and durvalumab, and weekly during radiation treatment.

[c] Chemotherapy dosing interval may be prolonged or dose withheld if deemed clinically appropriate by treating oncologist. Chemotherapy should start within 3 days of radiation therapy.

[d] Dosing interval may prolonged or dose withheld if deemed clinically appropriate by treating oncologist.

[e] Radiation to the primary tumor is delivered during week 1-3 of treatment. First dose of radiation should be within 3 days of first dose of chemotherapy. For patients who have residual disease in the mediastinum on repeat EBUS/mediastinoscopy, radiation to the mediastinum should ideally begin within 3 weeks of repeat EBUS/mediastinoscopy but may be up to 6 weeks..

[f] Either an EBUS or mediastiastinoscopy must be performed to provide pathologic evaluation of the mediastinal nodes prior to starting treatment. For patients who do not have systemic progression on repeat CT at week 9, a repeat EBUS or mediastinoscopy must be performed to evaluate the mediastinal lymph nodes. This should ideally take place within 3 weeks of the restaging CT at week 9 but may be up to 6 weeks.

[g] Study blood draws will take place prior to initiation of any therapy (within 45 days), 1 week after completion of radiation to the primary tumor (±7 calendar days), prior to mediastinal radiation (less than 4 weeks) for applicable patients, and every 4 months (±1 month) afterwards for 2 years or until disease progression.

[h] Optional repeat lung tumor biopsy will be performed 1 month after radiation to the primary tumor (±2 weeks).

[i] Standard of care lab assessments will be drawn prior to every cycle during chemotherapy and durvalumab therapy.

[j] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.

[k] Patients will have a pre-treatment scan, a scan at week 9 (±10 calendar days), and then Q12w ± 4w for the first 52 weeks (relative to the date of consent), and then standard of care thereafter.

[m] An optional research PET/CT will be offered to patients, which will be paid for by the study and not billed to insurance. This PET/CT can replace the standard of care CT scan at baseline and the week 9 scan.

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1. INTRODUCTION

We propose a trial of hypofractionated radiation to the primary lung tumor, with concurrent chemo-immunotherapy in patients with unresectable locally advanced NSCLC, followed by response-adaptive mediastinal radiation. We hope to decrease toxicity by eliminating mediastinal radiation in patients who have a complete response to the induction chemoimmunotherapy plus primary tumor radiation, and improve local control of the primary tumor by delivering a higher biologic dose of radiation.

1.1 Disease background

1.1.1 Limitations in standard of care chemoradiation for unresectable NSCLC

Current standard of care in the management of locally advanced non-small cell lung cancer (NSCLC) is concurrent chemo-radiation followed by a year of adjuvant durvalumab[1,2]. Standard radiation treatment is conventionally fractionated radiation therapy (1.8-2.0 Gy per day to total 60-70 Gy) to all visible sites of disease, which includes both the primary lung tumor and involved mediastinal lymph nodes[3]. This standard-of-care approach achieves local control in 30-50% of patients, but has several limitations[3].

First, mediastinal radiation is associated with significant toxicity, including those that predict for mortality in locally advanced NSCLC, specifically: radiation pneumonitis, cardiac dose, and esophagitis[3]. Radiation pneumonitis risk, counter-intuitively, is mostly due to mediastinal radiation and not due to radiation to the primary lung tumor. This is because the spinal cord can only tolerate 45-50 Gy of radiation, but enlarged mediastinal nodes are treated to 60-70 Gy; therefore, oblique beams that avoid the spinal cord are used to treat the mediastinum, which significantly increases dose spillage into normal lung[4]. When early stage lung tumors are radiated to high doses with hypofractionated radiation, such as stereotactic ablative radiotherapy (SABR), the rates of pneumonitis are low because the early stage tumors are node negative and do not typically involve mediastinal radiation, compared to radiation for stage III NSCLC, which typically treats a large region of the mediastinum[4,5].

A second significant disadvantage of mediastinal radiation in the era of immunotherapy, is the fact that the primary lymph node drainage basin for lung tumors is the mediastinum[6]. Radiation to the mediastinal nodes could suppress any mounting anti-tumor immune response in the region. Consequently, mediastinal radiation enhances toxicity and is likely immuno-suppressive when delivered in the setting of locally advanced NSCLC. This potentially detracts from a good clinical outcome, and the added toxicity likely impedes the ability to graft on combinatory immunotherapy.

Additionally, we also know from surgical series that approximately 31% of patients will clear their mediastinal and regional nodes and that an additional 29% of patients will clear their N2

nodal disease alone (ie downstaging to N1 disease) with chemotherapy alone and that this is associates with a median survival of 35 months or more.[7] The mediastinal nodal clearance rate with chemo-immunotherapy is not known, but likely higher given the greater efficacy of this regimen in advanced NSCLC when compared with chemotherapy alone.[8] It is unlikely that these downstaged patients derive a significant benefit from the addition of mediastinal radiation.

Finally, a third consequence of mediastinal radiation is that more effective radiation dosing regiments, such as SABR or hypofractionated approaches, cannot be utilized due to toxicity of hypofractionated radiation therapy when given to mediastinal normal tissues such as esophagus, blood vessels, and airways[9]. Although SABR and hypofractionated radiation have shown substantially higher local control rates (80-90%) than conventional fractionation radiation in early stage NSCLC, these dose regimens have not become standard of care in locally advanced NSCLC because of toxicity observed in the mediastinum[9-11].

1.1.2 Durvalumab in NSCLC

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/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document).). 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 (Stewart et al 2015). *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). 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.

In the landmark trial PACIFIC, patients with unresectable NSCLC who received adjuvant durvalumab after standard of care chemoradiation had improved survival compared to patients who received standard of care maintenance therapy.[1,2] Durvalumab is currently FDA approved for adjuvant therapy in patients receiving concurrent chemoradiation for NSCLC, and given for a year of adjuvant therapy per standard of care. Results from the randomized trial PACIFIC-2 are anticipated, which added the durvalumab to begin concurrent with chemoradiation, and for 2 years of therapy total. While results from this trial are still forthcoming, there have been no early toxicity signals from this trial. Our current study is based on the PACIFIC-2 regimen, with durvalumab beginning concurrent with chemoradiation (although we only radiate the primary and not the mediastinum, and the radiation is hypofractionated to deliver a higher biologic dose).

To date durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Even more patients are being treated per standard of care after results of the PACIFIC trial led to FDA approval of 1-year of adjuvant durvalumab after chemoradiation for unresectable NSCLC. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.3 Response rate to chemo-immunotherapy in NSCLC

Chemotherapy is effective in sterilizing mediastinal (N2) nodal disease in surgical series in about 60% of patients[7,12]. One would expect the mediastinal clearance rate to be higher when checkpoint inhibitors (PD-1 or PD-L1 inhibitors specifically) are employed in addition to chemotherapy. Large studies are currently underwent but encouraging results from smaller phase II trials show pathologic complete response rates in the mediastinum of up to 70% after neoadjuvant chemotherapy plus PD-1/PD-L1 inhibitors prior to surgical resection[13,14]. For patients with metastatic NSCLC, where chemotherapy plus checkpoint inhibitors have become standard of care first-line treatment, the objective response rates seen in large randomized trials are 48-57%[15,16]. Therefore, it is reasonable to question the added value of mediastinal radiation, specifically in those individuals who will achieve sterilization with chemo-immunotherapy alone, where the toxicity of mediastinal radiation will outweigh the benefit.

1.1.4 Rationale for hypofractionated radiation and immunotherapy combination

Radiation causes release of tumor antigens and cytokines into the tumor microenvironment, which leads to an inflammatory response and infiltration of immune cells including T-cells (both cytotoxic and regulatory), dendritic cells, macrophages, and myeloid-derived suppressor cells (MDSCs)[17]. Peripheral blood from patients with metastatic melanoma receiving standard photon radiation to a single site of disease while on ipilimumab show that radiation induces an increase in percentage of CD4+ T-cells, ratio of CD8+ T-cells to Tregs, decrease in MDSCs, and increase in HLA-DR expression on monocytes[18,19]. Clinical reports have been published with radiation to one tumor causing an abscopal effect that leads to systemic regression of disease outside the radiation field, even in patients who have previously progressed on immunotherapy[18,20,21]. Although the exact mechanism of the radiation induced abscopal effect is unclear, published data supports it is partially due to T-cell effector function in the irradiated tumor, especially CD8+ T-cells[19,22]. There is also growing evidence that cytokine release is a major mechanism, which can lead to a decrease in MDSCs[18,23,24].

In the landmark trial PACIFIC, that established adjuvant durvalumab after chemoradiation for unresectable NSCLC as standard of care, patients that initiated durvalumab after 2 weeks of radiation completion had improved survival compared with patients who waited longer to initiate durvalumab[1,2]. The exact cause of this phenomenon is unclear, but has been hypothesized to be related to immune changes after radiation that enhanced the efficacy of durvalumab. While the optimal radiation regimens for harnessing the proimmunogenic effects

of radiation remain to be defined, pre-clinical data suggests that the ability of radiation to promote anti-tumor immunity may be dependent on the dose and fractionation employed. Compared to conventionally fractionated radiation therapy (such as 60 Gy in 30 daily fractions typically employed to treat stage III NSCLC), hypofractionated radiotherapy at a higher dose per day over fewer days have been shown to result in a greater degree of stromal/vascular damage and increased apoptosis of tumor cells[25], which may ultimately lead to an environment of enhanced antigen presentation. Animal models support this theory and suggest that a threshold likely exists in regard to the radiation fraction size necessary to induce an optimal immune response with ablative doses generating greater immunostimulatory effects as compared to conventional radiation doses[26]. Clinically, the ability to deliver ablative doses to tumors with acceptable toxicity has become possible over the past decade with technologic advancements in image guidance and radiation dose delivery. In the setting of early-stage lung cancer, phase I/II trials demonstrate that the use of hypofractionated radiation yields improved survival as compared to conventional fractionated treatment with local control rates comparable to surgical resection[27]. Toxicity rates, including pneumonitis, esophagitis, and cardiac toxicity, are generally lower with hypofractionated ablative radiation to non-central tumors[27].

Therefore, we propose hypofractionated radiation to the primary tumor, which avoids the toxicity of mediastinal radiation, but potentially allows for a synergistic interaction between the radiation and immunotherapy, as part of the induction/initial phase of our trial schema.

1.1.5 Safety of combination chemoimmunotherapy plus radiation to the thorax

We propose a trial of hypofractionated radiation to the primary lung tumor, with concurrent chemo-immunotherapy in patients with unresectable locally advanced NSCLC, followed by response-adaptive mediastinal radiation.

The combination of chemotherapy and PD-1/PD-L1 checkpoint inhibition is currently standard of care in metastatic NSCLC, with a well characterized safety profile[15,16]. The safety profile of chemoradiation for NSCLC and adjuvant durvalumab is also well characterized and standard of care for unresectable stage III NSCLC[2]. PACIFIC-2 is a large randomized trial looking at concurrent chemoradiation, versus concurrent chemoradiation plus durvalumab, starting concurrent with radiation with a total of 2 years of durvalumab therapy. Results from this trial are pending, but there has been no early safety signals prompting early trial termination. Hypofractionated radiation for lung cancer is also well characterized and carries relatively low toxicity risk when not treating large regions of the mediastinum[27].

Numerous prospective and retrospective clinical series have been published assessing the safety of radiation plus immunotherapy, with the general conclusion that the combination is generally safe, and may lead to an improved response rate to immunotherapy. For example, the ETOP NICOLAS trial added nivolumab (a PD-1 inhibitor) concurrently to chemoradiotherapy in

standard first line treatment of stage III NSCLC, and saw no significant increase in toxicity after the first 82 patients.[28] A multicentric retrospective study of 104 patients looked at safety of combined PD-1 pathway inhibition and radiation therapy for non-small-cell lung cancer, where radiation was given within 6 months preceding, concomitantly, or 3 months after nivolumab administration[29]. There was no increased risk of severe or unexpected toxicities. A retrospective comparison of 50 patients who received checkpoint inhibitor and brain radiation, versus 113 patients who only received brain radiation, saw no difference in toxicity rates between patients who did and did not receive checkpoint inhibitors in addition to brain radiation[30]. Another retrospective study of 59 patients treated with hypofractionated body radiotherapy within 8 weeks of checkpoint inhibitor therapy concluded the combination is safe and promising[31]. A randomized phase 1 trial of pembrolizumab (a PD-1 inhibitor) with sequential versus concomitant stereotactic body radiotherapy in metastatic urothelial carcinoma also concluded that the combination treatment was well tolerated[32].

1.2 Research hypothesis

Adaptive radiation therapy to the mediastinum with hypofractionated radiation to the primary tumor (concurrent with chemo-immunotherapy), will improve progression-free survival (PFS) due to better local control of the primary lung tumor, as well as decrease toxicity when compared to historical controls (PACIFIC-2, randomized trial comparing chemoradiation versus chemoradiation plus concurrent durvalumab, and adjuvant durvalumab), in patients with unresectable locally advanced NSCLC.

1.3 Rationale for conducting this study

Rational for this study is to improve clinical outcomes, both by decreasing toxicity, and by improving disease control. Radiation to the mediastinum is the cause of most of the radiation toxicity in the treatment of unresectable NSCLC, including pneumonitis, esophagitis, and heart dose[3]. By eliminating this in a significant cohort of patients, who will experience a complete response from induction chemoradiation (plus radiation to the primary tumor), we propose to decrease toxicity, and potentially increase survival by allowing better tolerance of adjuvant immunotherapy. In the PACIFIC trial that showed a survival benefit to the addition of 1-year of durvalumab after chemoradiation for unresectable NSCLC, the number one toxicity requiring stopping durvalumab therapy was pneumonitis. If eliminating mediastinal radiation can decrease pneumonitis rates, that can lead to better tolerance of immunotherapy. We also propose to increase radiation dose to the primary tumor (accelerating the radiation from 60 Gy in 30 daily treatments to 15 daily treatments), which could improve local control of the primary tumor, improving disease outcome.

1.3.1.1 Radiation dose rationale

Hypofractionated radiation therapy to 60 Gy in 8-15 fractions has been shown in prospective trials to be safe and efficacious for lung cancer, especially tumors that do not involve large areas of the mediastinum.[27,33] This regimen results in a higher biological dose to the tumor than a slower, conventional fractionation course (60 Gy in 30 daily fractions), which can improve local control.[34,35]

Mediastinal radiation can be safely delivered to 60 Gy in 30 daily fractions with concurrent chemo per standard of care. There is also early data that this radiation regimen is also safe to deliver concurrent with chemoimmunotherapy.[28] Radiation alone in the mediastinum can be delivered safely in 25-30 fractions to around 60 Gy, as assessed by prospective dose escalation trials.[36]

1.3.1.2 Durvalumab dose rationale

A durvalumab dose of 20 mg/kg Q4W is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 17 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (For further information on immunogenicity, please see the current IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W (Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient

PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab Investigator's Brochure for a complete summary of clinical information including safety, efficacy and pharmacokinetics at the 20mg/kg Q4W regimen.

1.3.1.3 Rationale for fixed dosing

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 (Ng et al 2006, Wang et al 2009, Zhang et al 2012, Narwal et al 2013). 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 (Wang et al 2009)]. 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 (Zhang et al 2012).

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, we 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.

1.4 Benefit/risk and ethical assessment

1.4.1 Potential benefits

The goal of this clinical trial is to both improve survival and decrease toxicity. One potential benefit of this trial is improved survival, due to the following factors:

- Patients receive immunotherapy sooner than standard of care (at initial treatment, instead of after completion of chemoradiation and allowing time for recovering).

- Patients receive a higher biological dose of radiation to the primary tumor than standard of care, potentially improving local control (60 Gy in 8-15 daily fractions over 1.5-3 weeks, instead of in 30 fractions over 6 weeks).

Another potential benefit is decreased toxicity, since mediastinal radiation will not be given to patients with complete response in the mediastinum to induction therapy, therefore decreasing rates of esophagitis, pneumonitis, heart toxicity, etc.

1.4.2 Overall risks

While the goal of this clinical trial is to both improve survival and decrease toxicity, it is possible that the opposite results will be seen. Potential for increased toxicity could come from the following:

- Patients could have higher toxicity rates from receiving immunotherapy sooner than standard of care (at initial treatment, instead of after completion of chemoradiation and allowing time for recovering). Risks with durvalumab include, but are not limited to, diarrhea/colitis pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions, and infections/serious infections. For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.

- Patients could have higher toxicity rates from receiving radiation concurrent with immunotherapy in this study. Based on published clinical data, there does not seem to be new, unusual toxicities from the combination of radiation and immunotherapy, but the toxicity profiles do overlap, such as fatigue and pneumonitis.

- Patients could have higher toxicity rates from receiving a higher biological dose of radiation to the primary tumor (60 Gy in 8-15 daily fractions over 1.5-3 weeks, instead of in 30 fractions over 6 weeks).

Another potential risk is decreased survival due to worse cancer control, since mediastinal radiation is not given upfront in the induction phase, but given at week 12 if there is residual disease in the mediastinum. This could provide an opportunity for disease progression in the mediastinum, which otherwise might have been controlled by upfront radiation.

1.4.3 Overall benefit-risk

Overall, we believe the potential benefits of the trial outweigh the risks. This trial allows patients to receive the maximal systemic therapy upfront (platinum-doublet chemotherapy and checkpoint inhibitor immunotherapy), and metastatic disease is the number one mode of treatment failure after concurrent chemoradiation for unresectable NSCLC. Patients still receive radiation to all visible sites of disease on the trial, but those who have a favourable response to induction therapy can forgo mediastinal radiation, which is the source of most of the toxicity in radiation for unresectable NSCLC. This toxicity reduction on the radiation front, also potentially improves the patient's ability to tolerate more systemic therapy.

2. STUDY OBJECTIVES

2.1 Primary objective(s)

The primary objective is to compare the 1-year PFS rate in patients treated with concurrent chemotherapy, durvalumab and hypofractionated radiation therapy to the primary lung tumor followed by response adaptive mediastinal radiation and durvalumab relative to historical data on durvalumab maintenance therapy (PACIFIC-2 trial). The primary endpoint is progression-free survival (PFS): PFS is defined as the duration from study registration to progression, symptomatic deterioration, or death due to any cause, whichever comes first.
PFS for patients last known to be alive and progression free, will be censored at the date of last contact. Progression will be determined by the radiologist and treating physician.

2.2 Secondary objective(s)

A key secondary objective will be an evaluation of the frequency and severity of pneumonitis.

Additional secondary objectives include:

- To evaluate Overall survival (OS): OS is defined as the duration from study registration to death due to any cause. OS for patients last known to be alive will be censored at the date of last contact
- To evaluate the pathologic response rate of the mediastinum to chemo-immunotherapy plus primary lung tumor radiation
- To evaluate the objective response rate (CR or PR, confirmed and unconfirmed). Response rate will calculated as the percentage of patients achieving a PR or CR, and will be presented along with the 95% CI.
- To evaluate the frequency and severity of toxicities graded with CTCAE, version 5. Toxicities will be summarized as the proportion of patients with such toxicities, in addition to total number of toxicities (allowing for multiple toxicities within a patient) among all patients.

2.3 Exploratory objective(s)

Immune profile on peripheral blood and tumor, which can include but are not limited to the following:

- Changes in peripheral blood immune cell subpopulations measured via multi-parameter flow cytometry:
    - Important T-cell subsets using markers such as: CD3/CD8/CD4/Foxp3/CD45RA/CD45RO/CCR7/CD28/CD27/CD57/CD25/HLA-DR/CTLA4/PD-1

  - NK cells will be assessed using CD16/CD56/CD69.
  - B-cells and dendritic cells will be analyzed using: CD19, CD123, CD11c, CD86, MHC class I and II, CD70, and CD54.
  - MDSC will be assessed using: CD11b, CD 14, CD33.
- Next generation sequencing of the T-cell receptor-β locus in genomic DNA from sorted CD4+ and CD8+ T cell subsets from blood samples using the TRB ImmunoSeq kit (Adaptive Biotechnologies).
- Tumor biopsies (pre- and post-treatment of a non-radiated site) in select patients who consent will be assessed for: cell death, tumor infiltrating lymphocytes, expression of cell surface markers including HLA, PDL1, etc., and undergo multiparameter flow cytometry as well as TCR sequencing.

3. STUDY DESIGN

3.1 Overview of study design

This is a single-arm, phase II, multi-institutional trial for patients with unresectable NSCLC. Target accrual is 40 patients, distributed relatively evenly across 2-3 sites. Patients with unresectable NSCLC are typically treated with concurrent chemoradiation per standard of care, plus 1-year of adjuvant durvalumab.

The two investigation components of this study are: 1) giving durvalumab for 2 years starting with concurrent chemoradiation, which is being tested in a large randomized trial PACIFIC-2; and 2) instead of radiating all visible lung cancer to 60 Gy in 30 daily fractions over 6 weeks per standard of care, only the primary lung tumor will initially receive treatment with hypofractionated radiation therapy (60 Gy in 8-15 fractions given over 3 weeks). Mediastinal nodal disease will only receive radiation if there is persistent disease after initial induction therapy (chemo-immunotherapy plus radiation to the primary lung tumor).

3.2 Study schema

All patients will undergo standard of care staging with PET/CT, MRI/CT head, and mediastinal evaluation with EBUS or mediastinoscopy.

Induction therapy will include:

1a) Squamous cell carcinoma: cisplatin/etoposide every 4 weeks for 2 cycles (weeks 1 to 8, cisplatin 50 mg/m2 on days 1, 8, 29, and 36; etoposide 50 mg/m2 on days 1-5, and 29-33);

OR

1b) Non-squamous cell carcinoma: cisplatin/pemetrexed every 3 weeks for 3 cycles (weeks 1 to 8, cisplatin 75 mg/m2 and pemetrexed 500 mg/m2 on days 1, 22, and 43);

AND

2) durvalumab 1,500 mg q4 weeks

AND

3) hypofractionated radiation to the primary lung tumor (60 Gy in 15 fractions from weeks 1 to 3, or 60 Gy in 8 fractions from weeks 1-2, radiation fractionation depends on tumor anatomy).

At week 9, patients will be restaged with CT c/a/p, and those with pathologically enlarged mediastinal nodes will undergo repeat EBUS/mediastinoscopy. If pathologically positive lymph nodes are found, radiation will be given to the mediastinum (2 Gy/fraction to 60 Gy) starting week 12.

Durvalumab will continue be given every 4 weeks for 2 years from the start of concurrent chemoradiotherapy (as tested in PACIFIC-2 trial).

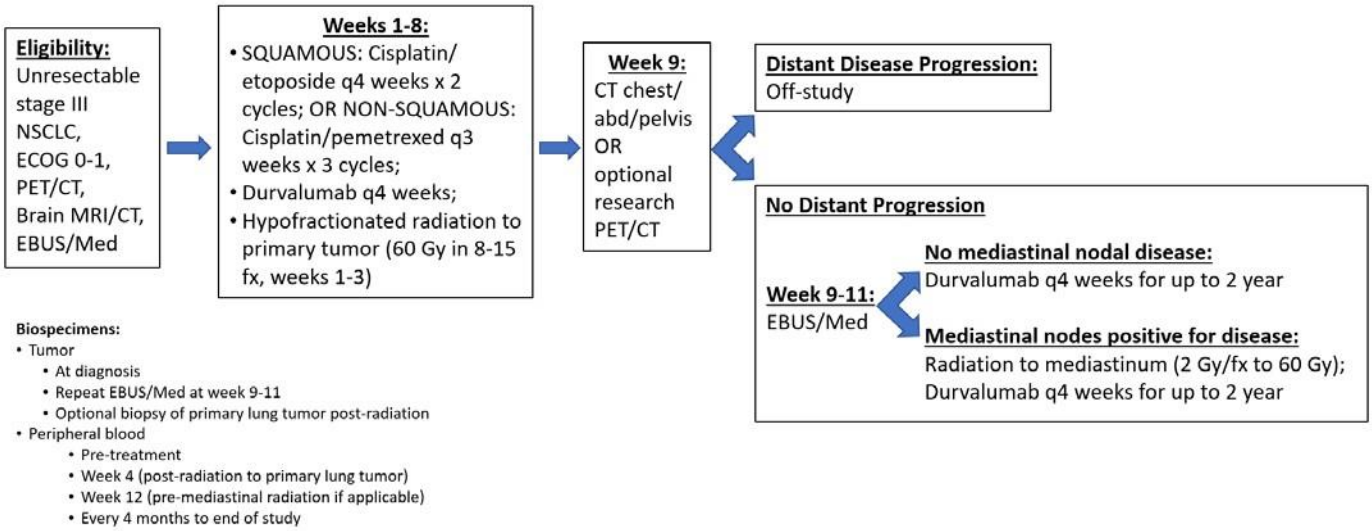

Figure 1. Study Schema.

3.3 Study oversight for safety evaluation

Oversight for this study will be provided by the Principal Investigator with delegation of appropriate responsibilities to sub-investigators and designated study personnel. They will ensure all entry criteria are met prior to the initiation of the protocol and all study procedures and reporting of adverse events are performed according to the IRB-approved protocol.

Early stopping of this trial will be 2 or more grade 5 adverse events (AEs) occurring within ≤ 30 days after the end of radiation treatment to the primary tumor, defined as possibly, probably, or definitely related to radiation treatment (per CTCAE, v.5.0). All AE's grade 4 or higher must be reported to the PI within 48 hours, except hematologic AEs (i.e. abnormal lab values).

4. PATIENT SELECTION

Eligible patients for this trial have unresectable non-small cell lung cancer, fit for treatment with concurrent chemoradiation and immunotherapy.

4.1 Inclusion criteria

For inclusion in the study patients must fulfill all of the following criteria:

1. Histologically or cytologically documented NSCLC

2. Stage III NSCLC according to AJCC staging v8

3. At least one mediastinal site of disease that is discontiguous from all other visible sites of disease and can be excluded from primary tumor site radiation (i.e. at least 10 mm separation between tumors)

4. A maximum of 20 patients with bulky mediastinal disease will be allowed on this trial, defined as at least one contiguous mediastinal mass with minimum diameter >2 cm, that is not contiguous with the primary tumor (and therefore would not be irradiated during radiation to the primary tumor)

5. No surgery for lung cancer for at least 3 years

6. No other malignancies for at least 3 years, excluding low grade or non-invasive malignancies such as skin cancers, prostate cancers, and DCIS

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

8. Age ≥ 18 years at time of study entry.

9. Life expectancy of ≥ at least 3 months

10. Body weight >30 kg

11. Adequate normal organ and marrow function as defined below:

    - Hemoglobin ≥9.0 g/dL
    - Absolute neutrophil count (ANC) 1.5 *(or 1.0)* x (≥ 1500 per mm^3)
    - Platelet count ≥100,000 per mm^3

- Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.

- AST (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤5x ULN

- Measured creatinine clearance (CL) >60 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

  Males:

  $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

  Females:

  $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

12. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

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 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 or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

- 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, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

14. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Prior anti-CTLA-4, PD-1 or PD-L1 antibodies including durvalumab
2. Prior chemotherapy in the past 3 years from consent
3. 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.
4. Prior thoracic radiation that would preclude curative-intent radiation dose as outlined in this study
5. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
6. History of allogenic organ transplantation.
7. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or

Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, 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 without active disease in the last 5 years may be included but only after consultation with the study physician

e. Patients with celiac disease controlled by diet alone

8. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent

9. History of leptomeningeal carcinomatosis

10. History of active primary immunodeficiency

11. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C.** Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

12. 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)

13. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

14. Female patients who are pregnant or breastfeeding 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.

15. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 4.3.

4.3 Withdrawal of patients from study treatment and/or study

Permanent discontinuation of study treatment

Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. A patient who decides to discontinue treatment will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who are permanently discontinued from further receipt of treatment, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up.

Patients who permanently discontinue durvalumab for reasons other than objective disease progression should continue to have scans performed q12w ±2w for the first 52 weeks, or death (whichever comes first).

If a patient is discontinued for progression documented by the radiologist and confirmed by the treating physician, then the patient should have 1 additional follow-up scan performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD.

All patients will be followed for survival until the end of the study.

Patients who decline to return to the site for evaluations should be contacted by telephone as an alternative.

Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

- Lost to Follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable CRF modules will be updated.)

- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable CRF modules will be updated.)

Withdrawal of consent

Patients are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- All further participation in the study including any further follow up (eg, survival contact telephone calls)
- Withdrawal to the use of any samples

5. TREATMENT PLAN

5.1 Study Registration

Potentially eligible patients will be identified by study investigators and screened for eligibility by the study team. Subjects will be registered by the FHCRC/UW Study Coordinator and entered into the OnCore System. Information regarding OnCore and the Clinical Trial Management System (CTMS) system is available at https://www.iths.org/ctms/. A complete, signed, study consent and HIPAA consent are required for registration.

5.2 Durvalumab

Durvalumab is FDA approved as standard of care adjuvant therapy for 1-year after chemoradiation for unresectable NSCLC. In this study, durvalumab is considered an investigational agent since it is being given concurrent with chemoradiation, and for 2-year duration. Drug administration details given in this study are generally consistent with current standard of care for FDA approved indications for durvalumab.

5.2.1 Formulation/packaging/storage

Durvalumab will be supplied by AstraZeneca as a 500- mg vial solution for infusion after dilution. 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 fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

5.2.2 Durvalumab doses and treatment regimens

All patients will receive 1500 mg durvalumab via IV infusion Q4W for up to a maximum of 24 months (up to 24 doses/cycles) until confirmed disease progression, or unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. If a patient's weight falls to 30 kg or below (≤30 kg) the patient should be withdrawn from study.

5.2.3 Study drug preparation

Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab (MEDI4736) 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 (MEDI4736) vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)

- 4 hours at room temperature

A dose of 1500 mg (for patients >30 kg in weight) 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 30.0 mL of durvalumab (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.

Standard infusion time is one hour. However, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

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.

5.2.4 Monitoring of dose administration

Patients will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Patients are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

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 during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature, with maximum total time at room temperature not exceeding 4 hours (otherwise requires new

infusion preparation). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in Appendix 1.

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.

5.2.5 Disposition of unused investigational study drug

The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be signed.

5.3 Chemotherapy

Chemotherapy for this study will be given per standard of care. The drugs and dosing regimen for this study will be:

Squamous cell carcinoma: cisplatin/etoposide every 4 weeks for 2 cycles (weeks 1 to 8, cisplatin 50 mg/m2 on days 1, 8, 29, and 36; etoposide 50 mg/m2 on days 1-5, and 29-33);

OR

Non-squamous cell carcinoma: cisplatin/pemetrexed every 3 weeks for 3 cycles (weeks 1 to 8, cisplatin 75 mg/m2 and pemetrexed 500 mg/m2 on days 1, 22, and 43);

Dose reductions and changes in dosing schedules are allowed at the discretion of the treating medical oncologist if clinically indicated.

5.4 Radiation Therapy

Radiation therapy delivered on this study will meet all requirements considered standard clinical care. All patients will be treated with conformal radiation treatment or intensity-modulated radiation techniques. Both photon therapy and proton therapy are allowed. All patients will be planned for both the initial phase of radiation to the primary lung tumor, and the subsequent mediastinal radiation (only given to patients who do not have a complete response in the mediastinum), at the time of initial simulation, to ensure that the mediastinal nodes will be able to be safely radiated without exceeding normal tissue constraints.

5.4.1 Simulation

All patients should undergo 4-D CT-based simulation with motion evaluation with slice thickness ≤3mm, scanning from at least C3 to below both kidneys (top of iliac crest). IV contrast use is encouraged but not required. Patients are treated supine with arms up with immobilization devices.

5.4.2 Definition of target volumes and margins

Contouring of gross tumor volume (GTV), internal gross tumor volume (IGTV), clinical target volume (CTV), and planning target volume (PTV) are per routine standard of care, and detailed in Table 1. Please see Figure 2 for example contours of GTV_primary, outlined in red, and GTV_mediastinum, outlined in green.

Table 1. Guidelines for target volumes.

Contour Name	Description	Margin
GTV_primary	Primary lung tumor, other lung parenchymal tumors if applicable (i.e. satellite nodules), and any contiguous involved lymph nodes.	None.
GTV_mediastinum	Any involved mediastinal nodes (defined per routine standard of care, either by CT enlargement, PET avidity, or positivity on pathologic evaluation with EBUS or mediastinoscopy) that are not included in the GTV_primary	None.
IGTV_primary	Encompass respiratory motion for GTV_primary based on 4-D CT	None.
IGTV_mediastinum	Encompass respiratory motion for GTV_mediastinum based on 4-D CT	None.
CTV_primary	IGTV_primary plus microscopic disease extension. When the CTV margin extends into critical normal organs, the volume can be reduced as clinically appropriate.	5-8 mm
CTV_mediastinum	IGTV_mediastinum plus microscopic disease extension. When the CTV margin extends into critical normal organs, the volume can be reduced as clinically appropriate.	5-8 mm
PTV_primary	CTV_primary plus margin for setup error. Value depends on institutional guidelines.	5-10 mm

PTV_mediastinum	CTV_mediastnum plus margin for setup error. Value depends on institutional guidelines.	5-10 mm

PTV_primary and PTV_mediastinum must not be contiguous for patients to be eligible for this trial (at least 1 mm separation between the two volumes). The trial inclusion criteria of a site of mediastinal disease that is >10 mm away from all other sites of disease selects for patients who will be able to have two separate PTV volumes.

For patients who need mediastinal radiation due to lack of complete response in the mediastinum to induction therapy, they will undergo repeat simulation and a new GTV_mediastinum, IGTV_mediastinum, CTV_mediastinum, and PTV_mediastinum must be contoured on the new scan.

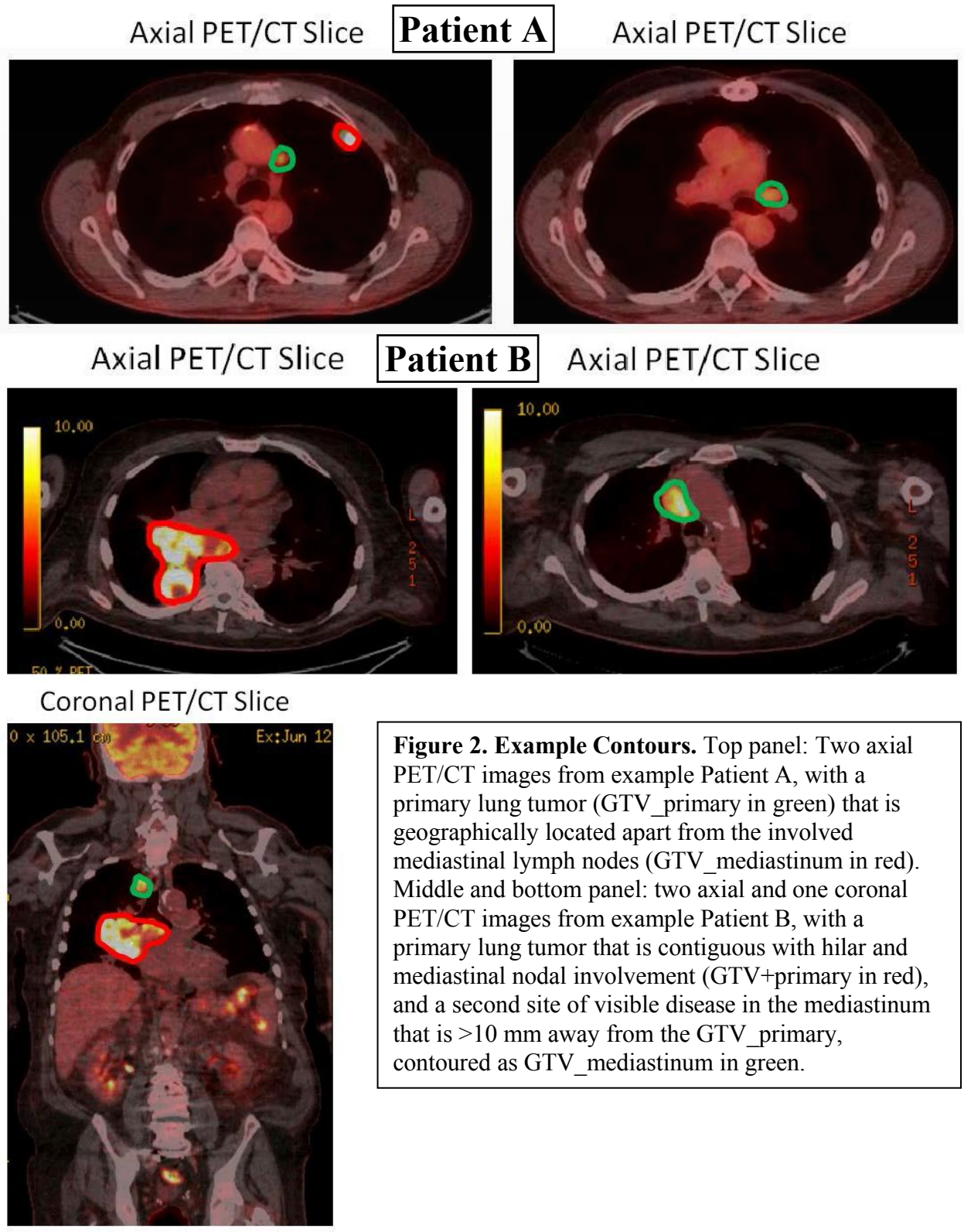

Figure 2. Example Contours. Top panel: Two axial PET/CT images from example Patient A, with a primary lung tumor (GTV_primary in green) that is geographically located apart from the involved mediastinal lymph nodes (GTV_mediastinum in red). Middle and bottom panel: two axial and one coronal PET/CT images from example Patient B, with a primary lung tumor that is contiguous with hilar and mediastinal nodal involvement (GTV+primary in red), and a second site of visible disease in the mediastinum that is >10 mm away from the GTV_primary, contoured as GTV_mediastinum in green.

5.4.3 Definition of critical structures

Normal organs will be contoured per RTOG contouring guidelines as published in the lung atlas: https://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx. Organs that must be contoured are listed and described in Table 2 below.

Table 2. Normal tissue contouring guidelines.

Contour Name	Description	Required/Required when applicable
BrachialPlex_L	Left brachial plexus, required if within 5 cm of PTV	Required when applicable
BrachialPlex_R	Right brachial plexus, required if within 5 cm of PTV	Required when applicable
Bronchus	Carina down to lobar bronchus, terminating at segmental bifurcation, including proximal 2 cm of trachea	Required when applicable
Esophagus	Entire extent of esophagus from below cricopharyngeus to gastroesophageal function	Required
GreatVessels	Required if within 5 cm of PTV	Required when applicable
Heart	Entire pericardial sac	Required
Liver	Required if within 5 cm of PTV	Required when applicable
Lung_L	All inflated and collapsed lung should be contoured. Does not include GTV.	Required
Lung_R	All inflated and collapsed lung should be contoured. Does not include GTV.	Required
Lungs	All inflated and collapsed lung should be contoured. Does not include GTV.	Required
Kidneys	Required if within 5 cm of PTV	Required when applicable
Skin	5 mm skin rhind	Required

SpinalCord	Bony limits of spinal canal	Required
Stomach	Required if within 5 cm of PTV	Required when applicable
Trachea	Trachea down to exclude proximal 2 cm	Required when applicable

5.4.4 Treatment planning

Prescription to PTV_primary is 60 Gy in 8-15 fractions. Choice of 8 or 15 fraction regimen will depend on ability to meet dose constraints (detailed in Table 3), and overall assessment of radiation treatment plan safety. The 8 fraction regimen is preferred, but the 15 fraction is allowed if there are safety concerns about the 8 fraction plan or inability to meet dose constraints as outlined in Table 3 below. The 8 fraction plan may not be safely delivered to ultra-central tumor volumes (defined as tumors touching the main bronchus), and the 15 fraction regimen is preferred in this setting.

Prescription to PTV_mediastinum is 60 Gy in 30 fractions. Treatment planning should meet all requirements considered standard clinical care. Planning technique is not specified on this trial, although highly conformal techniques that minimize normal tissue dose are encouraged (i.e. IMRT/VMAT, proton therapy). Treatment planning should account for respiratory motion (i.e. plan on 4D average CT, and/or 4D robustness optimization).

All patients will undergo treatment planning to two PTV volumes at the initial simulation: PTV_primary and PTV_mediastinum. Each individual plan and the composite plan must meet all dose constraints as specified in Table 3 below. Constraints are given for each organ for an 8 fraction treatment regimen, a 15 fraction treatment regimen (since PTV_primary is treated in 8-15 fractions), a 30 fraction treatment regimen (since PTV_mediastinum is treated in 30 fractions), and an equivalent dose in 2 Gy fractions (EQD2Gy) constraint for the composite plan. Alpha/beta ratio of 3 is used for EQD2Gy calculations for normal tissues. For patients who need mediastinal radiation due to lack of complete response in the mediastinum to induction therapy, they will undergo repeat simulation and a new GTV_mediastinum, IGTV_mediastinum, CTV_mediastinum, and PTV_mediastinum must be contoured on the new simulation scan. A composite plan must be generated with the initial PTV_primary radiation treatment, and the composite plan must meet all dose constraints as specified in Table 3 below.

Table 3. Treatment planning guidelines.

Structure	Goal for 8 fractions	Goal for 15 fractions	Goal for 30 fractions	Composite Goal in EQD2Gy
PTV_ primary	V57Gy>95% goal; V57Gy>90% accepted	V57Gy>95% goal; V57Gy>90% accepted		
PTV_ mediastinum			V57Gy>95% goal; V57Gy>90% accepted	
BrachialPlex_L, BrachialPlex_R	D0.035cc<32 Gy goal; D0.035cc<36 Gy accepted	D0.035cc<45 Gy goal; D0.035cc<50 Gy accepted	D0.035cc<66 Gy	D0.035cc<66 Gy
Bronchus	D0.035cc<32 Gy goal; D0.035cc<36 Gy accepted	D0.035cc<40 Gy goal; D0.035cc<45 Gy accepted	D0.035cc<66 Gy	D0.035cc<74 Gy
Esophagus	D0.035cc<32 Gy goal; D0.035cc<36 Gy accepted	D0.035cc<50 Gy goal; D0.035cc<55 Gy accepted	D0.035cc<66 Gy	D0.035cc<74 Gy
GreatVessels	D0.035cc<32 Gy goal; D0.035cc<36 Gy accepted	D0.035cc<48 Gy goal; D0.035cc<54 Gy accepted	D0.035cc<66 Gy	D0.035cc<74 Gy
Heart	D0.035cc<36 Gy goal; D0.035cc<40 Gy accepted	D0.035cc<40 Gy goal; D0.035cc<45 Gy accepted	D0.035cc<66 Gy	D0.035cc<74 Gy
Liver	Mean dose <10 Gy	Mean dose <18 Gy	Mean dose <20 Gy	Mean dose <20 Gy
Lungs	Mean dose <10 Gy; V20Gy < 10%; V5Gy<30%	Mean dose <18 Gy; V18Gy < 37%; V5Gy<60%	Mean dose <20 Gy; V20Gy < 37%; V5Gy<60%	Mean dose <20 Gy; V20Gy < 37%; V5Gy<60%
Kidneys	Mean dose <8 Gy goal	Mean dose <10 Gy goal	Mean dose <12 Gy	Mean dose <12 Gy
SpinalCord	D0.035cc<28 Gy	D0.035cc<36 Gy goal;	D0.035cc<50 Gy	D0.035cc<50 Gy

		D0.035cc<39 Gy accepted		
Stomach	D0.035cc<32 Gy goal; D0.035cc<36 Gy accepted	D0.035cc<45 Gy goal; D0.035cc<50 Gy accepted	D0.035cc<60 Gy	D0.035cc<60 Gy
Trachea	D0.035cc<32 Gy goal; D0.035cc<36 Gy accepted	D0.035cc<40 Gy goal; D0.035cc<45 Gy accepted	D0.035cc<66 Gy	D0.035cc<74 Gy

5.4.5 Patient specific quality assurance

Any patient-specific QA that needs to be acquired should follow institutional guidelines. For intensity-modulated techniques, patient specific QA is highly recommended.

5.4.6 Daily treatment localization/Image guided radiation therapy (IGRT)

Daily image guidance is required. This can be in the form of daily cone-beam CT (CBCT), or daily orthogonal x-rays. If daily orthogonal x-rays are used, weekly CT (CBCT or simulation CT) is required to verify anatomy. IGRT matching will be per routine clinical care.

5.4.7 Case review

Principal investigator will review first 3 cases per site prior to treatment initiation. All future cases will be reviewed without one week of treatment start.

5.5 Toxicity management guidelines

Durvalumab is FDA approved as adjuvant treatment after chemoradiation for unresectable NSCLC. Although this trial gives durvalumab for 2 years as opposed to the current FDA approval of 1 year, toxicities will be managed per standard of care. Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the durvalumab/tremelimumab Toxicity Management Guidelines (TMGs, current version dated November 2017, CTCAE version 5.0), included as Appendix 1.

Management of chemotherapy and radiation related toxicities will also be per standard clinical care. All toxicities will be graded according to NCI CTCAE, Version5.0.

6. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

6.1 Restrictions during the study

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

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 2) 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-sterilised 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.

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 2).

N.B 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 2. 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).

Table 1. 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

Blood donation

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

6.2 Concomitant treatment(s)

6.2.1 Permitted concomitant medications

Table 2. Supportive Medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

6.2.2 Excluded concomitant medications

Table 3. Prohibited Concomitant Medications

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment

Prohibited medication/class of drug:	Usage:
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
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	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs, • Short-term premedication for patients receiving other drugs (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. 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).
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly

7. STUDY PROCEDURES

7.1 Schedule of study procedures

7.1.1 Screening phase

Screening procedures will be performed up to 45 days before Day 1 of treatment, except for histology which has no time restriction. All screening procedures for this study are standard of care, there are no required study specific tests for screening. After signing the IRB approved informed consent, completing all screening procedures, and being deemed eligible for entry, patients will be enrolled in the study.

7.1.2 Treatment phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments. Treatment visits will be per standard of care, which is typically at least every 4 weeks during chemotherapy and durvalumab, and weekly during radiation treatment. Standard of care lab assessments will be drawn prior to every infusion during chemotherapy and durvalumab therapy. Study blood draws will take place prior to initiation of any therapy (within 45 days), 1 week after completion of radiation to the primary tumor (±7 calendar days), prior to mediastinal radiation (less than 4 weeks) for applicable patients, and every 4 months (±1 month) afterwards for 2 years or until disease progression. Either an EBUS or mediastiastinoscopy must be performed to provide pathologic evaluation of the mediastinal nodes prior to starting treatment, per standard of care. For patients who do not have systemic progression on repeat CT at week 9, a repeat EBUS or mediastinoscopy must be performed to evaluate the mediastinal lymph nodes. This should ideally take place within 3 weeks of the restaging CT at week 9 but may be up to 6 weeks. Optional repeat lung tumor biopsy will be performed 1 month after radiation to the primary tumor (±2 weeks).

End of treatment is defined as the last planned dosing visit within the 24-month dosing period. For patients who discontinue durvalumab prior to 24 months, end of treatment is considered the last visit where the decision is made to discontinue treatment.

7.1.3 Blood draws

Standard of care labs drawn during the study period includes hematology labs (Table 5), and clinical chemistry (Table 6). Study blood draws will take place a maximum of 9 times per patient during the 24 months study period, as detailed on the study calendar. Study blood draw will consist of 5 tubes.

Table 5. Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Table 6. Clinical Chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lipase [b]
Alanine aminotransferase	Magnesium
Amylase	Potassium
Aspartate aminotransferase	Sodium
Bicarbonate	Total bilirubin[a]
Calcium	Total protein
Chloride	Blood urea nitrogen
Creatinine [c]	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

[b] It is preferable that both amylase and lipase parameters are assessed, but one is acceptable.

[c] Creatinine Clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).

8. ASSESSMENT OF SAFETY

8.1 Early patient review for safety

Patients are seen and evaluated by the medical oncology team prior to each durvalumab infusion (every 4 weeks) for the entirely of the study duration per standard of care. During the chemotherapy portion of the study (weeks 1-8), patients are evaluated by the medical oncology team every one to two weeks as well. When patients are receiving radiation therapy (weeks 1-3 of the study, and weeks 12-18 for patients receiving mediastinal radiation), patients are evaluated weekly by the radiation oncology team per standard of care. Therefore, within the first 3 months of treatment for each patient, they will be assessed by the oncology teams at least 8 times.

8.2 Safety parameters

8.2.1.1 Definition of adverse events

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a patient's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the patient has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the patient being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both serious and non-serious AEs.

8.2.2 Definition of serious adverse events

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the patient
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.
    - Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this 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 causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

8.2.3 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 Perforation

- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eyeskin, haematological and rheumatological events, vasculitis, non-infectious meningitis and 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 aetiology 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 1). 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.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 1) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological

parameters etc) will be captured in <<specify where this information will be recorded e.g. eCRF, CRF, etc)>>

It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    - (i) ILD Markers (KL-6, SP-D) and β-D-glucan
    - (ii) Tumor markers: Particular tumor markers which are related to disease progression.

Additional Clinical chemistry: CRP, LDH

8.3 Assessment of safety parameters

8.3.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v5.0. The determination of severity for all other events not listed in the CTCAE should be made by the

investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below:

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the patient.
Grade 4 (life-threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the patient to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

8.4 Recording of adverse events and serious adverse events

AEs and SAEs will be collected from the time of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of durvalumab). If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study drug or the study has completed.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The following variables will be collected for each AE:

In addition, the following variables will be collected for SAEs as applicable:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating of whether treatment related
- Action taken with regard to cancer-directed treatment
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed

- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of the SAE

The grading scales found in the NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.4.1 Study recording period and follow-up for adverse events and serious adverse events

If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

8.4.2 Causality collection

The Investigator will assess causal relationship between the study treatments and each AE and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment?”

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as “yes.”

8.4.3 Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment–emergent (i.e., SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.

- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

8.4.4 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in CRF. When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.5 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs measurements will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study treatments.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting Investigator should use the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

8.4.6 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study treatments are 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.

8.4.7 New cancers

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 study treatments and have been identified after the patient's inclusion in this study.

8.4.8 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 to the Study Monitor/Physician at the next monitoring visit and should be documented. 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 to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented.
- The report should contain a comment regarding the co involvement of PD, 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.
- A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative.

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

AstraZeneca/MedImmune retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.4.9 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording.

AstraZeneca/MedImmune retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.4.10 Post-study events

After the patient has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study patients after the 90-day safety follow-up period for patients treated with durvalumab. However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor and AstraZeneca/MedImmune Patient Safety.

8.5 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

8.5.1 Reporting of deaths to AstraZeneca

All deaths must be recorded and reported as outlined in this protocol. 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

8.5.2 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 10.5 for contact information) within 7 calendar days or sooner when required (see Section 10.5). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 10.5). 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 10.5). There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

8.5.3 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 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.

8.5.4 Pregnancy

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 10.5 for contact information) within 7 calendar days or sooner when required (see Section 10.5), for pregnancies with SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.5.5 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.

8.6 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong patient received the medication
- Wrong drug administered to patient

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Patient accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs Sponsor within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The Sponsor works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days. The Sponsor must report to AstraZeneca Patient Safety using the

designated Safety e-mailbox within 7 calendar days or sooner when required if there is an SAE associated with the medication error and within 30 days for all other medication errors.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The primary objective of this study is to evaluate the one-year progression-free survival rate in patients with stage III non-small cell lung cancer treated with chemotherapy and hypofractionated radiation to the primary tumor and adaptive radiation to the mediastinum, along with up to 2 years of durvalumab. The design of the study is a single arm phase II and the design is based on a comparison with expected data with PACIFIC 2.

9.1 Description of analysis sets

9.1.1 Efficacy and safety analysis set

Given that this is a single arm phase II study, the primary analysis population (PAP) and the safety analysis population (SAP) are the same; the PAP and SAP will include eligible patients who started at least one therapy on trial (chemotherapy, or durvalumab, or radiation).

9.2 Methods of statistical analyses

9.2.1 Safety analyses

The primary toxicity of interest is grade 3 or higher pneumonitis. The incidence of grade 3 or worse pneumonitis attributable to treatment will be evaluated and compared against the PACIFIC trial results. All toxicities of all grades will be monitored on study and reported. Binary proportions will be calculated with associated confidence intervals for binary outcomes, such as toxicity.

9.2.2 Efficacy analyses

Efficacy analyses include an evaluation of PFS, OS, and response rate. The distribution of time to event outcomes will be evaluated using the method of Kaplan-Meier. Confidence intervals for median times will be determined using the Brookmeyer-Crowley method. Confidence intervals around landmark times will be determined using Greenwood's formula for the variance and based on a log-log transformation applied on the survival function. Binary proportions will be calculated with associated confidence intervals for binary outcomes, such as response. Means and/or medians will be calculated for continuous outcomes. Confidence bounds will be provided for means and quartiles and ranges for median values. All confidence bounds will be presented as 95% bounds.

9.2.3 Exploratory analyses

Exploratory outcomes will be summarized as described above for efficacy analyses. Change in patient reported outcomes will be summarized by means. The association between Immune profile measurements and efficacy outcomes (PFS, OS, response) will be evaluated using a Cox regression model for time-to-event outcomes and a logistic regression model for binary outcomes.

9.2.4 Interim analyses

This study will include interim monitoring for safety; the trial will not include interim monitoring to assess early stopping for futility. The study will not include interim monitoring for futility given that the primary endpoint is PFS at 1 years and insufficient information will be available to make interim decisions on this endpoint.

9.3 Determination of sample size

As stated above, the primary objective of this study is to compare the 1-year PFS rate (PFS1) from the start of induction chemoradiotherapy in this study to historical data. The estimated null historical rate with standard of care is 42%. This rate is based on the PFS1 in the PACIFIC trial and the estimated proportion of patients that will be able to proceed from induction chemoradiotherapy to maintenance durvalumab. In PACIFIC, PFS1, measured from the start of maintenance durvalumab, was 56%. To estimate the percentage of patients able to receive maintenacce therapy, we use the SWOG S0023 study in which 75% of stage III patients were able to receive consolidation chemotherapy following induction chemoradiotherapy. Further, we assume that all patients who were unable to receive consolidation therapy progressed prior to one year. Therefore, our estimate of the historical 1-year PFS rate with maintenance durvalumab following induction chemotherapy is 42% (75% x 56%). This number may be updated as more information from the trials become available.

The target sample size for this study is 40 eligible patients who receive at least one dose of radiation therapy. A design with 40 patients has 90% power to rule out a 1-year PFS rate of 42% at the 1-sided 5% level, if the true 1-year is 65%. The observation of at least 22 patients (55%) alive and progression free at 1 year would be considered evidence to rule out a 1-year PFS rate of 42%. Sample size calculations were performed using https://stattools.crab.org/Calculators/oneArmBinomialColored.html .

With 40 patients, binary proportions (response, toxicity) can be estimated within 16% with 95% confidence. Survival distributions will be estimated using the method of Kaplan-Meier. Confidence interval for median times will be estimated using the method of Brookmeyer-Crowley.

The estimated monthly accrual rate to the study is 2-3 patients per month, resulting in a total estimated duration of accrual of 18 months. The follow-up duration is 12 months. The total estimated time to analysis of the primary endpoint is 30 months.

10. ETHICAL AND REGULATORY REQUIREMENTS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

11. STUDY MANAGEMENT

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

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

12. DATA MANAGEMENT

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique patient number to assure subject confidentiality. Subjects will not

be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents.

Subject research files are stored in a secure place (or database). Access is restricted to authorized personnel.

13. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

13.1 Identity of investigational product(s)

Table 4. List of Investigational Products for This Study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	*50 mg/mL solution for infusion after dilution*	MedImmune/AstraZeneca

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Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v5.0)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** of the start of the immune-mediated adverse event (imAE) • Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution toGrade ≤1. 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. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (e.g., infliximab; also refer to the individual sections of the imAEs for specific type of

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v5.0)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
Grade 3 Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen. Note: For asymptomatic amylase or lipase levels of >2X ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Pediatric Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTC 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 the start of the immune-mediated event	− All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. − The recommendations for dosing of steroids (i.e., mg/kg/day) and for IV IG and plasmapheresis that are provided for adult patients should also be used for pediatric patients. − The infliximab 5 mg/kg IV dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For dosing in children younger than 6 years old, consult with a pediatric specialist. − For pediatric dosing of mycophenolate mofetil, consult with 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 (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures 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 CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	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 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious Disease consults.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • 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.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors

			(e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a] − Consider Pulmonary and Infectious Disease consults. − Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** − Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Obtain Pulmonary and Infectious Disease consults; consider, as necessary, discussing with study physician. − Hospitalize the patient. − Supportive care (e.g., oxygen). − If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Diarrhea/Colitis **Large intestine perforation/Intestine perforation**	**Any Grade**	**General Guidance**	**For Any Grade:** − 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 a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – 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. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event, including perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only; intervention not indicated)	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), and loperamide. Use probiotics as per treating physician's clinical judgment.
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day; limiting instrumental ADL) (Colitis: abdominal	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**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 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further

pain; mucus or blood in stool) (Perforation: invasive intervention not indicated)		workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; limiting self care ADL; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, fever; ileus; peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated)	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **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 . – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

	(Grade 3 Perforation: invasive intervention indicated; Grade 4 Perforation: life-threatening consequences; urgent intervention indicated)

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade**	**General Guidance**	**For Any Grade** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications). – Continue LFT monitoring per protocol.
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB >ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal)	• No dose modifications. • If it worsens, then treat as Grade 2.	
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline normal, >1.5-3.0×baseline if baseline abnormal)	• Hold study drug/study regimen dose until resolution to Grade≤1. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade≤1, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to ≤Grade 1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**

		– Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 3 (AST or ALT >5.0×ULN and ≤20×ULN if baseline normal, >5-20× baseline if baseline abnormal; and/or TB >3.0×ULN and ≤10.0×ULN if baseline normal, >3.0-10.0× baseline if baseline abnormal) **Grade 4** (AST or ALT >20×ULN if baseline normal, >20×baseline if baseline abnormal; and/or TB >10×ULN if baseline normal, >10.0×baseline if baseline abnormal)	For elevations in transaminases ≤8×ULN, or elevations in TB ≤5×ULN: • Hold study drug/study regimen dose until resolution to Grade≤1 • Resume study drug/study regimen if elevations downgrade to Grade≤1 within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade≤1 within 14 days. For elevations in transaminases >8×ULN or elevations in bilirubin >5×ULN, permanently discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3×ULN + bilirubin >2×ULN without initial findings of cholestasis [i.e., elevated alkaline P04] and in the absence of any alternative cause).[b]	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Request Hepatology consult, and perform abdominal workup and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** 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**	**Any Elevations of AST, ALT, or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with 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.	– 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 study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician 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 **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN 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 within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days Permanently discontinue study drug/study regimen for any case meeting	– 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 biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if

		Hy's law criteria, in the absence of any alternative cause.[b]	mycophenolate is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above (except would 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**	**General Guidance**	**For Any Grade:** – Consult with 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, decrease in urine output, or proteinuria).

	− Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.

Grade 1 (serum creatinine >ULN to 1.5×ULN)	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. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – If baseline serum creatinine is elevated above normal, and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.
Grade 2 (serum creatinine >1.5 to 3.0×baseline; >1.5 to 3.0×ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**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 (>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, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.

	Grade 3 or 4 (Grade 3: serum creatinine >3.0×baseline; >3.0 to 6.0×ULN) (Grade 4: serum creatinine >6.0×ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Carefully monitor serum creatinine on daily basis. − 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, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (refer to NCI CTCAE v 5.0 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** − Monitor for signs and symptoms of dermatitis (rash and pruritus). − IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**
	Grade 1	No dose modifications.	**For Grade 1:** − Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline.	**For Grade 2:** − Obtain Dermatology consult. − Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).

		• If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	– Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids promptly. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4 (or life-threatening):** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (or life-threatening):** – Consult Dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus,	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain,

hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	v5.0 for defining the CTC grade/severity)		unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – 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.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning 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	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan.

	• If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, 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 (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency)	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity.

		can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the CTC 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). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with Neurology consult as appropriate. –

Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above. – Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia)
Grade 2	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. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – 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 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
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. **For Grade 4:**	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain Neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.

		Permanently discontinue study drug/study regimen.	
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** – 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. – 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 Neurology consult. – 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 (Guillain-Barre [GB]: mild symptoms)	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician.

(Myasthenia gravis [MG]: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)		– Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult.
Grade 2 (GB: moderate symptoms; limiting instrumental ADL) (MG: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL)	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.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o 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. o 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. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *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.
	Grade 3 or 4 (Grade 3 GB: severe symptoms; limiting self care ADL; Grade 4 GB: life-threatening consequences; urgent intervention indicated; intubation) (Grade 3 MG: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL; Grade 4 MG: life-threatening consequences; urgent intervention indicated)	**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 or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** − Consider, as necessary, discussing with study physician. − Recommend hospitalization. − Monitor symptoms and obtain Neurology consult. *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 neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *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.

Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – 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). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, 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. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)

Grade 1 (asymptomatic or mild symptoms*; clinical or diagnostic observations only; intervention not indicated) *Treat myocarditis with mild symptoms as Grade 2.	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
Grade 2, 3 or 4 (Grade 2: Symptoms with moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms*) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, 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 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

	* Consider "new onset of symptoms" as referring to patients with prior episode of myocarditis.		
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – 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 new-onset 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 study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up 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. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	- 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. – Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	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.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – 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 3 to 5 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 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Grade 3 or 4 (Grade 3: pain associated with severe weakness; limiting self-care ADLs Grade 4: life-threatening consequences; urgent intervention indicated)	**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. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – 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 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
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 2:** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedication per institutional standard prior to subsequent doses. − Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
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 institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
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 institutional standard.
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 institutional standard.

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 Study Physician."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.