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STU 2019-1082
Phase II Concurrent Durvalumab (MEDI4736) and radiotherapy followed by consolidative Durvalumab (MEDI4736) for Stage III Non-Small Cell Lung Cancer (NSCLC)

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Study Drug/Treatment: Durvalumab (MEDI4736), IMFINZI

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Amendment/Version #_____4_____

STU-2019-1082
Phase II Concurrent Durvalumab (MEDI 4736) and radiotherapy followed by consolidative Durvalumab (MEDI 4736) for Stage III Non-Small Cell Lung Cancer (NSCLC)

Principal Investigator (PI) Name: **Yuanyuan Zhang**

PI Signature: _____

Date: _____

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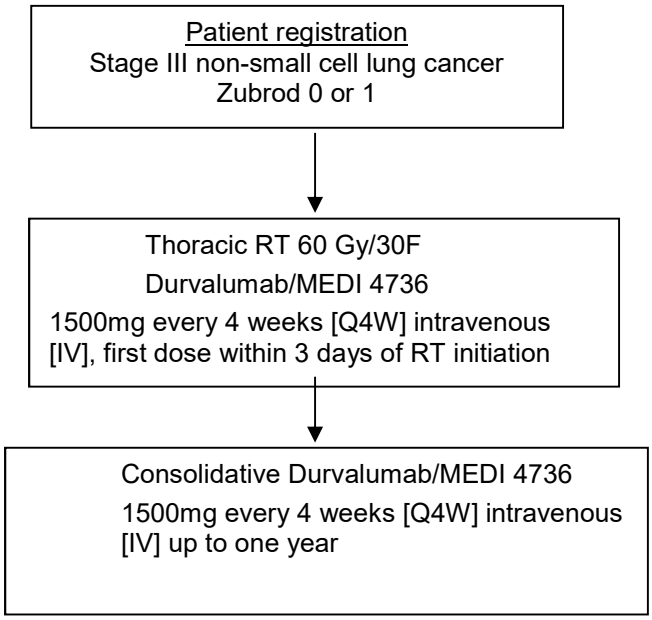
LIST OF ABBREVIATIONS (EXAMPLES)

AE	Adverse Event
ALT	Alanine Aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
IV (or iv)	Intravenously
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PD-L1	Programmed death-ligand 1
PET	Positron Emission Tomography
PFS	Progression Free Survival
PR	Partial Response
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	Single arm, Phase II trial of concurrent Durvalumab (MEDI 4736) and radiotherapy followed by consolidative Durvalumab (MEDI 4736) for Stage III Non-Small Cell Lung Cancer (NSCLC)
Short Title	TBD
Protocol Number	STU-2019-1082
Phase	Phase 2
Methodology	Open label
Study Duration	4 years
Study Center(s)	Single-center
Objectives	12-month progression-free survival (PFS) rate based on an assessment by an investigators according to RECIST 1.1 criteria
Number of Subjects	50
Diagnosis and Main Inclusion Criteria	Stage III non-small cell lung cancer Zubrod 0 or 1
Study Product(s), Dose, Route, Regimen	Durvalumab/MEDI 4736 1500mg every 4 weeks [Q4W] intravenous during concurrent radiotherapy, 1500mg every 4 weeks [Q4W] intravenous [IV] up to one year during consolidative phase. Thoracic RT 60 Gy/30F
Duration of administration	1 year
Reference therapy	Concurrent chemo-radiation
Statistical Methodology	Progression-free survival and overall survival will be estimated using the Kaplan-Meier approach and the corresponding confidence intervals will be estimated using Greenwood's formula. Distant metastases-free survival, local and regional control will be estimated using the Kaplan-Meier approach.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Until the recent developments of immunotherapy, we have reached a plateau in outcomes for locally advanced non-small cell lung cancer (LA-NSCLC). Despite aggressive therapy with concurrent chemoradiation, fewer than 20-25% of patients with stage III NSCLC achieve 5-year survival and are presumably cured. To date, modifications of chemotherapy or dose escalation of radiotherapy (RT) have not improved these outcomes.

Immunotherapy has significantly improved the survival outcomes of patients with various cancer types including thoracic malignancies. In the PACIFIC study, patients with locally advanced NSCLC were randomized to the anti-PDL1 antibody durvalumab or placebo for up to 12 months after completion of concurrent chemoradiation. Outcomes in the durvalumab arm were significantly better, regardless of tumor PDL1 status. Median PFS was 17.2 months in the durvalumab group (95% CI, 13.1 to 23.9) vs. 5.6 months (95% CI, 4.6 to 7.7) in the placebo group. The 24-month overall survival rate was 66.3% (95% confidence interval [CI], 61.7 to 70.4) in the durvalumab group vs. 55.6% (95% CI, 48.9 to 61.8) in the placebo group (two-sided P=0.005). (Antonia et al., 2018; Antonia et al., 2017). The time to death or distant metastasis was longer in the durvalumab group than in the placebo group (median, 28.3 months [95% CI, 24.0 to 34.9] vs. 16.2 months [95% CI, 12.5 to 21.1]; stratified hazard ratio, 0.53; 95% CI, 0.41 to 0.68). Following this study, consolidation durvalumab after chemoradiation received FDA approval and is now considered standard of care.

While NSCLC is typically considered relatively non-immunogenic, RT is thought to augment tumor immunogenicity(Iyengar & Gerber, 2013). The abscopal effect refers to the observation that RT to a local area results in an antitumor effect distant to the radiation site. One proposed mechanism for this phenomenon is inducing the release of circulating tumor antigen or inflammatory factors that could then mediate an augmented immune response against distant malignant lesions expressing similar tumor antigens. Supporting this hypothesis, local RT has been shown to increase the activity of natural killer cells (Uchida, Mizutani, Nagamuta, & Ikenaga, 1989).

Conversely, the therapeutic effects of ablative RT on local tumors are dependent on anti-tumor immune responses (Iyengar & Gerber, 2013). Of note, Formenti and colleagues demonstrated that the abscopal effect of radiotherapy is in part immune-mediated and that T cells are required to mediate distant tumor effects of radiotherapy (Demaria et al., 2004). In a preclinical model, ablative RT dramatically increased T-cell priming in draining lymphoid tissues, leading to reduction of the primary tumor or distant metastases in a CD8+ T-cell-dependent fashion. In the same model, these RT-initiated immune responses were greatly amplified by local immunotherapy (Lee et al., 2009). Particularly relevant to the current proposal, RT has been shown to increase tumor expression of PD-L1, and combined RT plus PD-1-pathway targeting results in synergistic suppression of tumor-infiltrating myeloid-derived suppressor cells (MDSCs), thereby promoting anti-tumor immunity (Deng et al., 2014).

In contrast to CTLA-4 (which exerts its regulatory effects in the priming phase of the immune response in regional lymph nodes), the negative regulatory effects of the PD-1/PD-L1 pathway occur in the effector phase of the immune response in peripheral tissues. Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2, resulting in dephosphorylation of multiple effector molecules involved in the CD3 T-cell signaling cascade (Talmadge, Donkor, & Scholar, 2007). PD-1 is expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regulatory cells (Tregs), and natural killer (NK) cells (Hodi et al., 2008; Hodi et al., 2010). Although healthy organs express little (if any) PD-L1, numerous cancers are known to express abundant levels of PD-L1. PD-1/PD-L1 has been suggested to regulate tumor-specific T-cell expansion in patients with melanoma, suggesting that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and therefore represents an attractive target for therapeutic intervention.

Blocking PD-L1 is a similar approach to that taken by CTLA4 inhibition with ipilimumab, but has some potential advantages. First, the expression of CTLA-4 and its ligands is restricted to the hematopoietic system; thus, the site of action for molecules targeting CTLA-4 is solely the peripheral lymphoid organs. In contrast, PD-L1 is expressed not only on cells of the hematopoietic system but also on a range of tumor types. Targeting of PD-L1 could therefore have additional effects within the tumor microenvironment. Secondly, CTLA-4 plays an early and critical role in controlling T-cell activation. This is reflected in the phenotype of CTLA-4 knockout mice, which die at an age of between 3 weeks and 4 weeks due to lymphoproliferative disease and tissue destruction. In contrast PD-L1, via binding to PD-1, acts later in the process of T-cell activation (Fife & Bluestone, 2008) and is considered more dispensable for the control of initial T-cell activation. This distinction is reflected in the phenotype of PD-L1 knockout mice, which are viable and have normal T-cell numbers and activation levels, but have increased T-cell activation in response to antigen and increased susceptibility in certain autoimmunity models (Dong et al., 2004; Latchman et al., 2004). Based on these data, inhibition of PD-L1 would be expected to have reduced toxicity relative to inhibition of CTLA-4. In support of this supposition, monotherapy clinical studies testing the tolerability of agents targeting PD-1 have shown a more favorable toxicity profile than ipilimumab (Berger et al., 2008; Brahmer et al., 2010; Wolchok et al., 2010).

The benefit seen in PACIFIC, along with the growing role of immunotherapy for the treatment advanced (stage IV) NSCLC, suggests that earlier exposure to durvalumab may improve outcomes and be well tolerated, thereby permitting de-escalation of therapy through removal of conventional chemotherapy from these regimens.

1.2 Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities

Durvalumab (Imfimzi; MEDI4736; AstraZeneca) is a human monoclonal antibody of the immunoglobulin (Ig) G1 kappa subclass that inhibits binding of PD-L1 (B7-H1, CD274) to PD-1 (CD279) and CD80 (B7-1). MEDI4736 is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. MEDI4736 contains a triple mutation in the constant domain of the Ig G1 heavy chain that reduces binding to complement protein C1q and the $F_c\gamma$ receptors involved in triggering effector function. Durvlumab binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80.

Risks with durvalumab include, but are not limited to, diarrhea/colitis and intestinal perforation, 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, vasculitis, non-infectious meningitis and non-infectious encephalitis. and infections/serious infections.

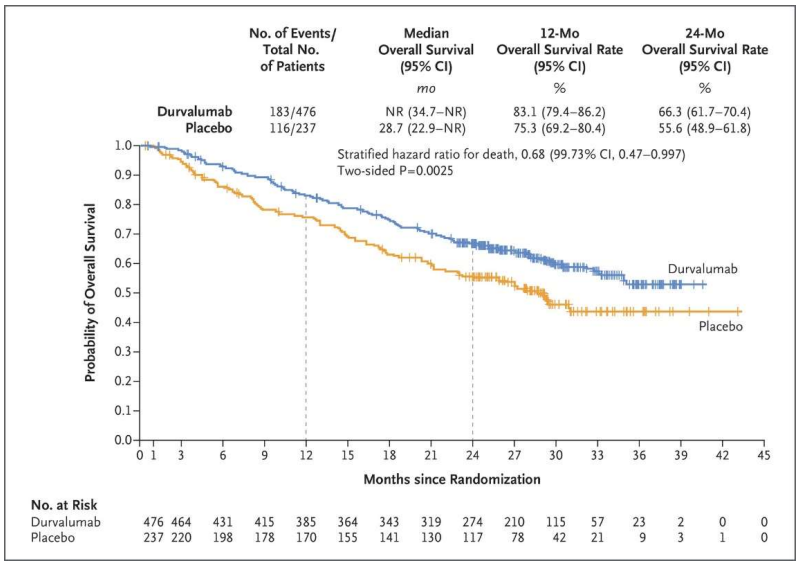
For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab Investigator Brochure (IB). Further information on these risks can be found in the current version of the durvalumab IB. In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 7% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.
The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated (Appendix II).

A Phase I, multicentre, open label, dose-escalation, and dose-expansion study was conducted to determine the MTD or optimal biologic dose, safety, PK, immunogenicity, and anti-tumour activity

of MEDI4736 in adult patients with advanced solid tumours, refractory to standard therapy (Study CD-ON-MEDI4736-1108). The safety profile of durvalumab in this population was consistent with that of other immunotherapies and with its known safety profile as monotherapy in patients with more advanced disease (stage IIIB or IV NSCLC)(Antonia SJ). Safety data are available for the 20 patients in the Q2W dose-escalation cohorts. Nineteen of the 20 patients treated at the Q2W schedule have reported at least 1 treatment-emergent AE. No patient has had a DLT at doses up to 10 mg/kg. The most frequent treatment-emergent AEs reported in 3 or more patients included fatigue (6 patients), constipation, decreased appetite, diarrhoea, dyspnoea and nausea (4 patients each), and cough, dehydration, hypertension, pyrexia and rash (3 patients each). Seven patients have had an AE that has been considered by the reporting investigator to be related to treatment: diarrhoea, vomiting, fatigue, dizziness and rash (2 patients each), and anaemia, nausea, influenza-like illness, infusion-related reaction, dehydration, and pruritus (1 patient each). The majority of AEs (in 15 of the 20 patients) have been Common Terminology Criteria for Adverse Event (CTCAE) Grade 1 or 2. There have been no Grade 3 or higher treatment-related AEs. One patient (in the 1.0 mg/kg cohort) had 2 events of Grade 3 hyponatremia, which occurred in the setting of dehydration. Four patients (1 patient in each of the 0.1, 0.3, 3.0, and 10.0 mg/kg cohorts) died due to AEs. None of the events were considered by the reporting investigator to be related to treatment. Three of these deaths were due to progression of disease (PD) recorded as serious adverse events (SAEs); the fourth death was due to retroperitoneal haemorrhage.

In addition to trials in advanced disease, durvalumab was investigated in stage III non-resectable NSCLC in the PACIFIC trial. In this study, patients were randomized to durvalumab 1500 mg IV or placebo every 14 days for up to one year, following completion of concurrent chemoradiation. The durvalumab arm demonstrated improved PFS and OS compared to the placebo arm (**Figure 1**). Tumor PD-L1 expression was tested retrospectively using archival tumor tissue obtained prior to chemoradiotherapy. Durvalumab improved overall survival for all but PD-L1 <1% group (**Figure 2A**). Durvalumab also improved progression-free survival in each of the PD-L1 subgroups **(Figure 2 B).** Limitations of PD-L1 subgroup analyses include the post-hoc nature with no pre-specified statistical adjustmetn, incomplete sample collection and small sample size of subgroups, the low number of events resulting in imbalances in baseline clinical characterisitics. The most common treatment-related adverse events included cough, pneumonitis, dyspnea, fatigue and diarrhea. Apparent immune-related adverse events included pneumonitis, pruritis and rash. **Table 1** lists AEs by treatment arm and severity. Pneumonitis, arguably the greatest concern in a trial combining sequential thoracic chemoradiation and immune checkpoint inhibition, was numerically increased in the durvalumab arm, but severe cases remained less than 5%: 33.9 (3.4% grade 3-4) in the durvalumab arm versus 24.8% (2.6% grade 3-4) in the placebo arm. Toxicity event terms that could represent similar processes, such as dyspnea and pneumonia, occurred at comparable rates between durvalumab and placebo arms, and reached grade 3-4 in fewer than 5% of patients. The use of combination therapies may contribute to the increased incidnece of penumonitis in the PACIFIC trial compared to the previously reported 3-5% (Suresh et al., 2018). Additionally, most cases of pneumonitis were reversible with stopping treatment, initiating glucocorticoids, or both.

Figure 1. Overall Survival (A) and Progression Free Survival (B) in PACIFIC study
(A)


No. of Events/ Total No. of Patients
Median Overall Survival (95% CI)
12-Mo Overall Survival Rate (95% CI)
24-Mo Overall Survival Rate (95% CI)
mo
%
%
Durvalumab 183/476 NR (34.7–NR) 83.1 (79.4–86.2) 66.3 (61.7–70.4)
Placebo 116/237 28.7 (22.9–NR) 75.3 (69.2–80.4) 55.6 (48.9–61.8)
Stratified hazard ratio for death, 0.68 (99.73% CI, 0.47–0.997)
Two-sided P=0.0025
Probability of Overall Survival
Durvalumab
Placebo
Months since Randomization
No. at Risk
Durvalumab 476 464 431 415 385 364 343 319 274 210 115 57 23 2 0 0
Placebo 237 220 198 178 170 155 141 130 117 78 42 21 9 3 1 0

(B)

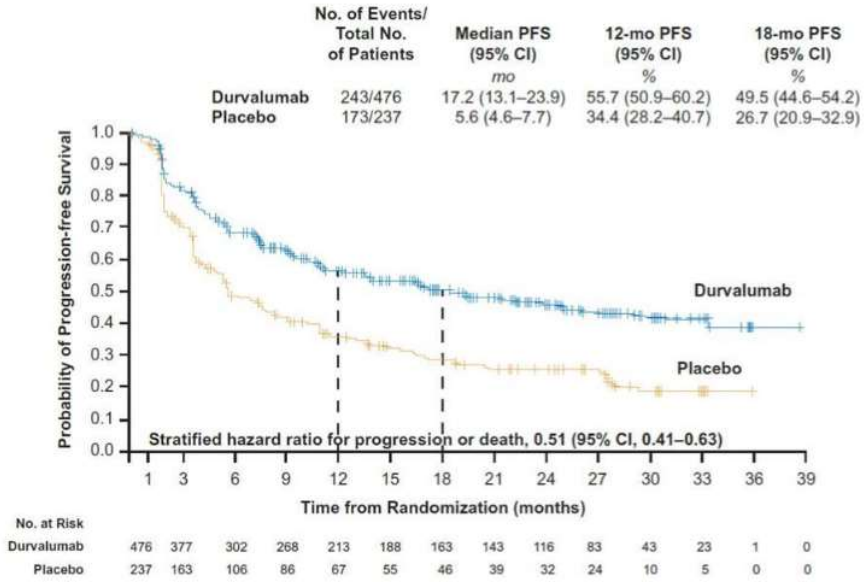
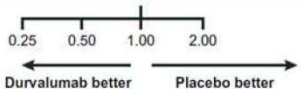

No. of Events/ Total No. of Patients
Median PFS (95% CI)
12-mo PFS (95% CI)
18-mo PFS (95% CI)
mo
%
%
Durvalumab 243/476 17.2 (13.1–23.9) 55.7 (50.9–60.2) 49.5 (44.6–54.2)
Placebo 173/237 5.6 (4.6–7.7) 34.4 (28.2–40.7) 26.7 (20.9–32.9)
Probability of Progression-free Survival
Durvalumab
Placebo
Stratified hazard ratio for progression or death, 0.51 (95% CI, 0.41–0.63)
Time from Randomization (months)
No. at Risk
Durvalumab 476 377 302 268 213 188 163 143 116 83 43 23 1 0
Placebo 237 163 106 86 67 55 46 39 32 24 10 5 0 0

Figure 2.Exploratory, Post-hoc Subgroup Analyses of Overall Survival (A) and Progression Free Survival (B) by PD-L1 Status (ITT population in PACIFIC study)

(A)

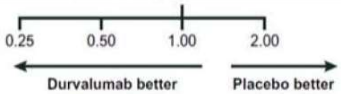
Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Death (95% CI)
	no. of events / no. of patients (%)		
All patients	183/476 (38.4)	116/237 (48.9)	0.68 (0.53–0.87)†
PD-L1 status			
≥1%	70/212 (33.0)	45/91 (49.5)	0.53 (0.36–0.77)
≥25%*	37/115 (32.2)	23/44 (52.3)	0.46 (0.27–0.78)
1–24%	33/97 (34.0)	22/47 (46.8)	0.60 (0.35–1.03)
<1%	41/90 (45.6)	19/58 (32.8)	1.36 (0.79–2.34)
Unknown	72/174 (41.4)	52/88 (59.1)	0.62 (0.43–0.89)



*Pre-specified subgroup.

(B)

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events / no. of patients (%)		
All patients	214/476 (45.0)	157/237 (66.2)	0.52 (0.42–0.65)†
PD-L1 status			
≥1%	84/212 (39.6)	59/91 (64.8)	0.46 (0.33–0.64)
≥25%*	48/115 (41.7)	31/44 (70.5)	0.41 (0.26–0.65)
1–24%	36/97 (37.1)	28/47 (59.6)	0.49 (0.30–0.80)
<1%	49/90 (54.4)	40/58 (69.0)	0.73 (0.48–1.11)
Unknown	81/174 (46.6)	58/88 (65.9)	0.59 (0.42–0.83)



*Pre-specified subgroup.

Table 1. Safety Summary of Pacific Trial

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

1.3 Other Agents

As of January 2019, six monoclonal antibodies targeting the PD1/PDL1 pathway have received FDA approval for the treatment of various malignancies, including nivolumab (Opdivo), pembrolizumab (Keytruda), atezolizumab (Tencentriq), durvalumab (Imfimzi), avelumab (Bavencio), cepilimumab (Yervoy). Nivolumab (Opdivo), pembrolizumab (Keytruda), and atezolizumab (Tecentriq) are approved for advanced (stage 4) NSCLC. Durvalumab is approved for locally advanced (stage 3) NSCLC.

Efficacy and toxicity among the various PD1- and PDL1-targeted agents in NSCLC are comparable. Single-agent response rates in previously treated patients range 15-20% (Reck et al., 2016; Rittmeyer et al., 2017; Rizvi et al., 2015; Tanvetyanon, Creelan, & Antonia, 2016; Zhou et al., 2016). Generally, biomarkers predicting benefit include tumor PDL1 expression, tumor mutational burden, and microsatellite instability (Dudley, Lin, Le, & Eshleman, 2016; Fabrizio et al., 2018; Patel & Kurzrock, 2015). Although immune checkpoint inhibitors are typically well tolerated, a minority of patients develop immune-related adverse events (irAEs). The overall incidence of irAEs has been low in clinical trials that evaluated monotherapy with anti-PD-1 and anti-PD-L1 therapies (typically <5%) (Suresh, Naidoo, Lin, & Danoff, 2018). These autoimmune toxicities occur when immune stimulation results in an immune-mediated attach on normal tissues and organs. In clinical studies enrolling 1889 patients with various cancers who received IMFINZI (AstraZeneca Safety information), pneumonitis occurred in 5% of patients, including Grade 3 (0.8%), Grade 4 (<0.1%), and Grade 5 (0.3%) pneumonitis; Hepatitis occurred in 12% of patients, including Grade 3 (4.4%),

Grade 4 (0.4%), and Grade 5 (0.2%) hepatitis; colitis or diarrhea occurred in 18% of patients, including Grade 3 (1.0%) and Grade 4 (0.1%) colitis.; hypothyroidism occurred in 11% of patients, while hyperthyroidism occurred in 7% of patients; adrenal insufficiency occurred in 0.7% of patients, including Grade 3 (<0.1%) adrenal insufficiency; Hypopituitarism leading to adrenal insufficiency and diabetes insipidus occurred in <0.1%; nephritis occurred in 6.3% of the patients including Grade 3 (1.1%), Grade 4 (0.2%), and Grade 5 (0.1%) nephritis; 26% of patients developed rash or dermatitis and 0.4% of the patients developed vitiligo. In rare cases (<<1%), autoimmune encephalitis (Burke, Hardesty, & Downs, 2018) and myocarditis (Semper, Muehlberg, Schulz-Menger, Allewelt, & Grohe, 2016) have been reported. Grade 3 irAEs are quite rare, occuring in fewer than 5% of patients (Antonia et al., 2018; Hellmann et al., 2017; Rizvi et al., 2015). Depending on severity, irAEs may be managed with treatment withholding and immunosuppression, most commonly corticosteroids.

1.4 Rationale

This study is designed to determine if adding durvalumab both during and after thoracic radiation for locally advanced NSCLC provides comparable outcomes to concurrent chemoradiation followed by consolidation durvalumab. Additionally, we hypothesize that the regimen under study will be better tolerated.

The benefit seen in PACIFIC, along with the growing role of immunotherapy for the treatment advanced (stage IV) NSCLC, suggests that earlier exposure to durvalumab may improve outcomes and be well tolerated, thereby permitting de-escalation of therapy through removal of conventional chemotherapy from these regimens. Indeed, the resulting improved outcomes from adding durvalumab to chemoradiation in the PACIFIC trial represent a greater magnitude of benefit from immunotherapy than was achieved from adding chemotherapy to thoracic radiation therapy. EORTC08844 compared radiotherapy alone, concurrent radiotherapy plus weekly low dose cisplatin and concurrent radiotherapy plus daily cisplatin (Schaake-Koning et al., 1992) showed improved overall survival rate of 12% with radiotherapy alone, 19% with weekly cisplatin and 26% with daily cisplatin. Another study showed similar improvement with the addition of carboplatin and VP16 (Jeremic, Shibamoto, Acimovic, & Djuric, 1995). They also represent a greater degree of benefit than has been observed from the addition of immunotherapy to chemotherapy in advanced NSCLC. Recently, IMpower131 trial enrolled 1,021 patients with stage IV squamous NSCLC randomly assigned to either atezolizumab plus carboplatin and nab-paclitaxel or carboplatin and paclitaxel alone. The median progression free survival is 6.3 months for atezolizumab plus chemotherapy compared to 5.6 months for chemotherapy alone (P=0.001) (Robert M. Jotte, 2018). Together, these observations suggest that thoracic radiation therapy and durvalumab represent a particularly favorable combination, supporting years of preclinical studies and case reports demonstrating synergy between radiation therapy and immunotherapy. PACIFIC2 and other ongoing trials provide evidence that concurrent thoracic radiation therapy and immune checkpoint inhibitor therapy is likely to be well tolerated. For example, concurrent palliative radiotherapy with durvalumab was well-tolerated in a cohort of patients included in a phase ½ trial in France (Levy, Massard, Soria, & Deutsch, 2016).

In this trial, enrollment is not restricted to patients with PD-L1-positive tumors for numerous reasons. In preclinical models, RT has been shown to increase tumor expression of PD-L1 (Deng et al., 2014) which would limit the correlation of outcomes with pre-RT tissue biomarkers. The observation that tumor PD-L1 expression may be prognostic in general lung cancer populations—but not among cases treated with radiation or chemotherapy (Sun J-M, 2014)—further suggests that baseline assessment of this biomarker may not adequately define the target population most likely to benefit. Despite early reports suggesting that PD-L1-positive patients appear to derive particular benefit from PD-1- and PD-L1-targeted therapies, the definition of PD-L1-positivity remains unclear. Finally, in the PACIFIC study, durvalumab was associated with improved PFS and OS in an unselected population. Durvalumab improved overall survival for all but PD-L1 <1% group and progression-free survival in each of the PD-L1 subgroups.

Compared to anti-CTLA-4 antibodies (eg, ipilimumab, tremelimumab), it has become clear that anti-PD-L1/anti-PD1 antibodies have greater anti-tumor efficacy in NSCLC, as evidenced by the unprecedented overall survival results in previously treated advanced NSCLC. Although drugs in these classes tend to have quite similar efficacy and safety profiles, by far the greatest experience in the locally advanced NSCLC and chemoradiation settings is with durvalumab, where it was U.S. FDA approved in February 2018. Furthermore, anti-PD-L1 antibodies may have hypothetical safety advantage over anti-PD1 antibodies. Anti-PD-L1 antibodies inhibit only PD-L1, while anti-PD1 antibodies inhibit PD-L1 and PD-L2. Durvalumab is highly selective for PD-L1 and does not bind to PD-L2, which plays a role in controlling inflammation in normal tissue, and which might potentially decrease the immune-related toxicity associated with the PD-L2 interaction (Mezquita & Planchard, 2018).

There is preclinical evidence supporting the administration of immunotherapy before, during, and after RT. However, administration of immunotherapy before radiation could delay potentially curative treatment for this aggressive disease. The benefit seen in PACIFIC, along with the growing role of immunotherapy for the treatment advanced (stage IV) NSCLC, suggests that earlier and greater exposure to durvalumab may improve outcomes and allow removal of conventional chemotherapy from these regimens. As no chemotherapy will be given with durvalumab in this study, no steroid premedication will be administered, thereby theoretically optimizing immune stimulation. The continuation of durvalumab after completion of thoracic radiotherapy is supported by the PACIFIC trial and several clinical and laboratory observations. For example, administration of the immunotherapeutic L-BLP25 vaccine after completion of concurrent chemoradiation was well tolerated and had efficacy in stage III NSCLC (Butts et al., 2014). Clinical observations of anti-CTLA-4 antibodies suggest that immunotherapy administration following RT may provide synergistic effects (Postow et al., 2012).

The administration of durvalumab for up to 1 year is based on apparent clinical benefit shown in the PACIFIC study, experience in advanced NSCLC, and available tolerability data. This duration covers the time-period when patients are at greatest risk of recurrence or progression. Furthermore, preclinical studies have demonstrated that continued stimulation of the immune system contributes to the anticancer effects of CTLA-4 blockade (Maker, Attia, & Rosenberg, 2005; Tarhini & Iqbal, 2010). The potential value of repeated dosing also has been seen in human studies of the anti-CTLA-4 antibody ipilimumab. In one dramatic and illustrative case, a heavily pretreated patient with ovarian cancer and increasing CA-125 (GVAX vaccine refractory) was enrolled onto a monotherapy ipilimumab (MDX-010) study (Hodi et al., 2008). After the first dose of ipilimumab (MDX-010), her CA-125 decreased dramatically. Re-dosing at the time of CA-125 increase resulted in an even more rapid decline in her CA-125. Repeated dosing following CA-125 increases occurred 4 times to date and with clear and dramatic reductions in CA-125.

Finally, disease-related considerations suggest that a one-year duration of durvalumab is optimal. Among patients with stage 3 NSCLC who achieve disease control after chemoradiation, approximately 75% of cases that eventually progress will do so within the first 12 months after completion of chemoradiation, indicating that this represents the highest risk period (Butts et al., 2014). Post-treatment fluorodeoxyglucose (FDG) uptake not representing disease recurrence or progression has occurred up to 15 months after completion of chemoradiation (Larici et al., 2011). If such radiographic findings correspond to physiologic effects related to tumor antigenic stimulation, then this period might represent the optimal period to capitalize on the abscopal effect.

In this trial, patients will receive a fixed dose of 1500mg IV infusion every four weeks with concurrent chemotherapy and then every 4 weeks in the consolidative phase. Although the PACIFIC trial administered durvalumab every 2 weeks for up to one year, monthly administration improves convenience, has been shown not to compromise safety or efficacy and is the dosing regimen employed in the PACIFIC2 trial. 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 1,000 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.

1.5 Correlative Studies

1.5.1 Tumor PD-L1 Expression

The effect of tumor PD-L1 expression on treatment response to anti-PD-L1 targeted immunotherapy is a key focus of ongoing investigation. Identification of predictive biomarkers of response to therapy protects patients from exposure to risks of ineffective therapies and improves cost-effectiveness. Submission of formalin-fixed and paraffin embedded tumor samples (blocks) from core or excisional biopsy is recommended for all patients at the time of study enrollment. Although PD-L1 expression has been associated with improved outcomes from anti-PD1/PD-L1 therapy in advanced NSCLC, the benefit has been less apparent in trials combining these agents with other therapies, including cytotoxic chemotherapy for stage 4 disease (Herbst et al., 2016; Langer et al., 2016; Socinski et al., 2018) or chemoradiation (Antonia et al., 2018). Based on the results of KEYNOTE-021 cohort G, a randomized phase II trial, the U.S. Food and Drug Administration has approved the triple combination of carboplatin, pemetrexed, and pembrolizumab in all patients with non–squamous cell NSCLC, regardless of PD-L1 expression levels (Langer et al., 2016). Previously reported results from the IMpower150 study showed that the combination of TECENTRIQ and Avastin plus carboplatin and paclitaxel has longer progression-free survival compared to Avastin plus carboplatin and paclitaxel in the first-line treatment of people with advanced non-squamous NSCLC (Socinski et al., 2018). This PFS benefit was observed across key subgroups, including those with varying levels of PD-L1 expression. Finally, as noted above, PDL1 levels may change after administration of radiation therapy. We therefore hypothesize that any association between tumor PD-L1 expression and clinical outcomes will be modest in this trial. Analysis of PD-L1 expression and other biomarkers may be evaluated as determined by additional data associated with disease progression or response to durvalumab.

1.5.2 Optional tumor tissue collection and studies

If a standard-of-care diagnostic biopsy to confirm recurrence is obtained, at least two core biopsies, minimum, should be obtained as part of this recurrence biopsy. Paraffin embedded tissue from this biopsy will be used for confirmation of recurrence and for additional research. Any remaining tumor tissue will be stored for additional research. Patients may consent to have tissue and/or blood submitted at recurrence.

The remaining tumor samples may be used to analyze the expression and spatial distribution of immune-related or response-related markers by multiplex immunohistochemistry, which may include but are not limited to PD-L1, CTLA-4, CD3, CD4, CD8, CD45RO, FOXP3, granzyme B,

OX40, PD1, cleaved caspase 3, and Ki67. Archived material (or biopsies if available) may also be analyzed for the presence of key genomic features such as *EGFR, KRAS,* and *ALK* alterations to evaluate their potential relevance and correlations with response to durvalumab.

1.5.3 Optional blood collection for blood born biomarkers

Blood samples will be analyzed to evaluate protein, nucleic acid, and cellular biomarkers that relate to durvalumab. PBMC will also be isolated from whole blood and will be preserved, and may be used for subsequent flow cytometry or assessment of the diversity of the immune cell repertoire based on VDJ coding region analysis, the relationship to clinical responses, and changes in response to treatment with durvalumab. Blood collected for analysis of immune cell gene expression profiles within the peripheral compartments will be evaluated for any relationship with efficacy endpoints. Serum samples may also be anlayzed for analysis of circulating soluble factors in relation to immune status at baseline and in response to treatment. Factors to be analyzed may include but are not limited to IFN-γ, tumour necrosis factor-α, interleukin (IL)-2, IL-6, IL-10, IL-8, IL-12, and levels of soluble PD-L1.

Recent studies have found that more than 25% of healthy individuals have strong IgG humoral immune responses to a variety of self-antigens, indicating that a “benign” form autoimmunity is much more common than autoimmune disease (Wandstrat et al., 2006). This autoimmunity is directed against a variety of self-antigens. These findings indicate that many healthy individuals exhibit significant autoimmunity that is regulated in the peripheral immune system by pathways such as those triggered by CTLA-4 and PD1. Consistent with this, CTLA-4 and PD1 are both known to potentiate autoimmune disease, suggesting that the inhibition of these regulatory pathways aggravates pre-existing autoimmunity. Based on this, we hypothesize that checkpoint therapy immune-related adverse events often result from the activation of pre-existing autoimmunity.

We have the capacity to this hypothesis by utilizing a variety of novel technologies to quantify autoimmune responses. Specifically, we have the ability to measure IgG autoantibody reactivity against more than 120 systemic and organ-specific antigens simultaneously.

The protein array system that we have developed for autoantibody screening can also be used to assess antibodies against any antigen. Consequently, a panel of tumor-type-specific antigens may be incorporated into these arrays so that we can follow the level and specificity of anti-tumor humoral immunity elicited by checkpoint therapy in individual patients and correlate this with disease progression.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the 12-month progression-free survival (PFS) rate for Stage III non-small lung cancer patients treated with concurrent durvalumab and radiotherapy followed by consolidative durvalumab;

2.2 Secondary Objectives

2.2.1 To assess the safety and tolerability of concurrent durvalumab and radiotherapy compared to historical data from patients treated with standard of care chemo-radiation;
2.2.2 To determine the overall survival (OS) defined as the time from study enrollment to death due to any cause;
2.2.3 To determine the distant metastases-free survival defined as the time from the study enrollment to any new distant lesion;
2.2.4 To determine the local and regional control defined as the time from the study enrollment to any local and regional lesion;

2.3 Exploratory Objectives

2.3.1 Biomarker and biomarker correlatives: To determine the OS and PFS in patients with (1) PD-L1-positive, (2) PD-L1-negative tumors and (3) PD-L1 not evaluable/undetermined tumors.

2.3.2 Proportion of patients alive at 12 and 24 months;

2.4 Endpoints

2.4.1 Primary endpoint of 12-month progression-free survival (PFS) rate is based on an assessment by an investigators according to RECIST 1.1 criteria; PFS is defined as the time from the study enrollment to documented progressive disease or death due to any cause, whichever occurs first;

2.4.2 Secondary endpoint of safety and tolerability will be assessed by adverse event according to CTCAE V.5;

2.4.3 Secondary endpoint of overall survival is defined as the time from study enrollment to death due to any cause;

2.4.4 Secondary endpoint of distant metastases free survival is defined as the time from the study enrollment to any new distant lesion;

2.4.5 Secondary endpoint of local and regional control defined as the time from the study enrollment to any local and regional lesion;

2.4.6 Exploratory endpoint of biomarker and biomarker correlatives;

2.4.7 Exploratory endpoint of proportion of patients alive at 12 and 24 months.

3.0 Subject ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of NSCLC with, medically inoperable (or patients who refuse resection) stage IIIA or stage IIIB disease (AJCC 8th edition);

3.1.1.1 Inoperable Stage IIIA disease is defined by multiple and/or bulky N2 mediastinal lymph nodes on computed tomography (CT) scan such that, in the opinion of the treating investigator, the patient was not a candidate for surgical resection.

3.1.1.2 N2 disease must have been documented by biopsy, or at a minimum by fluorodeoxyglucose positron emission tomography (PET) or CT if nodes were more than 2 cm in short axis diameter.

3.1.1.3 T4 disease is often considered resectable at the discretion of a thoracic surgeon. Patients with T4N0 or T4N1 disease can be enrolled if their case is reviewed by a thoracic surgeon and felt to be unresectable or if they are either medically inoperable or refuse surgery.

3.1.1.4 Stage IIIB patients have N3 or T4N2 status. N3 status must have been documented by the presence of a contralateral (to the primary tumor) mediastinal lymph node or supraclavicular or scalene lymph node proven by biopsy, or at a minimum by fluorodeoxyglucose uptake on PET or more than 2 cm in short axis diameter on CT scan. Patients with disease extending into the cervical region (defined as disease extending above cricoid cartilage) are not eligible.

3.1.2 Appropriate stage for study entry based on the following diagnostic workup:

3.1.2.1 History/physical examination, including documentation of height, weight and vital signs, within 30 days prior to registration;

3.1.2.2 CT scan with IV contrast (CT scan without contrast acceptable if IV contrast is medically contraindicated) of the lung and upper abdomen through the adrenal glands within 60 days prior to registration (recommended within 30 days prior to registration);

3.1.2.3 MRI of the brain with contrast (or CT with contrast if MRI is medically contraindicated) within 60 days prior to registration; note: the use of intravenous contrast is required for the MRI or CT (unless medically contra-indicated).

3.1.2.4 Whole-body FDG-PET/CT within 60 days prior to registration;

3.1.3 Age ≥ 18 years;

3.1.4 Life expectancy ≥ 12 weeks

3.1.5 Zubrod Performance Status of 0-1 within 30 days prior to registration;

3.1.6 Adequate respiratory function within 180 days prior to registration defined as follows: FEV1 > 1.2 liters; DLCO ≥ 50% predicted;

3.1.7 Patients with post-obstructive pneumonia are eligible provided they no longer require intravenous antibiotics at registration;

3.1.8 Patients with a pleural effusion that is transudative, cytologically negative and non-bloody, are eligible if the radiation oncologist feels the tumor can be encompassed within a reasonable field of radiotherapy; if pleural fluid is too small a volume to effectively sample by thoracentesis and does not show increased metabolic activity on CT/PET imaging, the patient will be remain eligible.

3.1.9 Adequate organ and marrow function as defined below

3.1.9.1 Absolute neutrophil count >1.5 × 10^9/L

3.1.9.2 Platelet count >100 × 10^9/L

3.1.9.3 Baseline or post-transfusion Hemoglobin ≥9.0 g/dL

3.1.9.4 Serum bilirubin≤ 1.5x upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.

3.1.9.5 Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5x ULN.

3.1.9.6 Measured creatinine clearance (CL) >40 mL/min or calculated CL >40 mL/min as determined by Cockcroft-Gault (using actual body weight);

Males:
Creatinine CL = Weight (kg) × (140 - Age)
(mL/min) 72 × serum creatinine (mg/dL)

Females:
Creatinine CL = Weight (kg) × (140 - Age) × 0.85
(mL/min) 72 × serum creatinine (mg/dL)

3.1.10 Negative serum pregnancy test within three days prior to registration for women of childbearing potential.

3.1.11 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for *90* days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.12.1 A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.12.2 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).

3.1.12 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Definitive clinical or radiologic evidence of metastatic disease;
3.2.2 Subjects may not be receiving any other investigational agents for the treatment of the cancer under study.
3.2.3 Current invasive malignancy (except non-melanoma skin cancer, localized, non-muscle invasive bladder and prostate cancer not requiring ongoing active therapy). Carcinoma in situ of the breast, oral cavity, or cervix are permissible regardless of timing;
3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields. For example, patients with prior breast radiotherapy treatments would likely be excluded;
3.2.5 Prior systemic treatment with chemotherapy, targeted therapy or an anti-PD-1, anti-PD-L1 including durvalumab, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways for locally advanced NSCLC. Prior chemotherapy and/or targeted therapy as adjuvant or neoadjuvant therapy for earlier-stage lung cancer is permitted as long as it was completed ≥6 months prior to enrollment. No prior anti-PD-1, anti-PD-L1 including durvalumab, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways is permitted;
3.2.6 A condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 7 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease;
3.2.7 Severe, active co-morbidity defined as follows:
3.2.7.1 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
3.2.7.2 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:
- Patients with vitiligo or alopecia

- Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
- Any chronic skin condition that does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the study physician
- Patients with celiac disease controlled by diet alone

3.2.7.3 Active infection including tuberculosis, hepatitis B, hepatitis C.
3.2.7.4 History of allogenic organ transplantation.
3.2.7.5 History of symptomatic or previously established interstitial lung disease;
3.2.7.6 History of severe hypersensitivity reaction to any monoclonal antibody or allergy to study drug components;
3.2.7.7 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.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirements.

3.2.9 Pregnancy, nursing females, or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.10 Patients whose radiation treatment plans are likely to encompass a volume of whole lung receiving ≥ 35% of lung volume. V20s up to 37% will be permitted and viewed as a minor deviation, provided that the treating radiation oncologist believes this level of exposure is within patient tolerance.

3.2.11 Planned radiation cardiac dose V50 >25%.

4.0 TREATMENT PLAN

4.1 Treatment Dosage, Preparation and Administration

4.1.1 Durvalumab/MEDI 4736 is administered 1500mg every 4 weeks (28±3 days) [Q4W] intravenous during concurrent radiotherapy, 1500mg every 4 weeks (28±3 days) [Q4W] intravenous [iv] up to one year during consolidative phase. Durvalumab/MEDI 4736 will be started within ± 3 days of the start date of radiation therapy.

4.1.2 A dose of 1500 mg (for patients >30kg 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.

If patient weight falls to ≤ 30 kg, weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

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.

4.1.3 The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab (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

4.2 Toxicities and Dosing Delays

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (section 5.4) Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0. There are no durvalumab dose modifications. However, durvalumab doses may be delayed or omitted. Dosing decisions and toxicity management should be made according to the system showing the greatest degree of toxicity as indicated in the toxicities and management algorithms (Appendix I).

4.3 Concomitant Medications/Treatments

4.3.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Other permitted supportive/ancillary medications include but are not limited to the following:

- Anticonvulsants
- Antiemetics
- Anticoagulants
- Antidiarrheals
- Analgesics
- Hematopoietic Growth Factors
- Nutritional supplementation
- Highly active antiretroviral therapy (HAART)

4.3.2 Prohibited Therapies

The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in above)
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of NSCLC)

4.3.3 Participation in Other Trials

Patients may not participate in other clinical trials that are intended to treat the diagnosed lung cancer or intended to reduce toxicity of therapy.

4.4 Other Modalities or Procedures

4.4.1 Radiotherapy Treatment Technology

This protocol requires the use of photons delivered either using 3D-CRT or IMRT techniques. The use of IGRT is highly encouraged but not required. No margin reduction will be allowed whether IGRT is used or not, and separate IGRT credentialing will not be required.

4.4.2 Radiotherapy Immobilization and Simulation

Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices.

Simulation Imaging

Contiguous CT slices of maximum 3 mm slice thickness should be obtained starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume. I.V. contrast-enhanced CT- simulation is recommended but not required in this study.

CTs and PET/CTs should be used to guide tumor and normal organ volume definition. In the event that contrast-enhanced datasets are used for treatment planning, the density of the contrast should be overridden to a representative background electron density.

Motion Management Technique

Motion management is highly recommended for this protocol. In instances in which motion management is not possible, larger expansion volumes will be used to adequately cover the motion-related uncertainties. The types of motion management allowed on this study are 4DCT with ITV, active breath-hold, gated treatment, and abdominal compression. IMRT will be restricted to patients with less than 1cm of tumor motion on 4D imaging or utilizing of gating, ABC, or breath hold methods. Abdominal compression as a method of minimizing respiratory motion is allowed.

4.4.3 Imaging for Structure Definition, Image Registration/Fusion and Follow up

A whole-body FDG-PET/CT and an IV contrast enhanced CT scan or MRI exam (if CT scan with contrast is medically contraindicated, when MR of the chest is submitted, a non-contrast chest CT should also be submitted) of the lung and upper abdomen through the adrenal glands are required within 60 days prior to registration. These exams will be used for disease staging and to assist in volume delineation in all eligible patients.

4.4.4 Accounting for Tumor Motion Approaches and Internal and Setup Margins

Internal margin (IM): The IM used will be dictated by the motion management decision made at time of simulation. It is required for all cases, with the exception of instances in which simulation is done with 4DCT to develop a MIP of tumor volume (see number 4 below).

- If the simulation is done with a free-breathing CT only, the IM will be 1 cm in the

superior- inferior direction and 0.5 cm in the axial direction.

- If simulation is done with abdominal compression, the IM will be 0.7 cm in the superior-inferior direction and 0.5 cm in the axial direction.
- If simulation is done using an active breath-hold or gated breathing technique, the IM will be 0.5 cm in all directions.
- If simulation is done using a 4DCT to develop a maximum intensity projection of the tumor volume based on the entire tumor motion, no IM is needed.
- *Setup Margin (SM)*: The SM will be 0.5 cm in all directions. No margin reduction will be allowed, even when using IGRT. The final PTV is constructed by expanding the just ITV or sum of the CTV + IM by the SM based on the definitions from Table A or B in section 5.2.5.

4.4.5 Definition of Target Volumes and Margins

All structures must be labeled for digital RT data submission as listed in the table below. Capital letters, spacing and use of underscores must be applied exactly as indicated. Resubmission of data may be required if labeling of structures does not conform to the DICOM standard name listed.

The structures marked as “Required” in the table must be contoured and submitted with the treatment plan.

There are two tables below. The first table applies to patients being treated using method 1, 2, or 3 from section 5.2.4. The second table applies only to patients being treated with method 4 of section 5.2.4 (4DCT with maximum intensity projection of the tumor volume based on the entire tumor motion)

Contouring of the ITV_6000 is necessary only when the ITV approach is used.

TABLE 2: FREE BREATHING / ABDOMINAL COMPRESSION / ACTIVE BREATH HOLD / GATING MOTION MANAGEMENT TECHNIQUES

DICOM Standard Name	Description	Detailed Specification
GTV_6000	GTV to receive 60 Gy **Required for free breathing, active breath hold or gating motion management techniques**	The primary tumor and clinically positive lymph nodes seen on the planning CT (> 1cm short axis diameter) and pre-treatment PET scan (SUV > 3) will constitute the GTV. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged. An ITV is defined at this point as the enveloping GTV motion over the course of a respiratory cycle.
CTV_6000	CTV to receive 60 Gy **Required**	The CTV is defined to be the GTV plus a 0.5 cm margin to account for microscopic tumor extension. If an ITV is used, then a 0.5 cm margin is added to the ITV to form a CTV. The CTV should be adjusted to not expand into other organs such as esophagus, major blood vessels, or bone.
PTV_6000	PTV to receive 60 Gy **Required**	The PTV will be equal to the CTV+IM+SM. IM and SM are defined in Section 5.2.4 above. In cases in which the PTV expansion extends outside of the skin, towards the spinal cord or into the spinal canal, it can be assumed that tumor motion will not occur in this direction, and the PTV margin in this direction can be limited. PTV margin can be limited up to 0.5 cm towards this particular dimension (skin or spinal cord).

TABLE 3: 4D CT WITH MAXIMAL INTENSITY TUMOR VOLUME TECHNIQUE (PREFERRED METHOD)

DICOM Standard Name	Description	Detailed Specification
iGTV_6000	Defined as the enveloping GTV motion over the course of the entire respiratory cycle **Required** when a 4DCT is used to encapsulate entire breathing cycle volume	The primary tumor and clinically positive lymph nodes seen on the planning CT (> 1 cm short axis diameter) and pre-treatment PET scan (SUV > 3) over the course of a respiratory cycle. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged.

ITV_6000	ITV to receive 60 Gy **Required** when iGTV is drawn	The ITV will be equal to the iGTV plus a 0.5 cm clinical margin as appropriate to account for microscopic tumor extension.
PTV_6000	PTV to receive 60 Gy **Required**	The PTV will be equal to the ITV+SM. SM is defined in Section 5.2.4 above. In cases in which the PTV expansion extends outside of the skin, towards the spinal cord or into the spinal canal, it can be assumed that tumor motion will not occur in this direction, and the PTV margin in this direction can be limited. PTV margin can be limited up to 0.5 cm towards this particular dimension (skin or spinal cord).

4.4.6 Definition of Critical Structures and Margins

Note: All required structures must be labeled for digital RT data submission exactly as listed in the first column of the table below. Capital letters and spacing must be used exactly as indicated. Resubmission of data may be required if labeling of structures does not conform to the DICOM Standard Name listed.

DICOM Standard Name	**Description**	**Detailed Specification**	
Spine Canal	Spinal Canal **Required**	Boundaries: The bony limits of the spinal canal	
		Cranial	Top of C1 (or first CT slice)
		Caudal	Bottom of L2 (or last slice of CT)
Lungs	**Both Lungs minus GTV_6000 (or iGTV_6000)** **Required**	Boundaries: Use Lung OAR Atlas*	
		Other notes: Both lungs merged into 1 structure and excluding the overlap with GTV_6000/iGTV_6000	
Esophagus	**Required**	Boundaries: The esophagus contour should include the mucosa, submucosa, and all muscular layers out to the fatty adventitia. Cranial: Bottom of cricoid cartilage Caudal: GE junction	
Brachial Plexus	**Required for upper lobe tumors**	The ipsilateral brachial plexus should be contoured for upper lobe tumors	
Heart	**Required**	Cranial: Ascending Aorta Caudal: Apex	
External	**Required**	External contour of patient encompassing all internal organs on each slice	
Non PTV	**Required**	External (as described above) minus PTV	

*Investigators can access the Lung OAR Atlas at
http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx

4.4.7 Dose Prescription

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priorities in Section 5.2.9 should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here. Cases will be scored using the Compliance Criteria table.

Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Dose specification technique**
PTV_6000	60	2.0	30	Covering exactly 95% of PTV

4.4.8 Compliance Criteria

The compliance criteria listed below will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

Target Volume Constraints and Compliance Criteria

Name of Structure	**Dosimetric parameter**	**Per Protocol**	**Variation Acceptable**
PTV_6000	D95%(Gy)	60	58.8 to 61.2Gy (excluding 60 Gy)
	*Dmin(Gy)	≥ 57	≥54 Gy
	*Dmax(Gy)	≤ 72	≤75 Gy

* Dmin and Dmax values are for a volume of 0.03 cc.

Normal Structure Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable*
Spine Canal	D0.03cc(Gy) (max)	≤ 50	none
Lungs	V5Gy(%)	≤ 65	≤ 70
	V20Gy(%)	≤ 35	≤ 37
	Dmean(Gy)	≤ 20	≤ 22
Esophagus	V35Gy(%)	≤ 50	≤ 55
	V70Gy(%)	≤ 20	≤ 25
	Dmean(Gy)	≤ 34	≤ 37
Brachial Plexus	Dmax(Gy)	≤63	≤ 66
Heart	V30Gy(%)	≤ 50	≤ 55
	V45Gy(%)	≤ 35	≤ 40
	D0.03cc(Gy) (max)	≤ 70 Gy	≤ 75 Gy **

*The Variation Acceptable category extends the Per Protocol category numbers to allow for more challenging treatment planning problems. The Variation Acceptable range does not include the Per Protocol values. Plans will be scored as Deviation Unacceptable when Per Protocol and Variation Acceptable constraints are not met.

** When this value cannot be achieved, treatment plans must be modified to move dose distribution hotspots away from the heart to avoid having the case scored as a Deviation Unacceptable.

Delivery Compliance Criteria

	Per Protocol	Variation Acceptable
Start date (days after step 1 registration)	14 days	15-30 days
RT Elapsed Days	< 45 days	46-51 days
Interruptions (other than holidays or weekends)	0-2 days	3-7 days

Note: Cases will be scored as Deviation Unacceptable when the time limits given above are not met.

4.4.9 Treatment Planning Priorities and Instructions

Critical Structure and Target priorities are listed in order of decreasing importance:

Spine Canal
PTV
Lungs
Esophagus
Heart
Brachial Plexus

If lung dose constraints are exceeded, several solutions can be entertained:

- For 3D-CRT: Increase the weighting of AP/PA treatments by 1, and reduce the obliques. This can be done as long as the cord dose, which takes precedence, is not exceeded.
- For 3D-CRT or IMRT: Reduce the CTV to the minimum range suggested above and/or reduce the PTV by choosing another motion management option with smaller internal margins.

It is recommended that the esophagus not be circumferentially irradiated with > 60 Gy (i.e.

the 60 Gy isodose line should not encompass the entire axial cross-section of the esophagus at any level).

4.4.10 Dose Calculations

Primary dataset for dose calculation

The primary dataset for dose calculation must be a free-breathing CT that was acquired along with 4DCT, an average intensity pixel CT (AveIP) generated from the 4DCT, the breath- hold/gated CT, or the free-breathing CT acquired with no other motion management. Maximum Intensity Pixel (MIP) generated images from 4DCTs may not be used as the primary dose calculation dataset.

Dose matrix resolution

Dose grid size should be ≤ 3 mm in all directions.

4.4.11 Daily Treatment Localization/IGRT

Image-guided radiation therapy (IGRT) is radiation therapy using imaging to facilitate accuracy and precision throughout its entire process from target and normal tissue delineation, to radiation delivery, to adaptation of therapy to anatomic and biological changes over time in individual patients. In this section we use the terminology IGRT to focus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment.

A reliable method of daily image guidance will be utilized. This can include but is not limited to daily cone beam imaging, fiducial marker tracking systems, kV – kV matching. Daily cone beam imaging aligned to the tumor and soft-tissue anatomy is considered the preferred approach.

4.4.12 Radiation Therapy Adverse Events

Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy.

Cardiac Toxicity

Radiation-induced myocarditis rarely occurs at doses lower than 50 Gy.

Neurologic Toxicity

Radiation-induced transverse myelitis rarely occurs at doses lower than 50 Gy.

Esophagitis

Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous Xylocaine, Carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required.

It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. If Grade 4 (CTCAE, v. 5) esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to ≤ 3 treatment days. Patients requiring hospitalization because of esophagitis may have their treatment interrupted.

Pulmonary Toxicity

Pneumonitis is possible in the later weeks of chemoradiotherapy and during the weeks that follow. In general, pneumonitis is a diagnosis of exclusion and is treated with a combination of corticosteroids and supportive care at the discretion of the treating physician.

Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving ≥ 20 Gy, usually within the first 6 months after initiation of treatment. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

4.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for one year or until

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

4.6 Duration of Follow Up

Subjects will be followed every 3 months until 2 years post concurrent durvalumab/RT then every 6mos during year 3-5, then yearly or until death, whichever occurs first.

Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed for overall survival until death, withdrawal of consent, or the end of the study (whichever occurs first). Subjects removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.7 Removal of Patients from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for treatment discontinuation and the date of discontinuation. The subject should be followed-up per protocol.

4.8 Subject Replacement

Subjects missing 7 or more doses due to toxicity will not be replaced since these subjects will be considered to have experienced a dose limiting toxicity.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 90 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 *Informed Consent*

5.1.2 *Medical history*

Complete medical and surgical history, history of infections

5.1.3 *Demographics*

Age, gender, race, ethnicity

5.1.4 *Review subject eligibility criteria*

5.1.5 *Review previous and concomitant medications*

5.1.6 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 *Performance status*

Performance status evaluated prior to study entry according to Appendix II.

5.1.8 *Adverse event assessment*

Baseline adverse events will be assessed. See section 7 for Adverse Event monitoring and reporting.

5.1.9 *Hematology*

5.1.10 *Blood draw for correlative studies*

See Section 9.0 for details.

5.1.11 *Serum chemistries*

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, amylase, lipase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

5.1.12 *Pregnancy test (for females of child bearing potential)*

See section 3.1.12 for definition.

5.1.13 *Tumor assessment*

5.2 Procedures During Treatment

5.2.1 Concurrent phase

- Physical exam including vital signs
- Performance status
- Adverse event assessment
- Serum chemistries (amylase and lipase do not need to be resulted prior to treatment administration in the absence of clinical symptoms)
- Adrenal function test and thyroid function test
- Optional blood collection

5.2.2 Consolidative phase

- Physical exam including vital signs
- Performance status
- Adverse event assessment
- Serum chemistries (amylase and lipase do not need to be resulted prior to treatment administration in the absence of clinical symptoms)
- Adrenal function tests and thyroid function tests
- Chest CT include adrenals
- Pulmonary function testing (PFT/DLCO)
- Optional blood collection

5.3 Follow-up Procedures

- Follow up visit every 3 months for 2 years; every 6 months for years 3-5; then yearly Procedure
- Physical exam including vital signs
- Performance status
- Adverse event assessment
- Complete blood count and serum chemistries
- Adrenal function tests and thyroid function tests
- Chest CT include adrenals

5.4 Time and Events Table

PRE-TREATMENT ASSESSMENTS

Assessments	Prior to Registration (calendar days)	Prior to Treatment (calendar days)
History and physical exam	30	
Zubrod performance status	30	
Tumor measurements	30	
Rad Onc exam	30	
Med Onc exam	30	
CBC	30	
CMP	30	
Thyroid function test	30	
AM cortisol, ACTH	30	
Urinalysis	30	
Serum pregnancy test if applicable	3	
Baseline Chest X-Ray	30	
Baseline EKG	30	
Cytology/Pathology Report confirming NSCLC	90	
Whole body FDG-PET/CT (base of skull to mid-thigh)	60	
CT chest with contrast and include adrenals*	60	
MRI of brain (CT if MRI contraindicated)	60	
Pulmonary function testing (PFTs/DLCO)	90	
Informed consent	Within 30 days including Day of registration	
Specimen collection for banking		If patient consents: See Section 9.

* Patients do not need to have a separate CT of chest and upper abdomen with contrast if FDG-PET/CT imaging includes a high quality CT chest with contrast

ASSESSMENTS DURING CONCURRENT TREATMENT

Assessments	Weekly (+/- 3 days)	At week 1 and 5 only (+/- 7 days)
Performance status	X	
CMP	X[1]	
Thyroid function test		X
Adrenal function test		X
Rad Onc Evaluation	X	
Med Onc evaluation		X[2]
Adverse event evaluation	X	
Specimen collection for banking		X[3]

[1] Biweekly
[2] Testing does not need to be repeated if performed within 7 days of starting protocol therapy.
[3]Day 1 and Day 42

ASSESSMENTS DURING CONSOLIDATIVE DURVALUMAB TREATMENT

Assessments	Every month at infusion	Every 3 months
Physical examination including vital signs (blood pressure, weight)	X	
Zubrod performance status	X	
CMP	X	
Thyroid function (TSH, T3 and T4);		Every 2 months
AM cortisol, ACTH		Every 2 months
Serum or urine Pregnancy test	X[1]	
AE evaluation	X	
CT of chest with contrast and include adrenals		X[2]
Pulmonary function testing (PFTs/DLCO)		X[3]
Blood collection for banking		X[4]

[1] Every 6 weeks
[2]After completion of concurrent durvalumab/radiotherapy, radiographic assessment with CT chest with contrast including adrenals will occur within 2 weeks. Further radiographic assessment will occur every 3 months for 2 years. After 2 years, radiographic disease assessment should be performed every 6 months during year 3-5 then annually thereafter. FDG-PET/CT should be done to confirm clinically uncertain progression or treatment related effects at the discretion of the treating investigator. This imaging may be done locally.
[3]At 6 months only.
[4]At 12 weeks and end of the study.

ASSESSMENTS IN FOLLOW UP

Assessments	Every 3 mos until 2 years post concurrent durvalumab/RT then every 6mos during year 3-5, then yearly
History and physical exam	X
Zubrod performance status	X
Tumor Measurement	X
Med Onc exam	X
AE Evaluation	X
CBC, BMP	X
CT Chest with contrast and include adrenals	X[1]

[1]After completion of concurrent durvalumab/radiotherapy, radiographic assessment with CT chest with contrast including adrenals will occur within 2 weeks. Further radiographic assessment will occur every 3 months for 2 years. After 2 years, radiographic disease assessment should be performed every 6 months during year 3-5 then annually thereafter. FDG-PET/CT should be done to confirm clinically uncertain progression or treatment related effects at the discretion of the treating investigator. This imaging may be done locally.

5.5 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Subject withdraws consent (termination of treatment and follow-up);

5.5.3 Subject is unable to comply with protocol requirements;

5.5.4 Subject demonstrates disease progression (unless continued treatment with study drug/treatment is deemed appropriate at the discretion of the investigator);

5.5.5 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician judges continuation on the study would not be in the subject's best interest;

5.5.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.5.9 Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

5.6 Study Restrictions

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

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.

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

Blood donation

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

6.0 Measurement of Effect

Antitumor Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) Committee [Eur J Cancer. 2009;45(2):228-247]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study therapy.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

6.1.2 Disease Parameters

Measurable Disease: Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease.
All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target lesions.
All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the five target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 60 days before the beginning of the treatment.

Conventional CT should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes). Determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): > 20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started (nadir) and minimum 5 mm increase over the nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. There can be no unequivocal new lesions.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Incomplete Response/Stable Disease (Non-CR/Non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

6.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the

treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Time point response: patients with target (+/– non-target) disease.			
Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease, PR = partial response, SD = stable disease.

Time point response: patients with non-target disease only.		
Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease

A 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

6.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

6.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from study enrollment to time of progression.

6.2 Safety/tolerability

Analyses will be performed for all subjects having received at least one dose of study therapy. The study will use the CTCAE version 5.0 for reporting of adverse events. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

For the most recent safety update (in drug studies), please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

7.1.1 Contraindications

There are no contraindications for IMFINZI® (durvalumab).

7.1.2 Special Warnings and Precautions for Use

IMFINZI can cause serious, potentially fatal adverse reactions including immune-mediated pneumonitis, hepatitis, colitis or diarrhea, endocrinopathies, nephritis, rash or dermatitis, other immune-mediated adverse reactions, infection, and infusion-related reactions.

7.1.3 Adverse Reactions

In patients with Stage III NSCLC in the PACIFIC study (IMFINZI n=475), the most common adverse reactions (≥20% of patients) were cough (40%), fatigue (34%), pneumonitis or radiation pneumonitis (34%), upper respiratory tract infections (26%), dyspnea (25%), and rash (23%). The most common Grade 3 or 4 adverse reaction (≥3%) was pneumonia (7%).

In patients with Stage III NSCLC in the PACIFIC study (IMFINZI n=475), discontinuation due to adverse reactions occurred in 15% of patients in the IMFINZI arm. Serious adverse reactions occurred in 29% of patients receiving IMFINZI. The most frequent serious adverse reactions (≥2% of patients) were pneumonitis or radiation pneumonitis (7%) and pneumonia (6%). Fatal pneumonitis or radiation pneumonitis and fatal pneumonia occurred in <2% of patients and were similar across arms.

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes

observed; or
- death.

7.2.1 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Adverse event of special interest

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)
- 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.

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 I). 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.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through 90 days post treatment will be considered acute adverse events.

Late Adverse Events (*as applicable*)

Adverse events occurring in the time period from the end of acute monitoring, to 5 years post treatment, will be defined as late adverse events. Immune-mediated adverse events such as adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, nephritis and renal dysfunction will be monitored by medical oncology and other specialists during follow up visit whereas radiation side effects will be monitored by radiation oncology.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring >24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

7.2.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.3 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC and/or HRPP

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy.
Attribution categories are as follows:

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

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

7.3.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW Radiation Oncology research office is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator and AstraZeneca. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required.

Written reports to:

Department of Radiation Oncology
Clinical Research Office
The University of Texas Southwestern Medical Center
FAX #: 214-645-8913

UTSW SCCC Data Safety Monitoring Committee Coordinator
Email: SCCDSMC@utsouthwestern.edu
Fax: 214-648-5949 or deliver to BLB.306

UTSW Institutional Review Board (IRB)
Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of PI awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

7.3.2 Reporting SAEs and UPIRSOs to AstraZeneca

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 and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The investigator and/or sponsor must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch/AdEERs report must be emailed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile

all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

* A cover page should accompany the MedWatch/AdEERs form indicating the following:
- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-##-#####)

* Sponsor must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.
* Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox: **AEMailboxClinicalTrialTCS@astrazeneca.com**
If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.
Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly. In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

Reporting of deaths to AstraZeneca
All deaths that occur during the study, or within the protocol defined 90 day post last dose of durvalumab safety follow up period must be reported to AstraZeneca as follows:
- Death that is clearly the result of disease progression should be documented but 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 AstraZeneca as a SAE within 24 hours. The report should contain a comment regarding the co involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE.

Deaths that occur following the protocol-defined 90-day post-last-dose of durvalumab safety follow-up period will be documented <<as events for survival analysis>>, but will not be reported as an SAE. 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 Drug Safety.

Medication errors
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

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 and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox within 7 calendar days or sooner when required. If the overdose results in an AE,

the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab. The investigator will use clinical judgment to treat any overdose.

Other events requiring reporting
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 and AstraZeneca Patient Safety using the designated Safety e-mailbox (see Section 10.3.2 for contact information), 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.

Pregnancy
Maternal exposure
If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.
Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.
If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, i.e., immediately, but no later than 24 hours of when he or she becomes aware of it.
The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.
The same timelines apply when outcome information is available.

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.

8.0 DRUG/TREATMENT INFORMATION

8.1 Durvalumab

- Other names for the drug(s): MEDI 4736, IMFINZI
- Classification - type of agent: Immunotherapy
- Mode of action: PD-L1 blockage
- Protocol dose: Durvalumab/MEDI 4736 is administered 1500mg every 4 weeks (28±3 days) [Q4W] intravenous during concurrent radiotherapy, 1500mg every 4 weeks [Q4W] (28±3 days) intravenous [iv] up to one year during consolidative phase. Durvalumab/MEDI 4736 will be started within ± 3 days of the start date of radiation therapy.
- Formulation/packaging/storage: Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 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.
- 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 1500mg (for patients >30kg 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 (ie, 1500mg of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.
- If weight falls to ≤ 30 kg, weight-based dosing at 20 mg/kg will be a 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 15mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.
- Standard infusion time 1 hour. In the event that 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.

- Side effects: Durvalumab can cause serious, potentially fatal adverse reactions including immune-mediated pneumonitis, hepatitis, colitis or diarrhea, endocrinopathies, nephritis, rash or dermatitis, other immune-mediated adverse reactions, infection, and infusion-related reactions. Refer the reader to the agent's package insert for a comprehensive list of adverse events.
- Monitoring of dose administration: Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Study Protocol.
- 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 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. 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

8.1.1 Return and Retention of Study Drug

Remaining drug will be destroyed according to institutional pharmacy instructions.

9.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to understand the effect of tumor PD-L1 expression on treatment response to anti-PD-L1 targeted immunotherapy

9.1 Sample Collection Guidelines

In this study, it is recommended that tissue be submitted to pathology department at UT Southwestern for PD-L1 expression analysis for all patients. It is highly recommended (but optional for the patient) that if any tissue remains after analysis, it will be stored at the Tissue Bank at UT Southwestern for future research. In addition, it is highly recommended (but optional for the patient) that fresh-frozen tumor biopsy, serum and peripheral blood specimens be submitted for the additional tests,

Optional Samples will be collected at the following time points (+/- 7 days):

- Tissue submission to pathology department at UT Southwestern for PD-L1 expression analysis for all patients (within 28 days) prior to study treatment.
- Collection of 8cc plasma at study enrollment, at week 6, week 12 and end of the study.

9.2 Assay Methodology

PDL-1 testing will utilize the Ventana SP263 assay and should be performed in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT). The remaining tumor samples may be used to analyze the expression and spatial distribution of immune-related or response-related markers by multiplex immunohistochemistry, which may

include but are not limited to PD-L1, CTLA-4, CD3, CD4, CD8, CD45RO, FOXP3, granzyme B, OX40, PD1, cleaved caspase 3, and Ki67. Archived material (or biopsies if available) may also be analyzed for the presence of key genomic features such as *EGFR, KRAS,* and *ALK* alterations to evaluate their potential relevance and correlations with response to durvalumab. Blood samples will be analyzed to evaluate protein, nucleic acid, and cellular biomarkers that relate to durvalumab. PBMC will also be isolated from whole blood and will be preserved, and may be used for subsequent flow cytometry or assessment of the diversity of the immune cell repertoire based on VDJ coding region analysis, the relationship to clinical responses, and changes in response to treatment with durvalumab. Blood collected for analysis of immune cell gene expression profiles within the peripheral compartments will be evaluated for any relationship with efficacy endpoints. Serum samples may also be analyzed for analysis of circulating soluble factors in relation to immune status at baseline and in response to treatment. Factors to be analyzed may include but are not limited to IFN-γ, tumor necrosis factor-α, interleukin (IL)-2, IL-6, IL-10, IL-8, IL-12, and levels of soluble PD-L1.

9.3 Specimen Banking

If any tissue remains after analysis, it will be stored at the Tissue Bank at UT Southwestern for future research. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of UT Southwestern for publication and any licensing agreement will be strictly adhered to.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UT Southwestern, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

10.1.1 Study design: The study is a single armed, phase II trial to evaluate concurrent Durvalumab and radiotherapy followed by consolidative Durvalumab for Stage III Non-Small Cell Lung Cancer (NSCLC).

10.1.2 Primary endpoint of 12-month progression-free survival (PFS) rate is based on an assessment by an investigators according to RECIST 1.1 criteria; PFS is defined as the time from the study enrollment to documented progressive disease or death due to any cause, whichever occurs first;

10.1.3 Secondary endpoint of safety and tolerability will be assessed by adverse event according to CTCAE V.5;

10.1.4 Secondary endpoint of overall survival is defined as the time from study enrollment to death due to any cause;

10.1.5 Secondary endpoint of distant metastases free survival is defined as the time from the study enrollment to any new distant lesion;

10.1.6 Secondary endpoint of local and regional control defined as the time from the study enrollment to any local and regional lesion;
10.1.7 Exploratory endpoint of biomarker and biomarker correlatives;
10.1.8 Exploratory endpoint of proportion of patients alive at 12 and 24 months.

10.2 Accrual

In the PACIFIC trial, patients who received consolidative durvalumab after chemoradiation had a 12-month PFS rate of 55%. PFS was measured starting after completion of chemoradiation, when anti-PDL1 treatment was started. This represents the assumed performance of the experimental arm in this study. We recognize that all patients who were randomized in the PACIFIC trial had tolerated and not progressed on chemoradiation, which represents some degree of selection bias. The possibility of early progression or treatment intolerance were taken into account when selecting the margins for the non-inferiority design of this study. A sample size of 47 achieves 80% power to detect a non-inferiority against an upper hazard ratio of 1.4 using a log-rank test at a 0.1 significance level when the actual hazard ratio is 1.0 and the standard of care group hazard rate is 0.5978 (which is equal to 1-year PFS rate of 55% using an exponential model). Three additional patients will be enrolled (total N=50) to account for 5% loss to follow-up. Patients will be accrued for a period of 3 years with 1-year follow-up.

10.3 Data Analyses

10.3.1 Survival outcome

Progression-free survival and overall survival will be estimated using the Kaplan-Meier approach and the corresponding confidence intervals will be estimated using Greenwood's formula. Distant metastases-free survival, local and regional control will be estimated using the Kaplan-Meier approach.

10.3.2 Toxicities:

Only adverse events assessed to be definitely, probably, or possibly related to protocol treatment will be considered. Toxicity rate and it confidence interval will be estimated using an exact binomial approach.

10.3.3 Exploratory Endpoints:

Exploratory data analysis will be conducted for the exploratory endpoints. Generalized estimating equation (GEE) approach will be used to investigate if there are significant changes in biomarkers over time. Proportion of patients alive at 12 and 24 months will be estimated using the Kaplan-Meier method.

10.3.4 Interim Reports to Monitor the Study Progress

Interim reports with descriptive statistics will be prepared twice a year until the initial manuscript reporting the treatment results has been accepted for publication. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; data quality; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of adverse events.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy

on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.3 Registration Procedures

All subjects must be registered with the Radiation Oncology Research Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Radiation Oncology Study Coordinator. To register a subject, call 214-546-1477 Monday through Friday, 9:00AM-5:00PM.

New subjects will receive a number beginning with 001 upon study consent such that the first subject consented is numbered 001, the second subject consented receives the number 002, etc.

Upon confirmation of eligibility and enrollment as per the afore-mentioned instructions, the subject will be assigned a secondary number in the order of enrollment. For example, subject 001 will become 001-01 upon enrollment. If subject 002 screen fails, and subject 003 is the next subject enrolled, subject 003 will become 003-02 and so-on.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

11.4 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project

The Medical Oncologist investigators and delegates, will perform an Immunotherapy Assurance Review of all patients in this trial. The Radiation Oncologist investigators and delegates, will perform an RT Quality Assurance Review after the first 20 cases enrolled. Subsequent reviews will continue in a periodic and timely fashion. The final cases will be reviewed within 3 months after this study has reached the target accrual. The goal of the review is to evaluate protocol compliance. The scoring mechanism is: Per Protocol, Variation Acceptable, and Deviation Unacceptable.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

11.5 Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.5.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

 Reporting requirement: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

11.5.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

 Reporting requirement: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

11.5.3 Major Deviations (also called **violations**): include any departure from IRB-approved research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

  Reporting requirement: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

11.5.4 Minor Deviations: include any departure from IRB-approved research that:

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

  Reporting requirement: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment

of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 APPENDICES

APPENDIX I. Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-immune-mediated reaction.

Toxicity Management Guidelines (TMGs)	
Drug Substance	Durvalumab and Tremelimumab
TMG Version	21 September 2023

ANNEX TO PROTOCOL

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

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

Version History

September 2023

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

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

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

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy –September 2023

General Considerations Regarding Immune-Mediated Reactions

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

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

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

Based on the severity of the imAE, durvalumab and/or tremelimumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider the need for glucose monitoring.

Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

Considerations for Prophylaxis for Long Term use of Steroids for Patients Receiving Immune Checkpoint Inhibitor Immunotherapy

- **Infection Prophylaxis: Pneumocystis jirovecii pneumonia (PJP), antifungal and Herpes Zoster reactivation**
- **Gastritis: Consider prophylaxis for patients at high risk of gastritis (e.g. NSAID use, anticoagulation) when the patient is taking steroid therapy**
- **Osteoporosis: Consider measures for prevention and mitigation of osteoporosis .**

Relevant Society Guidelines for Management of imAEs

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

1. Brahmer JR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021;9:e002435
2. Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology (ASCO) Guideline Update. J Clin Oncol 2022;39(36):4073-4126.
3. Haanen J, et al. Management of toxicities from immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guideline for diagnosis, treatment, and follow-up. Annals Oncol 2022;33(12):1217-1238.
4. Sangro B, et al. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol 2020;72(2):320-341.
5. Thompson JA, et al. National Comprehensive Cancer Network Guidelines: Management of immunotherapy-related toxicities version 2.2023. Published February 28, 2022.

Pediatric Considerations Regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTCAE grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid $\leq$ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks of** initiating corticosteroids.	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for steroid dosing (i.e., mg/kg/day) provided for adult patients should also be used for pediatric patients. – The recommendations for intravenous immunoglobulin (IVIG) and plasmapheresis use provided for adult patients may be considered for pediatric patients. – The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For subsequent dosing and dosing in children < 6 years old, consult a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology with similar clinical presentation (e.g. infection, progressive disease). – Monitor patients for signs (e.g. tachypnoea) and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related etiologies excluded, and managed as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up (including clinically relevant culture specimens to rule out infection), and high- resolution computed tomography (CT) scan. – Consider Pulmonary and Infectious Diseases consults.
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up, and then as clinically indicated.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1.	**For Grade 2** – Monitor symptoms daily and

		If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper (≤10 mg prednisone or equivalent).	consider hospitalization, as clinically indicated. – Consider Pulmonary and Infectious Diseases Consults; – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). Consider HRCT or chest CT with contrast, Repeat imaging study as clinically indicated – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy. such as tumor necrosis factor (TNF) inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider discussing with Clinical Study Lead.

	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Hospitalize the patient – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed. – Consider starting anti-infective therapy if infection is still a consideration on the basis of other diagnostic testing despite negative culture results – Supportive care (e.g., oxygen). – If no improvement within 2 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for *Clostridium difficile* toxin, etc. – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Consider further evaluation with imaging study with contrast. – Consult a gastrointestinal (GI) specialist for consideration of further workup. – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist, consider checking lactoferrin and/or calprotectin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 – If toxicity improves to Grade ≤1, then study drug/study regimen can be	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes

		resumed after completion of steroid taper (<10 mg prednisone, or equivalent).	(e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Consider further evaluation with imaging study with contrast. – Consider consult of a gastrointestinal (GI) specialist for consideration of further workup. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 days despite therapy with 1 to 2 mg/kg IV methylprednisolone, reconsult GI specialist and, if indicated, promptly start additional immunosuppressant agent such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines. **Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.** – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.** – Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤1 in 3 to 4 days.
	Grade 3 or 4	**Grade 3** – For patients treated with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper (≤10 mg prednisone per day, or equivalent). – For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study	**For Grade 3 or 4** – Urgent GI consult and imaging and/or colonoscopy as appropriate. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – If still no improvement within 2 days, continue steroids and promptly add further immunosuppressants. (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.

		investigator, in discussion with AstraZeneca Clinical Study Lead. **For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy:** **A. Permanently discontinue tremelimumab for Grade 3 diarrhea/colitis. HOLD durvalumab until resolution to Grade ≤ 1; durvalumab alone can be resumed after completion of steroid taper (<10 mg prednisone per day or equivalent)** **B. Permanently discontinue both durvalumab and tremelimumab for 1) Grade 4 diarrhea/colitis or 2) Any grade of intestinal perforation** **Grade 4** Permanently discontinue study drug/study regimen.	– **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**
Hepatitis ***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 hepatocellular carcinoma**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications). – Monitor and evaluate transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]) and total bilirubin .
	ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN	– No dose modifications. – If it worsens, then consider holding therapy.	– Continue transaminase and total bilirubin monitoring per protocol.
secondary tumour involvement of the liver with abnormal baseline values [BLV])	ALT or AST > 3 ≤ 5 x ULN or total bilirubin > 1.5 ≤ 3 x ULN	– Hold study drug/study regimen dose until ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN. Resume study drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent). – Permanently discontinue study drug/study regimen for any case meeting Hy's law laboratory criteria (AST or ALT >3 × ULN AND	– Regular and frequent checking of transaminases and total bilirubin (e.g., every 1 to 2 days) until transaminases and total bilirubin elevations improve or resolve. - Consider checking creatinine phosphokinase (CPK) and aldolase (to rule out myositis) – If no resolution to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN in 1 to 2 days, consider discussing with Clinical Study Lead, as needed.

		bilirubin ≥2 × ULN without initial findings of cholestasis (i.e., elevated ALP) and in the absence of any alternative cause.	– If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	ALT or AST > 5- ≤ 10 x ULN	– Hold study drug/study regimen. Resume study drug/study regimen if elevations downgrade to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN after completion of steroid taper (<10 mg prednisone, or equivalent). – **If in combination with tremelimumab, do not restart tremelimumab.**	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. - Check CPK and aldolase (to rule out myositis) – Perform Hepatology Consult, abdominal workup, and imaging as appropriate. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.**
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN OR total bilirubin > 3 x ULN	Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.** – Perform Hepatology Consult, abdominal workup, and imaging as appropriate.
Hepatitis **(elevated transaminases and total bilirubin)** ***Infliximab should not be used for management of immune-related hepatitis.***	**Any Elevations of AST, ALT, or T. Bili as Described Below**	**General Guidance**	**For Any Elevations Described** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – Monitor and evaluate AST, ALT, ALP, and T. Bili. – For hepatitis B (HBV) + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg).

THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])			– For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with Hepatitis B core antibody (HBcAb)+: Evaluate for both HBV and HCV as above.
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 >ULN and ≤2.5×BLV,	– 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**	
	ALT or AST > 2.5-≤ 5X BLV and ≤ 20xULN	– Hold study drug/study regimen dose until resolution to AST or ALT ≤2.5×BLV . – If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤2.5×BLV , resume study drug/study regimen after completion	– Regular and frequent checking of Transaminases and total bilirubin (e.g., every 1 to 3 days) until elevations of these are improving or resolved. - Consider checking creatinine phosphokinase (CPK) and aldolase (to rule out myositis) – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead.

	of steroid taper (<10 mg prednisone, or equivalent).	– If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting additional immunosuppressants. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
ALT or AST >5-7X BLV and ≤ 20X ULN OR concurrent 2.5-5X BLV and ≤ 20XULN AND total bilirubin > 1.5 - < 2 x ULN	- Withhold durvalumab and permanently discontinue tremelimumab – Resume study drug/study regimen if elevations downgrade to AST or ALT ≤2.5×BLV and after completion of steroid taper (<10 mg prednisone, or equivalent). – Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤2.5×BLV within 14 days	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. - Check CPK and aldolase (to rule out myositis) – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with Clinical Study Lead, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an additional immunosuppressant. (e.g.,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines). Discuss with Study Clinical Lead if mycophenolate is not available. **Infliximab should NOT be used.**

	ALT or AST > 7 X BLV OR > 20 ULN whichever occurs first OR bilirubin > 3ULN	Permanently discontinue study drug/study regimen.	**Same as above (except recommend obtaining liver biopsy early)**
Nephritis and/or renal dysfunction	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consider Consulting a nephrologist. – Consider imaging studies to rule out any alternative etiology – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decreased urine output, or proteinuria). Follow urine protein/creatinine ratio every 3-7 days
	Grade 1	No dose modifications.	**For Grade 1** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider hydration, electrolyte replacement, and diuretics, as clinically indicated. – Consider nephrologist consult if not resolved within 14 days, or earlier as clinically indicated
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion	**For Grade 2** – Consider including hydration, electrolyte replacement, and diuretics as clinically indicated – Follow urine protein/creatinine ratio every 3-7 days – Carefully monitor serum creatinine as clinically warranted.
		of steroid taper (<10 mg prednisone, or equivalent).	– Consult nephrologist and consider renal biopsy if clinically indicated. – Start prednisone 0.5 – 1 mg/kg/day if other causes are ruled out – If event is persistent beyond 5 days or worsens, increase to prednisone up to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup. When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Carefully monitor serum creatinine daily. – Follow urine protein/creatinine ratio every 3-7 days – 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 of steroids or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant
Dermatologic Adverse Events (Including Pemphigoid)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Monitor for signs and symptoms of dermatitis (rash and pruritus). **HOLD STUDY DRUG IF GRADE 3 PEMPHIGOID OR SEVERE CUTANEOUS ADVERSE REACTION (SCAR)[1] IS SUSPECTED.**

			– **PERMANENTLY DISCONTINUE STUDY DRUG IF SCAR OR GRADE 3 PEMPIGOID IS CONFIRMED.**
	Grade 1	No dose modifications.	**For Grade 1** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2** – Consider dermatology consult and skin biopsy, as indicated. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 1 week or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	Grade 3	**For Grade 3** – Hold study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. – Consider, as necessary, discussing with Clinical Study Lead.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 4** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.

			– Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. Consider, as necessary, discussing with Clinical Study Lead.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Consider consulting an endocrinologist for endocrine events. – Consider discussing with Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of endocrinopathies. (Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c)). If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide

			assessment of early morning adrenocorticotropin hormone (ACTH), cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2, 3, or 4	– For Grade 2-4 endocrinopathies <u>other than hypothyroidism and type 1 diabetes mellitus (T1DM)</u>, consider holding study drug/study regimen dose until acute symptoms resolve. – Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent). – Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or T1DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement. – **Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.** – **Isolated T1DM may be treated with appropriate diabetic therapy, and without corticosteroids. <u>Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis.</u>** – For patients with normal endocrine workup (laboratory assessment or magnetic resonance imaging (MRI) scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, viral infection, concomitant medications, substance abuse). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4** In consultation with relevant gastroenterology specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Consider Gastroenterology referral
	Grade 2	**Consider holding study drug/regimen**	**Grade 2** – Consider IV hydration – Consider Gastroenterology referral

	Grade 3, or 4	**For Grade 3** Hold study drug/study regimen until resolution of elevated enzymes and no radiologic findings If no elevation in enzymes or return to baseline values, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Nervous System Disorders			
Aseptic Meningitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include headache, photophobia, and neck stiffness, nausea/ vomiting which may resemble an infectious meningitis. – Patients may be febrile. – Mental status should be normal	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) - Consider antibiotic for bacterial coverage until cultures/panel results are back – Consider IV acyclovir until polymerase chain reactions are available
	Any Grade	Permanently discontinue study drug/study regimen	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) – Consider IV acyclovir until polymerase chain reactions are available – Consider, as necessary, discussing with Clinical Study Lead. – Consider hospitalization.

			– Once infection has been ruled out promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.
Encephalitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include Confusion, altered behaviour, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality. –	**For Any Grade** – Consider neurology consult – Consider testing including MRI of the brain with and without contrast, lumbar puncture, electroencephalogram (EEG) to evaluate for subclinical seizures, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin and additional autoantibodies to rule out paraneoplastic disorders. – Exclude bacterial and viral infections. (i.e. HSV)Consider IV acyclovir until polymerase chain reactions are available.
	Grade 2	**For Grade 2** Permanently discontinue study drug/study regimen.	**For Grade 2** – Consider, as necessary, discussing with the Clinical Study Lead. – Once infection has been ruled out methylprednisolone 1–2 mg/kg/day – For progressive symptoms or if oligoclonal bands are present consider methylprednisolone 1 g IV daily for 3–5 days plus IVIG or plasmapheresis
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider, as necessary, discussing with Clinical Study Lead. – Consider hospitalization. – Once infection is ruled out, start methylprednisolone 1 g IV daily for 3–5 days for progressive symptoms consider adding IVIG or plasmapheresis
Demyelinating Disease (optic neuritis, transverse myelitis, acute demyelinating encephalomyelitis (ADEM))	**Any Grade**	**General Guidance** – Permanently discontinue immunotherapy – Consider MRI of the spine and brain	**For Any Grade** – Consider neurology consult – Inpatient care – Consider prompt initiation of high methylprednisolone pulse dosing – Strongly consider IVIG or plasmapheresis

		– Once imaging is complete, consider lumbar puncture Consider testing to rule out additional aetiologies: B12, copper, HIV, rapid plasma reagin (RPR), ANA, anti-Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, paraneoplastic panel	
Peripheral neuropathy	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be evaluated to rule out any alternative etiology for neuropathy (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.
	Grade 1	No dose modifications.	**For Grade 1** – Consider discussing with the Clinical Study Lead, as needed. – Monitor symptoms for interference with ADLS, gait difficulties, imbalance, or autonomic dysfunction
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2** – Consult a neurologist. – Consider EMG/NCS

			– Consider discussing with the Clinical Study Lead, as needed. – Observation for additional symptoms or consider initiating prednisone 0.5–1 mg/kg orally – If progression, initiate methylprednisolone 2–4 mg/kg/day and treat as GBS – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider discussing with Clinical Study Lead, as needed. – Recommend hospitalization. – Monitor symptoms and consult a neurologist. – **Treat per Guillain-Barré Syndrome recommendations**
Guillain-Barré Syndrome (GBS)		General Guidance	– Recommend hospitalization – Obtain neurology consult – Obtain MRI of spine to rule out compression lesion – Obtain lumbar puncture – Antibody tests for GBS variants – Pulmonary function tests – Obtain electromyography (EMG) and nerve conduction studies – Frequently monitor pulmonary function tests and neurologic evaluations – Monitor for concurrent autonomic dysfunction – Initiate medication as needed for neuropathic pain
	Grade 2-4	Grade 2-4 Permanently discontinue	**Start IVIG or plasmapheresis in addition to methylprednisolone 1 gram daily for 5 days, then taper over 4 weeks.**
Myasthenia gravis		General Guidance	– Obtain neurology consult – Recommend hospitalization – Obtain pulmonary function tests

			– Obtain labs: ESR, CRP, creatine phosphokinase (CPK), aldolase and anti-striational antibodies – Consider cardiac exam, ECG, troponin, transthoracic echocardiogram for possible concomitant myocarditis – Obtain electromyography (EMG) and nerve conduction studies – Consider MRI of brain/spine to rule out CNS involvement by disease – Avoid medications that might exacerbate MG (e.g. beta blockers, some antibiotics, IV magnesium)
	Grade 2	Permanently discontinue	– Consider pyridostigmine 30mg three times daily and gradually increase based on symptoms (max dose 120mg four times daily) – Consider starting low dose prednisone 20mg daily and increase every 3-5 days. (Target dose 1mg/kg/day. Max dose 100mg daily)
	Grade 3-4	Permanently discontinue	– Start methylprednisolone 1-2mg/kg/day. Taper steroids based on symptom improvement – Start plasmapheresis or IVIG – Consider rituximab if refractory to plasmapheresis or IVIG – Frequent PFT assessments – Daily neurologic evaluations
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade** – Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (ECG), echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with

			baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
	Grade 2, 3 or 4	– If Grade 2-4, permanently discontinue study drug/study regimen.	**For Grade 2-4** – Monitor symptoms daily, hospitalize. – Consider cardiology consultation and a prompt start of high-dose/pulse corticosteroid therapy – Supportive care (e.g., oxygen). – If no improvement consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis or other therapies depending on the clinical condition of the patient, based on the discretion of the treating specialist consultant r or relevant practice guidelines. **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**
Myositis/ Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).

	defining the CTCAE grade/severity)		– 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, and; 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 Clinical Study Lead. - **Consider that patients may present with or progress to rhabdomyolysis. Treat signs and symptoms as per institutional protocol or local clinical practice.** – Initial work-up should include clinical evaluation, **creatine kinase, aldolase**, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) level, urine myoglobin, and additional laboratory 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.
	Grade 1	– No dose modifications.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult.

		– Consider, as necessary, discussing with the Clinical Study Lead.
Grade 2	– Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Consider Rheumatology or Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the Clinical Study Lead. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 days, consider additional – immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis, or other therapies based on the discretion of the treating specialist consultant or relevant practice guideline **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
Grade 3	**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 3** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussing with the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.
Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**Grade 4** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussing with the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**

[1] SCAR terms include Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema Multiforme, Acute Generalized Exanthematous Pustulosis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Drug-induced hypersensitivity syndrome.

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – The Clinical Study Lead may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	– Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. – If toxicity worsens, then treat as Grade 3 or Grade 4. – Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. – Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines. (See page 4).
Grade 3	Hold study drug/study regimen until resolution to Grade ≤1 or baseline	
Grade 4	Permanently discontinue study drug/study regimen	

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

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity 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 or study protocol prior to subsequent doses. – Consider steroids for patients who have previously experienced infusion reaction; use of steroid premedication may be permitted in these situations
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 standard, appropriate clinical practice guidelines, and society guidelines.

Non-Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity 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 2-3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	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 Clinical Study Lead."

APPENDIX II ECOG Performance Status

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

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.