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Official Title: Phase I/II study to assess the safety and efficacy of consolidative hypofractionated radiation therapy (hfRT) for boosting the residual primary lung cancer in combination with Durvalumab after definitive chemoradiation therapy for stage III non-small cell lung cancer (NSCLC)

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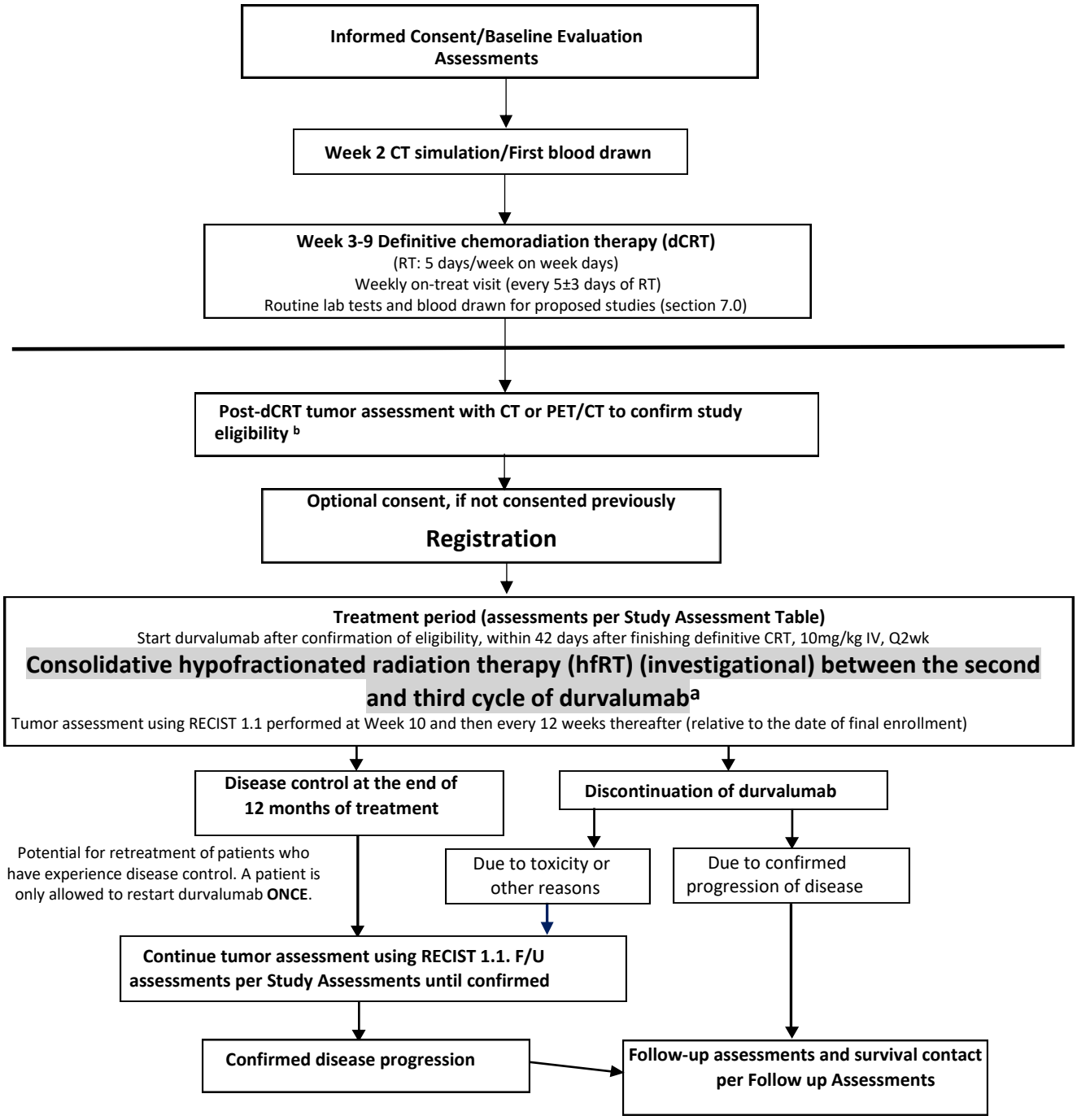
Study Schema



a A second CT simulation at radiation oncology will be performed within one week before the second cycle of durvalumab for planning of hfRT to be started and completed between the second and third cycle of durvalumab. Consolidative hfRT will start from 6.5Gy x 2 fractions and dose escalate to 10Gy x 2 fractions in a 3+3 design. See section 5.1.2

b To make it uniform, for patients enrolled either prior to or after dCRT, Day 0 is defined as the date when post-dCRT restaging imaging (CT or PET/CT) is performed.

AE Adverse event; CR Complete response; PD Progression of disease; PR Partial response; RECIST Response Evaluation Criteria In Solid Tumors; SAE Serious adverse event; SD Stable disease.

Abstract

This study is designed to determine if combining consolidative radiation therapy (RT) using a hypofractionated regimen (hfRT) of 10Gy x 2 fractions for boosting the residual primary lung cancer with adjuvant anti-PD-L1 therapy concurrently will provide better tumor control locoregionally and distantly than either modality alone. For safety reasons, consolidative hfRT will start from 6.5Gy x 2 fractions and dose escalate to 10Gy x 2 fractions in a 3+3 design. Consolidative hfRT will be delivered one to two months after finishing definitive chemoradiation therapy (dCRT) and concurrently with adjuvant anti-PD-L1 therapy using durvalumab in stage III non-small cell lung cancer (NSCLC).

At the final determined consolidative hfRT dose level, a total of thirty-two subjects with pathologically documented stage III NSCLC treated with two or more cycles of platinum-based doublet chemotherapy concurrently with dCRT will be enrolled for data analyses.

Follow-up assessments will occur every 3 months during durvalumab therapy and for 1 year following, then after 2 years from study day 0 every 4-6 months until confirmed disease progression or death. Primary endpoints include toxicities and safety of boost hfRT and anti-PD-L1 therapy adjuvantly following dCRT, and the 12-month progression-free survival to compare with historical results.

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ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aRP	acute radiation pneumonitis
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
CR	Complete response
ctDNA	Circulating Tumor DNA
CTV	Clinical Tumor Volume
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
dCRT	definitive chemoradiation therapy
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FFPE	Formalin fixed paraffin embedded
GTV	Gross Tumor Volume
HIV	Human immunodeficiency virus
hfRT	hypofractionated radiation therapy
IB	Investigator's Brochure
ICF	Informed consent form
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
imAE	Immune-mediated adverse event
IP	investigational product
IRB	Institutional Review Board
iSABR	Immunotherapy stereotactic ablative radiotherapy

ITV	Internal Tumor Volume
miRNA	Micro ribonucleic acid
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NED	No evidence of disease
NSCLC	Non-small cell lung cancer
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q12W	Every 12 weeks
QoL	Quality of life
QTcF	QT interval on ECG corrected using the Frederica's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Stable disease
sPD-L1	Soluble programmed cell death ligand 1
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
TTDM	Time to Death or Distant Metastasis
ULN	Upper limit of normal

Section 1.0 STUDY OBJECTIVES

1.1 Primary objective(s)

Primary objectives	Outcome measure
To evaluate the safety of combining hfRT and durvalumab	Adverse events (AEs) will be assessed during the entire course of study after study drug start by physical examinations, vital signs including blood pressure, pulse, electrocardiograms, etc., diagnostic imaging including CT, PET/CT, MRI, etc., and laboratory findings including clinical chemistry, hematology and urinalysis.
To evaluate 12-month PFS when combining hfRT with adjuvant anti-PD-L1 therapy	PFS based on assessments according to RECIST 1.1[a]

a The co-primary analysis of PFS will be based on programmatically derived PFS using tumor information recorded in the clinical database by the investigator according to RECIST 1.1
PFS Progression-free survival; RECIST Response Evaluation Criteria In Solid Tumors.

1.2 Secondary objective(s)

Secondary objectives	Outcome measure
To evaluate 18-month PFS when combining hfRT with adjuvant anti-PD-L1 therapy	PFS based on assessments according to RECIST 1.1[a]
To evaluate 12-month Overall survival (OS) when combining hfRT with adjuvant anti-PD-L1 therapy	OS
To evaluate the rate of local control (LC), locoregional control (LRC), DM, TTDM	LF12, LRF12 and DM12 rates will be calculated at the end of 12-month follow-up based on assessments according to RECIST 1.1[a]
To assess symptoms and health-related quality of life in patients treated with Durvalumab plus hfRT using EORTC QLQ- C30 v3 and LC13 module	EORTC QLQ-C30: Time to symptom deterioration (fatigue, pain, nausea/vomiting, dyspnea, loss of appetite, insomnia, constipation, and diarrhea). Time to QoL/function deterioration (physical function; role function; emotional function; cognitive function; social function and global health status/QoL) LC13: Time to symptom deterioration (dyspnea, cough, hemoptysis, chest pain, arm/shoulder pain, other pain) Changes in ECOG Performance Status will also be assessed

a Analysis of LC, LRC and DM will be based upon tumor information recorded in the clinical database by the investigator according to RECIST 1.1.

Abbreviations: AE Adverse event; DM distant metastasis; LF12 Proportion of patients alive and developed local failure within 12 months from day 0; LRF12 Proportion of patients alive and developed locoregional failure within 12 months from day0; DM12 Proportion of patients alive and developed distant metastasis within 12 months from day0; TTDM time to death or distant metastasis is defined as the time from the day0 until the first date of distant metastasis or death in the absence of distant metastasis; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire; LC13 Lung Cancer Module; QoL Quality of Life; RECIST Response Evaluation Criteria In Solid Tumours.

1.3 Exploratory objective(s)

Exploratory objectives	Outcome measure
To evaluate the effects of combined treatment on tumor microenvironment	Biomarker analysis of tissue biopsied after hfRT to assess exploratory markers which may include but is not limited to: immune cell gene expression profiles within the tumoral compartments, the presence of IFN-γ tumor necrosis factor-α, IL-2, IL-6, IL-8, IL-10, and IL-12 as well as expression of PD-L1 and the number and phenotype of immune cells such as T-cells, M1 and M2 subtypes of macrophage, and dendritic cells by immunohistochemistry methods.
To evaluate the systemic effects of combined therapy by testing circulating tumor RNA/DNA, and cytokine levels.	Biomarker analysis of blood collected before dCRT, during dCRT, after dCRT and before starting durvalumab, after starting durvalumab and before hfRT, and after hfRT to assess exploratory markers which may include but is not limited to: immune cell gene expression profiles in the peripheral blood, the presence of IFN-γ tumor necrosis factor-α, IL-2, IL-6, IL-8, IL-10, and IL-12 as well as antibodies against tumor, self, or viral antigens, and the number and differential of immune cells such as neutrophils, T-cells, B cells, monocytes, etc..
To explore potential biomarkers in residual biological samples (e.g., tumor, plasma and/or serum), which may influence the progression of cancer (and associated clinical characteristics) and/or prospectively identify patients likely to respond to Durvalumab/hfRT treatment	Correlation of biomarkers with response to durvalumab/hfRT treatment and/or the progression of cancer and/or toxicities
To evaluate the potential difference in pattern and treatment response and the potential relationship between acute radiation pneumonitis (aRP) during dCRT and shortly after hfRT.	The timing of onset, severity of symptoms, imaging features and treatment response to steroids for patients who develop aRP during or shortly after dCRT but prior to starting of durvalumab will be compared with aRP within three months after hfRT. Whether developing aRP during dCRT is predictive to aRP after hfRT will be explored in this study.

a PD-L1 expression determined by immunohistochemistry will be reported in the Clinical Study Report (CSR). Other exploratory biomarker research will be reported outside the CSR.

Section 2.0 INTRODUCTION

2.1 Disease background

Worldwide, lung cancer has been the most common cancer in the past few decades. In 2018, there were an estimated 2.1 million new cases, representing 11.6% of all new cancers. It was also the most common cause of death from cancer, with 1.8 million deaths (18.4% of the total) (GLOBOCAN 2018). Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers and 30% of patients present with Stage III disease.

- Standard treatment for patients with a good performance status and unresectable Stage III NSCLC is platinum- based doublet chemotherapy and radiotherapy administered with curative intent followed by maintenance durvalumab therapy.
- Unresectable stage III disease includes unresectable IIIA/B (N2) disease based on bulky (> 2 cm in short-axis diameter measured by chest CT) and multiple mediastinal nodal involvement and IIIB/C disease based on unresectable T4 involvement or any N3-disease in mediastinal nodes (Robinson et al 2007; Eberhardt et al 2015).

A meta- analysis of concurrent versus sequential chemoradiotherapy for unresectable stage III disease showed better outcomes with concurrent therapy, but even with concurrent chemoradiotherapy 5-year overall survival (OS) is approximately 15% (Butts et al 2014). Recently, results from the phase III PACIFIC trial have been reported comparing consolidative durvalumab vs. placebo after definitive concurrent chemoradiation therapy (dCRT) in patients with stage III unresectable NSCLC (Antonia et al 2017). Significantly improved progression-free survival (PFS) was seen for patients who received consolidative durvalumab therapy (17.2 months) compared to placebo (5.6 months), as well as 2-year overall survival (66.3% vs. 55.6%) (Antonia et al 2018). Although the long term survival data is not available, nearly 50% of patients will experience disease progression and/or death within 18 months after dCRT.

Thus exploring other consolidative therapies with durvalumab in an attempt to further extend disease control and improve overall survival in patients with stage III NSCLC is warranted.

2.1.1 Immunotherapy

Cancers are recognized by the immune system, and, under some circumstances, the immune system controls or even eliminates them (Dunn et al 2004). PD-L1 is one part of a complex system of receptors and ligands involved in controlling T- cell activation. The PD-1 receptor, (CD279) expressed on the surface of activated T cells (Keir et al 2008) has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki and Honjo 2007). When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages (Qin et al 2016). Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment (Pardoll 2012). PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T-cells leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti–PD-L1 agent to the PD- L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti–PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti–PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer et al, 2012; Hirano et al, 2005; Iwai et al, 2002; Okudaira et al, 2009; Topalian et al, 2012; Zhang et al, 2008) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al, 2014; Rizvi et al 2015; Segal et al 2015). In addition, high mutational burden (e.g., in bladder carcinoma [Alexandrov et al, 2013]) may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen- presenting cells (Fife and Bluestone, 2008). Blockade of CTLA-4 binding to CD80/86 by anti– CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti–CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data have supplemented a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity.

2.2. Durvalumab background/non-clinical and clinical experience

The non-clinical and clinical experience is fully described in the most current version of the durvalumab Investigator's Brochure.

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and has been developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (Stewart et al 2015). *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody- dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date durvalumab has been given to more than 9000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Appendix I. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

2.2.1 Clinical data demonstrating efficacy of consolidative durvalumab for stage III NSCLC

In the recently published results from PACIFIC trial, efficacy of durvalumab as consolidative therapy after definitive CRT for stage III nonresectable NSCLC has been demonstrated. From May 2014 through April 2016, a total of 713 patients underwent randomization, of whom 709 (99.4%) received at least one dose of durvalumab or placebo after chemoradiotherapy. Randomization occurred 1 to 42 days after the patients had received chemoradiotherapy in a 2:1 ratio to receive durvalumab at a dose of 10 mg per kilogram (mg/kg) of body weight intravenously or matching placebo every 2 weeks as consolidation therapy for up to 12 months. The 12-month overall survival rate was 83.1% in the durvalumab group, as compared with 75.3% in the placebo group. The 24-month overall survival rate was 66.3% in the durvalumab group, *versus* 55.6% in the placebo group (two-sided P=0.005). Durvalumab significantly prolonged overall survival, as compared with placebo (stratified hazard ratio for death, 0.68; 99.73% CI, 0.47 to 0.997; P=0.0025). The overall survival benefit with durvalumab was observed across all the pre-specified subgroups. Progression-free survival was also significantly longer with durvalumab than with placebo. The 12-month progression- free survival rate was 55.9% *versus* 35.3%, and the 18-month progression-free survival rate was 44.2% *versus* 27.0%.The median progression-free survival from randomization was 17.2 months in the durvalumab group, as compared with 5.6 months in the placebo group (stratified hazard ratio for disease progression or death, 0.51; 95% CI, 0.41 to 0.63). The overall response rate was 30.0% in the durvalumab group, as compared with 17.8% in the placebo group (P<0.001). 12-month distant metastasis-free survival was estimated to be 73% in durvalumab group compared with an estimated 59% in placebo group.

2.3 Immunostimulatory radiation therapy regimen

Radiation therapy (RT) has long been indicated to induce immune response as demonstrated by the abscopal effect, in which a systemic tumor response has been observed after local RT. Although previously thought to be an infrequent event, increasing cases of abscopal effects have been reported since immune checkpoint inhibitors were introduced along with recently increased use of stereotactic body radiation therapy (SBRT), which raised new interests in exploring immunoradiotherapy strategies. A wide variety of RT schemes were used in combination with immunotherapy in preclinical research ranging from conventional/low dose fractionation of 1.8 to 5Gy/fraction, to intermediate dose per fraction (6Gy/fraction x 5 fractions, 8Gy/fraction x 3 fractions, etc.), to high dose in single fraction (12-30Gy per fraction). In pre-clinical settings higher dose per fraction of RT such as the dose regimen used for SBRT is more likely to be immunostimulating than conventional fractionated RT (3-6). However, radiation dose and fractionation schedules for optimal synergy between radiotherapy and immunotherapy are not well defined in clinical settings. In pre- clinical including animal studies, RT was able to induce cell surface markers such as Fas, MHC I, ICAM-1, etc. Most of the animal model studies showed that the optimal increase in cell surface receptor expression resulted from a relatively large single dose of radiation (≥8 Gy) rather than conventional/low dose fractionation. Furthermore, the large

single fraction regimen also has a higher likelihood of altering the tumor microenvironment by facilitating infiltration of host immune cells such as macrophages, dendritic cells, or tumor antigen specific cytotoxic T lymphocytes (CTLs). Schaue et al showed that, when using a mouse melanoma model, treatment with single fractions of 7.5Gy or moderately higher doses was associated with an increase in anti-tumor CTLs and a decrease in regulatory T cells (Tregs), thus being immunosimulatory which is not seen in 5Gy x 1 regimen (Schaue et al 2012). Surprisingly, when the single fractional dose increased to 15Gy, RT not only increased the infiltration of anti-tumor CTLs but also the Tregs which may now in turn dampen the immunostimulation. However, when mice were irradiated with 15Gy total dose but fractionated in two, three or five fractions, ie., 7.5Gy x 2, 5Gy x3 or 3Gy x5 fractions, the 2-fraction regimen (7.5Gy x2 fractions) induced the highest level of anti-tumor CTLs and the lowest level of Tregs in the treated area, achieving the best tumor control. The authors hypothesized that the ratio of anti-tumor CTLs to Tregs might be a critical factor reflecting the aggregate effect of a particular RT regimen on the immunostimulatory and immunosuppressive pathways, with the most immunosimulating regimen being most likely ranging from 7.5Gy to 15Gy per fraction. When combining RT with immune checkpoint blockade such as using anti-CTLA-4 antibody in a mouse model, the most immunostimulating RT fractional dose falls into this range as well as reported by Demaria et al (7). In their study using a mouse breast model, tumor cells were injected subcutaneously in mice at a primary site which was irradiated and a secondary site that was distal and outside the RT field. Mice were randomized to RT alone, anti-CTLA-4 antibody 9H10 alone, or a combination of RT and 9H10 antibody. Three different fractionation regimen were tested: 20Gy x 1, 8G x3, or 6Gy x 5 fractions. 8Gy x3 in combination with anti-CTLA4 was significantly more effective than 6Gy x5 in inhibiting tumor growth at both the primary and secondary sites. 20Gy x 1, although showing primary site tumor control, was ineffective in inducing an immune-mediated response at the secondary site. As for combining RT with PD- 1/PD-L1 antibody studies, Zeng et al also confirmed the efficacy of a RT regimen of 12Gy x 1 fraction, when combined with anti-PD-1 antibody, produces long-term survival in a mouse glioma model which was not seen in either therapy alone (8). This dose regimen induced increased infiltration by cytotoxic T cells and decreased Tregs within the tumor microenvironment of gliomas. The same regimen of 12Gy x 1 has also shown synergistic inhibitory effects with anti-PD-L1 therapy in TUBO mammary carcinoma and colon adenocarcinoma mouse models, indicating the most immunostimulating RT dose range (7.5- 15Gy per fraction) shown by Schaue et al is very likely shared among different types of primary tumors (Deng et al 2014). We thus propose to conduct a phase I/II clinical trial testing a consolidative radiation therapy using a regimen within this range with a concurrent PD-L1 antibody, Durvalumab, in nonresectable stage III NSCLC, after definitive CRT. This is a trial designed as a follow-up study to the recently completed PACIFIC trial.

2.3.1 Clinical experience of the feasibility of consolidative lung SBRT after definitive chemoradiation therapy

One of the main concerns of adding consolidative RT with potential immunostimulatory effects after definitive CRT is pulmonary toxicity, particularly with anti-PD-L1 therapy. A prospective study has been conducted at University of Kentucky on thirty-seven patients with stage IIB/III NSCLC who underwent computed tomography (CT) or positron emission tomography–computed tomography (PET/CT) and were screened approximately 1 month after completion of definitive CRT (Kumar et al 2017). Limited residual disease (≤5 cm) within the site of the primary tumor received a stereotactic radiation therapy boost of either 10 Gy × 2 fractions or 6.5 Gy × 3 fractions to the primary tumor, to achieve a total Biologically Equivalent Dose

(BED) >100 Gy. This study did not include anti-PD-L1 therapy. The long term toxicities were reported, five patients (13.5%) experienced grade 3 pneumonitis, four developed acutely within three months after SBRT and one late onset. This is comparable to historical "moderate to severe" radiation pneumonitis rates of 8.0% to 15.3% per the authors. No grade 4 or 5 pneumonitis occurred. Predictors for grade 3 pneumonitis included age and mean lung dose during definitive CRT. For any grade of pneumonitis, current nonsmoking status was found to be protective (P<.01). Two patients experienced fatal bleeds. However, no significant dosimetric differences in RT were found between patients who developed a fatal hemorrhage and those who did not, with a calculated average maximum pulmonary artery dose of 175 Gy (BED3). Each hemorrhage was found to be related to local tumor recurrence in the hilum. Other grade 1 and 2 toxicities were observed including fatigue (7 patients), chest wall pain (5 patients), and esophagitis (4 patients). Hypofractionated RT boost or consolidative RT with SBRT after CRT is thus considered a safe treatment.

Possible improvement in local control for locally advanced NSCLC with SBRT boost was predicted. With a median follow-up of 25.2 months, overall 22% patients experienced local failure, 29% regional failure, 41% locoregional failure, and 65% distant failure. Median PFS was 6.5 months; 1-, 3-, and 5-year PFS was 30.9%, 16.8%, and 9.4%, respectively for the entire cohort. Interestingly, when comparing the outcome of boost dose regimens, although 6.5 Gy x3 fractions has a slightly lower BED (102.2 Gy including the definitive conventional fractionated RT dose) than 10 Gy x 2 fractions (110 Gy), both achieved similar rates of local control (22% vs. 21%, P=1.0). However, the survival for the 20 Gy boost (10 Gy x 2 fractions) were numerically better. Median OS was 19.2 months for the 19.5 Gy boost vs. 26.4 months for the 20 Gy boost (P=0.05). Although not statistically significantly different, the PFS curves of 19.5 Gy and 20 Gy boost treatment started to separate after 6 months with 20 Gy boost showing much better long-term disease control. Although no conclusion can be drawn from these data with the small number of patients in each group and a nonrandomized design, a possible stronger immunostimulatory effect from 10Gy x 2 fractions than 6.5Gy x 3 fractions could partly explain the difference.

2.3.2 Clinical evidence of the safety and abscopal effects of combining hfRT/SBRT with immunotherapy in lung cancer

Although no data at all available for combining hfRT/SBRT with immunotherapy after dCRT which makes our proposed study novel, there are small scaled prospective studies available on current use of immunotherapy including PD-1/PD-L1 inhibitors with SBRT in lung cancer and other solid tumors. The following two studies showed abscopal effects and low risks of grade 3 toxicities combining SBRT and immunotherapy particularly for lung cancer.

The University of Chicago recently completed a phase I study of SBRT followed by pembrolizumab (anti-PD-L1) in patients with multiple sites of metastatic solid tumors (Luke *et al* 2018). Two to four metastases were targeted with SBRT to 30–50 Gy in 3–5 fractions, and pembrolizumab was initiated 7 days after completion of SBRT. The cohort of 73 patients was heavily pre-treated, with a median of five prior therapies. Of the total 151 sites of metastases irradiated, 68 were in the lung, 24 in the liver, 28 in other abdomen/pelvis sites, 16 in the bone, and 15 near the spine. The abscopal response rate per RECIST criteria of any single non-irradiated target metastasis was an impressive 26.9%. This off-target effects, or abscopal effects, generated by combined SBRT and immunotherapy, if can be reproduced in our study, would

potentially significantly improve regional and distal control of stage III NSCLC. Grade 3 toxicity was seen in 6 patients (pneumonitis n=3; colitis n=2; hepatic toxicity n=1). So the overall grade 3 pneumonitis risk is only 4.4%. These promising results in a heterogenous group of tumors support further studies combining checkpoint inhibitors with SBRT.

More specifically, the short-term safety of combining thoracic SBRT and immunotherapy was recently explored in a combined analysis of two prospective trials ongoing at MD Anderson (Verma *et al* 2018). The first was the phase 1–2 trial testing SBRT with ipilimumab (anti-CTLA4). The second was another ongoing phase 1–2 trial testing SBRT with concurrent pembrolizumab (anti-PD-L1) in metastatic NSCLC. SBRT dose was 50 Gy in 4 fractions or 60 Gy in 10 fractions. Out of 60 patients with a median follow up of 6.9 months (range, 0.5–30.9 months), there were no grade ≥4 toxicities. Only 4 patients experienced grade 3 pulmonary toxicities with no difference between the ipilimumab and pembrolizumab groups. These short-term pulmonary toxicity rates were on par with RTOG 0236 which was a phase II study with SBRT only for stage I NSCLC, in which 8 of 55 patients developed grade 3 respiratory events (Timmerman *et al* 2010).

2.4 Research hypothesis

We hypothesize that combining consolidative RT using hypofractionated (hfRT) regimen of 10Gy x 2 fractions for boosting the residual primary lung cancer with adjuvant anti-PD-L1 therapy will further improve immunostimulation and provide better tumor control locoregionally and distantly than either modality alone. Consolidative RT will be delivered one to two months after finishing definitive chemoradiation therapy and concurrently with consolidative/adjuvant anti-PD-L1 therapy using durvalumab in stage III non-small cell lung cancer (NSCLC). Hypofractionated RT will be delivered between the second and third cycle of biweekly durvalumab.

2.5 Rationale for conducting this study

Immunotherapy has drastically changed the treatment of NSCLC and have established a new treatment paradigm for these patients. Recently results from the phase III PACIFIC trial have been reported comparing consolidative durvalumab vs. placebo after definitive chemoradiation therapy (dCRT) in patients with stage III unresectable NSCLC (Antonia et al 2017, 2018). Significantly improved PFS and OS were demonstrated for patients who received consolidative durvalumab therapy compared to placebo group. The FDA has now approved durvalumab as consolidation therapy for stage III NSCLC patients after definitive CRT. However, the PFS at 18 months was only 44.2% even with durvalumab treatment, which is consistent with the results from RTOG 0617 which tested dose escalation of RT without immunotherapy (36.6%). There is clearly room for further improvement in tumor control for locally advanced NSCLC. The proposed study of additional hfRT may potentiate/synergize the immunotherapy effects and further improve PFS.

2.5.1 Durvalumab monotherapy dose rationale

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

(D4190C00002). A durvalumab dose of 10 mg/kg Q2W intravenously was instead used in the phase III PACIFIC study.

PK/Pharmacodynamic data

Based on available PK/dynamics data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (For further information on immunogenicity, please see the current Investigator's Brochure (IB)).

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

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

2.5.2 Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase I study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated a minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Ng et al 2006, Wang et al 2009, Zhang et al 2012, Narwal et al 2013).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given the 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) can be considered for future studies.

2.5.3 Regimen of durvalumab for current study

To be able to best compare the results from this proposed clinical trial to the historic results from PACIFIC study, IV durvalumab of 10mg/kg Q2W used in the protocol of PACIFIC study will be the only regimen used in current study.

2.5.4 Rationale for exploratory research

Although numerous studies have been performed on tumor microenvironmental and systemic response to immunotherapies including PD-L1 blockade, there are scant data particularly from the lung cancer patients. The PACIFIC trial, which is the first clinical study that demonstrated the clinical benefit of adjuvant PD-L1 blockade after definitive chemoradiation therapy for stage III NSCLC, did not study the above mentioned questions which may be very valuable for predicting treatment response and important in selecting the right candidates for adjuvant immunotherapy both for maximizing the benefit of the treatment and for minimizing toxicities.

We thus propose to perform the exploratory research on both tumor tissues from biopsy of the residual lung parenchymal tumor two months after consolidative hfRT and patients' blood specimen.

Blood will be drawn from each patient in this study with the schedule described in section 5.2.3.2 for exploratory research on biomarker studies including sPD-L1, miRNA/mRNA, and cytokines, as well as ctDNA isolation for mutation and tumor burden studies and PBMC collection for flow cytometry.

For patients enrolled in the trial who consent to a repeat biopsy of residual lung tumor and/or lymph nodes (optional) two months after consolidative hfRT, the fresh tumor tissue from 2-3 core needle biopsy will be collected and processed to FFPE in a single block for PD-L1 testing as described in Section 5.2.3. If additional slides are available after PD-L1 staining, immunohistochemistry studies can be performed to study on immune cell infiltration into irradiated tumor microenvironment at Dr. Zhang's laboratory and pertinent core centers at our institution.

To evaluate the potential difference in pattern and treatment response and the potential correlations between acute radiation pneumonitis (aRP) during dCRT and shortly after hfRT, we plan to collect all aRP data from the start of dCRT to right before the first dose of durvalumab, and the acute onset of pneumonitis after the first fraction of hfRT and within three months after. Pneumonitis occurs three months after hfRT will be difficult to be assigned as late onset symptoms after dCRT or subacute after hfRT/immunotherapy thus will not be included in the comparison of aRPs caused by dCRT or hfRT, but will be captured for toxicities studies and counted as treatment-related AEs/SAEs. The timing of onset counting from the start of the first dose of RT (dCRT or hfRT respectively), severity of symptoms, imaging features and treatment response to steroids for patients who develop aRP during or shortly after dCRT but prior to starting of durvalumab will be compared with aRP within three months after hfRT. Whether developing aRP during dCRT is predictive to aRP after hfRT in timing or severity will be

explored in this study based on Spearman's rank correlation coefficients. We expect that no more than 20% patients are likely to be enrolled after completion of chemo-radiation (dCRT), in which case the effective sample size for correlative purposes will be 26 (80% of 32). We would be able to detect a correlation of 0.53 *vs* no correlation with 80% power using a significance level of 0.05.

2.6 Benefit/risk and ethical assessment

2.6.1 Potential benefits

2.6.1.1 Durvalumab

Results from the PACIFIC trial demonstrated the benefit of consolidative durvalumab in patients with stage III NSCLC after definitive CRT in DFS, PFS, and OS.

2.6.1.2 Consolidative RT

Both preclinical and clinical data suggest that the most immunostimulating regimen of RT most likely ranges from 7.5Gy to 15Gy per fraction. This effective dose range is likely shared among different types of cancer, and has been used commonly in stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) in early stage lung cancer with excellent clinical outcome. Unlike conventional fractionated RT which is usually lower than 4 to 5 Gy per fraction, or the super-high fractional dose used in stereotactic radiosurgery (SRS) with 18Gy or higher per fraction, this immunostimulating range of dosing will optimally induce expression of certain cell surface markers, such as Fas, MHC I, ICAM I, etc., induce cytotoxic T cell infiltration and decrease immunosuppressive regulatory T cells, with improved local as well as systemic tumor control. These effects have been observed in tumors treated with this immunostimulating range of RT alone or when combined with anti-CTLA-4 therapy, anti-PD-1, or anti-PD-L1 therapy as described in detail in section 2.3. Emerging data from clinical trials combining RT and immunotherapy have also shown promise (Gandhi et al 2015, Monjazeb and Schoenfeld 2016, Weichselbaum et al 2017). Particularly, a recent retrospective review has examined the OS, incidence of toxicities and the timing of radiation in advanced stage NSCLC (including metastatic disease) patients who received nivolumab and external beam radiotherapy (iEBRT), nivolumab and stereotactic ablative radiotherapy (iSABR) and nivolumab monotherapy (Hegde et al 2018). The study demonstrated a significant 29% absolute improvement in 18-month OS with iSABR Sandwich when compared to nivolumab monotherapy and no OS improvement with EBRT given prior to initiation of nivolumab. Of note, iSABR sandwich group of patients all received conventional fractionated EBRT and received SABR during nivolumab therapy (Sandwich). This result indicates that there might be synergistic effects of SABR (using the immunostimulating dose range of RT) and immune checkpoint blockade drug(s) after conventional fractionated EBRT, but not EBRT only, which supports the rationale of current clinical trial as designed.

The dose regimen selected for the consolidative RT in the current trial is unique in that it is not designed simply as for dose escalation. We propose to test the potential benefit of this immunogenic dosing of consolidative RT for further enhancing or even synergizing immunotherapy effects by durvalumab. More specifically, this immunogenic dose of consolidative RT to the residual primary tumor may alter the tumor microenvironment in residual primary tumor by increasing cytotoxic T cell infiltration to improve locoregional

control, as well as to enhance tumor antigen presentation by dendritic cells thus promoting immune reaction systemically to decrease distant metastasis, and ultimately improve survival.

2.6.2 Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system, however, there are potentially increased adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitors are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine therapy. These immune mediated effects can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

2.6.2.1 Durvalumab

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 (which may present with diabetic ketoacidosis), hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis (including pemphigoid), diabetes insipidus, encephalitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions and infections/serious infections and subcutaneous injection site reaction.
For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies, AEs (all grades) reported very commonly (≥ 20% 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 10% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6% 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 I) detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

2.6.2.2 Consolidative RT

Consolidative RT (10Gy x 2 fractions, QOD) after concurrent CRT with 60Gy of conventional fractionated EBRT to the residual lung cancer carries potential risks of increased rate of fatigue, chest wall pain, dermatitis, radiation pneumonitis, pneumonia, esophagitis, esophageal stenosis,

central airway necrosis, hemoptysis, spinal cord injury, arrhythmia and pericarditis, than definitive CRT only.
A prospective study has been conducted at the University of Kentucky on thirty-seven patients with stage IIB/III NSCLC with consolidative RT tested after completion of definitive CRT as described in section 2.3.1 (Kumar et al 2017). Limited residual disease (≤5 cm) within the site of the primary tumor after definitive CRT received a SBRT boost or consolidative RT of either 10 Gy × 2 fractions or 6.5 Gy × 3 fractions to the primary tumor, to achieve a total Biologically Equivalent Dose (BED) >100 Gy. This study did not include anti-PD-L1 therapy. The long term toxicities were reported, and five patients (13.5%) experienced grade 3 pneumonitis. There were no grade 4 or 5 pneumonitis events. After long-term follow-up, no additional cases of late fatal bleeding were found. Other grade 1 or 2 toxicities were observed including fatigue (7 patients), chest wall pain (5 patients), and esophagitis (4 patients).
Hypofractionated RT boost with SBRT after CRT is thus considered a safe treatment. However, with the hypothesis that hfRT using SBRT planning of immunostimulating fractional dose range may synergize immunotherapy drug such as durvalumab in tumor control, hfRT could potentially increase normal tissue toxicities such as tissues within or adjacent to RT field including lung, heart, esophagus, chest wall, spinal cord, etc., as well as distant organs including thyroid (thyroiditis), pituitary gland (hypophysitis), rash (dermatitis), gastrointestine (gastroenteritis), liver (hepatitis) and other autoimmune disease.

2.6.2.3 Overall benefit-risk

In summary, the potential for clinical benefit associated with combining hfRT using immunostimulating range of dose and inhibitor of PD-1/PD-L1 pathway such as durvalumab, supported by numerous preclinical studies and survival benefit observed in earlier clinical studies in patients with advanced stage NSCLC, outweighs the known and potential risks based on the AEs reported in patients treated with durvalumab and other PD- 1/PD-L1 inhibitors, or consolidative RT alone. Thus, the benefit/risk assessment favors the conduct of this proposed study.

Section 3.0 PATIENT SELECTION

3.1 Inclusion criteria

Inclusion Criteria:

1. Pathologically diagnosed NSCLC (squamous cell carcinoma, adenocarcinoma, large-cell carcinoma, or non-small-cell lung cancer not otherwise specified), clinical stage III (AJCC 8th Ed.)

2. At time of consent, potential subjects must be a candidate for dCRT
   OR
   Must have received dCRT with at least 2 cycles of platinum-based chemotherapy concurrent with conventional fractionated radiation therapy with a total dose of 5700 - 6300 cGy

3. Patients must be aware of the nature of his/her disease and willingly provide written, informed consent. Including compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (e.g., Health Insurance Portability and

Accountability Act in the US) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

4. Age ≥ 19 years at time of study entry

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at time of enrollment.

6. Life expectancy of > 12 weeks

7. Adequate normal organ and marrow function as defined below:
   - Hemoglobin ≥9.0 g/dL (5.59 mmol/L) (patients can be transfused to meet this criterion)
   - Absolute neutrophil count (ANC) ≥ 1500 per mm^3
   - Platelet count ≥100 x 10^9/L (≥100,000 per mm^3)
   - Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
   - AST (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal.
   - Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976)

     Males:

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

     Females:

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

8. Evidence of post-menopausal status or negative 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)

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

3.2 Exclusion criteria

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
2. Patients who have received prior anti–PD-1, anti PD-L1 or anti CTLA-4
3. Participation in another clinical study with an investigational product during the last 4 weeks
4. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
5. Mixed small cell and non-small cell lung cancer histology
6. Patients who receive sequential chemoradiation therapy for locally advanced NSCLC
7. Patients with locally advanced NSCLC who have progressed during definitive platinum based, concurrent chemoradiation therapy
8. Any unresolved toxicity (NCI CTCAE Grade >2) from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

    a. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
    b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician. For example, post-operative neurological deficits for previous benign brain tumors, urinary incontinence from radical prostectomy for prostate cancer, peripheral neuropathy from chemotherapy for breast cancer.

9. Any concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
10. Major surgical procedure (as defined by the investigator) within 28 days to the first dose of immunotherapy (excluding the placement of vascular access) that would prevent administration of study drug or radiation therapy.
11. History of allogenic organ transplantation.
12. Active or prior documented autoimmune or inflammatory disorders within the past 2 years (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    a. Patients with vitiligo or alopecia
    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome stable on hormone replacement or Graves' disease).

c. Any chronic skin condition including psoriasis that does not require systemic therapy (within the past 2 years).
d. Patients without active disease in the last 5 years may be included but only after consultation with the study physician.
e. Patients with celiac disease controlled by diet alone.

13. Known allergy or hypersensitivity to Durvalumab or any excipient.
14. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent
15. History of another primary malignancy except for
    a. Malignancy treated with curative intent and with no known active disease ≥5 years before the informed consent and of low potential risk for recurrence
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    c. Adequately treated carcinoma in situ without evidence of disease
16. History of primary immunodeficiency
17. Known history or active infection of **tuberculosis**, **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies).
18. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
    a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
    b. Systemic corticosteroids at doses ≤10 mg/day of prednisone or its equivalent
    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
    d. Systemic steroid administration required to manage toxicities arising from radiation therapy delivered as part of the chemoradiation therapy for locally advanced NSCLC is allowed.
19. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccines whilst receiving IP and up to 30 days after the last dose of IP.
20. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab therapy.
21. Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.
22. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1.
23. Previous history of RT (other than RT as part of the dCRT for the current course of NSCLC) involving any part of lungs, chest wall, thoracic spine or breast(s).
24. Judgment by the investigator that the patient is unsuitable to participate in the study for any condition and the patient is unlikely to comply with study procedures, restrictions and requirements.

25. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms. If QTcF ≥ 470 ms, the QTcF can be recalculated from 3 ECGs performed 2-5 minute apart. Triplicate ECGs should only be performed if screening ECG shows QTcF ≥ 470 ms.

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 3.3

3.3 Withdrawal of subjects from study treatment and/or study

An individual subject will not receive hfRT if any of the following occur in the subject in question:

1. Withdrawal of consent or lost to follow-up
2. Adverse event from durvalumab prior to start hfRT, in the opinion of the treating physician, contraindicates hfRT. The decision whether to discontinue durvalumab will be determined separately per Appendix I.
3. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational hfRT might constitute a safety risk
4. Pregnancy or intent to become pregnant, then durvalumab and hfRT (if not delivered or partly delivered) should be both permanently stopped
5. Any AE that meets criteria for discontinuation as defined in Section 5.3.3.5. and Appendix I
6. Adverse event related to hfRT after the first of the total two fractions, in the opinion of the investigator, contraindicates continuation of delivery of the second fraction.
7. Grade ≥3 infusion reaction from durvalumab, then both durvalumab and hfRT will be permanently stopped
8. Subject noncompliance that, in the opinion of the investigator, warrants withdrawal; e.g., refusal to adhere to scheduled visits, then both durvalumab and hfRT will be permanently stopped
9. Initiation of alternative anticancer therapy including another investigational agent, then both durvalumab and hfRT will be permanently stopped
10. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab. If that is confirmed prior to start of hfRT, cancel RT permanently. The subject(s) will remain in analysis set for toxicities and survival
11. Subjects who are permanently discontinued from receiving durvalumab or hfRT will be followed for safety per Section 9.2, including the collection of any protocol- specified blood specimens, unless consent is withdrawn or the patient is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Patients who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative

Withdrawal of consent

Subjects are free to withdraw from the study at any time (durvalumab, hfRT and assessments) without prejudice to further treatment.

Subjects who withdraw consent for further participation in the study will not receive any further durvalumab or hfRT if not delivered yet or further study observation, with the exception of follow- up for survival, which will continue until the end of the study unless the patient has

expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A subject who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. This is not mandatory. Subjects are under no obligation to give a reason. The Investigator will follow up AEs outside of the clinical study.

An individual subject will not receive any further IP (durvalumab therapy or hfRT) if any of the following occur in the patient in question:

- An AE that, in the opinion of the Investigator, contraindicates further dosing
- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Clinical progression, i.e. Investigator determination that the patient is no longer benefiting from treatment with IP, with or without radiological progression by RECIST 1.1.
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (Appendix I)

3.4 Replacement of patients

We estimate 15% withdrawal or discontinuation rate in this trial. It should not change the total number of enrollment.

Section 4.0 REGISTRATION PROCEDURES

Patients with NSCLC referred to the Nebraska Medical Center (NMC) / UNMC are evaluated in a multidisciplinary team conference. On initial presentation, a history and physical examination are performed, laboratory data obtained, and performance status is assessed. Imaging studies will be obtained as clinically indicated. Any pathologic specimens obtained at referring institutions are reviewed for accuracy. Patients with suspicious NSCLC will require a biopsy for confirmation of malignancy.

Patients with pathologically diagnosed NSCLC will be offered participation in the treatment portion of this trial.

The potential subject will be provided assistance by the research nurse coordinator in determining if the insurance carrier will decline coverage. Insurance carriers may or may not pay for study related expenses. The potential subject can then decide if he/she wishes to participate.

Subjects will be registered by contacting the UNMC Project Coordinator. Study personnel from UNMC will contact the IIT Office Research Project Coordinator if a subject appears to meet the eligibility criteria. They will email the following information:

- Registration request with Demographics cover sheet (located in the Study site Manual)
- Signed, completed eligibility checklist (Appendix B)

4.1 Eligibility Verification/Registration

The date of study enrollment is the date of consent. Before subjects are registered in the investigational treatment portion of the study, an eligibility checklist must be completed to verify the subject meets the eligibility criteria. The eligibility checklist will be maintained in the study file as source documentation only if it has been reviewed, signed by the treating physician. To make it uniform, for patients enrolled either prior to or after dCRT, Day 0 is defined as the date when post-dCRT restaging imaging (CT or PET/CT) is performed.

Once the UNMC Research Project Coordinator confirms that the subject meets criteria, and target accrual has not been met, approval for the subject will be given and study subject number assigned. An email confirmation of study registration will be forwarded by the UNMC Research Project Coordinator to the study personnel. The Project coordinator can assign a subject study number prior to final registration confirmation of a subject.

Each subject consented to the protocol is loaded into the UNMC Clinical Trial Management System (CTMS) within 7 days of consent. CTMS registration includes entering the required demographic information (included on the registration request form) as stated in the SRC policies and procedures. All subjects are CTMS registered (On Study) after the first time eligibility verification is complete and the IIT office provided the registration confirmation regardless if this occurs prior to or after dCRT.

Instructions for Subjects Who Do Not Start Assigned Protocol Treatment (Screen Failure)

A study subject number is still assigned to all consented subjects. If a subject does not receive any assigned protocol treatment after consenting, baseline data will still be collected and included in the electronic data capture system.

Section 5.0 TREATMENT PLAN

5.1 Schedule of study procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedule of Assessments during the screening and treatment period is provided in Section 7.0 of the protocol.

Tumor efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the Day 0 (not the date of therapy).

All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc., required for dosing should be performed within 3 days prior to dosing.

Subjects may delay durvalumab dosing under certain circumstances.

- Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible

5.1.1 Consent and Standard definitive CRT phase

All potential subjects must first read, understand, and sign the IRB/REB/IEC- approved ICF before any study-specific screening procedures are performed. Most patients will be consented prior to start of standard clinical care of definitive chemo-radiation therapy (dCRT). However, informed consent of study procedures may occur within the screening period after dCRT and prior to starting of durvalumab. All subjects will only consent to the study one time, however.

All subjects must have tumor pathology available prior to start of dCRT and reviewed at UNMC prior to consent. The collection of additional biopsies upon progression is encouraged. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient.

Initial consult day and CT simulation at radiation oncology usually occur one to two weeks before starting the dCRT phase.

For subjects to be consented prior to dCRT, the following procedures will be performed prior to the start of dCRT:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG (triplicate ECGs are done only if QTcF is ≥470 [2-5 minutes apart]), See section 5.2.1
- Tumor biopsy
- Review of prior/concomitant medications
- Imaging by CT/MRI/PET
- Clinical laboratory tests for:
  - Hematology (see section 5.2.2)
  - Clinical chemistry (see section 5.2.2)
  - TSH (Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.)
  - Coagulation (PT, INR)
  - Creatinine Clearance
  - Serum pregnancy test (for women of childbearing potential only)
  - Urinalysis (see section 5.2.2)
  - Disease-specific tumor markers such as PD-L1 (optional) which can be assessed after enrollment

5.1.1.2 Second/Final Eligibility Assessment—post-dCRT

This step is mainly a review for study eligibility for hfRT based on residual lung tumor size after dCRT phase. Subjects with CR (no target for planning hfRT) or tumor size in lung parenchyma >5cm in the largest axis (expecting high toxicities with hfRT) will not be eligible to continue on the study. Ideally final subject eligibility review should be completed after imaging study for tumor assessment (day 0). Subject consent should be as soon as possible following day 0. Infusion should start no more than 42 days post completion of dCRT.

The eligibility confirmation/assessment should be performed after the completion of dCRT with a CT chest/abdomen/pelvis with and without IV contrast or PET/CT (preferred), and ideally as close as possible before the start of durvalumab. For subjects who are recovering from toxicities associated with prior treatment, imaging for tumor assessments may be delayed by up to 14 days from the end of chemoradiation therapy. The eligibility confirmation procedures should be performed after the end of chemoradiation therapy.

The following procedures will be performed for the eligibility confirmation after dCRT:

- Informed consent
  - If the subject was enrolled after dCRT, then they must sign consent prior to any study specific screening procedures are performed.
  - If the subject was consented prior to dCRT phase, they will not sign a consent form again.
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height- only for subjects consenting after dCRT
- 12-lead ECG (triplicate ECGs are done only if QTcF is ≥470 [2-5 minutes apart]), See section 5.2.1
- concomitant medications
- EORTC QLQ-C30 v. 3 and LC13 module
- Imaging by CT chest/abdomen/pelvis or PET/CT (day 0)
- Clinical laboratory tests for:
  - Hematology (see section 5.2.2)
  - Clinical chemistry (see section 5.2.2)
  - TSH (Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.)
  - Coagulation (PT, INR)
  - Creatinine Clearance
  - Urinalysis (see Section 5.2.2)
  - Serum Pregnancy testing (for women of childbearing potential)
- Tumor pathology review, confirm NSCLC diagnosis
- Blood collection for exploratory studies

5.1.2 Treatment phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments. Screening lab procedures performed within 72 hours before of Cycle 1 Day 1

(C1D1) of durvalumab do not need to be repeated on C1D1.

Initial 3+3 design of dose escalation:

A stepwise dose escalation will be conducted for consolidative hfRT for safety reasons. hfRT will start with 6.5Gy x 2 fractions and increase to 10Gy x 2 fractions if Maximum Tolerated Dose (MTD) is not reached. Only up to these two dose levels will be tested. Up to six patients will be accrued to a given dose level to confirm that the dose level does not exceed MTD. The MTD will be defined as the dose below which 2 or more of 6 patients experience dose-limiting toxicity (DLT).

DLT includes the following:

- Any Grade 3+ non-hematologic toxicity. An exception is Grade 3 nausea/vomiting/diarrhea/electrolyte abnormality that is reduced to < Grade 3 with maximal supportive care within 3 days of onset.
- Any Grade 4 adverse event of any duration.
- Any Grade 3 adverse event that does not improve to baseline or Grade 1 within 7 days of onset.
- Any Grade 3 or 4 neutropenia associated with sepsis or fever > 38º C.
- Any Grade 4+ hematologic toxicity. An exception is Grade 4 neutropenia that improves to < Grade 4 within ≤ 7 days of onset.
- Grade 3 thrombocytopenia associated with clinically significant bleeding.

3+3 dose escalation design:

- If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the MTD has been exceeded and the next 3 patients will be treated at the next lower dose level (unless there have already been 6 accrued to that lower level).
- If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional patients (at least 2 of 6), the MTD will have been exceeded. If DLT is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.
- After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and defined as the previous dose level unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.
- If a patient fails to complete the initial course of therapy (hfRT) for reasons other than dose limiting toxicity defined adverse events, the patient will be regarded as uninformative in regard to the MTD goal and an additional patient will be treated at the current dose level
- If the starting dose level (6.5Gy x 2 fractions) already exceed MTD, dose de-escalation will NOT be performed due to the reasons as below.

Since the study is to look for potential synergy between consolidative hfRT and durvalumab and

because 6.5Gy/fraction is the likely minimal dose per fraction that is required to have immunostimulating effects per prior studies, no further dose de-escalation is proposed if 6.5Gy x 2 fractions exceed MTD. The trial will be stopped. Otherwise we will move on to test 10Gy x 2 fractions. If this dose exceeds MTD, we will choose the dose of 6.5Gy x 2 fractions for the next phase of the study. If 10Gy x 2 fractions regimen does not exceed MTD, we will choose 10Gy x 2 fractions as consolidative hfRT regimen for the next phase of the study. No additional dose escalation will be performed since the next dose level has not been clinically tested even by itself without immunotherapy and will likely start to induce immunosuppression per prior studies. After each cohort/dose level has been accrued the enrollment will temporarily pause to assess DLT status of each patient. An observation period of 4 weeks following completing hfRT is required to assess toxicity before enrolling a patient at the next dose level. The decisions to resume and at what level to resume the enrollment, are based on standard cohort 3+3 design.

All patients recruited in this step will be followed with biospecimen, *ie*, peripheral blood, collected as scheduled in section 7.0. Final data analyses such as PFS, OS, and exploratory aims will not include the patients treated at the dose level that is not selected for the second phase of the study.

The second phase of study
After determining which dose regimen to use for consolidative hfRT after the initial 3+3 dose escalation study, we will continue to enroll patients to a goal of 32 patients for final data analyses including those treated at the same dose level during dose escalation. Those patients in dose escalation step who are treated with the consolidative hfRT dose regimen that is not selected for the second phase will be followed in the study the same way as the rest of the cohort but will not be included in the final data analyses

Disease Progression:
Disease progression needs to be confirmed, the confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinical deterioration. Administration of study drug will continue between the initial assessment of progression and confirmation for progression.

For all subjects who are treated through progression, the investigator should ensure subjects do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the subject, and that the subject still meets all of the inclusion criteria and none of the exclusion criteria for this study including re- consenting to continue treatment. Subjects with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) will not be eligible to continue to receive study drug.

For more details about Follow-up of subjects after Disease progression see section 5.1.5 below.

5.1.3 End of treatment

End of treatment for current trial is defined as the last planned dosing visit within the 12-month dosing period of durvalumab. For subjects who discontinue durvalumab prior to 12 months, end

of treatment is considered the last visit where the decision is made to discontinue treatment, including the subjects who did not receive the second fraction of hfRT.

5.1.4 Follow Up for Subjects which have completed Durvalumab treatment with Disease Control

Assessments for subjects who have completed durvalumab treatment and achieved disease control, or have discontinued durvalumab due to toxicity in the absence of confirmed progressive disease are provided in Study Assessment tables (Section 7.0)

5.1.4.1 Re-treatment of subjects with 12-month disease control

Subjects who achieve and maintain disease control (ie, CR, PR, no evidence of disease, or SD) through to the end of the 12-month treatment period, may restart durvalumab upon evidence of confirmed PD (according to RECIST 1.1) during follow-up per treating physician discretion. Subjects would be considered off study.

5.1.5 Follow-up for subjects who have Confirmed Disease Progression

Subjects with confirmed PD that require discontinuing study drug, should have scans conducted according to local standard clinical practice (see Section 5.3.2.2.2.) until the subject commences a new treatment (these scans are optional).

Subjects with confirmed PD that continue to receive durvalumab at the discretion of the Investigator can receive study drug for a maximum of 12 months. For all subjects who are treated through progression, the investigator should ensure subjects do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the subject, and that the subject still meets all of the inclusion criteria and none of the exclusion criteria for this study including re-consenting to continue study drug. The same exceptions as noted in 5.1.2 apply. Subjects will follow the study assessments in Section 7.0 including tumor assessments every 12 weeks relative to Day 0 until study drug is stopped.

Assessments for subjects who have discontinued durvalumab treatment due to confirmed PD are presented in Study Assessment tables, Section 7.0.

All subjects will be followed for survival until the end of the study regardless of further treatments, or until the study ends.

5.2 Description of study procedures

5.2.1 Medical history and physical examination, electrocardiogram, weight, and vital signs

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examinations or focused physical examinations will be performed on study days noted in the Schedule of Assessments. A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph

nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems and at screening only, height. Focused exam is a physical exam with focus on AE reviews.

Resting 12-lead ECGs will be recorded at initial OR second screening (first time eligibility is determined) and as clinically indicated throughout the study. ECGs should be obtained after the subject has been in a supine position for 5 minutes and recorded while the subject remains in that position. In case of clinically significant ECG abnormalities, including a QTcF value ≥ 470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 2-5 minutes apart) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 9.1.
At baseline evaluation, a single ECG will be obtained on which QTcF must be <470 ms. The same is required at second screening after dCRT. In case of clinically significant ECG abnormalities, including a QTcF value ≥470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 2-5 minutes apart) to confirm the finding. Situations in which ECG results should be reported as AEs are described in Section 9.

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules.

5.2.2 Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments, for the timepoints of each test):

Hematology Laboratory Tests

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

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 0 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 0), and as clinically indicated.

[a] Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by DM if entered as percentage. Total white cell count therefore has to be provided.

Clinical Chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase[b]

Amylase[b]	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Creatinine Clearance[c]	TSH (Free T3 or free T4)[d]

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

[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.

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

[d] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day 0. Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system

Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Color and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells

If a subject shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, refer to Appendix I for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.
All subjects should have further chemistry profiles performed at 30 days (±3 days), 2 months (±1 week) and 3 months (±1 week) after permanent discontinuation of IP.
Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 9.2.

All subjects with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IP must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

All the above tests will be performed at local hospital clinical laboratories.

5.2.3. Biomarker/exploratory research and evaluation methods

5.2.3.1 PD-L1 testing

Sample collection for PD-L1 testing

- Samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (i.e., >100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.
- When the collection of a new sample is not clinically appropriate, archival samples may be utilized provided the specimen it is not older than 3 years of age. When archival samples are used to assess PD-L1 status, the age of the sample / date of collection should be captured.
- Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) are not appropriate for PD- L1 analysis.

Sample data collection for PD-L1 testing

The following fields of data should be collected from PD-L1 testing laboratory:

- Are the negative and positive controls stained correctly
- Is the H&E material acceptable
- Is morphology acceptable
- Total percent positivity of PD-L1 in tumor cells
- PD-L1 status (positive, negative or NA) in tumor cells
- Total percent positivity of PD-L1 in infiltrating immune cells

Sample processing and submission process for PD-L1 testing

Preparing Stored samples for testing

- Where samples already exist, they should be retrieved from the Bio-Bank storage location. These blocks should undergo quality review, prior to PD-L1 testing.

Preparing newly acquired samples for PD-L1 testing

- If subjects are undergoing a biopsy procedure that provides the option to submit newly acquired samples, this sample should be used to determine PD-L1 status. Where clinically acceptable, a minimum of 2 core biopsies should be collected and processed to FFPE in a single block. The provision of 2 cores is advised in order to provide sufficient tissue for PD-L1 assessment.
- It is recommended that core needle tumor biopsies are collected using an 18 gauge or larger needle and the process should be image-guided. Excisional or incisional samples are also adequate. If this is not per the institutions normal practice and a smaller gauge needle is used, then the number of cores collected should be increased to allow sufficient material for successful PD-L1 testing (>100 tumor cells) and embedded in the same block. If available, a single excisional biopsy of at least 4 mm in diameter may substitute for all core biopsies.

Fixation of biopsy samples for PD-L1 testing

- Previously frozen tissue is not acceptable for processing to FFPE for PD-L1 testing. To

fix newly acquired tissue, place immediately (within 30 min of excision) into an adequate volume of 10% v/v neutral buffered formalin (NBF). Samples should remain in fixative for 24 – 48 hours at room temperature.

- It is vital that there is an adequate volume of fixative relevant to the tissue (at least a 10-volume excess) and that large specimens (if any) are incised prior to fixation to promote efficient tissue preservation.

Embedding in paraffin for PD-L1 testing

- FFPE blocks should be stored at ambient temperature and protected from light at ambient temperature. FFPE blocks are stable under these conditions for an indefinite period

Quality control of samples to be used for PD-L1 testing

- Tissue should be assessed by the local pathologist prior to PD-L1 testing.
- Each sample should be reviewed for:
    - Adequate fixation
    - Good preservation of morphology
    - Presence of tumor tissue
    - Histopathology consistent with indication
    - Greater than 100 tumor cells are required to determine PD-L1 status – tumor cell content must be reviewed prior to testing in order for PD-L1 obtain a valid result.
- When submitting sample for PD-L1 testing the recommendation is to deliver the block in order for sectioning to occur at the laboratory. Blocks should be delivered - containing enough material to be provided to allow a minimum of 5, and preferably 10, sections to be cut (each 4-micron thick) to be used for PD-L1 testing.

Sectioning instructions

- It is recommended that slides are cut freshly prior to PD-L1 testing and they are used within 90 days of being cut to obtain PD-L1 status.

PD-L1 testing in this trial will be performed at the regional pathology service at Department of Pathology at University of Nebraska Medical Center

5.2.3.2 Exploratory research

Blood will be drawn from each subject in this study for exploratory research purpose such as biomarker studies including sPD-L1, miRNA/mRNA, and cytokines, as well as ctDNA isolation for mutation and tumor burden studies and PBMC collection for flow cytometry.

During standard of care dCRT, 20 cc of blood will be drawn each time at the schedule listed as below:

1. During the screening/baseline timepoint, ideally drawn together for other blood tests, e.g., routine pre-chemotherapy lab tests;

2. After 5 fractions but prior to the 6th fraction of RT. Draw on the day of the 6th fraction before delivery of the dose;
3. After 15 fractions but prior to the 16th fraction of RT. Draw on the day of the 16th fraction before delivery of the dose;
4. Within 72 hours after the last dose of RT. Prefer within 12 to 36 hours after the last dose.

After completing dCRT, 20cc of blood will be drawn each time at the schedule listed as below:

1. Within 24 hours of the CT simulation but prior to the procedure;
2. Day of the first fraction of hfRT prior to delivery of the dose;
3. Day of the second fraction of hfRT prior to the delivery of the dose;
4. Within 24-72 hours after delivery of the second fraction of hfRT but prior to the start of next cycle (the third cycle) of durvalumab;
5. At each subsequent follow-up visit, +/- 7 days. Q12w ± 1w for the first 48 weeks (relative to Day 0, and thereafter until confirmed objective disease progression/death (whichever comes first). The schedule of q12w ± 1 week for and thereafter MUST be followed regardless of any delays in dosing. If the visit/blood draw at 8 weeks after study treatment start is scheduled prior to one week after finishing of hfRT, then this appointment/blood draw can be cancelled.

5.2.3.3 Estimate of volume of blood to be collected

The total volume of blood that will be drawn from each subject in this study depends on the length of time that the subject receives durvalumab. The table below is a guide to the approximate volume of blood that will be drawn from each subject, based on the assumption that each subject remains in the study on treatment for 3 months after starting and attends all the planned visits, with additional volumes planned in before and during dCRT period prior to screening.

Volume of Blood to be Drawn From Each Subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	1.0	11	11.0
	Hematology	2.0	11	22.0
	Thyroid	1.0	10	10.0
	Coagulation	3.0	2	6.0
Biomarkers	Soluble PD-L1 (to assess target engagement)	5.0	10*	50.0
	Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumor and self antigens in circulation)	5.0	10	50.0
	miRNA/mRNA (to examine immune cell gene expression profiles in circulation)	5.0	10	50.0
	ctDNA	5.0	5	25.0

PBMC	Flow cytometry**	---	--	---
Total		37 mL	76	220.5 mL

HIV Human immunodeficiency virus; miRNA Micro RNA; mRNA Messenger RNA; PD-L1 Programmed death ligand 1.

* number of samples are estimated based on 12 months follow-up after Day 0.
** Cells for flow cytometry will be used from blood collected for the biomarkers.

5.2.3.4 Archival tumor samples and fresh tumor biopsies use beyond PD-L1

For subjects who consent to a repeat biopsy of residual lung tumor and/or lymph nodes (optional) two months after hfRT, the fresh tumor tissue from 2-3 core needle biopsy will be collected and processed to FFPE in a single block for PD-L1 testing as described in section 5.2.3. If additional slides are available after PD-L1 staining, immunohistochemistry studies can be performed to study on immune cell infiltration into irradiated tumor microenvironment if funding is available. The fresh specimen will be used up or disposed of after analyses or formalin-fixed and retained for further use as described here.

5.2.3.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented.

The Principal Investigator:

- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject is informed about the sample disposal.

5.2.4 Quality of Life questionnaire

A health-related Quality of Life questionnaire will be used throughout this study. For this study PRO, the European Organization for Research and Treatment of Cancer (EORTC) questionnaire to evaluate the quality of life of subjects with malignant disorders will be used. Nine multi-item scales were incorporated into QLQ-C30, including five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. The study coordinator will administer the EORTC QLQ-C30 to the subject at specific points throughout the study. Questionnaires will be administered at the time of screening and at CT simulation. Thereafter, questionnaires will be administered every 12 weeks (± 2 weeks) relative to Day 0 until confirmed disease progression or until treatment with durvalumab is discontinued.

5.3 Radiation Therapy

5.3.1 Radiation therapy planning for definitive chemoradiation therapy (standard care)

Eligible subjects should have histologically or cytologically documented stage III NSCLC according to the Staging Manual in Thoracic Oncology, version 7, of the International Association

for the Study of Lung Cancer. The subjects can be screened and enrolled preliminarily prior to starting the phase of definitive chemoradiation therapy (dCRT) and re-evaluated after the follow-up imaging post-dCRT (Day 0.) If no signs of disease progression with residual lung cancer size ≤5cm in largest axis, the subject will complete screening and be registered. The subject will start consolidative/adjuvant durvalumab within 42 days after the end of dCRT phase at 10mg/kg body weight intravenously every two weeks. Consolidative hfRT to the residual lung mass will be delivered between the second and third cycle of durvalumab. No specific dates are required for delivering hfRT between the two cycles.

Subjects should receive a course of dCRT prior to the final study eligibility confirmation. Subjects should receive treatment 5 days per week, one fraction per day, 1.8-2 Gy per fraction to a total dose of 59.8 to 60 Gy which is strongly recommended dosing although a total dose of 57 to 63 Gy is allowed for subjects to be enrolled to current trial. 3D conformal radiation therapy (3DCRT) or intensity modulated radiation therapy (IMRT) can be used per physician's choice for RT planning. Chemotherapy should be given concurrently with radiation therapy per standard care and institutional preference. More specifically, these subjects should receive two or more cycles (defined according to local practice) of platinum-based doublet chemotherapy (containing etoposide, vinblastine, vinorelbine, a taxane [paclitaxel or docetaxel], or pemetrexed) concurrently with RT. No adjuvant chemotherapy after concurrent CRT is allowed.

Meeting the following dose constraints with conventional fractionated RT as part of the definitive chemoradiation is mandatory for eligibility of the current trial.

Critical Organ	Max Dose Limit	Volume/Dose constraint
Total Lung-CTV	< 110% of PD	V20 Gy < 30%[a] (accept < 35%) mean dose <15 Gy (accept < 20Gy)
Esophagus	<105% of PD	mean dose <34 Gy
Cord	45 Gy	
Heart		V50 Gy < 25%; V45 Gy < 67%; V40 Gy < 100% mean < 35 Gy
Brachial plexus	60 Gy preferred, accept 66Gy	

a V20 Gy < 30%: no more than 30% of the volume of total lung minus the CTV should receive 20 Gy or more dose; CTV clinical tumor volume; PD prescribed dose;
Normal tissue constraints shall be prioritized in the following order for treatment planning: 1=spinal cord, 2=lungs, 3=esophagus, 4=brachial plexus, and 5=heart

5.3.2 Consolidative hypofractionated radiation therapy (investigational therapy)
5.3.2.1 Dose specifications
5.3.2.1.1 Stereotactic targeting and treatment

SBRT has now been formally defined and described in a published guideline from the American College of Radiology and American Society for Therapeutic Radiology and Oncology (Potters 2004). This protocol will respect that guideline. **NOTE:** 3-D conformal and intensity modulated radiation therapy (IMRT) are both allowed for planning of this step. The same planning method as in the course of dCRT is strongly recommended for medical billing purpose but not mandated.

5.3.2.1.2 Dose fractionation

All subjects will receive the radiation dose determined per the 3+3 dose escalation study (see section 5.1.2), with a total dose of either 13 Gy or 20 Gy in 2 fractions to the prescription line at the edge of the planning tumor volume (PTV), one fraction per day, every other day with the exception that, if the first fraction is delivered on a Friday, the second fraction is allowed on the following Monday (see Section 5.3.2.4. for more prescription details).

5.3.2.1.3 Premedications

It is not recommended to prescribe corticosteroid for premedication purpose (e.g., Dexamethasone) before or after each hfRT treatment due to concerns of interfering immunotherapy drug effects. Steroid use for symptomatic management is allowed as per Appendix I. Analgesic premedication to avoid general discomfort during long treatment durations also is recommended when appropriate.

5.3.2.2 Technical factors
5.3.2.2.1 Physical factors

Only photon (x-ray) beams produced by linear accelerators with photon energies of 4-10 MV will be allowed. Photon beam energies > 10 MV but not > 15 MV will be allowed only for a limited number (≤ 2) beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the target.

5.3.2.2.2 Minimum field aperture (field size) dimension

Because of uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, a minimum field dimension of 3.5 cm is required for any field used for treatment delivery for sites using standard 3-D conformal techniques where nearly all of the PTV is encompassed for each beam. It is understood that this may exceed the technical requirements listed in Section 5.3.2.4.2 Dosimetry for small lesions (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension). In such cases, the prescription dose is still prescribed to the edge of the defined PTV. This minimum field dimension does not apply to IMRT planning with a standard multileaf collimator or Tomotherapy or for the CyberKnife® unit where by design the entire PTV is not encompassed for each beam.

5.3.2.3 Localization, simulation and immobilization
5.3.2.3.1 Subject positioning

Subjects will be positioned in a stable position. A variety of immobilization systems may be used, including stereotactic frames used in our institute that surround the subject on three sides and large rigid pillows (conforming to subjects' external contours) with reference to the stereotactic coordinate system (Potters 2004). Subject immobilization must be reliable enough to insure that in combination with the techniques used to inhibit target motion, the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV) with any significant probability.

5.3.2.3.2 Inhibition of effects of internal organ motion

Special considerations must be made to account for the effect of internal organ motion (e.g., breathing) on target positioning and reproducibility. Acceptable maneuvers include reliable abdominal compression, accelerator beam gating with the respiratory cycle, tumor tracking, and active breath-holding techniques. Internal organ inhibition maneuvers must be reliable enough to insure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., < 5%).

5.3.2.3.3 Localization

Isocenter or reference point port localization images should be obtained on the treatment unit immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. These IGRT images can be obtained with planar kV imaging devices, an in-room helical CT device, tomotherapy helical CT, cone-beam CT equipment, of standard EPID imaging. In all cases, the RTOG Image Guidance Guidelines must be followed. For treatment systems that use kV imaging but also allow EPID imaging using the treatment beam, orthogonal images verifying the isocenter also should be obtained.

5.3.2.4 Treatment planning/target volumes

5.3.2.4.1 Image acquisition

Computed tomography will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the subject anatomy and fiducial system for stereotactic targeting. Intravenous (i.v.) contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels within 12 weeks of Day 0 on the trial. If not, i.v. contrast should be given during the planning CT; i.v. contrast at simulation may be omitted even in this case if contraindicated (e.g. allergy or renal insufficiency. Contrast will allow better distinction between tumor and adjacent vessels or atelectasis. Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 3.0 mm between scans. Images will be transferred to the treatment planning computers via direct lines.

The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume (GTV). The target will generally be drawn using CT pulmonary windows; however, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. 4-dimensional CT image guided GTV delineation to take tumor motion into consideration is mandated. This target will not be enlarged whatsoever for prophylactic treatment (including no “margin” for presumed microscopic extension); rather, include only abnormal CT signal consistent with gross tumor (i.e., the GTV and the clinical target volume [CTV] are identical).

With 4D CT-simulation, an internal target volume (ITV) around the GTV, accounting for tumor motion may be defined from the 4D CT dataset. The PTV will include the ITV plus an additional 0.5 cm margin uniformly applied to the ITV.

5.3.2.4.2 Dosimetry

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for

each case to deliver highly conformal prescription dose distributions. Non-opposing, noncoplanar beams are preferable. Typically, ≥ 10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of 7 non- opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. In order to obtain acceptable coverage, field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception should be when observing the minimum field dimension of 3.5 cm when treating small lesions (see above). As such, prescription lines covering the PTV will typically be the 67-90% line (where the maximum dose is 100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The treatment isocenter or setup point in stereotactic coordinates will be determined from system fiducials (and can be adjusted pre-treatment depending on the results from localization imaging studies) and translated to the treatment record.

For purposes of dose planning and calculation of monitor units for actual treatment, this protocol will require tissue density heterogeneity corrections. The particular algorithm used for such correction is per institutional protocol.

5.3.2.4.3 Prescription dose constraints for treatment planning

Successful treatment planning will require accomplishment of all of the following criteria:

1. Maximum dose: The treatment plan should be created such that 100% corresponds to the maximum dose delivered to the subject. This point must exist within the PTV.
2. Prescription isodose: The prescription isodose surface must be ≥ 67% and < 100% of the maximum dose.

3. Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 90% close to of the target volume (PTV) is conformally covered by the prescription isodose surface (PTV V100Rx = 90%) and 99% of the target volume (PTV) receives a minimum of 80% of the prescription dose (PTV V80%Rx > 99%). For ITV, V100Rx=95%; V80%Rx=100%.

4. High Dose Spillage:
   The cumulative volume of all tissue outside the PTV receiving a dose > 105% of prescription dose should be no more than 15% of the PTV volume.

5. Intermediate Dose Spillage

   The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:

   a. Location

   The maximum total dose over all fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction must be no greater than D2CM where D2CM is given by the table below.

b. Volume

The ratio of the volume of 50% of the prescription dose isodose to the volume of the PTV must be no greater than R50% where R50% is given in the table below. This table is used for all prescription requirements as stated above irrespective of calculation algorithm and total treatment dose.

Conformality of Prescribed Dose for Calculations Based on Deposition of Photon Beam Energy in Heterogeneous Tissue

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV Volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, $R_{50\%}$		Maximum Dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D_{2cm} (%)		Percent of Lung Receiving 20 Gy Total or More, V_{20} (%)	
	Deviation		Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor	None	Minor
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15
3.8	<1.2	.<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	<91.0	<10	<15
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	<94.0	<10	<15

Note 1: For values of PTV dimension or volume not specified, linear interpolation between table entries is required.
Note 2: Protocol deviations greater than listed here as "minor" will be classified as "major" for protocol compliance (see Section 5.3.3.4).

5.3.3 Critical structures

5.3.3.1 Critical organ dose-volume limits

The following table lists maximum dose limits to a point or volume within several critical organs. Except for the rib, these are absolute limits, and treatment delivery that exceeds these limits will constitute a protocol violation. The dose is listed as total delivered. These limits were formulated using tolerance data with biological equivalent dose (BED) conversion from prior SBRT experience including RTOG 0813 and historical data as published by Kumar et al 2017 from their experience on SBRT boost (without immunotherapy) for post-chemoradiation residual disease.

The esophagus, trachea, bronchi and heart may be situated adjacent to the treated GTV/PTV. As such, there is no specified limit as tumors that are immediately adjacent to that organ will not be able to be treated to any of the prescription doses without irradiating a small volume of that organ to the prescribed dose. **In such a case, safety takes priority** since the entire tumor has received standard dose of RT previously. The planning needs to be done so that all OARs meet the dose constraints as shown in the table below, even if that organ is part of the PTV, except for skin and rib. In addition, the volume of the OAR in question needs to be minimized, both in length and in the width (i.e., circumference), with efforts made to reduce the dose to the contralateral wall of the organ. **The volume limits (columns 2, 3 and 4) will be scored as protocol violations if exceeded by 5%, except for skin and rib which has dose constraints**

listed in the table below only as suggested for planning. For centrally located tumor, the constraints for "trachea & ipsilateral bronchus" is not required. PTV coverage should be attempted to meet recommendations with reasonable effort but can be compromised in order to meet the normal tissue constraints if needed.
For tumors that are not immediately adjacent to any OAR, centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures; we expect that the OAR doses will be as low as achievable (ideally, < 4 Gy/fraction).

Normal tissue constraints for consolidative RT

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)**	**Avoidance Endpoint**
Spinal Cord	<0.03 cc	5.5 Gy (2.75 Gy/fx)		Myelitis
Ipsilateral brachial plexus	<0.03 cc	6 Gy (3 G/fx)		neuropathy
Rib*	<1 cc	16 Gy (8 Gy/fx)	17.6 Gy (8.6 Gy/fx)	Pain or fracture
Skin*	<10 cc	14 Gy (7 Gy/fx)	12.8 Gy (6.4 Gy/fx)	ulceration
Stomach	<10 cc	7.2 Gy (3.6 Gy/fx)	12.8 Gy (6.4 Gy/fx)	Ulceration/fistula
Parallel Tissue	**Critical Volume**	**Critical Volume Dose Max (Gy)**		**Avoidance Endpoint**
Lung, Total	1500 cc	5 Gy (2.5 Gy/fx)		Basic Lung Function
Lung, Total	< 25% < 15% < 5% <1.5% 1000 cc	2.5 Gy (1.25 Gy/fx) 5 Gy (2.5 Gy/fx) 10Gy (5 Gy/fx) 20Gy (10 Gy/fx) 5.4 Gy(2.7Gy/fx)		Pneumonitis
Esophagus, non-adjacent wall	< 5 cc	11 Gy (5.5 Gy/fx)	16Gy (8 Gy/fx)	Stenosis/fistula
Heart/pericardium	< 15 cc	12.8 Gy (6.4 Gy/fx)	16Gy (8 Gy/fx)	pericarditis
Trachea and ipsilateral bronchus**	< 4 cc	6.6 Gy (3.3 Gy/fx)	14 Gy (7 Gy/fx)	Stenosis/fistula
Trachea and ipsilateral bronchus, non-adjacent wall	< 4 cc	7.2 Gy (3.6 Gy/fx)	12 Gy (6 Gy/fx)	Stenosis/fistula
Great Vessels, non-adjacent wall			12 Gy (6 Gy/fx)	aneurysm

PD prescription dose;
Exceeded any of these limits by 5% is a protocol violation except for skin and rib (*) with dose constraints provided for suggested planning.
** circumferential volume of trachea and ipsilateral bronchus dose constraints are only required for proximally located tumor as defined in Section 5.3.3.4. Also see Section 5.3.3. for more details.

In order to verify each of these limits, the organs must be contoured such that appropriate dose volume histograms can be generated. Instructions for the contouring of these organs are as follows in Section below.

5.3.3.2 Contouring or normal tissue structures

All structures listed in Sections 5.3.3.2.1 through 5.3.3.2.11 should be contoured in every subject irrespective of the location of the PTV. The structures listed in Sections 5.3.3.2.12 through 5.3.3.2.13 are only required if the named structure lies within 5 cm of the PTV.

5.3.3.2.1 Spinal cord
The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

5.3.3.2.2 Esophagus
The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

5.3.3.2.3 Brachial plexus
The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib.

5.3.3.2.4 Heart
The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.

5.3.3.2.5 Trachea and proximal bronchial tree
The trachea and proximal bronchial tree will be contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. For this purpose, the trachea will be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree. Differentiating these structures in this fashion will facilitate the eligibility requirement for excluding subjects with tumors within 2 cm of the proximal bronchial tree (see Section 5.3.3.2.10 below).

5.3.3.2.6 Proximal trachea
Contouring of the proximal trachea should begin at least 10 cm superior to the extent of the PTV or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.

5.3.3.2.7 Proximal bronchial tree

The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides. The following airways will be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.

5.3.3.2.8 Whole lung

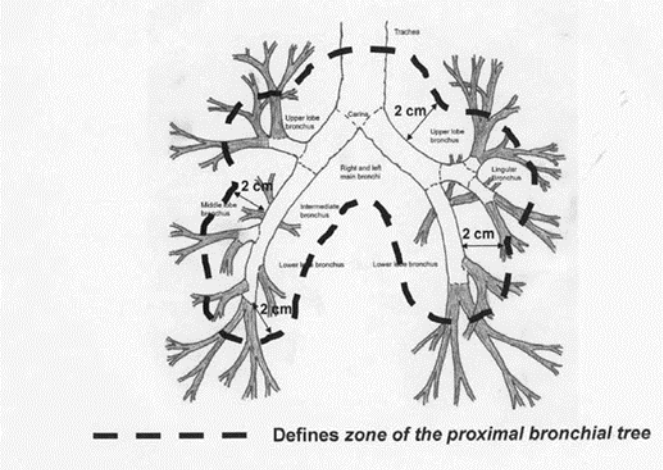
Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.

5.3.3.2.9 PTV plus 2 cm

As part of the QA requirements for "low dose spillage" listed in Section 5.3.3.5, a maximum dose to any point 2 cm away in any direction is to be determined. To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning.

5.3.3.2.10 Proximal bronchial tree plus 2 cm

To differentiate a "centrally located tumor" versus a "peripherally located tumor", it is convenient to define an artificial structure 2 cm larger in all directions from the proximal bronchial tree. If any part of the GTV falls within this artificial structure, the subject should be treated as "centrally located tumor". Otherwise the tumor is considered as "peripherally located tumor". Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. Defining the tumor as "centrally located tumor" versus a "peripherally located tumor" does not change prescription dose but affects tracheal and ipsilateral bronchus dose constraint requirement.



5.3.3.2.11 Skin

The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

5.3.3.2.12 Rib

Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow. Typically, several portions of adjacent ribs will be contoured as one structure. Adjacent ribs, however, should not be contoured in a contiguous fashion (i.e., do not include the intercostal space as part of the ribs).

5.3.3.2.13 Great vessels

The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV. For right sided tumors, the vena cava will be contoured, and for left sided tumors, the aorta will be contoured.

5.3.3.2.14 Other structures

The constraints tables above contain other structure, eg. stomach. These are required if the treated lesion is within 5 cm of the PTV.

5.3.3.3 Documentation requirements

In general, treatment interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record.

5.3.3.4 Compliance criteria

5.3.3.4.1 Dosimetry compliance

Section 5.3.2.4.3 describes appropriate conduct for treatment planning dosimetry for target coverage and the dose falloff. The Principal Investigator and co-investigators at radiation oncology of local institute will evaluate plans. Criteria for both Per Protocol (listed in the table as "None") and Variations Acceptable (listed under the heading of "Minor") are given in this table. Deviations Unacceptable occur when the stated Minor limits are exceeded. The table in Section 5.3.3.1 lists dose volume limits for specific organs and structures. Exceeding these dose limits by more than 2.5% constitutes a Variation Acceptable. However, exceeding these dose limits by more than 5% **(columns 2, 3 and 4 in the table) constitutes a Deviation Unacceptable, except for skin and rib which has dose constraints listed as suggested for planning. For centrally located tumor (see definition in Section 5.3.3.2.10), the constraints for "trachea & ipsilateral bronchus" is not required.**

5.3.3.5 Radiation therapy adverse events recording

Some of the toxicities from consolidative RT using immunostimulating dose regimen might be challenge to be distinguished from the ones from immunotherapy, e.g., durvalumab therapy such as pneumonitis, pericarditis, etc.. However, there is concern about effects mainly if not only from consolidative RT on organs at risk, most notably central airway, esophagus and heart/pericardium, as these organs can be in immediate proximity to some centrally-located tumors, or chest wall/rib pain or focal skin rash in RT field treating some peripherally-located tumors.

Currently there is no clearly defined guideline to separate RT- *vs*. immunotherapy-related AE's when both modalities are administered concurrently. For toxicities out of thorax and out of RT field, for the purpose of this study, we will define AE's as durvalumab-related. For AE's in tissues in thorax, i.e., chestwall/rib, esophagus, airway, great vessels and heart, or tissues adjacent to thorax such as liver and stomach, RT dose distributions in each organ will be reviewed from the sum plan combining RT plans of dCRT and hfRT. If TD5/5 dose constraint (the radiation dose that would result in 5% risk of severe complications within 5 years after irradiation based on QUANTEC, Marks *et al* 2010) is exceeded, we will define the SAE's as RT-related; otherwise as durvalumab-related. For the analyses on the incidence of treatment-related SAE's for the stopping rule, all SAE's will be summarized disregarding of whether it is RT- or durvalumab-related. Radiation pneumonitis is defined separately in section **5.3.3.5.4.**

5.3.3.5.1 Cardiac and pericardial injury

Although cardiac and pericardial injury is uncommon in the conventionally fractionated course of RT, with large doses per fraction of hfRT or SBRT, a number of possible side-effects can be seen especially when given during immunotherapy. Hospitalization or outpatient referral to cardiology is recommended depending on symptoms and acuity.

5.3.3.5.2 Gastrointestinal/esophageal injury

The radiation effects on the esophagus can be acute: esophagitis (i.e., dysphagia, causing pain on swallowing, typically relatively soon after RT course is completed, and typically resolves on its own within days to a week or longer), or chronic, typically manifesting with dysphagia due to stenosis, or esophageal ulceration, with perforation in the extreme cases. Acute esophagitis will be managed according to severity with dietary modification, liquid analgesics, oral pain medications with IV fluid support if necessary. Management of diarrhea which is unlikely from RT alone, should follow Appendix I.

5.3.3.5.3 Central airway/bronchial injury

This bronchial injury with subsequent focal collapse of lung may impair overall pulmonary status. It also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Because atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease while the actual tumor may be stable or shrinking. Investigators are referred to the strict criteria for progressive disease in Section 6.0 of this protocol to avoid such mis-characterization.
The consequences of bronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should all be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), v. 5.0.

5.3.3.5.4 Lung injury

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Radiation fibrosis is a late manifestation of radiation injury to the irradiated lung. Given the small amount of lung that is typically included in the SBRT portals, lung toxicity has not been shown to increase significantly delivered after chemoradiation therapy as reported by Kumar et al 2017. However, again no data is available now when doing hfRT or SBRT boost with immunotherapy after chemoradiation therapy as in current trial design. The symptoms may be confused with other causes of respiratory deterioration, including infections, and tumor recurrence. It is very important that Oncologists participate in the care of the patient,

as the clinical picture may be very similar to acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically "geometric" corresponding to the radiation portal, but may also be ill defined.

Since both RT and immunotherapy alone can cause pneumonitis, we further defined radiation pneumonitis per convention as:

The diagnosis of **radiation pneumonitis** is based on a combination of typical symptoms (eg, cough, dyspnea, and sometimes fever), compatible imaging findings per CXR and/or CT chest, dose distribution of radiation therapy, and exclusion of other causes, such as infection including the novel coronavirus SARS-CoV-2 (COVID-19), heart failure, pulmonary embolism, drug-induced pneumonitis, bleeding, and progression of the primary tumor. The opacities on imaging should conform to or at least overlap with the high isodose lines (IDLs) of radiation port/field defined by 50% IDL or above in either the initial dCRT or the hfRT plan (modified from Olivier *et al* 2020).

Accordingly, **durvalumab-related pneumonitis** is defined for those with typical symptoms, compatible imaging findings but with opacities showing no overlapping with high IDLs of radiation port/field defined by 50% IDL or above in either the initial dCRT or the hfRT plan, after clusion of other causes as defined above.

We recognize that there is no commonly accepted definition of "radiation pneumonitis" in the era of immunotherapy. Based on the above definition, the diagnosis is to be made upon physicians' clinical judgement based on factors listed, and commonly in a multi-disciplinary fashion.

In current proposed study, all pneumonitis will be defined as "radiation pneumonitis" vs. "Durvalumab-related pneumonitis" at our best judgement, but will be combined in toxicity analyses as in the PACIFIC trial and medically treated the same. Accordingly, CTCAE 5.0 only categorize "pneumonitis" as in one condition and does not differentiate the cause.

Subjects reporting symptoms as above will be promptly evaluated and treated. Mild pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised subjects. Details are provided in Section 5.3.3.5 and in Appendix I.

5.3.3.5 Toxicity management guidelines

Toxicities other than what are listed in Section 5.3.3.5 should be managed the same way as managing side effects from immunotherapy since it is likely contributed mostly from durvalumab which could be enhanced by the immunostimulating effects of consolidative RT. In the situation that subject develops significant side effects from the first fraction of consolidative RT such as acute worsening of dyspnea, cough (dry or productive), arrhythmia, etc., imaging study such as a chest X-ray and/or ECG should be ordered within 24 hours.

Hospitalization and/or steroid use will be determined per treating physician(s). **If the subject develops grade 2 pneumonitis, postponing the second fraction to up to one week after the first one is allowed in the trial if subject's condition returns to baseline within 3 days with maximum supportive care. If not, the second fraction of consolidative RT will be cancelled.** Any grade 3 pneumonitis developed after the first fraction of consolidative RT but prior to the second fraction immediately warrant cancelling of the second fraction. For other acute symptoms developed after the first fraction, cancelling of the second fraction of consolidative RT will be based on the recommendation of treating physician(s). The subject will remain on the protocol for assessment and other related follow-ups per protocol unless he/she decides to withdrawal. Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in Appendix I

Subjects should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis.. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see section 3.3. of this protocol and the Dosing Modification and Toxicity Management Guidelines in Appendix I).

Following the first dose of IP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in Appendix I provided by Astra Zeneca. These guidelines apply to AEs considered causally related to durvalumab monotherapy by the reporting investigators previously.

Dose reductions of durvalumab are not permitted.

Subjects should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

All toxicities will be graded according to NCI CTCAE, Version 5.0.

5.4 Restrictions during the study and concomitant treatment(s)

5.4.1 Restrictions during the study

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

Female subject of child-bearing potential

- Female subjects of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (table below) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Non-sterilised male partners of a female subject 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 subjects should also refrain from breastfeeding throughout this period.

Male subjects with a female partner of childbearing potential

- Non-sterilized male subjects 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). However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout this period.
- Female partners (of childbearing potential) of male subjects must also use a highly effective method of contraception throughout this period (table below).

Natural born 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 the table below. 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).

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

Barrier/Intrauterine methods	Hormonal Methods

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

[a] This is also considered a hormonal method

Blood donation
Subjects should not donate blood while participating in this study; or for at least 90 days following the last infusion of durvalumab or 90 days after receipt of the final dose of durvalumab, or at least six months after last dose of RT, whichever occurs longest.

5.5 Concomitant treatment(s)

5.5.1 Permitted concomitant medications

Supportive Medications

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

5.5.2 Excluded concomitant medications

Prohibited Concomitant Medications

Prohibited medication/class of drug:	**Usage:**
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the subject is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the subject is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the subject is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs, • Use in subjects with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the subject (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of durvalumab during the study
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Principal investigator

Section 6.0 MEASUREMENT OF EFFECT

6.1 Investigator RECIST 1.1-based assessments

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following (Wolchok et al 2009, Nishino et al 2013):

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after PD by conventional criteria
- The appearance of new lesions may not represent PD with immunotherapy
- SD while on immunotherapy may be durable and represent clinical benefit.

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anticancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anticancer compounds, the study may wish to implement the following in addition to standard RECIST 1.1 criteria:

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with durvalumab would continue between the initial assessment of progression and confirmation for progression.
- In addition, subjects may continue to receive durvalumab beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that subjects continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of durvalumab and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

* Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anticancer therapy other than durvalumab or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

All RECIST assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a subject discontinues study drug or receives another anti-cancer therapy.

At each visit, subjects will be programmatically assigned a RECIST 1.1 visit response of CR, PR, NED, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Subjects with no evidence of disease at follow-up in the absence of new lesions will be assigned a response of NED.

If a subject has had a tumor assessment which cannot be evaluated even after multi-disciplinary evaluation among treating physician(s), radiologist(s), etc., then the subject will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

Subjects who have disease control following completion of 12 months of treatment or subjects who are withdrawn from durvalumab treatment for reasons other than confirmed

PD will continue to have objective tumor assessments (see Study assessment tables, Section 7.0).

Confirmation of progression guidelines are set for the following reasons:

- for subject management and treatment decisions
- in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression
- when scans are evaluated by Investigator and by BICR, to reduce informative censoring by Investigator assessments (Investigator assesses PD at a time-point earlier than does BICR).

Confirmed objective disease progression refers to either of the following scenarios:

1. clinical progression/deterioration followed by a radiologic verification scan (PD by RECIST 1.1); or

2. in the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of progression criteria listed below. RECIST 1.1 modified for confirmation of progression refers to the second scenario above. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of PD with RECIST 1.1.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:

- ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir,

- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre- existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point),

- and/or additional new unequivocal lesions at the confirmatory scan time-point.

NOTE: In order to have confirmed objective disease progression, there should be two consecutive assessments meeting the PD definition: the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above). If the first assessment fulfilling the PD definition by RECIST 1.1 is not confirmed, continue with assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan. In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.

If progression is not confirmed, in the absence of significant clinical deterioration, then the subject should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. **If the first PD is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

6.1.1 Timing of Tumor Assessments

Tumor assessment must occur every 12 weeks (± 2 weeks) relative to Day 0 during the first 48 weeks following the first administration of durvalumab, and thereafter until confirmed objective disease progression or death.

Tumor assessment in subjects who achieve disease control following 12 months of durvalumab treatment will continue to be completed every 12 weeks (± 2 weeks) relative to Day 0 until confirmed disease progression, death, or until 2 years post-Day 0, whichever comes first. Tumor assessment following confirmed disease progression will be completed according to standard of care. Tumor assessment occurring beyond 2 years post-Day 0 will be completed according to standard of care.

Tumor assessment in subjects who discontinue treatment with durvalumab for any reason other than confirmed disease progression will continue to be completed every 12 weeks (± 2 weeks) relative to Day 0 until confirmed disease progression, death, or until 2 years post-Day 0, whichever comes first. Tumor assessment following confirmed disease progression will be completed according to standard of care. Tumor assessment occurring beyond 2 years post-Day 0 will be completed according to standard of care.

Tumor assessment in subjects who continue to receive durvalumab post-confirmed disease progression must be completed every 12 weeks (± 2 week) relative to Day 0 until treatment with durvalumab is discontinued. Upon discontinuation of durvalumab, tumor assessment will be completed according to standard of care.

Tumor assessment in subjects who discontinue durvalumab post-confirmed disease progression will be completed according to standard of care.

6.1.2 Efficacy variable in primary and secondary endpoints

6.1.2.1 Progression-free survival (PFS)

PFS (assessed per RECIST 1.1) will be defined as the time from Day 0 until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdraws from therapy or receives another anti-cancer therapy prior to progression. Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the subject progresses or dies after 2 or more missed visits, the subject will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the subject has no evaluable visits or does not have baseline data they will be censored at Day 1 unless they die within 2 visits of baseline.

The PFS time will always be derived based on scan/assessment dates not visit dates. RECIST 1.1 assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- The date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or of either reviewer where both select PD as a time point response.

- For investigational assessments, the date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that indicates progression

- When censoring a subject for PFS the subject will be censored at the latest of the dates contributing to a particular overall visit assessment.

Note: For target lesions, only the latest scan date is recorded in the RECIST eCRF out of all scans performed at that assessment for the target lesions and similarly for non-target lesions only the latest scan date is recorded out of all scans performed at that assessment for the nontarget lesions.
Additionally, PFS will be obtained using the algorithm described above by RECIST 1.1, but following a modification whereby any objective disease progression must be confirmed by the next scheduled scan. The confirmatory scan must be no sooner than 4 weeks after the initial suspected progression. If disease progression is confirmed (or disease progression occurs and no further scans are recorded) then the date of progression will be when it was originally observed. Subjects with a single disease progression and no further tumour assessment scans will be treated as PD in the analysis.
In the absence of clinically significant deterioration the investigational site is advised to continue the subject on study drug until progression has been confirmed.

6.1.2.2 Overall survival (OS)

OS is defined as the time from Day 0 until death due to any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.
Note: Survival calls will be made in the week following the date of DCO for the analysis, and if subjects are confirmed to be alive or if the death date is post the DCO date these subjects will be censored at the date of DCO. Death dates may be found by checking publicly available death registries.

6.1.2.3 Time to death or distant metastasis (TTDM)

TTDM will be defined as the time from Day 0 until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis is defined as any new lesion that is outside of the radiation field according to RECIST 1.1 or proven by biopsy. Subjects who have not developed distant metastasis or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the subject has distant metastasis or dies after 2 or more missed visits, the subject will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the subject has no evaluable visits or does not have baseline data they will be censored at Day 1 unless they die within 2 visits of baseline.

Section 7.0 STUDY PARAMETERS

SCHEDULE OF STUDY ASSESSMENTS

Baseline Evaluation assessments during standard care of definitive chemoradiation therapy (dCRT) (Only for patients consented prior to dCRT)

		definitive chemoradiation (dCRT) phase						
	Week 1and 2	Week 3 +/-3 days	Week 4 +/-3 days	Week 5 +/-3 days	Week 6 +/-3 days	Week 7 +/-3 days	Week 8 +/-3 days	Week 9 +/-3 days
Procedure/Scale	Screening	Visit No. 3	Visit No. 4	Visit No. 5	Visit No. 6	Visit No. 7	Visit No. 8	Visit No. 9[b]
Informed consent for preliminary enrollment	X							
Eligibility criteria	X							
Demographics	X							
Medical History	X							
Physical Exam (full)	X							
ECOG performance status	X							
Targeted physical exam based on symptoms		X	X	X	X	X	X	X
Vital Signs & Weight & Height[a]	X	X	X	X	X	X	X	X
ECG	X[c]							
Laboratory Assessments								
Clinical Chemistry	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	
Creatinine Clearance	X							
Hematology	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	
Coagulation (PT/INR)	X	---------- As clinically indicated ----------						
TSH, T4 (reflex free T3[g])	X	---------- As clinically indicated ----------						
Pregnancy test[f]	X							
Urinalysis	X							
Monitoring								
Adverse Event monitoring	X	X	X	X	X	X	X	X
Review of prior/concomitant medications	**X**							
Other assessments and assays								
Imaging by CT/MRI/PET	X							
Tumor pathology review	X							
CT simulation (for planning definitive CRT)	X							
Definitive CRT (30-33 fractions RT, with two or more cycles of chemotherapy)		X						

		definitive chemoradiation (dCRT) phase						
	Week 1and 2	Week 3 +/-3 days	Week 4 +/-3 days	Week 5 +/-3 days	Week 6 +/-3 days	Week 7 +/-3 days	Week 8 +/-3 days	Week 9 +/-3 days
Procedure/Scale	Screening	Visit No. 3	Visit No. 4	Visit No. 5	Visit No. 6	Visit No. 7	Visit No. 8	Visit No. 9[b]
PD-L1 (optional) testing from tissue	X							
Collect archival biopsy tissue for Immunohistochemistry staining (optional) for immune cell markers including confocal microscopy	X							
Blood draw for tumor marker research (exploratory endpoint)[e]	X		X		X			X

[a] Height will only be taken at initial study visit;
[b] Depending on the total number of fractions of RT, subjects may finish in week 8 or 9. For those finish in week 8, the No. 9 visit is not necessary;
[c] 12-lead ECG (triplicate ECGs are done only if QTcF is ≥470 [triplicate ECGs done 2-5 minutes apart]), See section 5.2.1
[d] Blood drawn per chemotherapy schedule and may vary per treating physician/standard care;
[e] Blood draw for exploratory research. See section 5.2.3.2. for details.
[f] For women of childbearing potential only. A serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of durvalumab and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion
[g] Free T3 will only be measured if TSH, and/or T4 is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

Schedule of new tumor baseline assessments, durvalumab + Consolidative hfRT after dCRT, treatment to progression

	Confirmation of Eligibility (Baseline Assessment[b])	C1	CT sim	C2	RT (1st boost)	RT (2nd boost)	C3 to C26 or PD
Week	**Screening**	**1**	**2**	**3**	**4**	**5**	**6 - 52**
Day	**Screening**	**1[a]**	**8-14**	**15-21**	**22-35**	**22-35**	**Q14 ± 3 days unless dosing needs to be held for toxicity reasons**
Informed consent[b]	(X)						
Review of Eligibility criteria	X						
Demographics	X						
Physical exam (full)	X						
Targeted physical exam (based on symptoms)/Routine follow-ups	X[r]		X[s]		X[t]		X[u]
Medical History	X						
ECOG performance status	X		X		X		X[u]
Vital signs (including weight and height)[c]	X	X		X	X		X
ECG[d]	X	As clinically indicated *For combinations with an agent with pro-arrhythmic potential or where effect of the combination on QT is not known more intense ECG monitoring than below may be required.*					
Laboratory Assessments							
Clinical chemistry[e]	X	X[f]		X			X
Creatinine Clearance	X	X[f]					
Hematology[e]	X	X[f]		X			X
Coagulation labs (PT/INR)	X	---------- As clinically indicated ----------					
TSH, T4[g], (reflex free T3 [h])	X	X[f]	---------- As clinically indicated ----------				
Pregnancy test[i]	X	X[f]		X			X
Urinalysis	X						
Monitoring							
Concomitant medications	X	<---------->					
AE/SAE assessment [l]		<---------->					
IP administration/ Therapy							
Durvalumab[m]		X		X			X

	Confirmation of Eligibility (Baseline Assessment[b])	C1	CT sim	C2	RT (1st boost)	RT (2nd boost)	C3 to C26 or PD
Week	**Screening**	**1**	**2**	**3**	**4**	**5**	**6 - 52**
Day	**Screening**	**1[a]**	**8-14**	**15-21**	**22-35**	**22-35**	**Q14 ± 3 days unless dosing needs to be held for toxicity reasons**
hfRT (QOD)[k]					X	X	
CT simulation (for planning hfRT)			X[p]				
Other assessments and assays							
EORTC QLQ-C30 v. 3 and LC13 module	X		X				X[u]
Tumor biopsy (archival or newly acquired)[a]	X						
Tumor biopsy (archival, if available, for patients who submit a newly acquired biopsy at screening for PD-L1 status)	X						
Tumor biopsy (after hfRT)[j] (optional)							X
Blood draws for exploratory research endpoint[q]	X		X		X	X	X
Efficacy evaluations							
Tumor assessment (CT/MRI/PET) (RECIST 1.1) [n,o]	X (Day 0)	Q12w ± 2w for the first 48 weeks (relative to Day 0, and thereafter until confirmed objective disease progression/death (whichever comes first). The schedule of q12w ± 2 week for first 48 weeks and thereafter MUST be followed regardless of any delays in dosing. See Section 6.1.1 for details regarding the timing of scans.					

[a] Every effort should be made to minimize the time between screening and starting durvalumab treatment. (i.e. within 1 day of completion of screening, but allow the first infusion to start up to 28 days after initial phase of radiation therapy (with concurrent chemotherapy))

[b] Most subjects will be consented prior to start of standard clinical care of definitive chemo-radiation therapy (dCRT). However, informed consent of study procedures may occur within the screening period after dCRT and prior to consolidative hfRT. Tumor pathology review will be performed only on new consented subjects. The collection of additional biopsies upon progression is strongly encouraged. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the subject.

[c] Body weight is recorded at each visit along with vital signs. Height is only at screening. For subjects that consented prior to dCRT, weight and height does not need to recorded for confirmation of eligibility again.

[d] Patients who signed consent prior to starting dCRT do not need to complete an additional ECG at this timepoint if the ECG requirements were satisfied prior to starting dCRT. If the baseline/screening ECG shows a QTcF ≥ 470 ms, the QTcF can be recalculated by performing triplicate ECGs completed 2-5 minutes apart. The recalculated QTcF must be < 470 ms to satisfy eligibility requirements.

[e] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.

[f] If screening clinical chemistry and hematology assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

[g] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day 1.

[h] Free T3 will only be measured if TSH and/or T4 is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[i] For women of childbearing potential only. Women of childbearing potential are required to have a pregnancy test within 7

days prior to the first dose of durvalumab and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion

[j] Tumor biopsy is scheduled two months after completing consolidative RT (±1 week), which is optional but strongly recommended.

[k] Consolidative hfRT is scheduled in between the second and third cycle of durvalumab, to be delivered every other day (QOD) with exception that, if the first dose is on a Friday, the second dose is allowed to be delivered on the following Monday.

[l] For AEs/SAEs reported, additional information such as medical history and concomitant medications may be needed

[m] Results for LFTs, electrolytes and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.

[n] RECIST assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands) and pelvis. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual subjects at baseline and follow-up. Baseline assessments (CT or PET/CT) should be performed no more than 28 days before the date of consent and, ideally, should be performed as close as possible to and prior to the start of IP. The confirmatory scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the subject has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit.

[o] See Section 6.1.1 for details regarding the timing of scans

[p] A CT simulation at radiation oncology will be performed within one week before the second cycle of durvalumab to allow sufficient time planning of consolidative RT.

[q] Blood drawn for exploratory research purpose, see section 5.2.3.2 for details.

[r] This follow-up visit is optional if no need of delay of starting the first cycle of durvalumab after being finally enrolled due to recovery from the initial phase of radiation therapy (with concurrent chemotherapy). If significant delay is required (up to 42 days after the end of the chemoradiation therapy), this visit is required to determined the eligibility of the subject for this trial based on his/her recovery status.

[s] Follow-up visit is within 24 hours before CT simulation.

[t] A follow-up visit on the same day of but prior to each fraction of consolidative RT (two visits).

[u] A follow-up visit will be scheduled q12 weeks within the first 48 weeks after study treatment start and thereafter until confirmed disease progression or death.

Note: All assessments on treatment days are to be performed prior to infusion of durvalumab or delivery of each fraction of consolidative RT, unless otherwise indicated.

Abbreviations: C Cycle; ECG Electrocardiogram; IM Intramuscular; LFT Liver function test; q12w Every 12 weeks; QOD Every other day; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

Follow-Up Assessments

Evaluation	Time Since Last Dose of durvalumab				
	Day (±3)	Months (±1 week)			12 Months and Every 6 Months (±2 weeks) until confirmed PD
	30	3	6	9	
Physical examination[a]	X	X	X	X	X
Vital signs	X	X	X	X	X
Weight	X	X	X	X	X
ECOG performance status	X	X	X	X	X
AE/SAE assessment[d]	X	----------X----------			
Concomitant medications	X				
Palliative radiotherapy	---------- As clinically indicated ----------				
Subsequent anticancer therapy	X	X	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted		X	X	X	X (every 2 months)
Hematology	X	X			X
Serum chemistry	X	X			
TSH, and fT4 (fT3)[b]	X				
Blood draws exploratory research[c]	X	X	X	X	X
Tumour assessment (CT or MRI)	For subjects who **achieve disease control following 12 months of treatment**, tumor assessments should be performed every 12 weeks (±2 weeks) relative to Day 0 until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Section 6.1 for timings of confirmatory scans. For subjects who **discontinue** durvalumab **due to toxicity (or symptomatic deterioration)**, tumor assessments should be performed relative to the relative to Day 0 as follows: every 12 weeks (±2 week) until confirmed disease progression, death, or until 2 years post-Day 0, whichever comes first. . Upon confirmed PD, scans should be conducted according to local standard clinical practice . For subjects who **continue on** durvalumab **post-confirmed progression** at the investigator's discretion, tumor assessments should be performed every 12 weeks (± 2 weeks) relative to Day 0 until treatment with durvalumab is discontinued. Upon discontinuation of durvalumab, tumor assessment will be completed according to standard of care. For subjects who **discontinue durvalumab following confirmed progression**, **scans should be conducted according to local clinical practice** .				

[a] Full physical exam
[b] Free T3 will only be measured if TSH and/or T4 is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.
[c] Blood drawn for exploratory research purpose, see section 5.2.3.2 for details. Subjects that have had disease progression will not have the samples drawn for research.
[d] Adverse events of special interest will be collected and reported through the duration of the follow-up phase. See section 9.0 for details.

Section 8.0 DRUG FORMULATION AND PROCUREMENT

8.1 Durvalumab

The Investigational Products Supply section of AstraZeneca will supply durvalumab to the investigator as a 500-mg vial solution for infusion after dilution. Although durvalumab now is FDA-approved for stage III NSCLC as standard consolidative/adjuvant therapy after definitive CRT, combined use with immunostimulating dose of consolidative hfRT has not been tested for safety or efficacy before.

8.1.1 Formulation/packaging/storage

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and a 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 secondary original packaging until use to prevent prolonged light exposure.

8.1.2 Durvalumab doses and treatment regimens

Subjects enrolled will receive Durvalumab 10 mg/kg via a 60-minute iv infusion Q2W ± 3 days for up to 12 months (maximum of 26 doses, last dose at Week 50) or until confirmed disease progression, whichever comes first, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

8.1.3 Study drug preparation

Preparation of durvalumab doses for administration with an IV bag

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

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

Standard infusion time is 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 and document if the line was not flushed.

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.

Preparation of durvalumab doses for administration with an iv bag

Doses of 10 mg/kg will be administered using an iv bag containing 0.9% (weight/volume) saline or 5% (w/v) dextrose, with a final durvalumab concentration of 15 mg/ml, and delivered through an iv administration set with a 0.2-µm or 0.22-µm in-line filter.

Subject weight at baseline should be used for dosing calculations unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard. An additional volume of 0.9% (weight/volume) saline equal to the calculated volume of durvalumab to be added to the iv bag must be removed from the bag prior to addition of durvalumab. The calculated volume of durvalumab is then added to the iv bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag. Add the calculated volume 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.

Dose calculation

Per institutional standard protocol. Refer to Appendix II.

8.1.4 Monitoring of dose administration

Subjects will be monitored before, during and after the infusion as specified in the Schedule of Assessment. Subjects are monitored per institutional standards during the infusion period.

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects 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. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 4 hours at room temperature, with maximum total time at room temperature not exceeding 4 hours (otherwise requires new infusion preparation). For management of subjects who experience an infusion reaction, please refer to the toxicity and management guidelines in Appendix I.
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 subjects to an intensive care unit if necessary.
Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

Dose modifications will not be required for AEs that are clearly not attributed to study drug (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. Dosing may continue despite concurrent vitiligo of any AE grade.

8.1.5 Accountability and dispensation

Per institutional standard protocol.

8.1.6 Disposition of unused investigational study drug

Per institutional standard protocol.

8.2 Investigational consolidative radiation therapy

Consolidative hfRT will be tested for its safety and efficacy in this trial concurrently with durvalumab. For detailed treatment planning, see Section 8.0.

Section 9.0 TOXICITY REPORTING GUIDELINES

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC Fred & Pamela Buffett Cancer Center Data Monitoring plan. The protocol will adhere to the institutional and FDA guidelines for the toxicity reporting.

All subjects will be closely followed for toxicity from the time of the first administration of study medication until 90 days after last administration of study medication. For the subjects enrolled prior to dCRT, adverse events (AE's) will not be captured during standard dCRTsince it is not relevant to the investigational therapy (consolidative hfRT with concurrent durvalumab). However, baseline information for this population in the form of internal or outside facility documentations will be captured by retrospective review of the medical records internally or to be requested from outside facilities. Subjects during dCRT routinely are evaluated by their radiation oncologists during weekly on-treatment visits (OTVs) with safety concerns documented. All AE reporting will begin on the date of the first administration of study medication through the entire follow-up period of each subject. For subjects enrolled prior to dCRT that are determined ineligible post-dCRT, AEs will not be reported or recorded since they received no study medication. We acknowledge that AE's/SAE's may not follow the more typical cytotoxic 30 day duration of occurrence, and that this requires ongoing vigilance by the investigators to report later AE's/SAE's as events of medical importance if there is any plausible likelihood of a relationship with study therapy because of the type/specificity of the AE/SAE relative to anti-PD-L1 therapy.

Adverse events will be assessed by reports from subjects to their physician/Investigator and by physical examinations. Per NCI guidelines, SAEs and AEs will be graded and toxicity assessed using the revised NCI CTCAE version 5.0. All adverse events (AE) and serious adverse events (SAEs) will be followed until resolution, a return to baseline or ≤ grade 1 levels, or until no reasonable improvement is expected. During the course of the study, all AEs and SAEs should be proactively followed up for each subject for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the subject has discontinued study drug or the study has completed.

Deaths occurring within 30 days of study treatment regardless of relationship will be reported to the UNMC Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC).

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

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

9.1 Definitions Adverse Events

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

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE. Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received first cycle of durvalumab.

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

Unexpected Adverse Event

An AE in which the specificity, severity, or frequency is not consistent with (a) the IRB application and detailed protocol; (b) Risk information in the ICF; (c) the current investigator's brochure; or (d) Investigational plan or protocol
The term AE is used to include both serious and non-serious AEs.

Serious Adverse Events

A serious adverse event is one that at any dose (including overdose) and regardless of causality:

- Results in death
- Is a serious threat to life, health, safety or welfare-fare of subject [1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Requires intervention to prevent permanent impairment or damage
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is another serious important medical event[3]
- Is any medical event in an investigational drug study that requires treatment to prevent one of the outcomes listed above
- Seriously jeopardizes the rights, safety, or welfare of subjects

[1]Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. AESI are defined as AEs that include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism that may require more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy. An AESI may be serious or non-serious. Adverse events of special interest will be collected and reported through the duration of the follow-up phase.

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
- Intestinal perforations
- Pneumonitis / ILD
- Hepatic events
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Guillain-Barré syndromeMyasthenia gravis
- Rash / Dermatitis
- Renal events
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- 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 eye, skin, haematological and rheumatological events. vasculitis, non-infectious meningitis and non-infectious encephalitis.

It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs. In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochures. 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 Astra-Zeneca to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix I) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

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

- Physical examination
  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.

- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:

    (i) ILD Markers (KL-6, SP-D) and β-D-glucan

    (ii) Tumor markers: Particular tumor markers which are related to disease progression.

9.2 Adverse Event Reporting Requirements Per University of Nebraska Medical Center, IRB and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) and Astra Zeneca Reporting

9.2.1 IRB Reporting

All internal adverse events (AEs) will be reported to the local IRB promptly per institutional human research protection program policies.

9.2.2 Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) Reporting

Reporting of the following will be done in accordance with DSMC guidelines:

- All SAEs and toxicity will be reported to the DSMC. However, no SAEs will be reported prior to the start of study medication.

- All AE grade 3 or higher (expected or unexpected, regardless of attribution) will be reported to the DSMC. In certain investigator-initiated institutional trials where virtually 100% of subjects are guaranteed to experience very specific known grade 3 or higher toxicities (e.g., hematologic toxicity in stem cell transplant studies), the requirement for reporting of those toxicities may be waived at the discretion of the DSMC based on initial protocol review and in conjunction with investigator input if required. For this trial, no AEs will be reported prior to the start of study medication.

Attribution of AE: The likelihood of relationship of the AE to the study drugs will be determined by the investigator based on the following definitions:

Not related: The subject was not exposed to the study treatment or another cause that is obvious.
Probably not related: The AE is most likely explained by another cause, and the time of occurrence of the AE is not reasonably related to the study treatment.
Possibly related: Study treatment administration and AE occurrence reasonably related in time, and the AE is explained equally well by causes other than study treatment, or treatment administration and AE occurrence are not reasonably related in time, but the AE is not obviously a result of other causes.
Probably related: Study treatment administration and AE occurrence are reasonably related in time, and the AE is more likely explained by study treatment than by other mechanisms.
Definitely related: The occurrence and timing of the AE are clearly attributable to the study treatment.

A guide to the interpretation of the causality question is found in Appendix I.
AEs will be collected from the time the subject starts study medication and ending 90 days following the final dose of study medication. All AEs will be followed until resolution or until no further improvement is expected. AEs judged by the investigator as not related or probably not related to the treatment will NOT be followed beyond the 90 days after the final dose of study drug.
All SAEs and AE reporting will be completed using DSMC approved forms. Detailed policy and procedures for this section may be reviewed at:
http://www.unmc.edu/cancercenter/clinical/prms.html

9.2.3 Astra Zeneca Reporting

The investigator and/or sponsor must inform the FDA, via the MedWatch 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 report must be emailed to AstraZeneca at the time the event is reported to the FDA.

It is the responsibility of the investigator of each study site 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*** 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-18-13876)

***** Site investigator 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

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

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.

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

9.2.3.1 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 (see Section 9.3.2 for further details). 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.

9.2.3.2 Other events requiring reporting

Overdose

An overdose is defined as a subject 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 subject with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to AstraZeneca Patient Safety or designee using the designated Safety e-mailbox. If the overdose results in an AE, the AE must also be recorded as an AE (see Section 9.2). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section 9.2). There is currently no specific treatment in the event of an overdose of durvalumab.
The investigator will use clinical judgment to treat any overdose.

Hepatic function abnormality
Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to AstraZeneca Patient Safety using the designated Safety e-mailbox (see Section 9.2.3 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 (with or without consolidative RT) 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 subject will be based on the clinical judgment of the investigator.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject 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 AstraZeneca.

Pregnancy

No patients currently pregnant is eligible for the trial.

Maternal exposure

If a subject becomes pregnant during the course of the study, the durvalumab should be discontinued immediately, and planned consolidative hfRT should be cancelled.

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 subject was discontinued from the study only if the subject agrees to such follow-up.

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 subjects should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab or 180 days after the last dose of consolidative RT, whichever is the longer time period.

Pregnancy of the subject'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 monotherapy, whichever is the longer time period should, if possible, be followed up and documented.

9.3 Monitoring

Various methods will be implemented to exchange information with study personnel:

- Site Initiation/Orientation
- Investigator meetings as feasible
- Email distributions/reports as needed

9.3.1 Data Monitoring

For this study, data monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirement(s). Monitoring is a Quality Control, continuous process during the entire trial.

9.4 Auditing

Auditing is a systematic and independent examination of trial-related activities and documents to determine:

- whether the evaluated trial-related activities were conducted
- the data were recorded, analyzed, and accurately reported, according to the protocol, to the sponsor's SOPs, GCP, and applicable regulatory requirement(s).

Auditing is a Quality Assurance, one point process during the trial.

This study will undergo audit on at least a semi-annual basis by the UNMC Fred & Pamela Buffett Cancer Center Audit Committee.

Detailed policy and procedures for this section may be reviewed at: https://www.unmc.edu/cancercenter/clinical/prms.html .

Section 10.0 STATISTICAL CONSIDERATIONS

10.1 Description of analysis sets

A comprehensive statistical analysis plan (SAP) will be prepared and finalized before first subject in. The efficacy Analysis Set and the Safety Analysis Set described below will be applied to all subjects that start study treatment.

10.1.1 Safety analysis set

All subjects who received at least one dose of durvalumab and received or were planned to receive the selected hfRT dose level determined by the initial 3+3 dose escalation study after being enrolled will be included in the safety population. Throughout the safety results sections, subjects who develop severe adverse effects (SAEs) who would not be candidate for hfRT after final eligibility confirmation will be still counted in the set so that the rate of SAEs will not be underestimated in this study.

When assessing safety and tolerability, summaries will be produced based on the safety analysis set.

10.1.2 Efficacy analysis set

All subjects who received at least one dose of durvalumab and received or were planned to receive the selected hfRT dose level determined by the initial 3+3 dose escalation study after being enrolled and for whom any post-dose data are available will be included in the efficacy analysis set. This intention-to-treat approach will provide the best comparison between data from the current trial to the historical data from the PACIFIC study.

10.2 Methods of statistical analyses

Descriptive statistics will be used for all variables. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the entire correlated analysis set.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first infusion of study drug, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to day 0.

Time to event variables will be summarized using Kaplan-Meier Curves; this includes OS, time to onset of symptoms, PFS and TTDM. Chi-square or Fisher's exact test (as appropriate) will be used to compare treatment response to steroids for subjects who develop aRP during or shortly after dCRT but prior to starting of durvalumab to those having aRP within six months after hfRT. Imaging features will be compared using two-sample or paired t-tests (or an appropriate non-parametric test) as appropriate to the hypothesis being tested. Unless otherwise stated, a significance level of 0.05 will be assumed for all tests.

All data collected will be listed.

Results of all statistical analysis will be presented using a 95% confidence interval (CI) and p-value, unless otherwise stated.

10.2.1 Safety analyses

Toxicities data will be analyzed as categorical variables which will be summarized by frequency counts and percentages for each category as one of the primary endpoints of the study to compare numerically with historical data. Percentages will be calculated out of the population total for the safety analysis set. Due to the unique biology of potential interaction between certain range of immunostimulating RT with immunotherapy drug such as PD-L1 inhibitor, this study is not designed with dose escalation for RT but rather use a fixed dose regimen that has been tested as being safe when applied alone in previous study. No statistical comparison will be performed on safety data obtained in this study.

10.2.2 Efficacy analyses

12-month PFS is one of the primary endpoints and the study has been sized to compare the results from current trial to historical results from PACIFIC study. 18-month PFS, 12-month OS and QoL/Function improvement rate using EORTC QLQ-C30 tests are secondary endpoints. Kaplan-Meier analysis will be used to compare PFS at 12 and 18 months and OS at 12 months between historical PACIFIC study data and combination therapy.

Efficacy data will be summarized and analyzed on the efficacy analysis set.

Survival data obtained from current study will be compared with historical data in PACIFIC trial with z-test based on the methods from Parkin and Haukulinen1991, with P value < 0.05 defined as being statistically significant.

10.2.3 Exploratory analyses

Expression levels of biomarkers including PD-L1 levels in tumor microenvironment from immunohistochemistry studies or peripheral sPD-L1 before and after hfRT will be analyzed as continuous or categorical variables which will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. The relationship of these variables with disease progression will be studied by univariate analyses with log-rank tests. Variables that had a log-rank p-value of 0.15 were considered for inclusion in a Cox Proportional

Hazards regression if appropriate.

10.2.4 Interim analyses

An interim analyses is planned for current study for primarily estimating efficacy to facilitate trial completion. Interim analyses will be performed 6 months (± 15 days) after the 12th subject at the selected hfRT dose level determined by the initial 3+3 dose escalation study is enrolled counting from his/her first day of study treatment. When the 12th patient has completed 6 months, then accrual will be held for interim analysis. The design will allow reasonable long median follow-up for meaningful data analysis. Disease progression will be summarized and analyzed for the first 12 subjects enrolled. If 7 or more subjects have disease progression or died, the trial will be terminated or halted before further discussion with statistician and AstraZeneca. Otherwise the trial will proceed to finish enrollment.

10.3 Determination of sample size

To shorten the duration of the proposed study, we will evaluate the 12-month PFS data for the potential benefit of adding consolidative RT with hypofractionated fractionation (hfRT) to be compared with the historical data but incorporating an interim analysis after recruiting thirteen subjects. In our case, the historical data from PACIFIC trial will be used. An additional 20% PFS increase is expected when adding hfRT to durvalumab, i.e., a one- year PFS of 75.9% or higher is predicted for this study. The sample size was estimated with the assistance from our statistician to achieve 80% statistical power.

Sample size justification: Simon's optimal two-stage design to test the null hypothesis of the progression free survival proportion of P<=55.9% versus the alternative of P>=75.9% has an expected sample size of 18.2 and a probability of early termination of 0.675. If the treatment is actually not effective, there is a 0.096 probability of concluding that it is (the target for this value was 0.10). If the treatment is actually effective, there is a 0.19 probability of concluding that it is not (the target for this value was 0.20). After testing the treatment on 12 subjects at the selected hfRT dose level determined by the initial 3+3 dose escalation study in the first stage, the trial will be terminated or halted before further discussion with statistician and AstraZeneca if 7 or more subjects have disease progression, defined by locoregional or distal progression per RECIST criteria 1.1, or death. If the trial goes on to the second stage, a total of 32 subjects will be studied (12). If the total number responding is less than or equal to 20, the drug is rejected. If 15% dropout rate, then total is subjects are 37, to achieve a power of 82% and alpha or significant level 0.10.

Considering the initial 3+3 dose escalation step, an additional 6 patients may be enrolled and treated at hfRT dose level that will not be selected for the second step of efficacy study, a total of 37+6=43 patients could be needed for this project.

10.4 Stopping rule

The trial will be stopped if, at any time, a total of two cases developed grade 5 toxicity after consolidative RT from side effects caused by immunotherapy and/or consolidative RT if other causes including tumor progression can be ruled out. With grade 5 toxicities only occurred in

4.4% of patients in the durvalumab arm in PACIFIC trial, having an increased mortality rate to above 6%, if happened in this trial, would most likely offset any potential survival benefit adding consolidative RT rendering continuing the trial be meaningless as well as raise concerns of safety.

At the initial 3+3 dose escalation step of the trial, if the starting dose level of hfRT (6.5Gy x 2 fractions) exceeds MTD, the trial will be terminated.

An interim analysis will be conducted at six months after enrolling the 12th patient treated with the final selected dose of hfRT. The trial will be terminated if 7 or more have disease progression including death caused by disease progression. Of note, if patient(s) died of disease progression, the number of death caused by disease progression will be counted; If patient(s) died of toxicities caused by immunotherapy and/or consolidative RT, the number of death will not be counted. If, as stated above, a total of two cases developed grade 5 toxicity after consolidative RT from side effects caused by immunotherapy and/or consolidative RT if other causes including tumor progression can be ruled out, the trial will be terminated no matter how many cases with disease progression occur.

Section 11.0 Records to be Kept

Information regarding the actual treatments, adverse effects, radiographic and laboratory information will be recorded on appropriate forms in the Advarra electronic data capture system detailed below. Additionally, serious adverse events, when noted, will be recorded on site via the standard serious adverse event reporting as noted in Section 9 of this protocol.

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

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Site investigator files shall be retained for a time as indicated by their individual institutional requirements or as outlined in the study agreement or required by regulatory authorities.

11.1 Quality Assurance

Complete records must be maintained in a research chart on each patient treated on the protocol. Research chart can be maintained either as an electronic record, paper chart or a combination or both. These records should include primary documentation (e.g., lab. report slips, physician notes, etc.) which confirm that:

- The subject met the eligibility criteria.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given & reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).

- Response was assessed according to protocol (dated notes on clinical assessment, lab reports as appropriate).

11.2 Responsibilities of the Principal Investigator

The PI is responsible for ensuring that the protocol and its appendices are followed, particularly when other departments are involved in the trial. The PI oversees the quality of the data collected in the electronic case report forms. The data obtained during the trial are recorded directly, with all modifications of data signed, dated, and justified as stated above. Modifications must conform to the procedures defined for paper and electronic records.
For the entire group of persons involved in carrying out the trial (day, night and emergency personnel), the PI is responsible for the following:

1. Ensuring that the personnel are informed of the protocol used and that they understand the part they are responsible for implementing.
2. Training personnel if necessary.
3. Designating individual(s) specifically responsible for the administrative management of the trial.

Ensuring that other departments or services involved in this trial are informed of the trial and determining with them the specific operating procedures necessary to conduct the trial.

11.3 Advarra Electronic Data Capturing (EDC) System

Data will be stored electronically for this study in the Advarra EDC system contained on the company's secure server. Data forms will not differ from the paper versions with the exception of an electronic format containing the UNMC Fred & Pamela Buffett Cancer Center and Advarra logo.

Advarra EDC provides for remote data collection that meets FDA 21 CFR Part 11 requirements as well as HIPAA and other regulatory requirements designed to enhance data security and protect subject confidentiality. Authorized users log into Advarra through a secure connection and must provide a valid username, password, and database ID. This data may be made available to the public at large.

SECTION 12.0 PATIENT CONSENT

12.1 Human Subjects Research Protection Training

All personnel involved in this research project will have completed the OHRP-approved computer based training course on the Protection of Human Research Subjects. All clinical and correlative research included in this application will have approval by the institutional review board.

12.2 Study Population

Subjects are from all socio-economic groups and will be entered into the study without bias with respect to gender or race. Attempts will be made to recruit minorities. No vulnerable subjects will be included in the study.

12.3 Sources of Material

Pathology material (frozen tissue if available, if not then 5-6 unstained slides or a block) must be reviewed, and the diagnosis confirmed by University Nebraska Medical Center pathology department as outlined in the protocol.(retrospectively).

12.4 Recruitment and Informed Consent
Subjects with an initial diagnosis of stage III non-small cell lung cancer (NSCLC) seen and evaluated at Nebraska Medicine (NM) will be available for recruitment These subjects will be informed of the nature of this study, and will be asked to participate on a voluntary basis after informing them of the possible risks and benefits of the study. A number of public registries may be accessible to health care providers and prospective subjects as listed on the protocol title page.

12.5 Subject Competency
Subjects will be eligible to participate in the study only if they are competent to give informed consent. A subject that the investigators judges to be incompetent will not be enrolled.

12.6 Process of Informed Consent
If the patient chooses to be a participant in this study, informed consent will be obtained by the investigators. The study and procedures involved including the risks will be explained in detail to each subject. It will be clearly explained to the subject that this is a research study and that participation is entirely on a voluntary basis. Subjects will be given the option to discuss the study with a family member, friend, counselor or, another physician. The participating investigators will be available to discuss the study with them.

12.7 Subject/Representative Comprehension
When the process of informed consent is completed, the subject will be asked to state in his/her own words, the purpose of the study, the procedures that will be carried out, potential risk, potential benefits to the subject, the alternatives and the right to withdraw from the study. If there is any indication that a given subject's comprehension is anything less than accurate, the points of confusion will be discussed and clarified.

12.8 Information Purposely Withheld
The results of the tests done solely for research purposes will not be disclosed to the subject. No other information will be purposely withheld from the subject.

12.9 Potential Benefits of the Proposed Research to the Subjects
It is anticipated that the combination of hfRT and durvalumab would result in prolonged survival in this subject population.

12.10 Potential Benefits to Society
Information obtained from this study may help other subjects by contributing to the knowledge of NSCLC and whether this treatment offers potential advantages over other treatments currently available.

12.11 Potential Risks
The use of Durvalumab and hfRT are associated with numerous potential risks. Combined immunotherapy/radiation is considered a valid treatment option for patients with NSCLC. It is

believed the treatment option outlined in the study will not pose significant additional risks compared to conventional treatment.

12.12 Therapeutic Alternatives

If patients choose not to participate in this study they may elect to receive standard therapy as per their primary oncologist, which may include surgery, chemotherapy, or radiation, or a combination of these approaches. The treatment recommendations may or may not be similar to treatment as described in this protocol. As yet, there is no proven benefit to the use of Durvalumab and hfRT in this patient population as outlined in this protocol document is considered investigational.

12.13 Risk/Benefit Relationship

Although there are inherent risks involved because of the use of chemotherapy and radiotherapy we anticipate that subjects who receive the treatment phase of the protocol will do no worse than expected with standard therapy, and may experience an improved outcome. The risk is considered to be acceptable in the setting of cancer.

12.14 Consent Form Documents

No information will be purposely withheld from the subjects. The consent document used in this study will include the adult consent document. See attached consent form.

Section 13.0 REFERENCES

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Section 14.0 Data Collection Forms

A data collection plan for electronic data capture forms (eCRF) is submitted as part of this protocol for the scientific review committee review.

In addition, the study team has the following items provided, at the time of site activation, as an accompaniment to the protocol. These items are provided electronically as a study site manual and Manual of Operations (MOP) to guide the study operations.

Appendix I - Dosing Modification and Toxicity Management Guidelines

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

Table of Contents

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 protocol- specific treatment regimen. The TMGs provide information for the management of immune- mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with monotherapy or combination 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 non-immune–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.

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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.

4.

Pediatric Considerations Regarding Immune-Mediated Reactions

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

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology 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	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression,

	study protocol for defining the CTCAE grade/severity)		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. **<u>For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy:</u>** **<u>A.</u> <u>Permanently discontinue tremelimumab for Grade 3 diarrhea/colitis. HOLD durvalumab until resolution to Grade σ; 1; durvalumab alone can be resumed after completion of steroid taper (<10 mg prednisone per day or equivalent)</u>** **<u>B.</u> 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	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression,

	study protocol for defining the CTCAE grade/severity)		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	**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.

		days or if there are signs of respiratory insufficiency.	– 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 inflammatory or	Note: It is possible that events with an 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 resolution to	– Hold study drug/study regimen until ≤Grade 1 or baseline. – If toxicity worsens, then treat as Grade 3 or Grade 4. – Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. – Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality	when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper
Grade 3	Hold study	

	drug/study regimen until resolution to Grade :<1 or baseline	**For Grade 2, 3, or 4**
	Grade 4 Permanently discontinue study drug/study regimen	Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines. (See page 4).

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

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity 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
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.).	institutional standard. 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."

List of Abbreviations

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

ICI(s)	Immune checkpoint inhibitor(s)	ULN	Upper limit of normal

APPENDIX II. Durvalumab Weight-based Dose Calculations

Durvalumab Dosing

For subjects weighing >30 kg, durvalumab should be dosed at 10 mg/kg Q2W in the protocol of this trial

Example:

1. Cohort dose: 10 mg/kg
2. Subject weight: 30 kg
3. Dose for subject: 300 mg = 10 (mg/kg) × 30 (kg)
4. Dose to be added into infusion bag: [rounded to the nearest tenth mL (0.1 mL)]: Dose (mL) = 300 mg / 50 (mg/mL) = 6.0 mL
5. The number of vials required for dose preparation: Number of vials = 6.0 (mL) / 10.0 (mL/vial) = 1 vial

APPENDIX III
Eligibility Checklist

	Site #	Subject ID:
IRB# 004-21 **Title:** Phase I/II study to assess the immunostimulatory effects of consolidative hypofractionated radiation therapy (hfRT) for boosting the residual primary lung cancer in combiniation with Durvalumab after definitive chemoradiation therapy for stage III non-small cell lung cancer (NSCLC)		Waiver #: Astra Zeneca Ref #: ESR-18-13876
		Investigator: Dr. Chi Zhang

Inclusion Criteria: **Response should be YES**	Yes	No	N/A
1. Pathologically diagnosed NSCLC (squamous cell carcinoma, adenocarcinoma, large-cell carcinoma, or non-small-cell lung cancer not otherwise specified), clinical stage III (AJCC 8th Ed.)	[ ]	[ ]	[ ]
2. At time of consent, subjects must be a candidate for dCRT. OR Must have received dCRT with at least 2 cycles of platinum-based chemotherapy concurrent with conventional fractionated radiation therapy with a total dose of 5700 – 6300 cGy.	[ ]	[ ]	[ ]
3. Patients must be aware of the nature of his/her disease and willingly provide written, informed consent. Including compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act in the US) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.	[ ]	[ ]	[ ]
4. Age ≥ 19 years at time of study entry	[ ]	[ ]	[ ]
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at enrollment.	[ ]	[ ]	[ ]
6. Life expectancy of > 12 weeks.	[ ]	[ ]	[ ]

7. Adequate normal organ and marrow function as defined below: a.Hemoglobin ≥ 9.0 g/dL (5.59 mmol/Lb.ANC 1.5 (≥ 1500 per mm^3) c. Platelet count ≥ 100 x 10^9/L (≥ 100,000 per mm^3) Hemaglobin: _____ ANC: _____ Platelet count: _____ d. Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician. Bilirubin_____ e. AST (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal (ULN). AST_____ALT_____ f. Measured creatinine clearance (CL) > 40 mL/min or calculated creatinine CL > 40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976). Creatinine:_____ Calculated creatinine clearance:_____	[ ] [ ] [ ]
8. Evidence of post-menopausal status or negative serum pregnancy test for female pre-menopausal patients. Status: _____ Pregnancy test date: _____	[ ] [ ] [ ]
9. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up	[ ] [ ] [ ]
Exclusion Criteria: **Response should be NO**	Yes No N/A
1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)	[ ] [ ] [ ]
2. Patients who have received prior anti–PD-1, anti PD-L1 or anti CTLA-4	[ ] [ ] [ ]
3. Participation in another clinical study with an investigational product during the last 4 weeks.	[ ] [ ] [ ]
4. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.	[ ] [ ] [ ]
5. Mixed small cell and non-small cell lung cancer histology	[ ] [ ] [ ]
6. Subjects who receive sequential chemoradiation therapy for locally advanced NSCLC.	[ ] [ ] [ ]
7. Subjects with locally advanced NSCLC who have progressed during definitive platinumbased, concurrent chemoradiation therapy.	[ ] [ ] [ ]

8. Any unresolved toxicity (NCI CTCAE Grade >2) from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria a. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician. b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician. For example, post-operative neurological deficits for previous benign brain tumors, urinary incontinence from radical prostatectomy for prostate cancer, peripheral neuropathy from chemotherapy for breast cancer	[ ] [ ] [ ]
9. Any concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.	[ ] [ ] [ ]
10. Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of immunotherapy (excluding the placement of vascular access) that would prevent administration of study drug or radiation therapy.	[ ] [ ] [ ]
11. History of allogenic organ transplantation.	[ ] [ ] [ ]
12. Active or prior documented autoimmune or inflammatory disorders within the past 2 years (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis hypophysitis, uveitis, etc]). The following are exceptions to this criterion: a. Patients with vitiligo or alopecia b. Patients with hypothyroidism (e.g., following Hashimoto syndrome stable on hormone replacement or Graves' disease). c. Any chronic skin condition including psoriasis that does not require systemic therapy (within the past 2 years). d. Patients without active disease in the last 5 years may be included but only after consultation with the study physician. e. Patients with celiac disease controlled by diet alone.	[ ] [ ] [ ]
13. Known allergy or hypersensitivity to Durvalumab or any excipient.	[ ] [ ] [ ]
14. Any uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirements, substantially increase risk of incurring AEs or compromise the ability of the subject to give written informed consent.	[ ] [ ] [ ]

15. History of another primary malignancy except for: a. Malignancy treated with curative intent and with no known active disease ≥5 years before the informed consent and of low potential risk for recurrence b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease c. Adequately treated carcinoma in situ without evidence of disease	[ ] [ ] [ ]
16. History of primary immunodeficiency.	[ ] [ ] [ ]
17. Known history or active infection of **tuberculosis**, **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies).	[ ] [ ] [ ]
18. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion: a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection) b. Systemic corticosteroids at doses ≤10 mg/day of prednisone or its equivalent c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication) d. Systemic steroid administration required to manage toxicities arising from radiation therapy delivered as part of the chemoradiation therapy for locally advanced NSCLC is allowed.	[ ] [ ] [ ]
19. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients , if enrolled, should not receive live vaccines whilst receiving IP and up to 30 days after the last dose of IP.	[ ] [ ] [ ]
20. Female subjects who are pregnant or breastfeeding or male or female subjects of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab therapy.	[ ] [ ] [ ]
21. Prior randomization or treatment in a previous durvalumab and/or tremilimumab clinical study regardless of treatment arm assignment.	[ ] [ ] [ ]
22. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or unresolved irAE >Grade 1	[ ] [ ] [ ]
23. Previous history of RT (other than RT as part of the dCRT for the current course of NSCLC) involving any part of the lungs, chest wall, thoracic spine or breast(s).	[ ] [ ] [ ]
24. Judgment by the investigator that the subject is unsuitable to participate in the study for any condition and the subject is unlikely to comply with study procedures, restrictions and requirements.	[ ] [ ] [ ]
25. Mean QT interval corrected for heart rate using Fredericia's formula (QTcF) ≥470 ms. Only one ECG is required at screening if the QTcF < 470 ms. Triplicate ECGs performed 2-5 minutes apart should only be performed if screening ECG shows QTcF ≥470 ms	[ ] [ ] [ ]

Eligibility: [ ] Subject satisfies all criteria
[ ] Subject not formally eligible, but admitted to this study because (state reason):

_____

[ ] Subject DID NOT Meet Eligibility Criteria

Subject Initials: _____ DOB:_____

ELIGIBILITY reviewed and confirmed by:

Investigator Signature _____Date_____

Printed Name of Investigator: _____