Clinical Study Protocol
Drug Substance: Durvalumab (MEDI4736)
Study Number ESR-18-14205
Edition Number 5
Date 05/09/2023

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Phase II Trial of concurrent, split course chemoradiation followed by Durvalumab (MEDI4736) in poor risk and/or elderly patients with newly diagnosed stage III non-small cell lung cancer

Sponsor: Dr. Gaurav Marwaha

Collaborator/Funder: AstraZeneca

PROTOCOL SYNOPSIS

Clinical Protocol ESR-18-14205

Study Title: Phase II Trial of concurrent, split course chemoradiation followed by Durvalumab (MEDI4736) in poor risk and/or elderly patients with newly diagnosed unresectable stage III non-small cell lung cancer
Protocol Number: ESR-18-14205
Clinical Phase: II
Study Duration: 18 months enrollment
Investigational Product(s) and Reference Therapy: Durvalumab (MEDI4736) will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration/infusion after dilution. Radiation (60 Gy in 30 fractions administered over 12 weeks with 1-1.5 week breaks between cycles) and chemotherapy (once every 3 weeks for 4 cycles) will precede Durvalumab (MEDI4736) utilization.
Research Hypotheses: 1. We hypothesize that concurrent four phase, split course chemoradiation followed by Durvalumab is feasible (safe and tolerable) in elderly / poor risk unresectable stage III NSCLC patients. 2. Specifically, we hypothesize that 80% of patients enrolled will safely complete 4 cycles of concurrent split-course CRT, and in those to go on to receive Durvalumab, we expect no more than 20% of patients to have to therapy terminated for Durvalumab-related toxicities. 3. Without Durvalumab, the median survival is known to be 20 months in this patient population; we expect that adding Durvalumab in the treatment regimen will improve the median survival to 30 months. 4. Without Durvalumab, the median progression free survival (PFS) is known to be 11 months in this patient population; we expect that adding Durvalumab in the treatment regimen will improve the median PFS to 17 months.
Objectives:

Primary Objectives: 1. To determine the percentage of poor risk and/or elderly unresectable stage III NSCLC patients who complete split course chemoradiation; 2. To determine the safety and tolerability of durvalumab (MEDI4736) after completion of chemoradiation in this group of patients.

Secondary Objective(s):

1. To determine the 1-year overall survival rate
2. To determine the 1-year progression-free survival rate
3. To determine the 1-year loco-regional progression-free survival rate
4. To determine rate of grade 3 and 4 toxicities with this regimen in the selected patient population

Study Design: Non-Randomized, Prospective

Number of Centers: 2 – RUMC & ROPH

Number of Patients: 30

Study Population:

Elderly (age 70 years or older) or >18 years old AND poor risk (ECOG 2) stage IIIA-C (AJCC 8th edition) inoperable non-small cell lung cancer (NSCLC)

Inclusion Criteria:

- Participants must have histologically or cytologically confirmed stage IIIA-C (AJCC 8th edition) non-small cell lung cancer that will be treated with curative intent.
- Participants must have been deemed medically inoperable by multidisciplinary team/tumor board
- Participants must have been staged with a PET/CT or CT within 45 days of enrollment (if PET/CT out of window, CT Chest/Abdomen/Pelvis within 21 days of enrollment is acceptable)
- Participants must be elderly (age 70 years or older) or >18 years old AND poor risk (ECOG 2) see section 4.1.1
- Participants ideally have endobronchial ultrasound biopsy (EBUS) or mediastinoscopy to confirm nodal status, but can be deferred if PET/CT imaging characteristics are highly suggestive of nodal metastases
- Participants must have normal organ and marrow function: Leukocytes >3000/mcL; ANC >1500/mcL; PLT >100000/mcL; total bilirubin within normal limits (≤1.5x); AST/ALT <2.5x institutional upper limit of normal; creatinine clearance ≥30
- Body weight >30kg
- Mean lung dose < 20 Gy and lung V20<35%
- No disease progression after CRT

- See Section 4 for full detail

Exclusion Criteria:

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study:

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to carboplatin, pemetrexed (for patients with adenocarcinoma), etoposide (for patients with squamous cell carcinoma), or immunotherapy
- Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic CHF.
- Angina pectoris, cardiac arrhythmia, or psychiatric/social situations that would limit compliance with study requirements.
- Pregnant women
- Known HIV+ patients
- See section 4 for full detail

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

Patients who have completed four cycles of chemoradiation will go on to receive durvalumab (MEDI4736) monotherapy as 1500mg durvalumab (MEDI4736) via IV infusion Q4W for up to a maximum of 12 months (up to 13 doses/cycles) with the last administration on week 48 until confirmed disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. (N.B If a patient's weight falls to 30kg (≤30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W after consultation between Investigator and Study Physician, until the weight improves to above 30 kg >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W).

Weight-based dosing (20 mg/kg) should be utilized for patients whose body weight falls to ≤30 kg while on study.

Study Assessments and Criteria for Evaluation:

Safety Assessments: Safety will be monitored continually throughout the protocol. Assessments include adverse events, serious adverse events, vital signs, and physical and laboratory examinations, as well as immune-mediated adverse events.

Chemotherapy safety measurements are described in detail in the protocol. Briefly, any grade 3-5 toxicities will be reported. Repeat chemotherapy doses will be administered only if hematologic treatment parameters and patient has recovered adequately from previous cycles of chemotherapy.

SAEs possibly, probably or definitely related to RT (including grade 3-4 congestive heart failure, pneumonitis, arrhythmias, and myocardial infarction, grade 4 esophagitis, and any AEs that lead to hospitalization) that causes either an interruption or early termination of RT will be reported. The proportion of patients who have tolerated the treatment will be provided. All adverse events will be graded according to CTCAE v 5.0

Durvalumab safety measurements are described in detail in protocol. The tolerability of therapy is defined as having one or no safety events defined as: 1) grade 4-5 non-hematologic serious adverse events (SAEs) as defined in CTCAE v5.0, probably or definitely related to protocol treatment by 90 days from the start of Durvalumab; 2) Any adverse events that lead to prolonged dose delays (defined as skipping at least 2 doses of Durvalumab; 3) Permanent discontinuation of Durvalumab due to toxicity within the first 30 days of starting Durvalumab.

1.) **Rate of completion of therapy** (Defined as percentage of patients able to: A. Complete 4 cycles of concurrent split course CRT and B. Receive adjuvant course of Durvalumab)

Efficacy Assessments:

2.) **Survival analyses:** Kaplan Meier

3.) **Response to trimodality therapy (chemoradiation plus Durvalumab),** which will be evaluated in this study using the revised RECIST guideline (https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf) with the following definitions:

- Complete Response (CR): Disappearance of all target lesions
- Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to quality for Progressive Disease (PD), taking as reference the smallest sum LD since the treatment started.

Progression is defined as change in a known lesion(s) not related to post-treatment effects as defined below:
• At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Additionally, the absolute increase must be greater than 5 mm.
• Appearance of ≥1 new lesions not related to post-treatment effect.

Progression is further divided into local, regional or distant progression:
• Local: Progression within the PTV.

• Regional: Progression outside the PTV but within the same lobe of the lung as the primary tumor or in regional lymph nodes (AJCC 8th edition)
• Distant: Progression at any other site (including pleural or pericardial effusion)

Statistical Methods/Sample Size Determination/Data Analysis:

For the primary endpoint of completion rate of chemotherapy/split course chest radiation, where we anticipate 80% completion, a sample size of n=30 provides power of about 0.8 in a non-inferiority test with non-inferiority margin of 0.18 and alpha =0.05. This will allow estimation of the completion rate within ±0.13 using a 90% confidence interval (normal approximation) or within a total width of 0.30 (using exact Binomial interval).

For the endpoint of completion of durvalumab post-chemoradiation, we estimate post-chemoradiation n of 24 (assuming 80% completion of chemoradiation). This will allow estimation of durvalumab completion rate within ±0.13 using a 90% confidence interval (normal approximation) or within a total width of 0.30 (using exact Binomial interval).

For the secondary endpoints, with n=30 subjects, we estimate 70% power to detect improvement in PFS for adding Durvalumab and 55% power to detect improvement in OS, each at a liberal 0.10 level of significance and without adjusting for multiplicity. (Without Durvalumab, the median survival is known to be 20 months in this patient population; we expect that adding Durvalumab in the treatment regimen will improve the median survival to 30 months. Without Durvalumab, the median progression free survival (PFS) is known to be 11 months in this patient population; we expect that adding Durvalumab in the treatment regimen will improve the median PFS to 17 months.)

SCHEDULE OF STUDY ASSESSMENTS

	Screening (prior to CRT)	**During 4 cycles of CRT (12 weeks)**	**C1 Durva**	**C2 Durva**	**C3 Durva**	**C4 Durva**	**C5 to C12 Durva or PD**	**C13 Durva or final visit**	**Follow-up (q3mths for year 1 from end of durvalumab, q4mths for year 2 from end of durvalumab)[u]**
Week		**1-12**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**						
Day		**1-84**	**Q28days ±3 days unless dosing needs to be held for toxicity reasons**						
Informed consent: study procedures[b]	X								
Physical Exam	X	X[x]							X
Quality of life (QOL) [v]		X[v]	X			X	X[v]		
Targeted physical exam (based on symptoms)			X	X	X	X	X	X	
Vital signs[c]	X	X[x]	X	X	X	X	X	X	
Concomitant medications	X	X[x]	X	X	X	X	X	X	
ECG[d]	X (optional)		As clinically indicated						

	Screening (prior to CRT)	During 4 cycles of CRT (12 weeks)	C1 Durva	C2 Durva	C3 Durva	C4 Durva	C5 to C12 Durva or PD	C13 Durva or final visit	Follow-up (q3mths for year 1 from end of durvalumab, q4mths for year 2 from end of durvalumab)[u]
Week		**1-12**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**						
Day		**1-84**	**Q28days ±3 days unless dosing needs to be held for toxicity reasons**						
Pulmonary Function Tests (FEV1 and DLCO)[t]	X (optional)								
Demography and Medical History, including baseline characteristics and tobacco use	X								
Eligibility criteria	X								
Clinical chemistry[e]	X		X[f]	X	X	X	X	X	
Hematology[e] (CMP and CBC with differential)	X	X[x]	X[f]	X	X	X	X	X	
TSH[g], (reflex free T3 or free T4[h])	X	X[n]	X			X	Every 3 cycles unless clinically indicated	X	X[p]
Hepatitis B and C and HIV[r]	X								
TB test[s]	X								

	Screening (prior to CRT)	During 4 cycles of CRT (12 weeks)	C1 Durva	C2 Durva	C3 Durva	C4 Durva	C5 to C12 Durva or PD	C13 Durva or final visit	Follow-up (q3mths for year 1 from end of durvalumab, q4mths for year 2 from end of durvalumab)[u]
Week		**1-12**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**						
Day		**1-84**	**Q28days ±3 days unless dosing needs to be held for toxicity reasons**						
Pregnancy test[i]	X		X	X	X	X	X	X	
WHO/ECOG performance status	X		X	X	X	X	X	X	X
AE/SAE assessment [j]		X[v]	X	X	X	X	X	X	X
Durvalumab (monotherapy) [k]			X	X	X	X	X	X	
Tumor biopsy (newly acquired or archival ≤3 months old)[a]	X								
Tumor biopsy (archival, if available, for patients who submit a newly acquired biopsy at screening for PD-L1 status)	X								
CT scan chest (through adrenals)			X[o]						X

	Screening (prior to CRT)	**During 4 cycles of CRT (12 weeks)**	**C1 Durva**	**C2 Durva**	**C3 Durva**	**C4 Durva**	**C5 to C12 Durva or PD**	**C13 Durva or final visit**	**Follow-up (q3mths for year 1 from end of durvalumab, q4mths for year 2 from end of durvalumab)[u]**
Week		**1-12**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**						
Day		**1-84**	**Q28days ±3 days unless dosing needs to be held for toxicity reasons**						
Tumor evaluation (CT or PET/CT) (RECIST 1.1) [l,m]	X		CT or PET/CT within 4 weeks of starting C1 Durva. Q3m ± 1w for the first 48 weeks (relative to the date of starting Durva), and then q3-6m ± 1w thereafter until confirmed objective disease progression/death (whichever comes first). The schedule of q3m ± 1 week for first 48 weeks and then q3-6m ±1 w thereafter MUST be followed regardless of any delays in dosing						
Brain MRI with contrast or brain CT with contrast if there is a contraindication for MRI	X								X[W]

[a] Every effort should be made to minimize the time between trial enrollment and starting treatment. (i.e. within 14 days of enrollment)

[b] Informed consent of study procedures and tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization

[c] Body weight is recorded at each visit along with vital signs as per institutional guidelines. Measured height recorded at screening only.

[d] Any clinically significant abnormalities detected require triplicate ECG results. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart) <<for durvalumab monotherapy.

[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 7 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 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.

[i] For women of childbearing potential only. A urine or 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 study drug 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] For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed

[k] 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.

[l] RECIST assessments will be performed on images from CT (preferred), 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 patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of randomization 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 patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit.

[m] Patients will have scans done q3m for the first 48 weeks, and then q3-6m thereafter (relative to the date of randomization) until confirmed objective disease progression. Patients with confirmed PD who continue to receive durvalumab at the discretion of the Investigator (following consultation with AstraZeneca) can receive treatment for a maximum of 12 months until no longer having clinical benefit.

[n] As clinically indicated.

[o] or to progression, whichever occurs first.

[p] until return to normal limits and then as clinically indicated.

[r] Testing performed for known disease and perform testing at screening to determine eligibility. Please refer to exclusion criteria number 16.

[s] Testing performed for known disease or investigator suspicion of exposure, perform testing at screening.

[t] Only performed if deemed tolerable by the investigator

[u] Detail follow up schedule attached on appendix 3 and appendix 4

[v] All patients enrolled in the study who read English or Spanish will complete the EORTC QLQ-C30 quality of life (QOL) assessment at the start of CRT, C1D1 of Durvalumab, and then every 12 weeks during Durvalumab. QOL for patients who are at treatment completion, discontinued due to DLT's, discontinued due to progressive disease see Appendix 3 or Appendix 4.

[w] Brain MRIs will be performed annually on follow-ups or for new neurological symptoms.

[x] Perform PE, vital signs, Con Med's, AE's, Hematology on Day 1 of each cycle of chemotherapy.

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.

C Cycle; ECG Electrocardiogram; IM Intramuscular; LFT Liver function test;; qXw Every X weeks; qXw Every X weeks; SNP Single nucleotide polymorphism; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

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THE STUDY CHAIRS WILL MEET EVERY 6 MONTHS TO MONITOR THE TRIAL FOR SAFETY. INTERIM REPORTS WITH DESCRIPTIVE STATISTICS WILL BE PREPARED TWICE A YEAR UNTIL THE INITIAL PAPER REPORTING THE TREATMENT RESULTS HAS BEEN ACCEPTED FOR PUBLICATION. IN GENERAL, THE INTERIM REPORTS WILL CONTAIN INFORMATION ABOUT THE

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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
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APC	Antigen-presenting cells
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
CDC	Complement-dependent cytotoxicity
CI	Confidence interval

CL	Clearance
C_{max}	Peak concentration
$C_{max,ss}$	Peak concentration at steady state
C_{min}	Trough concentration
$C_{min,ss}$	Trough concentration at steady state
CNS	Central nervous system
CR	Complete response
CRT	Concurrent chemotherapy and radiation therapy
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DC	Disease control
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Disodium edetate dihydrate
GCP	Good Clinical Practice
Gy	Gray (J/kg) – measure of radiation therapy dose
HCl	Hydrochloride
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IGF	Insulin-like growth factor
IHC	Immunohistochemistry

IL	Interleukin
imAE	Immune-mediated adverse event
IMRT	Intensity Modulated Radiation Therapy
IRB	Institutional Review Board
IV	Intravenous(ly)
MAb	Monoclonal antibody
MDT	Multi-disciplinary Team
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro ribonucleic acid
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural killer
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
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
PRO	Patient-reported outcome

Q2W	Every 2 weeks
Q3M	Every 3 months
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
$t_{½}$	Half life
TIL	Tumor infiltrating lymphocyte
T_{max}	Time to peak concentration
$T_{max,ss}$	Time to peak concentration at steady state
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
USA	United States of America
WHO	World Health Organization

1. INTRODUCTION

1.1 Background and Rationale

Definitive chemoradiation followed by durvalumab is the standard of care treatment for inoperable stage III non-small cell lung cancer. For the first time in twenty years (since the adoption of concurrent chemoradiation), a breakthrough in terms of overall survival was made in this patient population, thanks to the addition of durvalumab (Antonia 2018). The landmark study published by Antonia, et al suggested a statistically significant improvement in overall survival: The 2 year overall survival rate was 66.3% (95% CI, 61.7 to 70.4) in the durvalumab group versus 55.6% (95% CI, 48.9 to 61.8) in the placebo group (two-sided P = 0.005). Additionally, progression free survival (PFS) increased from 5.6 to 17.2 months with the addition of durvalumab. Notably only 15% of patients on the Durvalumab arm had to discontinue therapy due to adverse events (Antonia 2017). The landmark study included high functioning patients only, that is World Health Organization performance status of 0-1, and the median age of patients enrolled was 64 years. In the cohort of patients ≥65 years, the durvalumab arm remained superior (HR for disease progression or death of 0.74; CI0.54-1.01).

With many newly-diagnosed stage III NSCLC patients ineligible for this new standard of care regimen due to poor performance status (ECOG 2), competing risks, or advanced age with or without other comorbidities, treatment is often deescalated and/or “non-curative therapies” are offered instead. These alternate regimens often omit chemotherapy or immunotherapy, and/or use an abbreviated radiotherapy regimen.

Expanding the eligibility criteria is one potential way to increase the access and utilization of curative therapies (Bonomi 2018). Certain comorbidities, prior cancer histories, and/or prior oncologic therapies, may not necessarily obviate curative strategies in this patient population. In addition, an emerging need exists to optimize the therapeutic window for poor risk/elderly patients, such that they may derive the greatest benefit.

Continuous course chemoradiation is difficult to tolerate for poor risk patients, given the compounded side effects of multimodality treatment without a break. One large study from Hoosier and US Oncology suggested significantly higher rates of grade 3 and 4 toxicities and higher rates of hospitalization compared to younger patients <70yo treated with a definitive CRT regimen (Jalal 2011). In a larger scale, pooled analysis of individual patient data from cooperative group studies of concurrent CRT, significantly fewer elderly (≥70yo) compared

with younger patients: completed treatment, discontinued treatment because of AEs, died during treatment, and refused further treatment (Stinchcombe 2017).

As such, alternative strategies for administering curative doses of chemotherapy and radiation therapy have been explored. Split-course radiation with chemotherapy, in particular, has been described with favorable outcomes, approximating those seen in continuous regimen approaches (Garg 2014; Gielda 2011).

In the split course approach largely adopted by a single high-volume institution, patients receive a full four cycles of chemotherapy, with radiation concurrently for 7-8 fractions at the start of each cycle (such that 1-1.5 week breaks from radiation are built into each cycle). These patients do not, however, receive any adjuvant or maintenance therapies after completion of chemoradiation, as they would be ineligible for durvalumab off study.

One of the radiation developments that has helped more patients complete their course of radiation is intensity modulated radiation therapy (IMRT); it has also been shown to have an association with improved survival and lesser toxicities when utilized in the treatment of locally advanced NSCLC (Koshy 2017; Chun 2017). More conformal techniques have enabled less heart and lung doses, specifically, reducing the short and long term impact of high dose radiotherapy in this patient population (Koshy 2017; Chun 2017). IMRT, coupled with improvements in image guidance have facilitated highly individualized, precise, and often adaptable (based on real-time cone beam CTs) radiotherapy plans.

We thus propose this phase II trial using four-phase, split course chemoradiation using IMRT, followed by up to 12 months of Durvalumab in elderly (greater than or equal to 70 years old) and/or poor-risk (ECOG PS 2; Creatinine clearance <60) patients with newly diagnosed stage III NSCLC.

1.2 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (Dunn et al 2004).

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (CD279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki and Honjo 2007). The PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T cell response. 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 (**Error! Reference source not found.**; 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 [**Error! Reference source not found.**]) 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 now been added to with 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. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies, whilst nivolumab and pembrolizumab, two anti–PD-1 agents, and atezolizumab, an anti–PD-L1, agent have been granted approvals by agencies such

as the US FDA and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, there are data from agents in the anti–PD-1/PD-L1class showing clinical activity in a wide range of tumor types.

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

To date durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 0 and Section 6.2. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.4 Research hypotheses

1. We hypothesize that concurrent four phase, split course chemoradiation followed by Durvalumab is feasible (safe and tolerable) in elderly / poor risk stage III NSCLC patients.

2. We hypothesize that >80% of patients enrolled will complete split course chemoradiation, and be eligible to receive adjuvant Durvalumab

3. Without Durvalumab, the median survival is known to be 20 months in this patient population; we expect that adding Durvalumab in the treatment regimen will improve the median survival to 30 months.

4. Without Durvalumab, the median progression free survival (PFS) is known to be 11 months in this patient population; we expect that adding Durvalumab in the treatment regimen will improve the median PFS to 17 months.

1.5 Rationale for conducting this study

The rationale for the study is to identify another cohort of stage III NSCLC for whom adjuvant Durvalumab can be safely given, expanding its utilization and benefits. With a unique, extremely well-tolerated 4-phase split course CRT regimen preceding the administration of Durvalumab, we expect to be able to offer adjuvant Durvalumab to a significant proportion of patients on study.

1. **Primary Objectives:** To determine the completion rate of 4-cycle split course CRT and to determine the feasibility (safety/tolerability) of durvalumab post chemoradiation in poor risk and/or elderly stage III NSCLC patients.

2. **Secondary Objectives**

   a. To determine the 1-year overall survival rate

   b. To determine the 1-year progression-free survival rate

   c. To determine the 1-year loco-regional progression-free survival rate

   d. To determine rate of grade 3 and 4 toxicities with this regimen in the selected patient population

1.5.1.1 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).

PK/Pharmacodynamics data

Based on available PK/pharmacodynamics 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 IB).

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

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

Clinical data

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

1.5.1.2 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 only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Ng et al. 2006, Wang et al. 2009, Zhang et al. 2012, Narwal et al. 2013). Wang and colleagues investigated 12 monoclonal antibodies

and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al. 2009)]. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters (Zhang et al. 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

1.6 Benefit/risk and ethical assessment

1.6.1 Potential benefits

1.6.1.1 Durvalumab

Durvalumab may improve survival and progression-free survival in this patient population as it did in the favorable-risk patients enrolled on the landmark NEJM study. Additionally, Durvalumab may reduce incidence of distant metastases and brain metastases.

1.6.2 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 is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressant 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.

1.6.2.1 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, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases

in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicity, infusion-related reactions, hypersensitivity reactions and infections/serious infections.

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

Further information on these risks can be found in the current version of the durvalumab IB.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9% 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

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

1.6.2.2 Overall benefit-risk

Given the overall well-tolerated nature of Durvalumab (most often better tolerated than chemotherapy), and its potential to improve survival, the benefits for this trial far outweigh the risks.

2. STUDY OBJECTIVES

2.1 Primary objective(s)

To determine the percentage of poor risk/elderly stage III NSCLC patients who complete chemotherapy/split course chest radiation and are able to proceed to treatment with durvalumab and to determine safety/tolerability of durvalumab post chemoradiation in this group of patients.

2.2 Secondary objective(s)

a. To determine the 1-year overall survival rate

b. To determine the 1-year progression-free survival rate

c. To determine the 1-year loco-regional progression-free survival rate

d. To determine rate of grade 3 and 4 toxicities with this regimen in the selected patient population

3. STUDY DESIGN

3.1 Overview of study design

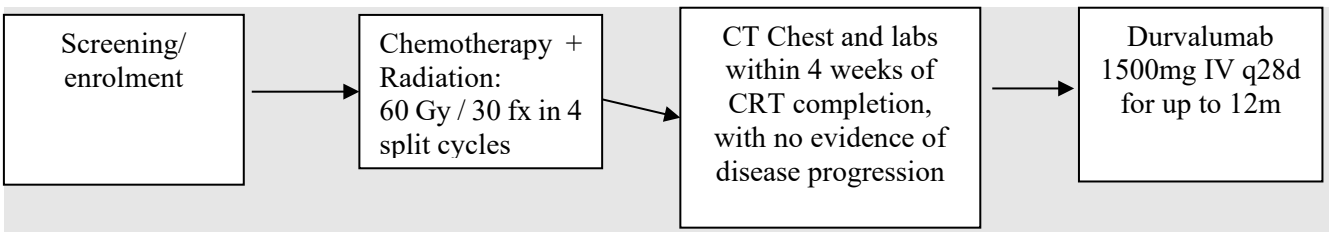
This is a non-randomized, prospective phase II clinical trial.

Radiation and chemotherapy will begin on the same day (Day 1) and be administered on an outpatient basis. On days on which both modalities are being delivered, the sequence of treatments does not matter. Radiation will commence and continue for 7-8 fractions over the first 2 weeks on weekdays only (e.g. M-F, M-W), and then be held for the remainder of the second week and the third week. Radiation will resume at the start of cycle 2 (Day 22 +/- 2 days) of therapy at the same time of initiation of cycle 2 of chemotherapy. During this second phase of radiation, 7-8 (to total 15+/- 2 days) fractions will be delivered before the next break (second half of week 5 and week 6). At the start of cycle 3 (Day 43 +/- 2 days), radiation will resume with 7-8 consecutive weekday treatments alongside cycle 3 of chemotherapy. The last phase of therapy will begin cycle 4 (Day 64 +/- 2 days) with 7-8 (to total 30) consecutive weekdays of radiotherapy alongside cycle 4 of chemotherapy. The radiation treatments should thus alternate 8/7/8/7 or 7/8/7/8 to complete 30 total fractions over the four phases of chemoradiation. Chemotherapy will consist of four, 21 day cycles of an FDA approved carboplatin doublet (pemetrexed for pemetrexed eligible patients and paclitaxel or etoposide for those pemetrexed ineligible as outlined in section 5.3 of the protocol). Within 4 weeks of completion of chemoradiation, provided no progression on restaging CT chest scans, patients will start their course of Durvalumab (1500mg IV every 28 days (+/- 2 days for up to 12 months).

Radiation, chemotherapy, and durvalumab will be held/adjusted according to the protocol (see section 3.3)

3.2 Study schema

Figure 1.



3.3 Study oversight for safety evaluation / discontinuation of therapies

Safety will be monitored by Rush University Medical Center's internal Data Safety Monitoring Board on a 6 month basis or if any grade 5 toxicities occur. If three or more grade 5 toxicities occur, the study will be halted.

Radiation-Related Toxicities:
Any grade 3-4 cardiopulmonary SAEs (congestive heart failure, pneumonitis, arrhythmias, and myocardial infarction), grade 4 esophagitis, or any AEs that lead to radiation therapy related hospitalizations that make continued RT infeasible should require RT to be held. RT could be resumed if AEs return to grade 2 or less, but if the AEs do not return to grade 2 or less within 14 days, RT will be permanently discontinued.

Chemotherapy-Related Toxicities:
Dose modifications of 20%: for weight loss greater than 10% of initial body weight, for grade 4 toxicity, or for delay in treatment due to parameters not being met (see 5.3).

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used to grade adverse events. Patients will be evaluated clinically and with standard laboratory tests before each cycle of chemotherapy as specified in Study Calendar & Evaluations. Subjects will be evaluated for serious adverse events, and adverse events requiring chemotherapy drug interruption or discontinuation as specified in Study Calendar & Evaluations. Specifically, any grade 3 non-hematologic toxicities and any grade 4 hematologic toxicities will be reported.

Chemotherapy will be held/modified for the following:

A. With any cardiopulmonary SAEs (congestive heart failure, pneumonitis, arrhythmias, myocardial infarction), grade 4 esophagitis, or any AEs that lead to radiation therapy related hospitalization that make continued RT infeasible. Chemotherapy will be resumed with the following cycle of radiation, thus potentially extending chemotherapy cycle length beyond 21 days.
B. As outlined in section 5.3

MEDI4736 (Durvalumab) Related-Toxicities:
For MEDI4736 (durvalumab), there will not be any dose escalation or de-escalation. If the MEDI4736 (durvalumab) dose is held or interrupted, it will not be made up. If the patient meets retreatment criteria, the full dose of 1500 mg will be administered. If the patient does not meet retreatment criteria before the next scheduled dose, if/when the toxicity resolves to the point where treatment is possible, the doses of MEDI4736 (durvalumab) are applied off schedule every 4 weeks. MEDI4736 (durvalumab) must be withheld for drug-related toxicities and severe or life-threatening AEs as per the CTCAE v5.0. The drug will be permanently discontinued for the following conditions: Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day

(or equivalent) within 12 weeks after last dose of study drug; recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing. Please see Toxicity Management Guidelines.

4. PATIENT SELECTION

4.1.1 Inclusion criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

1. Participants must have histologically or cytologically confirmed stage IIIA-C (AJCC 8th edition) non-small cell lung cancer that will be treated with curative intent.

2. Participants must have been deemed medically inoperable by multidisciplinary team/tumor board.

3. Participants must have been staged with a PET/CT within 45 days of enrollment (if PET/CT out of window, CT Chest/Abdomen/Pelvis within 21 days of enrollment is acceptable).

4. Patients must have undergone an MRI Brain w/IV contrast, or CT brain if MRI not feasible, confirming no evidence of brain metastases, within 30 days of enrollment.

5. Participants must be elderly (age 70 years or older and PS 0-1) or >18 years old AND poor risk (ECOG 2)

6. Participants ideally have endobronchial ultrasound biopsy (EBUS) or mediastinoscopy to confirm nodal status, but can be deferred if PET/CT imaging characteristics are highly suggestive of nodal metastases

7. Participants should have a life expectancy of >6 months

8. Participants must have normal organ and marrow function: Leukocytes >3000/mcL; ANC >1500/mcL; PLT>100000/mcL; Hemoglobin ≥9.0 g/dL

9. Serum bilirubin ≤1.5x institutional upper limit of normal (ULN)

10. AST/ALT <2.5x institutional upper limit of normal

11. Measured creatinine clearance (CL) >30 mL/min or Calculated creatinine CL>30 mL/min by the Cockcroft-Gault formula

Males:

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

Females:

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

12. Patients must be capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

13. Body weight >30kg

14. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or

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

15. 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.

16. Concurrent enrollment on RUSH IIT Protocol EERENs: A Phase II Single Arm Study is allowed for those patients enrolled in this trial.

4.1.2 Exclusion criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study:

1. History of allergic reactions attributed to compounds of similar chemical or biologic composition to carboplatin, pemetrexed (for patients with adenocarcinoma), etoposide (for patients with squamous cell carcinoma), or immunotherapy

2. **If deemed by treating oncologic physicians,** Patients that have uncontrolled intercurrent illness, including but not limited to: ongoing or active infection, symptomatic congestive heart failure, symptomatic 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

3. Pregnant women

4. Patients known to be HIV+

5. 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

6. Receipt of the last dose of anticancer therapy (CRT) ≤7 days prior to the first dose of study drug. If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by AstraZeneca/MedImmune and the investigator

7. 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.

17. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

18. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

19. History of allogenic organ transplantation.

20. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

    a. Patients with vitiligo or alopecia

    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement

    c. Any chronic skin condition that does not require systemic therapy

    d. Patients without active disease in the last 5 years may be included but only after consultation with the study physician

    e. Patients with celiac disease controlled by diet alone

21. History of another primary malignancy except for

    a. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP 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

22. History of leptomeningeal carcinomatosis

23. History of active primary immunodeficiency

24. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

25. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:

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

    b. Systemic corticosteroids at physiologic doses not to exceed <<10 mg/day>> of prednisone or its equivalent

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

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

27. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy.

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

29. Prior randomisation or treatment in a previous durvalumab clinical study regardless of treatment arm assignment.

30. Patients who have received prior anti–PD-1, anti PD-L1, including durvalumab or anti CTLA-4:

    a. Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy.

b. All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study.

c. Must not have experienced a ≥Grade 3 immune related AE or an immune related neurologic or ocular AE of any grade while receiving prior immunotherapy. NOTE: Patients with endocrine AE of ≤Grade 2 are permitted to be enrolled if they are stably maintained on appropriate replacement therapy and are asymptomatic.

d. Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day.

31. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 4.2

Withdrawal of patients from study treatment and/or study

Permanent discontinuation of Durvalumab

An individual patient will not receive any further investigational product if any of the following occur in the patient in question:

1. An individual patient will not receive any further durvalumab if their weight falls to 30kg or less.

2. Withdrawal of consent or lost to follow-up.

3. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing.

4. Patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.

5. Pregnancy or intent to become pregnant.

6. Any AE that meets criteria for discontinuation as defined in Section 6.3

7. Grade ≥3 infusion reaction

8. Patient noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits

9. Initiation of alternative anticancer therapy including another investigational agent

10. Confirmation of PD and investigator determination that the patient is no longer benefiting from treatment with durvalumab.

11. Patients who are permanently discontinued from receiving investigational product will be followed for safety per Section 10.3.1, 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 patients 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

4.2 Withdrawal of consent

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

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

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

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

- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing.
- Pregnancy or intent to become pregnant.
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (e.g., 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 1)

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

- all further participation in the study including any further follow up (e.g., survival contact telephone calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples

4.2.1 Replacement of patients

5. PATIENTS WHO DO NOT REMAIN ON THE STUDY UP TO THIS TIME FOR REASONS OTHER THAN DLT WILL BE REPLACED WITH ANOTHER PATIENT AT THE SAME DOSE LEVEL. INVESTIGATIONAL PRODUCT(S)

5.1 Durvalumab

5.1.1 Formulation/packaging/storage

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

5.1.2 Durvalumab doses and treatment regimens

Patients will receive 1500 mg durvalumab via IV infusion q4w for up to 12 months unless criteria for discontinuation are met. Patients will receive 20mg/kg if weight drops and participants are allowed to stay in the study.

5.1.3 Study drug preparation

Patients will receive 1500mg durvalumab (MEDI4736) via IV infusion Q4W for up to a maximum of 12 months (up to 13 doses/cycles) with the last administration on week 48, or until confirmed disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. (If a patient's weight falls to 30kg or below the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500mg Q4W.

See Figure 2.

Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab (MEDI4736) for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

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

A dose of 1500mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, 1500mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If patient weight falls to ≤ 30 kg weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

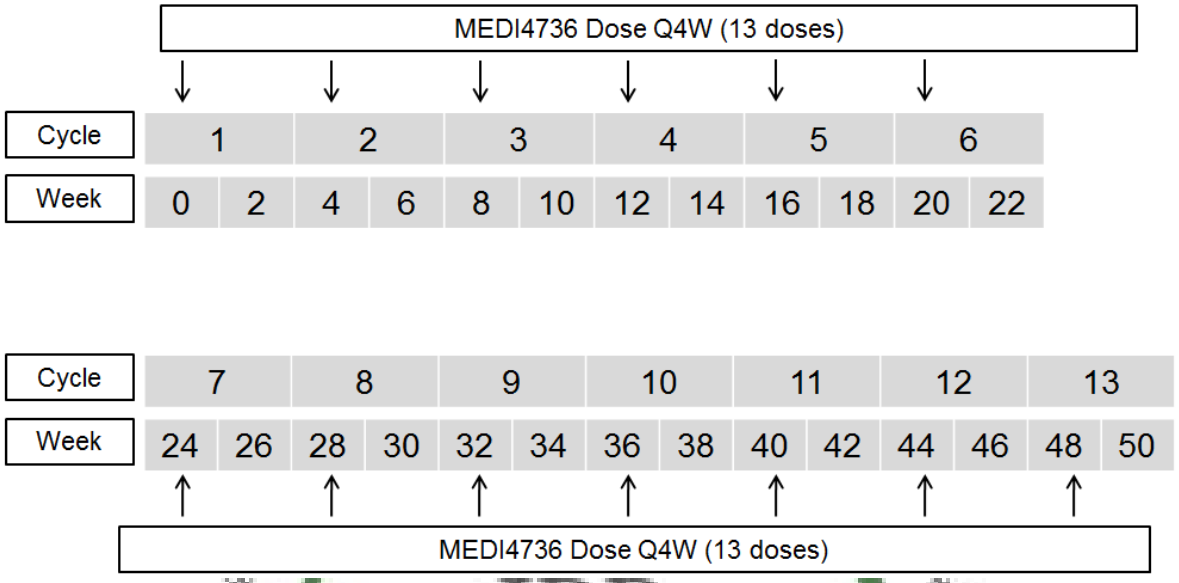
Standard infusion time 1 hour, however. In the event that if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

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

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

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

Figure 2. Durvalumab (MEDI4736) Monotherapy Dosing Schedule



5.1.4 Monitoring of dose administration

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

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued. Standard infusion time 1 hour, however. In the event that if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. If time exceeded, then new preparation will be required.

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

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study

personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

5.1.5 Accountability and dispensation

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab (MEDI4736) to the investigator as a 500-mg vial solution for infusion after dilution. After last patient is placed in follow up, pharmacy will follow internal SOP for destroying drug.

5.1.6 Disposition of unused investigational study drug

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

5.2 RADIATION THERAPY DETAILS:

CT simulation for radiation will be acquired alongside 4DCT, i.e. 4 dimensional CAT scan (which incorporates tumor motion into planning). The free breathing scan will be performed using 1-3mm cuts with or without IV contrast (based on discretion of Radiation Oncologist for target delineation). Radiation therapy will be administered with photons, 6-18 MVs. Effort should be made to maximize the utilization of 6MV photons as the primary treatment energy. Prescription will be 60 Gy / 30 fractions to the

PTV, such that at least 93% of the PTV is receiving the prescription dose of 60 Gy. No elective coverage will be part of the planning process, unless there are intervening areas of concern deemed clinically necessary to cover by treating Radiation Oncologist (e.g. coverage of level 4R LN if 2R and 7 are both positive). Hot spots outside the PTV will be limited to no more than 10% hot and no more than 15% hot within the PTV.

Intensity modulated radiation therapy (IMRT), step-and-shoot or VMAT (volumetric modulated arc therapy) will be a requirement with daily CBCTs (cone beam cat scans) for image guidance. Adaptive re-planning will be allowed after a minimum of 2 phases (i.e. 30 Gy) of concurrent chemoradiation if deemed appropriate by the treating Radiation Oncologist. The following organs at risk will be routinely contoured: heart, lungs, brachial plexus, esophagus, spinal cord. The GTV will be contoured and include gross disease (biopsy proven, PET-avid, or CT criteria for nodal disease - >1cm in short axis). The CTV will include a 5mm expansion on the primary lung tumor respecting anatomic boundaries and an expansion of nodal volume to include involved LN station. The ITV will reflect MIP and 4DCT/gated imaging acquired at the time of CT simulation, and an ICTV will be created reflecting the physiological motion of the CTV. The PTV will be at least 3, but no more than 5mm margin expansion on the ICTV.

The following OAR parameters will be required:

Spinal Cord dmax <50 Gy

Heart mean dose < 30 Gy and/or V50<25%

Total Lungs mean dose <20 Gy and V20<32% and V5<75%

Brachial Plexus dmax <66 Gy

Esophagus mean dose <30 Gy and dmax <66 Gy

5.3 Chemotherapy Details:

5.3.1 Non-squamous histology

Chemotherapy will be Carboplatin/Pemetrexed (delivered on one day, every three weeks for four cycles) for adenocarcinoma histology and creatinine clearance > 45. For patients with creatinine clearance <45 patients will receive carboplatin/paclitaxel (carboplatin AUC =4 day 1, paclitaxel 80mg/m2 day 1 and day 8 or 21 day cycle or Carboplatin/Etoposide (carboplatin AUC =4 day 1, etoposide 80mg/m2 days 1-3, every three weeks for four cycles), per decision of investigator.

Dose adjustments can be made at the discretion of the treating Medical Oncologists.

5.3.2 Squamous cell carcinoma histology

Patients will receive carboplatin/paclitaxel (carboplatin AUC =4 day 1, paclitaxel 80mg/m2 day 1 and day 8 or 21 day cycle or Carboplatin/Etoposide (carboplatin AUC =4 day 1, etoposide 80mg/m2 days 1-3, every three weeks for four cycles), per decision of investigator.

Dose adjustments can be made at the discretion of the treating Medical Oncologists.

5.3.3 Treatment parameters:

Treatment will be based on most recent weight prior to each cycle of chemotherapy.

Treatment parameters for each cycle:

1. Absolute neutrophil count above 1000/microliter

2. Platelets above 100,000 per microliter

3. Dose modifications of 20%: for weight loss greater than 10% of initial body weight, for grade 4 toxicity, or for delay in treatment due to parameters not being met

6. TREATMENT PLAN

6.1 Patient enrollment

Patient registration can occur only after evaluation for eligibility is complete and eligibility criteria have been met. Patients must have signed and dated all applicable consents and authorization forms. There will be no randomization in this study.

Dosage and administration

See section 5 for chemotherapy, radiation therapy, and Durvalumab treatment parameters.

6.2 Definition of DLT

Dose-limiting toxicities (DLTs) will be evaluated during the trial. The period for evaluating DLTs will be from the time of first administration of durvalumab until 3 months after last administration. Patients who do not remain on the study up to this time for reasons other than DLT will be replaced with another patient at the same dose level. Grading of DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Prior to the DLT definition section in a protocol, the rules for identifying the maximum tolerated dose should be clearly defined (e.g., if ≥2/6 DLTs occur in a dose escalation cohort).

A DLT is defined as the occurrence of an adverse event (AE) that is **at least possibly related to the investigational product (IP) or investigational regimen (IR)**, with two exceptions: any grade of vitiligo or alopecia will not qualify as a DLT. AEs that are **at least possibly related to durvalumab- and/or tremelimumab-containing regimens** shall be assessed as DLTs if they meet any of the following criteria:

Hematologic toxicity:

- Grade ≥3 neutropenia complicated by fever >38.3°C
- Grade 4 neutropenia (lasting more than 7 days)
- Grade ≥3 thrombocytopenia with significant bleeding
- Grade 4 thrombocytopenia (regardless of duration)
- Grade 4 anemia (regardless of duration)

Non-hematologic toxicity:

- Any Grade 4 non-immune-mediated AE
- Any Grade 4 immune-mediated AE, excluding endocrinopathies
- Any Grade 3 non-immune mediated AE that does not resolve to ≤Grade 1 or baseline within 30 days with optimal medical management

- Any Grade 3 immune-mediated AE – excluding diarrhea/colitis, pneumonitis, hepatitis, rash, neurotoxicity, myocarditis, myositis/polymyositis, endocrinopathies and nephritis – that does not resolve to ≤Grade 1 or baseline within 30 days after onset of the event despite optimal medical management including systemic corticosteroids
- Grade 3 diarrhea or colitis that does not resolve to ≤Grade 1 within 14 days [*both* immune- *and* non-immune-mediated indicated here; the same is the case if not specified in remaining bullet points below]
- Grade 3 noninfectious pneumonitis
- Grade 2 noninfectious pneumonitis that does not resolve to ≤Grade 1 within 3 days of the initiation of maximal supportive care
- **Aspartate** aminotransferase (AST) or **alanine** aminotransferase (ALT) ≥3×ULN with concurrent increase in total bilirubin (TBL) ≥2×ULN without evidence of cholestasis or alternative explanations (e.g., viral hepatitis, disease progression in the liver; i.e., "Hy's Law")
- ALT or AST >8×ULN or TBL>5×ULN
- Grade 3 immune-mediated rash that does not resolve to ≤Grade 1 or baseline within 30 days
- Grade 2 rash covering > 30% BSA that does not resolve to ≤Grade 1 or baseline within 30 days
- Any grade of immune-mediated rash with bullous formation
- Grade 3 immune-mediated neurotoxicity (excluding Guillain-Barre and myasthenia gravis) that does not resolve to ≤Grade 1 within 30 days
- Grade 2 or 3 immune-mediated peripheral neuromotor syndrome (such as Guillain-Barre and myasthenia gravis) that does not resolve to ≤Grade 1 within 30 days or that exhibits signs of respiratory insufficiency or autonomic instability
- Grade 3 immune-mediated myocarditis
- Any symptomatic immune-mediated myocarditis that does not become asymptomatic within 3 days of initiating optimal medical management including systemic corticosteroids
- Grade 2 or 3 immune-mediated myositis/polymyositis that does not resolve to Grade ≤1 within 30 days of initiating optimal medical management including systemic corticosteroids or that exhibits signs of respiratory insufficiency regardless of optimal medical management
- Immune-mediated increase in creatinine >3×ULN, or >3×baseline for patients with a baseline creatinine elevated above ULN

The DLT assessment period is from the time of first dose of IP/IR and ends upon administration of the first dose of IP/IR on Cycle 2, Day 1 (28 day cycle).

Any treatment-related toxicities that first occurred during the DLT period must be followed for resolution to determine if the event qualifies as a DLT as specified in the DLT criteria above.

Immune-related AEs are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

6.3 Toxicity management guidelines

6.3.1 Durvalumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the durvalumab Toxicity Management Guidelines (TMGs).

Patients 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 4.1.2 and the Dosing Modification and Toxicity Management Guidelines in Appendix 1).

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 1. These guidelines have been prepared 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 durvalumab monotherapy by the reporting investigator

> **NOTE: Dose reductions are not permitted.** In case of doubt, the Investigator should consult with the Company.

Patients 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, Version5.0.

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

7.1 Restrictions during the study

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

Female patient of child-bearing potential

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

Male patients with a female partner of childbearing potential

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

- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 1).

N.B Females of childbearing potential are defined as those who are not surgically sterile (i.e., 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 (i.e., less than 1% per year) when used consistently and correctly are described in Table 1. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

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

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

[a] This is also considered a hormonal method

Blood donation

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

7.2 Concomitant treatment(s)

7.2.1 Permitted concomitant medications

Table 2. Supportive Medications

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

7.2.2 Excluded concomitant medications

Table 3. Prohibited Concomitant Medications

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

Prohibited medication/class of drug:	Usage:
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])

Prohibited medication/class of drug:	Usage:
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: • Usage during CRT • Use of immunosuppressive medications for the management of IP-related AEs, • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

8. STUDY PROCEDURES

8.1 Schedule of Events

See page 7 for the Schedule of Events.

For all treatment arms

- PRO, QoL (in Spanish for Spanish speakers), and tumor efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of randomization (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.

For durvalumab monotherapy

- Patients may delay 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
  - Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) and PRO assessments. Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives of durvalumab (see current Investigator Brochure for durvalumab).

8.1.1 Screening phase

Screening procedures will be performed up to 5 days before Day 1 of CRT, unless otherwise specified. All patients must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, patients will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the Screening Visit:

- Informed Consent

- Review of eligibility criteria
- Medical history and demographics, tobacco use
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG
- Pulmonary function testing performed if deemed tolerable by the investigator
- Hep B/ Hep C testing
- HIV testing for known HIV positive patients
- Tumor biopsy
- Review of prior/concomitant medications
- Brain Imaging by CT/MRI
- Tumor evaluation PET/CT
- Clinical laboratory tests for:
    - Hematology (see Table 4)
    - Clinical chemistry (see Table 5)
    - TSH
    - Creatinine Clearance
    - Serum or Urine pregnancy test (for women of childbearing potential only)
    - Urinalysis (see Table 6) **discretion** of the **investigator**

8.1.2 Treatment phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

8.1.3 End of treatment

End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For patients who discontinue durvalumab prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ±7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

Assessments for patients 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 Appendix 3.

Assessments for patients who have discontinued durvalumab treatment due to confirmed PD are presented in Appendix .

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

8.2 Description of study procedures

8.2.1 Medical history and physical examination, 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 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), genital/rectal, and neurological systems and at screening only, measured height.

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Bodyweight is also recorded at each visit along with vital signs.

First infusion of Durvalumab

On the first infusion day, patients will be monitored, and vital signs collected/recorded in eCRF prior to infusion of IP.

Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab.

Subsequent infusions of Durvalumab

BP, pulse and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored, and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments, Appendix 3 and Appendix 4 for the timepoints of each test):

Table 4. Hematology Laboratory Tests

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

Note: [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.

Table 5. Clinical Chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
	Uric acid

[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] Bicarbonate (where available), chloride, creatinine clearance, and magnesium testing are to be performed at baseline, on Day 0 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 0), and if clinically indicated.

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

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

Table 6. Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells for clinical signs of infection. Obtain per primary investigator's discretion.

If a patient shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, refer to Appendix 1 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.

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 10.3.5.

All patients 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.

8.3 Biological sampling procedures

8.3.1 Immunogenicity sampling and evaluation methods

PD-L1 testing

Perform PD-L1 testing per local assay

- Tissue will be processed per institutional policies.

8.3.2 Archival tumor samples and fresh tumor biopsies use beyond PD-L1 (not mandated)

8.3.2.1 Fresh tumor biopsies

Tumor biopsies will be performed prior to the start of therapy. Methods for obtaining biopsy can include: image-guided core needle biopsy. Tissue will be processed per institutional policies. Analyses to be conducted with biopsy and archival tumor samples include: immunohistochemistry, tumor mutation analysis, RNA analysis.

9. DISEASE EVALUATION AND METHODS

Rate of completion of therapy (defined as percentage of patients able to receive adjuvant course of Durvalumab)

Response to trimodality therapy (chemoradiation plus Durvalumab), which will be evaluated in this study using the revised RECIST guideline (https://www.eortc.be/Recist/documents/RECISTGuidelines.pdf) with the following definitions:

- Complete Response (CR): Disappearance of all target lesions
- Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to quality for Progressive Disease (PD), taking as reference the smallest sum LD since the treatment started.

Progression is defined as change in a known lesion(s) not related to post-treatment effects as defined below:
• At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Additionally, the absolute increase must be greater than 5 mm.
• Appearance of ≥1 new lesions not related to post-treatment effect.

Progression is further divided into local, regional or distant progression:
• Local: Progression within the PTV.
• Regional: Progression outside the PTV but within the same lobe of the lung as the primary tumor or in regional lymph nodes (AJCC 8th edition)
• Distant: Progression at any other site (including pleural or pericardial effusion)

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, patients may continue to receive durvalumab beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that patients 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).

Patients who have disease control following completion of 12 months of treatment or patients who are withdrawn from durvalumab treatment for reasons other than confirmed PD will continue to have objective tumor assessments (see Appendix).

9.1.1 Efficacy variable

Confirmation of progression guidelines are set for the following reasons:

- For patient 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 pseudo progression 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 RECIST 1.1 PD.

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 patient 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.**

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression.

Following confirmed progression, patients should continue to be followed up for survival status every 3 months as outlined in the follow-up schedules of assessments in Appendix 4

10. ASSESSMENT OF SAFETY

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

10.1.1 Safety parameters

10.1.1.1 Definition of adverse events

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

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

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

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

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

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

10.1.2 Definition of serious adverse events

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the patient
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above
- Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations, or development of drug dependency or drug abuse

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

10.1.3 Definition of adverse events of special interest (AESI)

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

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

AESIs observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases

- Pancreatitis/ serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- 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.

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

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 1.) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc.) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitis carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

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

- Physical examination

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

- SpO2
  - Saturation of peripheral oxygen (SpO2)

- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    - (i) ILD Markers (KL-6, SP-D) and β-D-glucan
    - (ii) Tumor markers: Particular tumor markers which are related to disease progression

Additional Clinical chemistry: CRP, LDH

10.2 Assessment of safety parameters

10.2.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v5.0.
The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

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

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

10.2.2

Per internal Rush Cancer Center Standard Operating procedures, Rush Cancer Center Data Safety Monitoring committee with be overseeing patient safety for this trial.

10.3 Recording of adverse events and serious adverse events

Grade 3-4 non hematologic and grade 4 hematologic SAEs will be collected from the time of the patient starting concurrent chemotherapy and radiation until the follow-up period is completed (90 days after the last dose of durvalumab). If an event that starts post the defined safety, follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

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

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

The following variables will be collected for each AE:

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

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 10.3.2
- Description of the SAE

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

- Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

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

Adverse events and serious adverse events will be recorded from initiation of treatment period and including the follow-up period (90 days after the last dose of durvalumab).

During the course of the study all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

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

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

10.3.2 Causality collection

The Investigator will assess causal relationship between the IPs and each AE and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

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

A guide to the interpretation of the causality question is found in Appendix 1.

10.3.3 Relationship to protocol procedures

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

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

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

10.3.4 Adverse events based on signs and symptoms

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

10.3.5 Adverse events based on examinations and tests

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

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

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

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

10.3.6 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix 1 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

10.3.7 Disease progression

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

10.3.8 New cancers

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

10.3.9 Deaths

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

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

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

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

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. After 90 days, only patients with ongoing investigational product related SAEs will continue to be followed for safety.

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

Post-study events

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

10.3.10 Reporting of serious adverse events

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

Note that all serious or unexpected adverse events must be reported to AstraZeneca regardless of the country where the study is conducted:

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

***** A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address

- The trial name/title and AstraZeneca ISS reference number (ESR-18-14205)

***** Sponsor must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.

**** Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:*** AEMailboxClinicalTrialTCS@astrazeneca.com
If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

10.3.11 Reporting of deaths to AstraZeneca

All deaths that occur during the study, or within the protocol (defined 90day 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 10.3.2 10 for further details). The report should contain a comment regarding the coinvolvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE.

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

reported as an SAE. However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

10.3.12 Other events requiring reporting

10.3.13 Overdose

An overdose is defined as a patient receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study patient with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 10.3.2 10 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 10.3). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section 10.1.2 and Section 10.3.2 10). There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

10.3.14 Hepatic function abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca Patient Safety using the designated Safety e-mailbox (see Section 10.3.2 10 for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study patient will be based on the clinical judgment of the investigator.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

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

10.3.15 Pregnancy

10.3.16 Maternal exposure

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

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

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

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

The same timelines apply when outcome information is available.

10.3.17 Paternal exposure

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

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab

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

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

10.4 Medication error

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

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

Medication error includes situations where an error:

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

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

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

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

- Errors related to or resulting from IVRS/IWRS - including those that lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) e.g. forgot to take medication

- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

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

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs 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 works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 10.3.10) and within 30 days for all other medication errors.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

11.1.1 Safety analysis set

Safety Assessments: Safety will be monitored continually throughout the protocol. Assessments include serious adverse events, vital signs, and physical and laboratory examinations, as well as immune-mediated adverse events.

Chemotherapy safety measurements are limited to grade 3-4 non hematologic toxicities and grade 4 hematologic toxicities.

SAEs possibly, probably or definitely related to RT (including grade 3-4 congestive heart failure, pneumonitis, arrhythmias, and myocardial infarction, grade 4 esophagitis, and any AEs that lead to hospitalization) that causes either an interruption or early termination of RT will be reported. Proportion of patients who have tolerated the treatment will be provided. All adverse events will be graded according to CTCAE v 5.0.

Durvalumab safety measurements are described in detail in protocol (section 10. The tolerability of therapy is defined as having one or no safety events defined as: 1) grade 4-5 non-hematologic serious adverse events (SAEs) as defined in CTCAE v5.0, probably or definitely related to protocol treatment by 90 days from the start of Durvalumab; 2) Any adverse events that lead to prolonged dose delays (defined as skipping at least 2 doses of Durvalumab; 3) Permanent discontinuation of Durvalumab due to toxicity within the first 30 days of starting Durvalumab.

We expect 80% of patients enrolled to complete 4 cycles of concurrent split-course CRT, and in those to go on to receive Durvalumab, we expect no more than 20% of patients to have therapy terminated for Durvalumab-related toxicities.

11.1.2 Efficacy analysis set

Efficacy analysis is part of the secondary objectives of the study. Efficacy endpoints include (i) overall survival (OS) and 1-year overall survival rate; (ii) progression-free survival and 1-year progression-free survival rate and (iii) loco-regional progression-free survival (PFS) and its 1-year rate. The efficacy endpoint of OS will be measured as time from diagnosis to death from any cause. PFS is defined as the time from diagnosis to the first occurrence of disease progression, as determined by investigator review of tumor assessments by RECIST, v1.1 or death from any cause, whichever occurs first. Loco-regional progression-free survival will be defined in a similar way. Data for patients without disease progression or death will be censored at the last follow-up date.

11.2 Methods of statistical analyses

11.2.1 Safety analyses

The safety analyses will include all treated patients. Safety will be assessed through summaries of AEs, changes in test results, changes in vital signs, and exposures. The results will be reported by tabulation and by descriptive summaries.

The two primary objectives of the study are (i) completion of chemotherapy/split course chest radiation; and (ii) safety/tolerability of the durvalumab post-chemoradiation. The first objective will be assessed as a binary endpoint of yes/no completion for each patient. The completion rate, overall as well as stratified by demographic and clinical characteristics will be reported in tabular forms.

The second primary objective of safety/tolerability of durvalumab will be measured by (a) the number of cycles of durvalumab received for each treated patient and (b) the binary endpoint of discontinuation of durvalumab. Each of these endpoints will be reported by descriptive summaries and tabulation.

A secondary objective of the study is determination of grade 3 and 4 toxicities in the selected population. The binary endpoint of (yes/no) grade 3 and 4 toxicities will be tabulated.

For each of the binary endpoints, the overall rate will be reported with 90% confidence interval. Due to the limited sample size, both asymptotic (such as Agresti-Coull) and exact Binomial confidence intervals will be reported. Similarly, the endpoint of number of cycles of durvalumab received will also be reported with 95% confidence interval.

11.2.2 Efficacy analyses

The efficacy analyses will include all treated patients, grouped according to treatment actually received (those patients that completed all study treatments vs those that had study treatments discontinued). Efficacy endpoints include (i) overall survival (OS) and 1-year overall survival rate; (ii) progression-free survival and 1-year progression-free survival rate and (iii) loco-regional progression-free survival and its 1-year rate. OS, PFS and loco-regional-PFS will be analyzed and described by the Kaplan-Meier method. Median survival and, 25th and 75th percentiles will be reported along with confidence intervals, as appropriate. 1-year OS, 1-year PFS and 1 year loco-regional-PFS will be estimated based on the Kaplan-Meier approach.

11.3 Determination of sample size

For the primary endpoint of completion rate of chemotherapy/split course chest radiation, where we anticipate 80% completion, a sample size of n=30 provides power of about 0.8 in a non-inferiority test with non-inferiority margin of 0.18 and alpha =0.05. This will allow estimation of the completion rate within ±0.13 using a 90% confidence interval (normal approximation) or within a total width of 0.30 (using exact Binomial interval).

For the endpoint of completion of durvalumab post-chemoradiation, we estimate post-chemoradiation n of 24 (assuming 80% completion of chemoradiation). This will allow estimation of durvalumab completion rate within ±0.13 using a 90% confidence interval (normal approximation) or within a total width of 0.30 (using exact Binomial interval).

12. FOR THE SECONDARY ENDPOINTS, WITH N= 30 SUBJECTS, WE ESTIMATE 70% POWER TO DETECT IMPROVEMENT IN PFS FOR ADDING DURVALUMAB AND 55% POWER TO DETECT IMPROVEMENT IN OS, EACH AT A LIBERAL 0.10 LEVEL OF SIGNIFICANCE AND WITHOUT ADJUSTING FOR MULTIPLICITY. (WITHOUT DURVALUMAB, THE MEDIAN SURVIVAL IS KNOWN TO BE 20 MONTHS IN THIS PATIENT POPULATION; WE EXPECT THAT ADDING DURVALUMAB IN THE TREATMENT REGIMEN WILL IMPROVE THE MEDIAN SURVIVAL TO 30 MONTHS. WITHOUT DURVALUMAB, THE MEDIAN PROGRESSION FREE SURVIVAL (PFS) IS KNOWN TO BE 11 MONTHS IN THIS PATIENT POPULATION; WE EXPECT THAT ADDING DURVALUMAB IN THE TREATMENT

REGIMEN WILL IMPROVE THE MEDIAN PFS TO 17 MONTHS.)ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

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.

12.2 Ethics and regulatory review

Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

The PI / Radiation Oncologist, Dr. Marwaha, will perform a pre-treatment RT Quality Assurance Review for each case enrolled.

The Co-PI / Medical Oncologist, Dr. Fidler, will perform a pre-treatment chemotherapy / immunotherapy Quality Assurance Review for each case enrolled.

The scoring mechanisms is: 1) Per Protocol, 2) Acceptable Variation, 3) Unacceptable Deviation, and 4) Not Evaluable.

12.3 Informed consent

Patients must have signed and dated all applicable consents and authorization forms prior to enrollment and before performing screening procedures. The form will be signed and personally dated by the subject, parent, legal guardian or caretaker and by the Investigator, Sub investigator or study coordinator designated by the Investigator to conduct the informed consent discussion. Informed consent form used during the process must be the latest version IRB approved. A copy of the form is require to be given to the subject and the original version will be kept in the subject research chart.

12.4 Changes to the protocol and informed consent form

Changes to the protocol and informed consent forms are permitted but must be approved by PI and Co-PIs and be in compliance with study site / AstraZeneca regulations. IRB approval of changes is required.

13. STUDY MANAGEMENT

13.1 Training of study site personnel

Study site personnel will all have access to the protocol, and receive any specific training as deemed fit by the PI and Co-PIs.

13.2 Data collection

Data collected during this study will be entered into a secure database (REDCap) using electronic case report forms, eCRF. Principal investigator is responsible for ensuring eCRFs are completed accurately and in a timely manner. Original records of observations, clinical findings and evaluations that are subsequently recorded as data will be made available to support the subject's research record. The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents and study-related documents. Records are to be retained and securely stored until the later of: (a) two (2) years following the date a New Drug Application is approved for the Study Drug that is the subject of the Clinical Trial; or (b) two (2) years after the Investigational New Drug Application for such Study Drug is terminated or withdrawn, or such longer period of time as may be required by site policies, applicable laws, rules or regulations.

13.3 Monitoring of the study

13.3.1 Source data

Source data for every subject will be kept in the subject's research chart at the coordinator's office under double lock doors with accordance to FDA regulations. These files can be made available during monitoring visits to provide source verification for EDC correlation. Incorrect or missing entries on to the CRFs will be required and must be corrected immediately upon finding.

13.4 Study timetable and end of study

The study chairs will meet every 6 months to monitor the trial for safety. Interim reports with descriptive statistics will be prepared twice a year until the initial paper reporting the treatment results has been accepted for publication. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; data quality; compliance rate of treatment delivery with the distributions of important prognostic baseline

variables; and the frequencies and severity of adverse events. The interim reports will not contain results. These reports will be submitted to the Rush Protocol Review and Monitoring Committee.

14. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

14.1 Identity of investigational product(s)

Table 1. List of Investigational Products for This Study

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

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APPENDIX 1.

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions Version (CTCAE v5.0)

General Considerations

Dose Modifications

Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0.

In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions:

- Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen
- Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing

Grade 1 No dose modification

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

If toxicity worsens, then treat as Grade 3 or Grade 4.

Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper.

Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:

1. The event stabilizes and is controlled.

Toxicity Management

It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table:

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines.

- Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow.
- Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events.
- For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
- Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation.
- If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of

2. The patient is clinically stable as per Investigator or treating physician's clinical judgement.
3. Doses of prednisone are at ≤10 mg/day or equivalent.

Grade 3 Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.

Grade 4 Permanently discontinue study drug/study regimen.

Note: For asymptomatic amylase or lipase levels of >2X ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed.

Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade ≤1 upon treatment with systemic steroids and following full taper

Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).

symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper).

– More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids.

– With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.

– Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

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


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Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors

			(e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea/Colitis	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or

		blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only; intervention not indicated)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day; limiting instrumental ADL) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm

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

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any elevation in AST, ALT or TB > ULN**	**General Guidance**	– Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN	• No dose modifications. • If it worsens, then treat as described for elevations in the row below.	– Continue LFT monitoring per protocol.
	AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤3.0×ULN	• Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN. • If toxicity worsens, then treat as described for elevations in the row below. • If toxicity improves to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN, or baseline, resume study drug/study regimen after completion of steroid taper.	– Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

AST or ALT >5.0×ULN and/or TB >3.0×ULN	For elevations in transaminases ≤8 × ULN, or elevations in TB ≤5 × ULN: • Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN, or baseline • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN, or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN or baseline within 14 days. For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, permanently discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3×ULN + bilirubin >2×ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	– Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (serum creatinine > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – If baseline serum creatinine is elevated above normal, and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated.

		drug/study regimen after completion of steroid taper.	– If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 5.0 for definition of severity/grade	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus).

depending on type of skin rash)		– IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids sooner. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days,	**For Grade 3 or 4 (or life-threatening):** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible.

	then permanently discontinue study drug/study regimen. **For Grade 4 (or life-threatening):** Permanently discontinue study drug/study regimen.	– Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance** **For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For 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. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.

Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short term- corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

		3. Doses of prednisone are ≤10 mg/day or equivalent.	– For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications).

autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	for defining the CTC grade/severity).	– Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate. –
Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above. – Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia)
Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization.

		Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and “repetitive stimulation” if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically

		considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.
Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.

Grade 3 or 4	
	For Grade 3: Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.

For Grade 3 or 4 (severe or life-threatening events):

- Consider, as necessary, discussing with study physician.
- Recommend hospitalization.
- Monitor symptoms and obtain neurological consult.

MYASTHENIA GRAVIS:

- Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist.
- Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG.
- If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.

GUILLAIN-BARRE:

- It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.
- Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

GUILLAIN-BARRE:

- It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.
- Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1 (asymptomatic or mild symptoms*; clinical or diagnostic observations only; intervention not indicated)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.

*Treat myocarditis with mild symptoms as Grade 2.		
Grade 2, 3 or 4 (Grade 2: Symptoms with moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms*) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)) * Consider "new onset of symptoms" as referring to patients	If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

	with prior episode of myocarditis.		
Myositis/Polymyositis (“Poly/myositis”)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).

Grade 1 (mild pain)	- No dose modifications.	
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician. **For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Grade 3 or 4 (Grade 3: pain associated with severe	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation.

weakness; limiting self-care ADLs Grade 4: life-threatening consequences; urgent intervention indicated)	Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** – Permanently discontinue study drug/study regimen.	– Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

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

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

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

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

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

Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

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

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

Appendix 2. Durvalumab Weight-based Dose Calculations

Durvalumab Dosing

For patients weighing ≤ 30 kg, durvalumab should be dosed at 20 mg/kg

Example:

1. Cohort dose: 20 mg/kg

2. Patient weight: 30 kg

3. Dose for patient: 600 mg = 20 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag: [rounded to the nearest tenth mL (0.1 mL)]:

Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL

5. The number of vials required for dose preparation:

Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

Appendix 3. Schedule of Study Procedures: Follow-Up for Patients Who Have Completed Durvalumab Treatment and Achieved Disease Control (Until Confirmed Progression of Disease) and Patients Who Have Discontinued Durvalumab Due to Toxicity in the Absence of Confirmed Progression of Disease

Evaluation	Time Since Last Dose of durvalumab					
	Day (±3)	Months (±1 week)				Every 4 Months (±2 weeks) for 2 years
	30	3	6	9	12	
Physical examination[a]	X	X	x	x	x	x
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X	X				
Weight	X	X				
Urine hCG or serum βhCG [d]	X	X				
AE/SAE assessment	X	X				
Concomitant medications	X	X				
<<World Health Organisation>> <<ECOG>> performance status	X	X	X	x	x	X
Subsequent anticancer therapy	X	X	X	X	X	X
Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted		X	X	X	X	X (every 2 months)
Hematology	X	X				X
Serum chemistry	X	X				
Thyroid function tests (TSH, and fT3 and fT4)[b]	X					

Appendix 3. Schedule of Study Procedures: Follow-Up for Patients Who Have Completed Durvalumab Treatment and Achieved Disease Control (Until Confirmed Progression of Disease) and Patients Who Have Discontinued Durvalumab Due to Toxicity in the Absence of Confirmed Progression of Disease

Evaluation	Time Since Last Dose of durvalumab								
	Day (±3)	Months (±1 week)							Every 4 Months (±2 weeks) for 2 years
	30	3	6	9		12			
Quality of life (QOL)[c] and health resource use, if applicable	X		X	For patients who achieve disease control following 12 months/48 weeks of treatment, quality of life and information relating to health resource use should be completed every 12 weeks relative to the date of randomisation until confirmed PD by RECIST 1.1 by investigational site review. For patients who discontinue study drug due to toxicity or a reason other than confirmed PD, quality of life and information relating to health resource use should be completed relative to the date of randomisation as follows: every 8 weeks for the first 48 weeks, then every 12 weeks until confirmed PD by RECIST 1.1 by investigational site review.				

Appendix 3. Schedule of Study Procedures: Follow-Up for Patients Who Have Completed Durvalumab Treatment and Achieved Disease Control (Until Confirmed Progression of Disease) and Patients Who Have Discontinued Durvalumab Due to Toxicity in the Absence of Confirmed Progression of Disease

Evaluation	Time Since Last Dose of durvalumab					
	Day (±3)	Months (±1 week)				Every 4 Months (±2 weeks) for 2 years
	30	3	6	9	12	
Tumor assessment (CT or PET/CT)	For patients who **achieve disease control following 12 months of treatment**, tumor assessments should be performed every 12 weeks (±1 week) relative to the date of **first infusion** thereafter until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Schedule of Study Assessments for timings of confirmatory scans. For patients who **discontinue** MEDI4736 **due to toxicity (or symptomatic deterioration)**, tumor assessments should be performed relative to the relative to the date of **first infusion** as follows: every 8 weeks (±1 week) for the first 48 weeks (per Schedule of Assessments), then every 12 weeks(±1 week) until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Schedule of Assessments for timings of confirmatory scans. Upon confirmed PD, scans should be conducted according to local standard clinical practice and submitted for central review until a new treatment is started (these scans are optional).					
MRI Brain	Annually in follow-up or for new neurological symptoms.					

[a] Full physical exam

[b] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[c] All patients enrolled in the study who read English or Spanish will complete the EORTC QLQ-C30 quality of life (QOL) assessment

[d] For women of childbearing potential only.

Appendix 4. Schedule of Study Procedures: Follow-Up for Patients Who Have Discontinued Durvalumab Treatment Due to Confirmed Progression of Disease at the Discretion of the Investigator

Evaluation	Time Since Last Dose of durvalumab					
	Day (±3)	Months (±1 week)				Every 4 Months for 2 years (±2 weeks)
	30	3	6	9	12	
Physical examination[a]	X	X				
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X					
Weight	X					
AE/SAE assessment	X	X				
Concomitant medications	X	X				
<<World Health Organisation>> <<ECOG>> performance status[b]	X	X				
Subsequent anticancer therapy	X	X				
Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted		X	X	X	X	X
Urine hCG or serum βhCG [e]	X					
Hematology	X	X				
Serum chemistry	X	X				
Thyroid function tests (TSH, and fT3 and fT4)[c]	X					
Quality of life (patient reported outcomes)[d] and health resource use, if applicable	X		X			

Appendix 4. Schedule of Study Procedures: Follow-Up for Patients Who Have Discontinued Durvalumab Treatment Due to Confirmed Progression of Disease at the Discretion of the Investigator

Evaluation	Time Since Last Dose of durvalumab					
	Day (±3)	Months (±1 week)				Every 4 Months for 2 years (±2 weeks)
	30	3	6	9	12	
Tumor assessment (CT or PET/CT)	For patients who **continue on** durvalumab **post-confirmed progression** at the investigator's discretion (following consultation with the sponsor), tumor assessments should be performed relative to the date of **first infusion** per until durvalumab is stopped. For patients who **discontinue durvalumab following confirmed progression**, **scans should be conducted according to local clinical practice** and submitted for central review until a new treatment is started (these scans are optional).					

[a] Full physical exam
[b] PS to be collected if available at the 2 monthly calls to obtain subsequent anticancer therapy and survival status
[c] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.
[d] All patients enrolled in the study who read English or Spanish will complete the EORTC QLQ-C30 quality of life (QOL) assessment
[e] For women of childbearing potential only.