Protocol Title

A Phase II Study Evaluating Safety and Efficacy of Durvalumab (MEDI4736) Following Multi-Modality Therapy in Esophageal Cancer: Big Ten Cancer Research Consortium BTCRC-ESO14-012

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to BRTCRC Administrative Headquarters and keep a record for your files.

_____ _____
Signature of Site Investigator Date

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Investigator Name (printed)

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Investigator Title

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Name of Facility

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Location of Facility (City and State)

_____ ❑ Not Submitting to IRB
Expected IRB Approval Date

PLEASE COMPLETE AND EMAIL TO BIG TEN CRC ADMINISTRATIVE HEADQUARTERS

STUDY SYNOPSIS

TITLE	A Phase II Study Evaluating Safety and Efficacy of Durvalumab (MEDI4736) Following Multi-Modality Therapy in Esophageal Cancer
SHORT TITLE	A Phase II Study of Durvalumab (MEDI4736) in Esophageal Cancer
PHASE	II
OBJECTIVES	**Primary Objective:** • To determine if postoperative adjuvant therapy with durvalumab improves 1 year relapse free survival (RFS) compared to historical rates in patients with persistent esophageal cancer following neoadjuvant chemoradiotherapy and esophagectomy **Secondary Objectives:** • To assess the toxicity and tolerability of durvalumab following trimodality therapy in patients with esophageal cancer. **Correlative Objectives:** • To assess changes in PD-L1 expression with chemoradiotherapy in esophageal cancer. • To analyze possible predictive biomarkers of 1 year RFS including PD-L1 expression (at diagnosis and in residual disease) in tumor cells and tumor infiltrating lymphocytes (by histology and gene expression analysis – by pathway analysis and CIBERSORT), both within the tumor and in surrounding connective tissue. • To assess the Immunoscore (based on numeration of lymphocyte populations - CD3/CD45RO, CD3/CD8, CD8/CD45RO) – within the center and invasive margins of the tumor – and correlate with 1 year RFS. • To analyze the correlation between changes in circulating tumor cell numbers in response to PD-L1 inhibition and 1 year RFS in patients with residual esophageal cancer.
OUTCOME MEASURES	• Primary: Relapse free survival (RFS) at 1 year • Secondary: Incidence and severity of adverse events overall and related to the study drug. • Exploratory outcomes as above.
STUDY DESIGN	Phase II, open-label, single arm, single-stage study. A total of 23 evaluable patients will be enrolled (26 total to account for 10% unevaluable). If total number of patients free of disease relapse at 1 year is less than or equal to 15, the drug would not be considered for further study in this setting. To improve accuracy for estimating the primary endpoint (1 year RFS) with a 95% confidence interval, an additional 11-16 patients beyond the initial planned 23 evaluable will be enrolled for a target of 34-39 enrolled to have at least 34 patients evaluable for 1 year RFS.

	After six patients are treated with at least one dose of study drug, they will be observed for a minimum of 60 days. During the 60-day observation period, further accrual will be halted to evaluate "unacceptable toxicities warranting early closure of the trial" defined as: 1) Any definitive durvalumab-related death. A durvalumab-related death will be continuously monitored throughout the trial and the trial will be suspended for re-evaluation whenever such an event is confirmed. 2) Any unexpected and previously unreported grade 4 toxicities definitely related to durvalumab. If such events are observed in one subject, the DSMB will discuss and provide recommendations to the sponsor-investigator. If such events are observed in two or more subjects, the trial will be suspended for re-evaluation. Pneumonitis of grade 3 and 4 will be continuously monitored. An overall rate of 20% or above would be considered unacceptable. If the probability of the grade 3/4 pneumonitis rate being less than 20% drops below 0.1, the trial will be suspended for re-evaluation.
ELIGIBILITY CRITERIA	Inclusion Criteria: - Esophageal cancer with persistent residual disease in the surgical sample following neoadjuvant concurrent chemoradiotherapy (carboplatin and paclitaxel or cisplatin and 5-FU) followed by surgical resection. - Must have had R0 resection (defined as resection with negative margins) - Minimum of 1 month and maximum of 3 months from surgical resection with no evidence of disease recurrence at the time of enrollment - ECOG Performance status 0-1 - Adequate bone marrow, renal and hepatic function - Must have adequately recovered from chemoradiation and surgery Exclusion Criteria: - Prior therapy with a PD-1, PD-L1, or CTLA-4 inhibitor or cancer-specific vaccine therapy - Patients with R1 resection (defined as positive margins after resection) or R2 resection (defined as presence of macroscopic residual disease after resection) - Evidence of active autoimmune disease requiring systemic treatment within preceding 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires ongoing use of systemic steroids or immunosuppressive agents. Exceptions to this rule include vitiligo, resolved childhood asthma/atopy, requirement of intermittent bronchodilators or local steroid injections, hypothyroidism stable on hormone replacement, Sjogren's syndrome. - Presence of interstitial lung disease or history of pneumonitis requiring treatment with corticosteroids

	- Patients with diagnosis of immunodeficiency or those receiving chronic systemic corticosteroid therapy or other immunosuppressive therapy (except inhaled steroids) within 28 days of the first dose of study drug - History of psychiatric illness/social situations that would limit compliance with study requirements. - Clinically significant infections as judged by the treating investigator. Clinically significant is defined as an active infection requiring IV antibiotics - Known HIV infection or chronic hepatitis B or C.
STATISTICAL CONSIDERATIONS	Null Hypothesis: 1 year RFS with postoperative adjuvant durvalumab therapy in patients with persistent esophageal cancer following neoadjuvant chemoradiotherapy and esophagectomy is 50% or less. Alternative Hypothesis: 1 year RFS with postoperative adjuvant durvalumab therapy in patients with persistent esophageal cancer following neoadjuvant chemoradiotherapy and esophagectomy is 75% or greater. Acceptable Type I (alpha) error: 5% Acceptable Type II (beta) error: 20% Power: 80% Phase II, open label, single arm, single-stage study.
TOTAL NUMBER OF SUBJECTS	Total n=39, 34 efficacy evaluable and allowing for up to 5 unevaluable. Subjects who receive less than 6 months of durvalumab for reasons unrelated to disease progression or toxicity will be replaced.
ESTIMATED ENROLLMENT PERIOD	Estimated 18 months
ESTIMATED STUDY DURATION	Estimated 39 months

INDEX

SCHEMA

A Phase II Study Evaluating Safety and Efficacy of Durvalumab (MEDI4736) Following Multi-modality Therapy in Esophageal Cancer:
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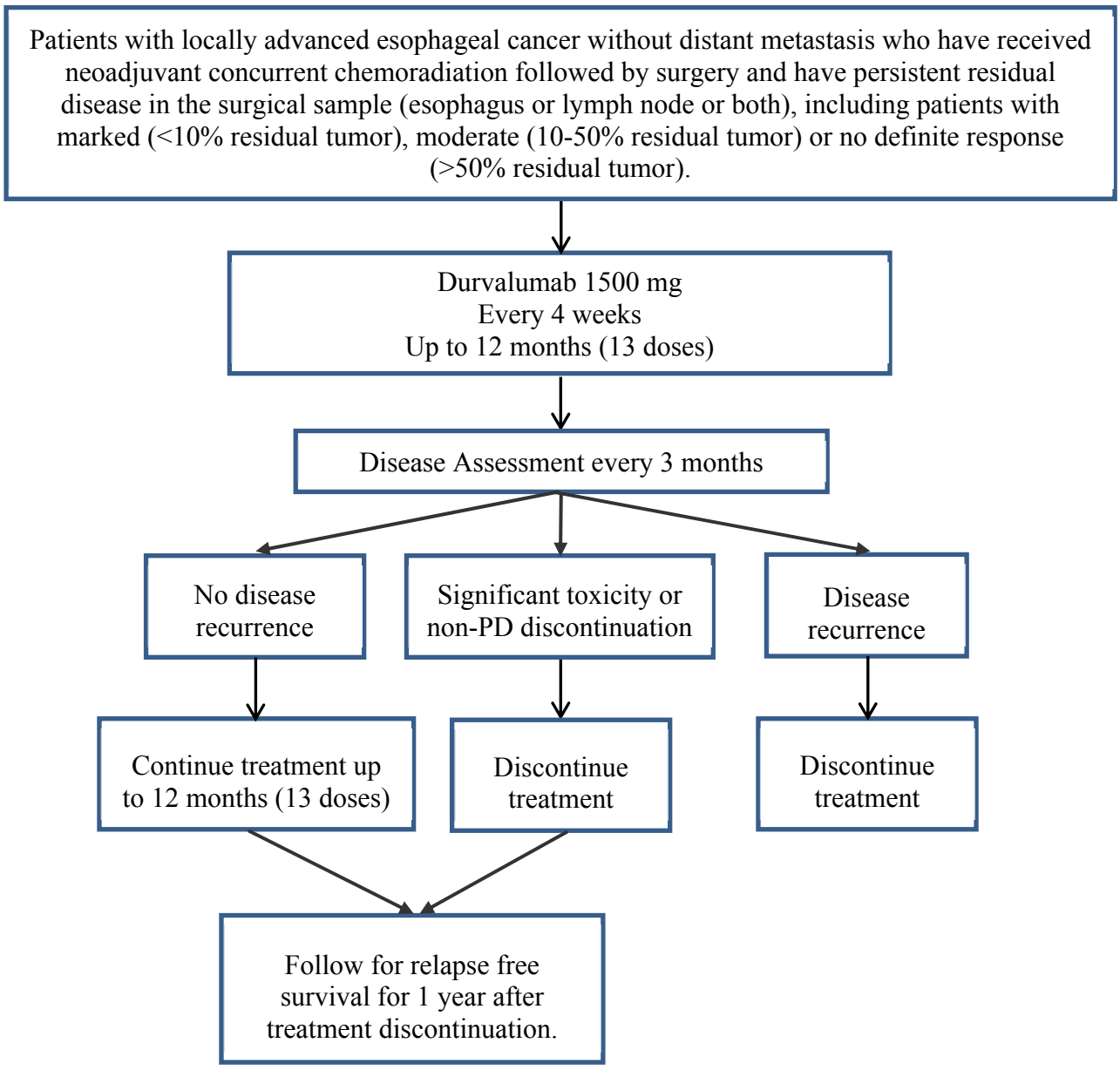

1. BACKGROUND & RATIONALE

1.1 General Background:

Esophageal cancer has been recently described as 'the silent epidemic' because of its rapidly rising incidence. It is the 6th leading cause of cancer related mortality in men in the United States (1). Approximately 16,980 new cases and 15,590 deaths are estimated to occur from esophageal cancer in U.S. in 2015, with a 5- year survival rate of 17.9% (2). Multiple factors contribute to the poor prognosis associated with esophageal cancer. These include a) the advanced stage at the time of diagnosis b) the complex biology of the disease with large mutational burden, and c) resistance to currently available therapies (3). Two-thirds of the patients with esophageal cancer have locally advanced disease. A standard of care for fit patients with locally advanced esophageal cancer is tri-modality therapy with concurrent platinum-based chemotherapy and ionizing radiation followed by surgical resection. With this approach, only about 29% of the patients achieve a complete pathologic response (4). The majority of patients with persistent residual disease noted on surgical specimen will recur leading to a poor prognosis with median survival of 12 months. No post-operative therapy has been shown to improve outcomes in this patient population. With its grim prognosis, there is a pressing need for novel agents in the treatment of esophageal cancer that can decrease the risk of relapse following tri-modality therapy.

Chemotherapy agents with activity in locally advanced esophageal cancer are limited to 5 classes of agents. These include taxanes (docetaxel or paclitaxel), fluoropyrimidines (capecitabine or 5-FU), platinums (oxaliplatin, carboplatin, cisplatin), topoisomerase I inhibitors (irinotecan) and anthracyclines (epirubicin). Standard chemotherapy regimen in combination with ionizing radiation for the treatment of locally advanced esophageal cancer is either weekly carboplatin and paclitaxel or cisplatin and 5-FU (4, 5). Outcomes with these regimens are comparable. There is currently no proven role for adjuvant chemotherapy in esophageal cancer patients following tri-modality therapy.

The importance of an intact immune surveillance in controlling outgrowth of neoplastic processes has been known for decades (6). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies (7-13). In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors (14). Similar correlation has been found in esophageal squamous cell carcinoma as well (15).

The programmed cell death protein 1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress host immune response to the tumor. The normal function of PD-1, expressed on the cell surface of activated T- cells under physiologic conditions, is to down-modulate unwanted or excessive immune responses especially in peripheral tissues, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (16). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immune-receptor tyrosine- based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade (16-19). The mechanism by which PD-1 down

modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells (20). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues (16, 21). Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor (18, 22). Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor including esophageal cancer. PD-1 has also been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (23). It has also been shown that blockade of PD-1 pathway leads to T cell activation and cytokine release (24).

This evidence suggests that the PD-1/PD-L1 pathway plays a critical role in evasion of host immune system by tumor and should be considered as an attractive target for therapeutic intervention. Recent data have shown that inhibition of the PD-1 pathway leads to durable tumor regression (25). Several immune checkpoint inhibitors in the form of monoclonal antibodies to PD-1 and PD-L1 are currently being tested in various malignancies, both in combination with other therapies and as single agents. Growing clinical evidence demonstrates activity of PD-1 pathway inhibitors in esophageal cancer including pembrolizumab (PD-1 inhibitor) and durvalumab (MEDI4736). Durvalumab is a fully human IgG1 monoclonal antibody against PD-L1 with preliminary data demonstrating activity in a variety of tumors including esophageal cancer (26, 27).

The dynamic PD-1 pathway is impacted by various cancer directed treatment modalities including ionizing radiation. Ionizing radiation induces a local inflammatory response that enhances the infiltration of tumor-specific T cells and simultaneously upregulates PD-1/PD-L1 pathway in the tumor microenvironment thereby inhibiting immune activation. This upregulation limits some of the radiation induced toxicities but at the same time markedly weakens radiation induced antitumor immunity facilitating disease relapse. In addition, previous data have consistently shown that neoadjuvant chemoradiotherapy results in a decrease in the number of tumor infiltrating lymphocytes (28). It is also known that higher number of tumor infiltrating lymphocytes have been shown to be a prognostic marker associated with decreased distant recurrence rate (29).

Based on these data and the activity of durvalumab in esophageal cancer, we hypothesize that adjuvant PD-L1 inhibition following chemoradiotherapy and surgery in esophageal cancer patients who do not achieve a complete pathological response with trimodality therapy will decrease the risk of cancer recurrence and improve relapse free survival through simulation of the immune system to eradicate residual disease. This phase II trial aims to evaluate the safety and efficacy of durvalumab in patients with persistent esophageal cancer following chemoradiotherapy and surgical resection.

1.2 Therapeutic Durvalumab (MEDI4736) Background

MEDI4736 is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). MEDI4736 is composed of 2 identical heavy chains and 2 identical light chains, with an overall

molecular weight of approximately 149 kDa. MEDI4736 contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

1.2.1 Summary of Non-clinical Experience:

The non-clinical experience is fully described in the current version of the durvalumab (MEDI4736) Investigator's Brochure (IB).

MEDI4736 binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. *In vitro* studies demonstrate that MEDI4736 antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-γ). Additionally, MEDI4736 demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays. In vivo studies show that MEDI4736 inhibits tumor growth in a xenograft model via a T lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) resulted in tumor regression in a mouse model of colorectal cancer.

Cynomolgus monkeys were selected as the only relevant species for evaluation of the pharmacokinetics (PK)/pharmacodynamics and potential toxicity of MEDI4736. Following intravenous (IV) administration, the PK of MEDI4736 in cynomolgus monkeys was nonlinear. Systemic clearance (CL) decreased and concentration half-life (t1/2) increased with increasing doses, suggesting saturable target binding-mediated clearance of MEDI4736. No apparent gender differences in PK profiles were observed for MEDI4736.

In general, treatment of cynomolgus monkeys with MEDI4736 was not associated with any MEDI4736-related adverse effects that were considered to be of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) PK/pharmacodynamics and dose range-finding study, and a GLP 4-week repeat-dose toxicity study were consistent with antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK/pharmacodynamics, and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction. The spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA:MEDI4736 immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry study. Similar observations were reported in cynomolgus monkeys administered human mAbs unrelated to MEDI4736. Given that immunogenicity of human mAbs in nonclinical species is generally not predictive of responses in humans, the ADA-associated morbidity and mortality were not considered for the determination of the no-observed-adverse-effect level (NOAEL) of MEDI4736.

Finally, data from the pivotal 3-month GLP toxicity study with MEDI4736 in cynomolgus monkeys showed that subchronic dosing of MEDI4736 was not associated with any adverse effects. Therefore, the NOAEL of MEDI4736 in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies. In addition to the *in vivo* toxicology data, no unexpected membrane binding of MEDI4736 to human or cynomolgus monkey tissues was

observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues.

1.2.2 Summary of Clinical Experience:

Clinical experience with durvalumab (MEDI4736) is fully described in the current version of the durvalumab (MEDI4736) Investigator's Brochure.

As of the data cutoff dates (15Apr2015 to 12Jul2015), a total of 1,883 subjects have been enrolled and treated in 30 ongoing MEDI4736 clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,883 subjects, 1,279 received MEDI4736 monotherapy, 440 received MEDI4736 in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

1.2.3 Pharmacokinetics and Product Metabolism

MEDI4736 monotherapy exhibited nonlinear (dose-dependent) PK. The area under the concentration-time curve from 0 to 14 days (AUC0-14) increased in a greater than dose-proportional manner over the dose range of 0.1 to 15 mg/kg and approached linearity at ≥ 3 mg/kg, suggesting that the nonlinear PK of MEDI4736 is likely due to saturable target-mediated clearance. Exposures following multiple doses (currently up to a maximum of 26 doses) demonstrated accumulation consistent with PK parameters estimated from the first dose. Suppression of free soluble PD-L1 (sPD-L1) was correlated with MEDI4736 PK concentrations. Following administration of MEDI4736 monotherapy, free sPD-L1 levels were below the lower limit of quantitation (LLOQ) in the majority of subjects with available data (n = 38) at all timepoints following IV doses ≥ 1 mg/kg every 2 weeks (Q2W).

Overall, a low incidence of ADA was observed. Of the 220 subjects who received MEDI4736 monotherapy and for whom PK/ADA data were available, 5 were detected ADA positive, with an impact on PK/pharmacodynamics reported in 1 subject.

1.2.4 Safety:

The safety profile of MEDI4736 as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-mediated AEs (imAEs), which are important risks of immune checkpoint inhibitors, have been observed with MEDI4736 and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with MEDI4736 and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in the study protocols.

AEs reported with MEDI4736 monotherapy and MEDI4736 and tremelimumab combination therapy in key clinical studies are described below.

1.2.4.1 Adverse Event Profile of Durvalumab (MEDI4736) Monotherapy

Study CD-ON-MEDI4736-1108: The safety profile of MEDI4736 monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108 has been broadly consistent with that of the overall 1,279 subjects who have received MEDI4736 monotherapy (not including subjects treated with blinded investigational product) across the clinical

development program. 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 toxicity. As of 07May2015, among the 694 subjects treated with MEDI4736 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108, a total of 378 subjects (54.5%) experienced a treatment-related AE, with the most frequent (occurring in ≥ 5% of subjects) being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with ≥ Grade 3 events occurring in 65 subjects (9.4%). Treatment-related ≥ Grade 3 events reported in 3 or more subjects (≥ 0.4%) were fatigue (12 subjects, 1.7%); increased aspartate aminotransferase (AST; 7 subjects, 1.0%); increased gamma-glutamyltransferase (GGT; 6 subjects, 0.9%); increased alanine aminotransferase (ALT; 5 subjects, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 subjects, 0.4% each). Six subjects had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject had a treatment-related Grade 5 event (pneumonia). Treatment-related serious adverse events (SAEs) that occurred in ≥ 2 subjects were colitis and pneumonitis (3 subjects each). A majority of the treatment-related SAEs were ≥ Grade 3 in severity and resolved with or without sequelae. AEs that resulted in permanent discontinuation of MEDI4736 were considered as treatment related in 18 subjects (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 subjects). A majority of the treatment-related AEs resulting in discontinuation of MEDI4736 were ≥ Grade 3 in severity and resolved with or without sequelae.

Study D4191C00003/ATLANTIC: The safety profile of MEDI4736 monotherapy in Study CD-ON-MEDI4736-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) treated with MEDI4736 10 mg/kg Q2W. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study D4191C00003/ATLANTIC. Overall, events reported in ≥ 10% of subjects were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current MEDI4736 study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment-related AEs (all grades) reported in ≥ 2% of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in ≥ 2 subjects were pneumonitis (3 subjects) and increased GGT (2 subjects). There was no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in ≥ 1.0% of subjects were dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to MEDI4736. Each treatment-related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to MEDI4736. Twenty-three of 303 subjects (7.6%) permanently discontinued MEDI4736 treatment

due to AEs. Events that led to discontinuation of MEDI4736 in ≥ 2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

1.2.5 Efficacy:

Partial efficacy data are available for 2 monotherapy studies (CD-ON-MEDI4736-1108 and D4190C00007) and 2 combination therapy studies (CD-ON-MEDI4736-1161 and D4190C00006). Clinical activity has been observed across the 4 studies.

Study CD-ON-MEDI4736-1108: Overall, 456 of 694 subjects treated with MEDI4736 10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22, 18.2%). In the PD-L1-positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%).

Study D4190C00007: Of the 32 subjects with myelodysplastic syndrome (MDS) treated in Study D4190C00007, 21 subjects had at least 1 post-baseline disease assessment. Among these subjects, the best overall responses were marrow complete remission (mCR) in 4 subjects (19.0%); stable disease (SD) in 4 subjects (19.0%); and progressive disease (PD) in 5 subjects (23.8%). The remaining 8 subjects (38.1%) did not meet the criteria for complete remission (CR), mCR, partial remission (PR), SD, or PD at the date of assessment.

Study CD-ON-MEDI4736-1161: Of the 65 subjects with metastatic or unresectable melanoma treated with the combination of MEDI4736 and BRAF inhibitor (BRAFi; dabrafenib)/MEK inhibitor (MEKi; trametinib), 63 subjects were evaluable for response. A total of 35 subjects (55.6%) had a best overall response of confirmed or unconfirmed PR. The disease control rate (DCR; CR + PR [regardless of confirmation] + SD ≥ 12 weeks) was 79.4%.

Study D4190C00006: Of the 102 subjects with advanced NSCLC treated with MEDI4736 in combination with tremelimumab in Study D4190C00006, 63 subjects with at least 16 weeks of follow-up were evaluable for response (defined as measurable disease at baseline and at least 1 follow-up scan; this included discontinuations due to disease progression or death without follow-up scan). Of the 63 evaluable subjects, 17 (27%) had a best overall response of PR, 14 (22%) had SD, 22 (35%) had PD, and 10 (16%) were not evaluable. The ORR (confirmed and unconfirmed CR or PR) was 27% and the DCR (CR, PR, or SD) was 49% as assessed by RECIST v1.1.

1.3 Durvalumab (MEDI4736) Fixed Dosing

A population PK model was developed for MEDI4736 using monotherapy data from a Phase 1 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 PK of MEDI4736 (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of MEDI4736 was evaluated by comparing predicted steady state PK concentrations (5^{th}, median and 95^{th} 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-subject variability with fixed dosing regimen.

Similar findings have been reported by others. 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. 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-subject variability in pharmacokinetic/pharmacodynamics parameters. (30)

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W MEDI4736 (equivalent to 20 mg/kg Q4W) is included in the current study. Fixed dosing of durvalumab is recommend only for subjects with > 30kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule.

2. OBJECTIVES, ENDPOINTS AND OUTCOME MEASURES

2.1. Objectives

2.1.1. Primary Objective:

- To determine if postoperative adjuvant therapy with durvalumab improves 1 year relapse free survival (RFS) compared to historical rates in patients with persistent esophageal cancer following neoadjuvant chemoradiotherapy and esophagectomy.

2.1.2. Secondary Objectives

- To assess the toxicity and tolerability of durvalumab following trimodality therapy in patients with esophageal cancer.

2.1.3. Correlative/ Exploratory Objectives

- To assess changes in PD-L1 expression with chemoradiotherapy in esophageal cancer.
- To analyze possible predictive biomarkers of 1 year RFS including PD-L1 expression (at diagnosis and in residual disease) in tumor cells and tumor infiltrating lymphocytes (by histology and gene expression analysis – by pathway analysis and CIBERSORT), both within the tumor and in surrounding connective tissue.

- To assess the Immunoscore (based on numeration of lymphocyte populations - CD3/CD45RO, CD3/CD8, CD8/CD45RO) – within the center and invasive margins of the tumor – and correlate it with 1 year RFS.
- To analyze the correlation between changes in circulating tumor cell numbers in response to PD-L1 inhibition and 1 year RFS in patients with residual esophageal cancer.

2.2. Endpoints

2.2.1. Primary Endpoint

1 year relapse free survival

2.2.2. Secondary Endpoints

Toxicity and tolerability of PD-L1 inhibition after trimodality therapy in patients with esophageal cancer.

2.3. Outcome Measures

2.3.1. Primary Outcome Measure

Relapse free survival at 1 year. History and physical examination to be performed every 4 weeks while the patient is receiving durvalumab. CT scan of the chest and abdomen will be performed every 3 months to assess for disease recurrence.

2.3.2. Secondary Outcome Measures

Incidence and severity of adverse events related to the study drug – to be assessed at every visit, which will be every 4 weeks prior to the next dose of durvalumab.

We will also collect data on regimen received (carboplatin/paclitaxel or cisplatin/5-FU), histology (adenocarcinoma), and amount and site of residual disease (primary tumor only or with lymph node involvement) for descriptive purposes.

3. ELIGIBILITY CRITERIA

3.1. Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

3.1.1 Written informed consent and HIPAA authorization for release of protected health information obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.

NOTE: HIPAA authorization may be included in the informed consent or obtained separately.

3.1.2 Age ≥ 18 years at the time of consent.

3.1.3 ECOG Performance Status of 0-1 within 28 days prior to registration for protocol therapy.

3.1.4 Females of childbearing potential and males must be willing to use two effective methods of contraception (See section 5.5.1) from the time consent is signed until 3 months after treatment discontinuation.

3.1.5 Females of childbearing potential must have a negative serum pregnancy test within 14 days prior to registration for protocol therapy.

NOTE: Female subjects are considered of childbearing potential unless they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are ≥60 years old and naturally postmenopausal for at least 12 consecutive months. See section 5.5.1.

3.1.6 Histological evidence of persistent residual esophageal adenocarcinoma including gastroesophageal junction adenocarcinoma following definitive concurrent chemoradiotherapy (carboplatin and paclitaxel or cisplatin and 5-FU) in the surgical sample (esophagus or lymph node or both) obtained at the time of esophagectomy.
NOTE: Persistent residual disease is defined as follows (modified from College of American Pathologists Guidelines):

- No residual tumor (Grade 0, complete response, 0% tumor). This group will not be included in this study.
- Marked response (Grade 1, 0-<10% residual tumor)
- Moderate response (Grade 2, 10-50% residual tumor)
- No definite response (Grade 3, >50% residual tumor)

3.1.7 Minimum of 1 month and maximum of 3 months from surgical resection with no evidence of disease progression at the time of enrollment.

3.1.8 Must have adequately recovered from surgery as judged by the treating investigator.

3.1.9 Laboratory values must be obtained within 28 days prior to registration for protocol therapy.

- White blood cell count (WBC) $\geq$ 3 K/mm^3
- Hemoglobin (Hgb) > 9 g/dL. Transfusion is allowed, if needed, since patients are post esophagectomy.
- Platelets > 100 K/mm^3
- Absolute neutrophil count (ANC) $\geq$ 1.5 K/mm^3
- Calculated creatinine clearance of $\geq$ 40 cc/min using the Cockcroft-Gault formula or by 24-hour urine collection for determination of creatinine clearance:

  Males: $\frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$

  Females: Estimated creatinine clearance for males × 0.85

- Bilirubin $\leq$ 1.5 × ULN
- Aspartate aminotransferase (AST, SGOT) $\leq$ 2.5 × ULN
- Alanine aminotransferase (ALT, SGPT) $\leq$ 2.5 × ULN

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

3.2. Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

3.2.1 Prior therapy with a PD-1, PD-L1, or CTLA-4 inhibitor or cancer-specific vaccine therapy.

3.2.2 Evidence of active autoimmune disease requiring systemic treatment within preceding 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Exceptions to this rule include vitiligo, resolved childhood asthma/atopy, requirement of intermittent bronchodilators or local steroid injections, hypothyroidism stable on hormone replacement, psoriasis not requiring systemic treatment (within the past 2 years), Graves's disease and Sjogren's syndrome.

3.2.3 Prior malignancy is not allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, Gleason score $\leq$ 7 prostate cancers, or other cancer for which the subject has been disease-free for at least 3 years.

3.2.4 Active or prior documented inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis).

3.2.5 Presence of interstitial lung disease or history of pneumonitis requiring treatment with corticosteroids.

3.2.6 Patients with diagnosis of primary immunodeficiency.

3.2.7 Patients receiving chronic systemic corticosteroid therapy or other immunosuppressive therapy within 28 days prior to registration for protocol therapy. Exceptions include intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

3.2.8 History of allogeneic organ or stem cell transplant.

3.2.9 Receipt of live attenuated vaccine within 30 days prior to registration for protocol therapy.

3.2.10 Mean QT interval corrected for heart rate (QTc) > 470 msec calculated from 3 ECGs by Bazett's Correction.

3.2.11 Ventricular arrhythmias requiring medication(s).

3.2.12 Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, or active bleeding diatheses.

3.2.13 History of psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

3.2.14 Known HIV infection or chronic hepatitis B or C.

3.2.15 Known history of previous clinical diagnosis of tuberculosis.

3.2.16 Clinically significant infections as judged by the treating investigator. Clinically significant is defined as an active infection requiring IV antibiotics.

3.2.17 Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother, breastfeeding should be discontinued. In addition, breast milk cannot be stored for future use while the mother is being treated on study.

3.2.18 Treatment with any investigational agent within 28 days prior to registration for protocol therapy.

3.2.19 History of hypersensitivity to durvalumab or any excipient.

3.2.20 Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

3.2.21 Previous enrollment in the present study.

4. SUBJECT REGISTRATION

All subjects must be registered and randomized through Big Ten CRC Administrative Headquarters' electronic data capture (EDC) system. A subject is considered registered when an 'On Study' date is entered into the EDC system.

Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy within five business days of registration.

Blinding
This study treatment is not blinded to the subject or the investigator.

5. TREATMENT PLAN

5.1. Pre-medication
None

5.2. Drug Administration

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Durvalumab	1500 mg[1]	Every 4 weeks (1 cycle)	Intravenous	Maximum 13 doses (12 months), or until unacceptable toxicities or disease recurrence

[1]: Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study. Fixed dosing of durvalumab is recommended only for subjects with > 30kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule.

NOTE: Infusions may be given ±3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. It should be clearly documented in subject's chart and case report forms.

The body surface area and drug dose should be recalculated only if subject's weight changes by ≥ 10% during the course of the study.

5.2.1. Missed doses:
Missed doses can be made up within 8 days of the missed dose.

5.3. Supportive Care:
Institutional standards should be followed for hydration and transfusions.

5.4. Concurrent Therapy
None

5.5. Restrictions during the study

The following medications are considered **exclusionary** during the study.

1. Any investigational anticancer therapy other than the protocol specified therapy
2. Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment, other than any stated comparator or combination regimens. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
3. Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).
4. Live attenuated vaccines within 30 days of durvalumab dosing (ie, 30 days prior to the first dose, during treatment with durvalumab and for 30 days post discontinuation of durvalumab.) Inactivated viruses, such as those in the influenza vaccine, are permitted.

5.5.1. Contraception

Females of childbearing potential who are sexually active with a nonsterilized male partner must use 2 methods of effective contraception from screening, and must agree to continue using such precautions for 3 months (90 days) after the final dose of investigational product, or for at least 90 days following the last infusion of durvalumab; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

- Female subjects are considered of childbearing potential unless they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are ≥60 years old and naturally postmenopausal for at least 12 consecutive months.
- Subjects must use 2 acceptable methods of effective contraception as described in the table below.
- Nonsterilized males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 1 below) from Day 1 and for 90 days after receipt of the final dose of investigational product.

Table 1 Effective methods of contraception (two methods must be used)

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T[a]	Hormone injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	Combined pill Minipill Patch

[a] This is also considered a hormonal method.

5.5.2.Blood donation

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

6. DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in the Study Calendar and Evaluations section.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring protocol therapy interruption or discontinuation at each study visit for the duration of their participation in the study.

Subjects discontinued from the treatment phase of the study for any reason will be evaluated at least 30 days (+ 7) after the last dose of protocol therapy.

6.1. Dose Modifications

6.1.1. Dose Modifications and Toxicity Management for Durvalumab:

For adverse events (AEs) that are considered at least partly due to administration of durvalumab the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab (see below).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued.

Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed (see Tables 2, 3 and 4 below). Dose reductions are not permitted.

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune-mediated Adverse Events (imAEs) during the conduct of this study. Potential imAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of imAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Dose modification recommendations and toxicity management guidelines for immune-mediated adverse events, for infusion-related reactions, and for non-immune-mediated adverse events are detailed in Tables 2, 3, and 4, respectively.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 10.1.3. All toxicities will be graded according to NCI CTCAE v4.

Table 2 Dosing Modifications and Toxicity Management Guidelines for Immune-Mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)

General Considerations

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4. In addition to the criteria for permanent discontinuation of study drug/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/regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.	It is recommended that management of immune-mediated adverse events (imAEs) follow 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 (greater than 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 2-4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms,
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. 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, may permanently discontinue study drug/study regimen. Please refer to guidelines below Grade 4 Permanently discontinue study drug/study regimen **Note**: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen. **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	

Table 2 Dosing Modifications and Toxicity Management Guidelines for Immune-Mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)

General Considerations	
Dose Modifications	**Toxicity Management**
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).	then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (eg, infliximab) (also refer to individual sections of the immune-related adverse event 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 is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug 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.

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**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 modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** (Radiographic Changes Only) - Monitor and closely follow up in 2-4 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/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). - Reimaging as clinically indicated. - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. - If still no improvement within 3-5 days despite IV methylprednisolone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (infliximab at 5 mg/kg every 2 weeks). **Caution**: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungal or anti

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
			PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[i] - Consider pulmonary and infectious disease consult. - Consider, as necessary, discussing with study sponsor-investigator via the Big Ten CRC project manager.
	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 sponsor investigator. - Hospitalize the patient - Supportive Care (eg, oxygen) - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5mg/kg every 2 weeks dose) started. **Caution**: rule out sepsis and refer to infliximab label for general guidance before using infliximab - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[i]
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

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
			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 per day over baseline) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1**: – Close monitoring for worsening symptoms – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4-6 per day over baseline) (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 3-5 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 3-5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
			immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[i]. **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 sponsor-investigator (via the Big Ten CRC project manager) if no resolution to ≤ Grade 1 in 3-4 days. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[i].
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 per day over baseline) (Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening	Grade 3 Permanently discontinue study drug/study regimen 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 3-5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg 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 improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti-PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[i].

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)

Adverse Event	Event Grade (CTCAE v. 4)	Dose Modifications	Toxicity Management
	consequences, urgent intervention indicated)		
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of immune-related hepatitis** **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade**	General Guidance	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin (T bili) – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)
	Grade 1 (AST or ALT > ULN and ≤ to 3 × ULN and/or T bili > ULN < 1.5 × ULN)	No dose modification If it worsens, treat as Grade 2 event	**For Grade 1** – Continue LFT monitoring per protocol
	Grade 2 (AST or ALT > 3 to 5 × ULN and/or T bili >1.5- 3.0 × ULN)	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 improves to ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. – If no resolution to ≤ Grade 1 in 1-2 days, consider, as necessary, discussing with sponsor-investigator (via the Big Ten CRC project manager). – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3-5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3-5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil)[i]. Discuss with sponsor-investigator (via the Big Ten CRC project manager) if mycophenolate mofetil is not available.

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
			Infliximab should NOT be used. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[i].
	Grade 3 or 4 (Grade 3: AST or ALT >5-20 × ULN and/or T bili > 3.0-10 × ULN) **Grade 4** (AST or ALT > 20 × ULN and/or T bili > 10 × ULN)	**For Grade 3**: For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN: - -Hold study drug/study regimen dose until resolution to ≤ Grade 1 or baseline - -Resume study drug/study regimen if elevations downgrade ≤ Grade 1 or baseline within 14 days and after completion of steroid taper - Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, 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	**For Grade 3 or 4:** - Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. - If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study sponsor-investigator (via the Big Ten CRC project manager) if mycophenolate is not available. **Infliximab should NOT be used.** - Hepatology consult, abdominal workup, and imaging as appropriate. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[i].

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)

Adverse Event	Event Grade (CTCAE v. 4)	Dose Modifications	Toxicity Management
		(i.e. elevated alkaline phos) and in the absence of any alternative cause[ii] **For Grade 4:** Permanently discontinue study drug/study regimen.	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. See instructions at **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/liver decompensation	**Any Grade**	**General Guidance**	**For Any Grade:** - Monitor and evaluate liver function test: AST, ALT, ALP, and TB. - Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). - For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg - For HCV+ patients: evaluate quantitative HCV viral load - Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml - Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
	Grade 1 (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event. For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/liver decompensation	
	Grade 2 (Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. **If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.**	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline) (Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	**For Grade 3:** – Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[i]
	Grade 4 (Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	• Permanently discontinue study drug/study regimen.	**For Grade 4:** Same as above (except would recommend obtaining liver biopsy early)
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise - Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise			

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
- Grade 3-4: Permanently discontinue study drug/study regimen			
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	**Any Grade**	General Guidance	**For Any Grade:** − Consult with Nephrologist − Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum Creatinine > 1-1.5× baseline; > 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 it worsens, depending on the severity, treat as Grade 2 or Grade 3 or 4. − Consider symptomatic treatment including hydration, electrolyte replacement, and diuretics.
	Grade 2 (Serum Creatinine>1.5-3.0× baseline; >1.5-3.0×ULN)	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline. • If toxicity worsens then treat as Grade 3 or Grade 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 2-3 days and as clinically warranted. − Consult Nephrologist and consider renal biopsy if

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
		drug/study regimen after completion of steroid taper.	clinically indicated. - If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. - If event is not responsive within 3-5 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 improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[i]. - 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; >3.0-6.0 × 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 3-5 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 improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[i]

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
Rash (excluding Bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4 for definition of severity/grade depending on type of skin rash)	General Guidance	**For Any Grade**: - Monitor for signs and symptoms of dermatitis (rash and pruritus). - **IF THERE IS ANY BULLOUS FORMATION, THE STUDY SPONSOR-INVESTIGATOR SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****
	Grade 1	No dose modification	**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- 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 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 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid. Consider, as necessary, discussing with sponsor-investigator (via the Big Ten CRC project manager) and promptly start systemic steroids prednisone 1 to 2 mg/kg/day or IV equivalent. - Consider skin biopsy if persistent for >1-2 weeks or recurs.

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4	**For Grade 3**: Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue Study drug/study regimen. **For Grade 4**: Permanently discontinue study drug/study regimen.	**For Grade 3 or 4**: - Consult dermatology - Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. - Consider hospitalization. - Monitor extent of rash [Rule of Nines]. - Consider skin biopsy (preferably more than 1) as clinically feasible. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[i] - Consider, as necessary, discussing with study sponsor-investigator (via the Big Ten CRC project manager).
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, and adrenal insufficiency Type 1 diabetes mellitus, hypophysitis, exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4 for defining the CTC grade/severity)	General Guidance	**For Any Grade**: - Consider consulting an endocrinologist for endocrine events. - Consider, as necessary, discussing with study sponsor-investigator (via the Big Ten CRC project manager). - 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, hypotension polydipsia, polyuria 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 T_3 and free T_4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c).

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
			– 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, 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 T_4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until subject 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.	**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. – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
		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.	with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. - For all patients with abnormal endocrine work up, except for those with isolated hypothyroidism, or Type I DM, and as guided by endocrinologist, consider short-term, corticosteroids (e.g., 1-2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. hydrocortisone, or sex hormones). - 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 (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[i] - For patients with normal endocrine work up (lab or MRI scans), repeat labs/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 Resume study drug/study regimen administration 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:	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). - Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids - Isolated Type 1 diabetes mellitus may be treated with

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
		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.	appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity. – 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 (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[i]
Neurotoxicity (includes but not limited to limbic encephalitis. autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (Please refer to CTCAE v 4 for definition of severity/grade depending on type of neurotoxicity)	General Guidance	– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations). – Symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications	For Grade 1: – See "Any Grade" recommendations above.
	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. o If toxicity worsens then treat as	– Consider, as necessary, discussing with the study sponsor-investigator (via the Big Ten CRC project manager). – 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 3-5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
		Grade 3 or Grade 4 • Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIgG).
	Grade 3 or 4	**For Grade 3:** • Hold Study drug/study regimen dose until resolution to ≤ Grade 1. • Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to ≤ Grade 1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen	**For Grade 3 or 4**: − Consider, as necessary, discussing with study sponsor-investigator (via the Big Ten CRC project manager). − Obtain neurology consult. − Consider hospitalization. − Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. − If no improvement within 3-5 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 which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which 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

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
			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 IVIG.
	Grade 1	No dose modification	**For Grade 1**: - Consider, as necessary, discussing with the study sponsor-investigator (via the Big Ten CRC project manager). - 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.	Grade 2 - Consider, as necessary, discussing with the study sponsor-investigator (via the Big Ten CRC project manager). - 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

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
			Gravis. 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 IVIG. 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 acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
	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 sponsor-investigator (via the Big Ten CRC project manager). - Recommend hospitalization. - Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It 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 plasmapharesis or IVIG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE*: o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
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

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)			
Adverse Event	**Event Grade (CTCAE v. 4)**	**Dose Modifications**	**Toxicity Management**
			(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 with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 Grade 2: Symptoms with mild to moderate activity or exertion Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention	• 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.	**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

Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)

Adverse Event	Event Grade (CTCAE v. 4)	Dose Modifications	Toxicity Management
	indicated Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	If Grade 3-4, permanently discontinue study drug/study regimen.	(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]).[i]

i: ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Pestow MD.
ii: FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

Table 4. Dosing Modification and Toxicity Management Guidelines for Infusion-Related Reactions for Durvalumab Monotherapy (1 November 2017 Version)

Severity Grade	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Management 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 Grade 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).

Table 5. Dose Modification and Toxicity Management Guidelines for Non-Immune Mediated Reactions for Durvalumab Monotherapy (1 November 2017 Version)		
CTC Grade/ Severity	**Dose Modification**	**Toxicity Management**
Any Grade	Note: dose modifications are not required for adverse events 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
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline.	Treat accordingly as per institutional standard
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 at next scheduled dose. Otherwise, discontinue study drug/study regimen.	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note: for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per treating Investigator's clinical judgment and in consultation with the sponsor-investigator.).	Treat accordingly as per institutional standard

Abbreviations:
AChE = acetylcholine esterase; ADA = American Dietetic Association; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; imAE = immune-mediated adverse event; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

7. STUDY CALENDAR & EVALUATIONS

Study Day	Screen	Cycle 1 Cycle = 28 days	Cycles 2-13	30 Days Post Treatment	Follow up
	-28 days	Day 1 (-3)	Day 1 (±3)	30 days (+7) after last dose	Every 3 months (±7 days)
REQUIRED ASSESSMENTS					
Informed Consent	X				
Diagnosis and Staging[1]	X				
Medical history	X				
Physical exam and ECOG PS	X	X	X	X	X
Vital Signs[2]	X	X (x5)	X (x3)	X	
ECG[3]	X (x3)	pre, post: C1D1	pre, post: C4D1	X	
LABORATORY TESTS					
Complete Blood Cell Count (CBC) with diff[5]	X	X[4]	X	X	
Comprehensive Metabolic Profile (CMP), including GGT, LDH, magnesium, uric acid[6]	X	X[4]	X	X	
Amylase, lipase[6]	X	X[4]	X		
Urinalysis[7]	X	X[4]	X	X	
TSH. If TSH abnormal, check free T3, free T4.[8]	X		every even cycle		
Prothrombin Time, aPTT, INR[9]	X				
Calculated creatinine clearance	X				
Serum pregnancy (WOCP)[10]	-14 days				
AEs, imAEs, AESIs & concomitant meds	X		X	X	
DISEASE ASSESSMENT[5]					
CT chest, abdomen/pelvis	X		Q 3 months[11]		Q 3 months[11]
TREATMENT EXPOSURE					
Durvalumab		X	X		
CORRELATIVE STUDIES					
CTC blood sample[12] (Indiana University ONLY)- optional		Pre-dose	pre-dose C4D1	At recurrence	
Archived tissue samples[13]- mandatory		X			
Whole blood sample[14]- mandatory		Pre-dose			
BANKING STUDIES					
Whole Blood[15]– optional		X			
Unstained Slides (diagnosis and surgery) [16]- optional		X			
Serum and Plasma[17]- optional		X		X	
FOLLOW-UP					
Survival					X

Footnotes:

1: Diagnosis and Staging to include pathology report and TNM staging

2: Vital signs to include temperature, blood pressure, pulse rate, respiratory rate, weight, and height (screen only).

3: ECGs are required during screening, pre and post treatment on C1D1, pre and post treatment at C4D1, end of treatment, and at any other time point when clinically indicated.

4: Cycle 1 Day 1 labs do not need to be repeated if done within 7 days prior to Day 1.

5: CBC with diff and platelets to include: hemoglobin, platelet count, red blood cell count, total white cell count.

6: CMP to include: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, calcium, chloride, creatinine, gamma glutamyl transferase (GGT), glucose, lactate dehydrogenase (LDH), magnesium, potassium, sodium, total bilirubin, total protein, urea or blood urea nitrogen (depending on local practice), uric acid. If total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome), fractionate into direct and indirect bilirubin. GGT at baseline and as clinically indicated. Amylase and lipase will be checked at screening; amylase and/or lipase (depending on local practice) will be checked prior to Day 1 of each cycle.

7: Urinalysis performed at Screening, Day 1 of every cycle, and as clinically indicated. Urinalysis to include: bilirubin, blood, glucose, ketones, pH, protein, and specific gravity. Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

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

9: Prothrombin time, aPTT and INR only performed at Screening and as clinically indicated.

10: Pregnancy test: Within 14 days of registration.

11: Disease assessment will be performed every 3 months ±7 days (prior to Cycle 4, 7, 10, etc.). During follow up, disease assessment will be performed every 3 months (±7 days) for up to 1 year from the time of treatment discontinuation (if they have not withdrawn consent).

12: OPTIONAL - CTC blood samples will be collected at pre-dose Cycle 1 Day 1, pre-dose Cycle 4 Day 1 (3 months), and at the time of disease recurrence during treatment or follow up. Please note that CTC blood samples will only be collected on consenting subjects enrolled at the Indiana University Melvin and Bren Simon Cancer Center.

13: Submission of unstained slides from the subject's archived initial diagnostic tumor tissue and tissue from the time of surgery is mandatory (if available). See the Correlative Laboratory Manual (CLM) for collection, processing, labeling, and shipping instructions.

14: Mandatory submission of whole blood for gene expression analysis is to be collected at Pre-Treatment Cycle 1 Day 1. See CLM for collection, processing, labeling, and shipping instructions.

15: Optional whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. See CLM for collection, processing, labeling, and shipping instructions.

16: Optional unstained slides for banking from archived FFPE tumor blocks from the time of diagnosis and the time of surgery are requested (if available). See CLM for collection, labeling, and shipping instructions.

17: Optional serum and plasma for banking are to be collected at Pre-Treatment Cycle 1 Day 1 and at the 30 Day Post Treatment visit. See CLM for collection, labeling, processing, and shipping instructions.

7.1. Screening

7.1.1. Within 28 days prior to registration for protocol therapy:

- Screen for the eligibility for the trial. Patient must satisfy all the inclusion criteria and must not have any exclusion criterion.
- Informed consent
- Diagnosis and staging: pathology report and TNM staging.
- Medical history
- Physical exam and ECOG PS
- Vital signs: temperature, blood pressure, pulse rate, respiratory rate, weight, and height (screen only).
- 12-lead ECG (in triplicate, 2-5 minutes apart). All 12-lead ECGs should be obtained after the subject has been resting in a supine position for at least 5 minutes in each case.
- Complete blood count with differential (CBC): to include hemoglobin, platelet count, red blood cell count, total white cell count.
- Comprehensive metabolic panel (CMP): to include albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, calcium, chloride, creatinine, gamma glutamyl transferase (GGT), glucose, lactate dehydrogenase, magnesium, potassium, sodium, total bilirubin, total protein, urea or blood urea nitrogen (depending on local practice), uric acid. If total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome), fractionate into direct and indirect bilirubin. GGT at baseline and as clinically indicated.
- Amylase and lipase
- Urinalysis: to include bilirubin, blood, glucose, ketones, pH, protein, and specific gravity. Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.
- Thyroid stimulating hormone. Free T3 and free T4 will only be measured if TSH is abnormal.
- Prothrombin time, aPTT and INR
- Calculated creatinine clearance using the Cockcroft-Gault formula or by 24-hour urine collection for determination of creatinine clearance.
- [Within 14 days of registration] Serum pregnancy test for women of childbearing potential (WOCP)
- Baseline signs and symptoms; concomitant medications.
- Baseline CT scan of chest, abdomen and pelvis

7.2. On Treatment

7.2.1. Cycle 1 Day 1 (or within 3 days prior):

- Physical exam and ECOG PS, weight
- Vital signs: blood pressure and pulse rate will be measured before, during and after the infusion at the following times (based on a 60-minute infusion):
  1. At the beginning of the infusion (at 0 minutes ± 5 minutes)
  2. at 30 minutes after the start of infusion (± 5 minutes),
  3. at the end of infusion (at 60 minutes ± 5 minutes)

4. at 30 minutes post-infusion (90 minutes from the start of the infusion ± 5 minutes)
5. at 60 minutes post-infusion (120 minutes from the start of the infusion ± 5 minutes)
   - The 1-hour post-infusion observation period will apply to the first infusion only and then for subsequent infusions as clinically indicated.
   - If the infusion takes longer than 60 minutes, blood pressure and pulse measurements should follow the principles described here (e.g. every 30 minutes), or more frequently if clinically indicated.

- ECG within an hour prior to start of infusion and at least one time point 0 to 3 hours after the infusion. ECGs recorded during the treatment phase will be single tracing. The same method of assessment should be used throughout the study. Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes in each case.
- Complete blood count with differential (CBC)
- Comprehensive metabolic panel (CMP)
- Amylase and/or lipase (depending on local practice)
- Urinalysis
- Durvalumab administration
- Correlative studies:
  - CTC blood sample – optional (pre-dose) (collected only on subjects enrolled at Indiana University)
  - Whole blood- optional
  - Archived tissue samples from diagnosis and surgery (mandatory, if available)
- Banking studies:
  - Whole blood- optional
  - Unstained slides from archived tumor blocks from diagnosis and surgery - (optional, if available)
  - Serum and plasma- optional

Notes: Cycle 1 Day 1 lab testing need not be repeated if completed within 7 days of starting protocol therapy.
See CLM for collection, processing, labeling and shipping instructions.

7.2.2. Cycle 2+ Day 1 (±3 days):

- Physical exam and ECOG PS, weight
- Vital signs: blood pressure and pulse rate will be measured before, during and after the infusion at the following times (based on a 60-minute infusion):
  1. At the beginning of the infusion (at 0 minutes ± 5 minutes)
  2. at 30 minutes after the start of infusion (± 5 minutes),
  3. at the end of infusion (at 60 minutes ± 5 minutes)
     - If the infusion takes longer than 60 minutes, blood pressure and pulse measurements should follow the principles described here (e.g. every 30 minutes), or more frequently if clinically indicated.
- Complete blood count with differential (CBC)
- Comprehensive metabolic panel (CMP)
- Amylase and/or lipase (depending on local practice)

- Urinalysis
- Adverse events, immune-related adverse events, adverse events of special interest and concomitant medications
- Durvalumab administration
- Every 3 months (prior to Cycle 4, 7, 10, etc.): CT of chest, abdomen and pelvis
- Cycle 4 Day 1: (in addition to procedures listed above)
  - ECG within an hour prior to start of infusion and at least one time point 0 to 3 hours after the infusion. ECGs recorded during the treatment phase will be single tracing. The same method of assessment should be used throughout the study. Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes in each case.
  - Pre-dose C4D1 Correlative studies:
    - CTC blood sample - optional (pre-dose) (collected only on subjects enrolled at Indiana University)

7.3. Protocol therapy discontinuation

A subject will be discontinued from the protocol therapy under the following circumstances:

- Grade ≥ 3 infusion reaction
- If there is clear evidence of disease relapse (per RECIST 1.1). NOTE: If pseudoprogression is suspected, a subject will be allowed to continue durvalumab until biopsy or repeat radiographic scans confirm disease relapse.
- If the treating physician thinks a change of therapy would be in the best interest of the subject
- If the subject requests to discontinue protocol therapy
- If the protocol therapy exhibits unacceptable toxicity
- If a female subject becomes pregnant
- If protocol therapy is interrupted for ≥ 42 days due to a treatment-related adverse event.

7.4. Safety Follow-up: 30 days (±7 days) after last dose of protocol therapy

Subjects discontinued from the treatment phase of the study for any reason will be evaluated 30 days (± 7) after the last dose of study drug or as soon as possible thereafter (ex. protocol therapy interruption for ≥ 42 days). If a subject is discontinued due to disease relapse, the subject will be off study after the Safety Follow-up visit and no further follow up will be performed.

- Physical exam and ECOG PS
- Vital signs: temperature, blood pressure, pulse rate, respiratory rate and weight
- 12-lead ECG. ECG should be obtained after the subject has been resting in a supine position for at least 5 minutes. The same method of assessment should be used throughout the study.
- Complete blood count with differential (CBC)
- Comprehensive metabolic panel (CMP)
- Urinalysis
- Adverse events, immune-related adverse events, adverse events of special interest and concomitant medications
- Banking studies:
  - Serum and plasma- optional

7.5. At Recurrence:

- Correlative studies:
  - CTC blood sample - optional (collected only on subjects enrolled at Indiana University) at the time of disease recurrence during treatment or follow up.

7.6. Follow-up

Subjects can stop study participation at any time. All subjects without documented disease relapse will be followed every 3 months for 1 year from the time of treatment discontinuation (if they have not withdrawn consent) for assessment of survival, disease relapse, and occurrence of any late AEs.

- Physical exam and ECOG PS
- CT scan of the chest and abdomen/ pelvis every 3 months for up to 1 year from the time of treatment discontinuation (if they have not withdrawn consent).

Subjects will be off study after 1 year of follow-up from discontinuation of the study drug or at documented disease relapse, whichever comes first.

8. CRITERIA FOR DISEASE EVALUATION

In some circumstances it may be difficult to distinguish disease recurrence and relapse from inflammatory findings. It is recommended that a repeat disease assessment be performed if needed to confirm disease relapse prior to taking a subject off study. The disease assessment should be performed no sooner than 4 weeks after the criteria for relapse is first met. During this interim period, subjects should continue to be followed per protocol, including continued dosing of the study drug.

8.1. Definitions for Disease Evaluation –RECIST version 1.1 [*Eur J Ca* 45:228-247, 2009]

8.1.1. Disease Relapse:

Any clinical or radiographic finding(s) that meet the criteria for measurable or non-measurable lesions (confirmed by histology/cytology if solitary) according to RECIST 1.1.

- If pseudoprogression is suspected, relapse will be confirmed by either a biopsy or repeat radiographic scans.

8.1.2. Overall Survival:

Overall Survival is defined by the date of registration to date of death from any cause.

8.1.3. Relapse Free Survival:

Time from the date of surgery until the criteria for disease relapse is met or death occurs.

8.2. Methods of Measurement

Both imaging-based evaluation and clinical examination will be used for assessment. The same imaging modality must be used throughout the study to measure disease. Baseline imaging should be available within 28 days of the first dose of study drug.

8.2.1. CT and MRI:

CT and MRI are the best currently available and most reproducible imaging methods for assessing solid organ malignancy. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data, which may bias an investigator if it is not routinely or serially performed.

8.2.2. Chest X-Ray:

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by an aerated lung (CT is preferable).

8.2.3. Clinical Examination:

Clinically detected lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained at the institution.

8.2.4. Cytology and Histology:

Cytologic and histologic techniques can be used to confirm disease relapse (e.g. detection of an enlarged lymph node on imaging, to differentiate neoplastic from reactive etiology). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required if the effusion happens to be the sole suspected site of relapse.

9. BIOLOGICAL CORRELATIVES

9.1 Planned Correlative Studies:

- Assessment of changes in PD-L1 expression with chemoradiotherapy in esophageal cancer and correlate with 1 year RFS.
- Analysis of possible predictive biomarkers of 1 year RFS including PD-L1 expression (at diagnosis and in residual disease) and tumor infiltrating lymphocytes (by histology and gene expression analysis – by pathway analysis and CIBERSORT), both within the tumor and in surrounding connective tissue.
- Assessment of the Immunoscore (based on numeration of lymphocyte populations - CD3/CD45RO, CD3/CD8, CD8/CD45RO – within the center and invasive margins of the tumor – and correlate it with 1 year RFS
- Analysis of the correlation between changes in circulating tumor cell numbers in response to PD-L1 inhibition and 1 year RFS in patients with residual esophageal cancer

9.2 Source of Tissue Specimens for Correlative Studies:

Specimens from the time of initial diagnosis (archived tissue) and the specimens obtained at the time of surgery (residual tumor and any positive lymph node) are mandatory (if available) for correlative studies.

9.3 PD-L1 expression using Tissue Microarrays (31)

FFPE specimens obtained at the time of initial diagnosis as well as at the time of surgical resection.

Automated QIF analysis using the AQUA method utilizing commercially available antibody.

9.4 Generation of Gene Expression Data

9.4.1 Blood:

Whole blood will be collected in standard BD Vacutainer EDTA tubes and frozen at -80C. Refer to the Correlative Laboratory Manual (CLM) for collection, processing, labeling, and shipping instructions.

9.4.2 Tumor Specimens:

Specimens from the time of initial diagnosis (archived tissue) and the specimens obtained at the time of surgery (residual tumor and any positive lymph node) will be submitted by sites to the Big Ten CRC biorepository. Refer to the CLM for collection, processing, labeling, and shipping instructions.

9.4.3 Sequencing Methods:

For each sample, DNA & RNA will be extracted using the Qiagen All Prep Universal DNA/RNA/miRNA kit (Qiagen, Valencia CA). Briefly, 100ng of DNA will undergo a highly multiplexed PCR reaction to amplify all exons of 409 genes known to be mutated in cancer (Sanger Gene Census) using the Ion Ampliseq Comprehensive Cancer Panel. The Ion Ampliseq Comprehensive Cancer Panel is specifically designed for amplification of both formalin-fixed paraffin embedded samples as well fresh/frozen tissue. Subsequent to amplification, libraries will be sequenced on an Ion Proton Sequencer using 200bp fragment chemistry and an Ion

Proton I chip. An estimated 90 million reads per run will be generated. It is estimated that each sample will have 1500-2000X average coverage of each cancer gene, enabling low allele frequency somatic mutation detection. Each sequencing run will be evaluated for technical quality control metrics. For bioinformatics analysis, reads will be mapped to the human genome using the TMAP algorithm, which is integrated into the Ion Torrent Suite Software. After mapping, somatic variants will be called (point mutations, indels, and copy number variation), using the Ion Torrent Variant Caller (Life Technologies) and Ion Reporter (Life Technologies) software packages by identifying those mutations present in the tumor samples that are absent in the germline DNA derived from blood. Annotation of identified variants will be performed by cross-referencing the following databases: NIH dbSNP, 1000 genomes project, COSMIC (Catalog of Somatic Mutations in Cancer), and TCGA (The Cancer Genome Atlas). Identification of cancer driver variants, association with therapeutic interventions, and mutational network analyses will be performed using Ingenuity Variant Analysis (Ingenuity Systems). All data and analyses will be stored on the HIPPA-compliant Indiana University Scholarly Data Archive.

For expression analysis, 10ng of RNA (extracted as described above) will undergo library preparation using the Ion Ampliseq Transcriptome Human Gene Expression Kit. This will allow for accurate quantitative expression of ~20,000 genes in the human genome. Standard workflow for gene-level expression will be conducted using Torrent Suite Version 5.0. The AmpliSeq Transcriptome Plugin tool will be used to generate standard expression files.

9.5 Tumor Infiltrating Lymphocytes

Unstained slide of the specimen obtained at time of diagnosis and at the time of surgical resection including central area of the tumor and the invasive margin (32).

9.6 Immunoscore

Two regular whole slide FFPE sections of the specimen obtained at time of diagnosis and at the time of surgical resection (33).

9.7 Optional Sample Banking for Future Studies

Subject consent will be obtained for additional optional samples collected for future Big Ten Cancer Research Consortium studies. Hoosier Cancer Research Network, as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository.

This includes:

- Whole blood:
  - Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma:
  - Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at the 30 Day Post Treatment Visit.
- Pre- and Post-treatment serum:
  - Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at the 30 Day Post Treatment Visit.
- Unstained slides: (If Available)
  - Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor blocks from the time of diagnosis and from the surgical specimen.

Please refer to the CLM for all sample collection, processing, labeling, and shipping instructions.

10. DRUG INFORMATION

Please refer to the latest version of the IB, provided as a document separate from this protocol, for detailed information on toxicity associated with durvalumab.

10.1. Drug Names:
MEDI4736, durvalumab

10.2. Drug Class:
Durvalumab is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1).

10.3. Formulation, Packaging and Storage
Durvalumab is formulated at 50 mg/mL in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, pH 6.0.

The investigational product is supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL (500 mg/vial). The solution will be diluted with 0.9% (w/v) saline for IV infusion.

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure. Durvalumab must be used within the individually assigned expiry date on the label.

In-use storage and stability
Total in-use storage time from needle puncture of durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration. Durvalumab does not contain preservatives and any unused portion must be discarded.

10.4. Availability and Distribution
AstraZeneca/MedImmune will supply durvalumab at no charge to subjects participating in this clinical trial.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.5. Preparation

The dose volume of durvalumab and number of vials needed for the subject to achieve the accurate dose will be calculated according to the durvalumab dose calculation worksheet found in the Documents/Info tab of the EDC.

Preparation of infusion bags

The preparation of infusion bags should be done under aseptic conditions by trained personnel; it should **not** be prepared on the ward.

An additional volume of 0.9% (w/v) saline equal to the calculated volume of durvalumab to be added to the IV bag must be removed from the bag prior to addition of durvalumab.

The calculated volume of durvalumab is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

Vials should be used for specific subjects and should not be shared between subjects.

10.6. Administration

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral vein.

Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm in-line filter.

The IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Since the compatibility of durvalumab with other IV medications and solutions, other than normal saline (0.9% [weight/volume] sodium chloride for injection), is not known, the durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered.

10.7. Precautions

Owing to the drug's mechanism of action and nonclinical findings, subjects should be monitored for the development of immune-mediated adverse events such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, neuropathy, serious infection, infusion-related reactions, anaphylaxis or serious allergic reaction, and immune complex disease.

10.8. Side Effects

For a comprehensive list of adverse events, please refer to the current version of the Investigator's Brochure.

Adverse events for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These adverse events are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy.

The identified risks with durvalumab monotherapy include the following: cough/productive cough, pneumonitis, ILD, dysphonia, ALT/AST increased, hepatitis, diarrhea, abdominal pain, colitis, hypothyroidism, hyperthyroidism, blood TSH increased, blood TSH decreased, adrenal insufficiency, hypophysitis/hypopituitarism, type 1 diabetes mellitus, diabetes insipidus, blood creatinine increased, dysuria, nephritis, rash, pruritus, night sweats, dermatitis myocarditis, pyrexia, peripheral edema, upper respiratory tract infections, pneumonia, oral candidiasis, dental and oral soft tissue infections, influenza, myalgia, myositis, polymyositis and infusion related reaction.

The following events have been seen with other checkpoint inhibitors (Naidoo et al 2015, Champiat et al 2016) and/or may possibly occur due to the mechanism of action of the PD-1/PD-L1 class or mAb therapeutics in general.

- Potential imAEs including:
  - Pancreatitis
  - Other rare or less frequent events with a potential immune-mediated aetiology, eg, pericarditis, sarcoidosis, uveitis, and other events involving the eye (eg, keratitis and optic neuritis), skin (eg, scleroderma and vitiligo), and haematological (eg, haemolytic anaemia and immune thrombocytopenic purpura), rheumatological events (polymyalgia rheumatic and autoimmune arthritis), neuropathy/neuromuscular toxicities (eg, myasthenia gravis, Guillain Barre syndrome), vasculitis, non-infectious meningitis and non-infectious encephalitis.
- Hypersensitivity reactions including:
  - Anaphylaxis and allergic reaction
  - Cytokine release syndrome
  - Immune complex disease
- Other infections

Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this drug.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1. Adverse Event (AE):

Any untoward medical occurrence in a subject or clinical trial participant which does not necessarily have a causal relationship with the treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

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

Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or 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 subject has received investigational product.

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

11.1.2. Serious Adverse Event (SAE):

A serious adverse event is any adverse event that:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3. Definition of Immune-Mediated Adverse Events (imAEs)

Immune-related AEs are adverse events associated with the treatment of patients with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. Based on these potential imAEs, AstraZeneca/Medimmune has defined a list of specific adverse event terms (see AESIs below) that are selected adverse events that **must be reported to Big Ten Cancer Research Consortium Administrative Headquarters (Big Ten CRC AHQ) within 24 hours** from the time the site investigator is aware of such an occurrence, regardless of whether or not the site investigator considers the event to be related to study drug(s). See Section 11.2 for reporting criteria.

11.1.4. Definition of Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the durvalumab safety profile and require close monitoring and rapid communication by the investigator to the sponsor-investigator and Big Ten CRC AHQ.

Durvalumab AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product. Adverse events that are both an SAE and an AESI should be reported one time as an SAE only.

AESIs for 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 etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye/skin, hematological and rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis.

11.1.4.1. Pneumonitis

Adverse events of pneumonitis are of interest for AstraZeneca/Medimmune, as pneumonitis has been reported with anti-PD-1 MAbs (Topalian et al, NEJM 2012). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

Guidelines for the management of subjects with immune-mediated adverse events including pneumonitis are outlined in Section 6.1.1.

11.1.4.2. Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness.

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Section 6.1.1.

11.1.4.3. Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies (Brahmer et al 2012). Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea, and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in Section 6.1.1.

Cases where a subject shows an AST **or** ALT ≥3×ULN **or** total bilirubin ≥ 2×ULN may need to be reported as SAEs, 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.

Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo
- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

11.1.5. Unexpected Adverse Event:

An adverse event not mentioned in the Investigator's Brochure or Prescribing Information or the specificity or severity of which is not consistent with the Investigator's Brochure or Prescribing Information, or is not included in the informed consent document as a potential risk.

11.1.6. Related Adverse Event

There is a reasonable possibility the drug caused the adverse experience.

Unrelated	The Adverse Event is *clearly not related* to the investigational agent(s)
Unlikely	The Adverse Event is *doubtfully related* to the investigational agent(s)
Possible	The Adverse Event *may be related* to the investigational agent(s)

Probable	The Adverse Event is *likely related* to the investigational agent(s)
Definite	The Adverse Event is *clearly related* to the investigational agent(s)

11.2. Reporting

11.2.1. Adverse Events (AEs)

Adverse events (AEs) will be recorded from the time of consent and for at least 90 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting. A copy of the current CTCAE version can be downloaded from the CTEP website at http://ctep.cancer.gov.

During the course of the study all AEs should be proactively followed up for each subject. The investigator is responsible for following all AEs until resolution, return to baseline status, or stabilization with the expectation that it will remain chronic, even if this extends beyond study drug administration.

11.2.2. Serious Adverse Events (SAE)

11.2.2.1. Site Requirements for Reporting SAEs:

Investigators and other site personnel must report all SAEs occurring during the course of the study within **one business day** of discovery of the event. This includes events both related and unrelated 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 completed SAE Submission Form (see Documents/Info tab of the EDC) must be sent electronically to SAFETY@hoosiercancer.org at Big Ten Cancer Research Consortium (Big Ten CRC) Administrative Headquarters (AHQ) within one business day of discovery of the event. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

The original copy of the SAE Submission Form and the e-mail correspondence must be kept within the study file at the study site.

Follow-up information must be sent electronically to Big Ten CRC AHQ at SAFETY@hoosiercancer.org, using a new SAE Submission Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

The follow-up information should describe:

- whether the event has resolved or continues,
- if and how it was treated,
- whether the subject continued or withdrew from study participation.

11.2.3. Big Ten CRC AHQ Requirements for Reporting SAEs:

11.2.3.1. Big Ten CRC AHQ Reporting to AstraZeneca/ MedImmune

Big Ten CRC AHQ will submit all FDA reportable SAEs to AstraZeneca **within one business day** of receipt of the SAE Submission Form from the site. Big Ten CRC AHQ will submit a MedWatch Form to AstraZeneca and will provide follow-up information as reasonably requested.

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.

Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com

11.2.3.2. Big Ten CRC AHQ Reporting to the Food and Drug Administration (FDA)

Big Ten CRC AHQ will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of Shadia Jalal, M.D., Sponsor-investigator. Big Ten CRC AHQ will cross-reference this submission according to local regulations to the AstraZeneca Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, Big Ten CRC AHQ will submit a copy of these reports to AstraZeneca at the time of submission to FDA.

Big Ten CRC AHQ will be responsible for all communication with the FDA including but not limited to 7 and 15 Day Reports, as well as an Annual Progress Report. Big Ten CRC AHQ will report to the FDA, regardless of the site of occurrence, any AE that is serious, unexpected, and reasonably related (i.e., possible, probably, definite) to the study treatment. The sponsor-investigator will review these reports and determine if any revisions are needed to the protocol or consent.

7-Day Reports:

- Big Ten CRC AHQ will report unexpected fatal or life-threatening events associated with the use of the study treatment will be reported to the FDA.
- Big Ten CRC AHQ will report these events either by fax or by phone as soon as possible but in no event later than 7 calendar days after the initial receipt of the information regarding the event. The fax should be sent to the FDA project manager assigned to the IND. A comprehensive written report will be submitted as an amendment to the IND within an additional 8 days (15 calendar days, total).

15-Day Reports:

- Big Ten CRC AHQ will submit all other serious unexpected events associated with the use of the study treatment to FDA as an amendment to the IND as soon as possible but in no event later than 15 calendar days after initial receipt of the information regarding the event.

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

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA

- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-14-10654)

***** Sponsor must also indicate, either in the SAE report or in 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.

Annual Progress Reports

- Big Ten CRC AHQ will submit an annual progress report within 60 days of the anniversary of the date that the IND went into effect.

11.2.4. Other events requiring immediate reporting

11.2.4.1. Requirements for Reporting Overdose

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

Any overdose of a study subject with durvalumab, with or without associated AEs/SAEs, is required to be reported to Big Ten CRC AHQ within 24 hours of knowledge of the event. Big Ten CRC AHQ will report the event to AstraZeneca/MedImmune Patient Safety or designee within 24 hours using the designated Safety e-mailbox. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

11.2.4.2. Requirements for Reporting Hepatic function abnormality

Hepatic function abnormality (as defined in Section 11.1.4.3) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to Big Ten CRC AHQ, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. Big Ten CRC AHQ will report the event to AstraZeneca/MedImmune Patient Safety or designee within 24 hours using the designated Safety e-mailbox.

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

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

11.2.4.3. Requirements for Reporting Pregnancy

Pregnancy itself, or pregnancy of a subject's partner, is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 any conception occurring from the date of the first dose until 90 days after the last dose (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was withdrawn from the study drug.

Pregnancy in a female subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to Big Ten CRC AHQ on the Pregnancy Report form (See Documents/Info tab of the EDC). Big Ten CRC AHQ will report the event to AstraZeneca/MedImmune Patient Safety or designee within 24 hours using the designated Safety e-mailbox.

Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to Big Ten CRC AHQ after outcome. Big Ten CRC AHQ will report the event to AstraZeneca/MedImmune Patient Safety or designee within 24 hours using the designated Safety e-mailbox.

Male subjects should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported ***within 24 hours of knowledge of the event*** to Big Ten CRC AHQ on the Pregnancy Report form (See Documents/Info tab of the EDC). The site investigator will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

11.3. IND Safety Reports Unrelated to This Trial

IND safety reports not occurring on this trial but involving the study intervention (outside SAEs) received from outside sources will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines. The sponsor-investigator will review these reports and determine if any revisions are needed to the protocol or consent.

12. STATISTICAL CONSIDERATIONS

12.1. General Considerations

Statistical analysis of this study will be the responsibility of Biostatistics and Data Management Core at Indiana University Melvin and Bren Simon Cancer Center (IUSCC). Parameter estimates and relevant summary statistics will be reported where appropriate. For continuous variables, summary statistics will include number of subjects, mean, median, standard deviation, minimum and maximum. Categorical endpoints will be summarized using number of subjects, frequency, and percentages. Missing data will not be imputed. Data analysis will be performed in SAS Version 9.4.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Changes from this analysis plan will not require an amendment to the protocol unless it changes a significant feature of the protocol.

12.2. Study Design

This is an open label single-arm single-stage phase II trial.

12.3. Definition of Primary Endpoint

- Relapse free survival: Time from the date of surgery until the criteria for disease relapse is met or death occurs.
- One year relapse free survival: Subject is alive and relapse free at one year post-surgery.

12.4. Definitions of Secondary Endpoints

- Toxicity and tolerability: The occurrence and rate of any AEs, SAEs, AESIs, or imAEs while being on study drug and up to 30 days of receiving the final dose of the study drug.

12.5. Definitions of Correlative Endpoints

- Programmed death ligand -1 expression at cellular level in the specimen of residual tissue obtained at the time of esophagectomy
- Assessment of tumor infiltrating lymphocytes by histologic analysis within the tumor and in surrounding connective tissue
- Immunoscore (based on numeration of lymphocyte populations – CD3/CD45RO, CD3/CD8, CD8/CD45RO) within the tumor and in surrounding connective tissue
- Changes in the circulating tumor cells collected at baseline, at 3 months, and at the time of disease recurrence (during treatment or follow up).

12.6. Sample Size/Accrual/Study Duration/Replacement Rules

Historical outcomes of patients who receive chemoradiotherapy followed by surgical resection and are noted to have persistent disease at the time of surgery are poor with 50% of them recurring in the first year (34). We expect durvalumab to improve the relapse free survival at 1 year rate by 25%. The null hypothesis is that 1 year RFS with postoperative adjuvant durvalumab therapy in patients with persistent esophageal cancer following neoadjuvant chemoradiotherapy and esophagectomy is 50% or less. Alternative hypothesis is that 1 year RFS with postoperative adjuvant durvalumab therapy in patients with persistent esophageal cancer following neoadjuvant chemoradiotherapy and esophagectomy is 75% or greater. With a maximum acceptable type I error (the probability of concluding that the drug is effective when it is actually not effective) of 0.05, and acceptable type II error (the probability of concluding that the drug is not effective when it is actually effective) of 0.20, the calculated sample size is 23 evaluable patients. If the total number of patients free of relapse at 1 year is less than or equal to 15, the drug would not be considered for further study. Up to 26 will be enrolled to allow for 10% unevaluable for efficacy. Subjects who receive less than 6 months of durvalumab for reasons unrelated to disease progression or toxicity will be replaced. Estimated accrual period is 18 months; follow up period of 12 months. To improve accuracy for estimating the primary endpoint (1 year RFS) with a 95% confidence interval, an additional 11-16 patients beyond the initial planned 23 evaluable will be enrolled for a target of 39 enrolled and at least 34 patients evaluable for 1 year RFS (to allow for approximately 10% unevaluable). With n=34

evaluable, if the 1 year RFS is 75%, a 95% two-sided confidence interval will have a half-width of 15% (using normal-approximation).

12.7. Criteria for Stopping the Study

Safety: The first six subjects treated with at least one dose of study drug will be observed for a minimum of 60 days. During the 6th subject's 60-day observation period, further accrual will be halted to evaluate "unacceptable toxicities warranting early closure of the trial" defined as:

1) Any definitive durvalumab-related death. A durvalumab-related death will be continuously monitored throughout the trial and the trial will be suspended for re-evaluation whenever such an event is confirmed.
2) Any unexpected and previously unreported grade 4 toxicities definitely related to durvalumab.

If such events are observed in one subject, the DSMB will discuss and provide recommendations to the sponsor-investigator. If such events are observed in two or more subjects, the trial will be suspended for re-evaluation.

Pneumonitis of grade 3 and 4 will be continuously monitored. An overall rate of 20% or above would be considered unacceptable. If the probability of the grade 3/4 pneumonitis rate being less than 20% drops below 0.1, the trial will be suspended for re-evaluation.

12.8. Analysis Datasets

Population	Definition
Enrolled	This will comprise all patients who meet the eligibility criteria and are registered onto the study.
Efficacy Evaluable	This will comprise all patients who receive at least one dose of trial drug and either undergo at least one post-baseline assessment or die before any evaluation.
Safety	This will comprise all patients that receive at least one dose of durvalumab

12.9. Subject Characteristics and significant protocol violations

Subject demographics and subject baseline clinical characteristics will be listed and summarized for all subjects enrolled, including age, gender, and race by phase. Counts, means, medians, standard deviation, minimum and maximum values will be presented. Significant protocol violations will be listed.

12.10. Concomitant Medication

Concomitant medication use will be tabulated.

12.11. Disposition

Subject disposition will be tabulated and will show the number of subjects enrolled, and the number of subjects completing the study. All reasons for discontinuation will be listed and summarized.

12.12. Analysis Plan for Primary Objectives/Aims

In the efficacy evaluable population, our primary analysis will be to estimate RPS at 1 year with a 95% confidence interval. Kaplan-Meier curve will also be estimated for the relapse free survival curve.

12.13. Analysis Plan for Secondary Objectives/Aims

In the safety population, toxicity will be summarized by rates and 95% confidence intervals. Toxicity analysis will be carried out after 30 days following receipt of the final dose of the study drug by the last study patient. We will tabulate AEs, AESIs, and imAEs, both with and without considering drug attribution.

12.14. Analysis Plan for Correlative/Exploratory Objectives

In the efficacy evaluable population, change in PD-L1 expression from diagnosis to surgery will be assessed using a paired t-test or Wilcoxon signed-rank test as appropriate.

Changes in PD-L1 expression, Immunoscore values, and changes in CTCs over time will be correlated with 1 year RFS using two-sample tests or Wilcoxon rank sum tests as appropriate. We will also explore time to event analyses with RFS using log-rank tests.

Differential gene expression will be performed in R using DESeq2. These files will be downloaded and uploaded to Partek Genomics Suite v6.6 for visualization. Pathway analysis will be performed using Ingenuity Pathway Analysis. CIBERSORT analysis to identify the immune cell make up based on gene expression will also be performed.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with Indiana University Melvin and Bren Simon Cancer Center Institutional Data and Safety Monitoring Plan (DSMP) for High Risk Phase II Trials.

Big Ten CRC AHQ facilitated oversight activities for High Risk Phase II Trials include**:**

- Review and processing of all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator, including a weekly update of aggregate AE data. For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the sponsor investigator will notify Big Ten CRC AHQ who will notify the DSMC Chair and Compliance Officer immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.
- Coordinate *monthly* (Phase II) meetings which will include representation from each accruing site.
    - These meetings should include review of data, the number of subjects and significant toxicities as described in the protocol. Big Ten CRC AHQ should maintain meeting minutes and attendance for submission to the DSMC.

- Conduct the trial across all participating sites in accordance with the requirements set forth in the IUSCC DSMP.

13.1.1 Big Ten CRC AHQ Study-Specific Data and Safety Monitoring Board (DSMB)

This study will have a study-specific Data and Safety Monitoring Board (DSMB) managed through Big Ten CRC AHQ. The Big Ten CRC AHQ DSMB will review and monitor study progress, toxicity, safety, and other data from this trial. The board is chaired by an independent medical oncologist or another qualified individual external to this trial.

The DSMB will meet semi-annually during the active treatment and safety follow-up portion of the trial to review the following:

- Monthly Summary Reports
- Reports of the following, if not already included in the Monthly Summary Report:
  - Adverse event summary (including serious adverse events)
  - Study accrual patterns
  - Protocol deviations
- Audit and/or monitoring results, if applicable
- Data related to stopping rules described in study design
- Big Ten CRC AHQ meeting minutes/ attendance

After all information has been reviewed, the Big Ten CRC AHQ DSMB will provide a determination to the sponsor-investigator. The report may indicate one or more of the following decisions:

- Continuation of the trial without change
- Continuation of trial with modifications as outlined by the board
- Immediate suspension of trial for safety reasons with recommended plan of follow-up to minimize subject harm
- Termination of trial

Big Ten CRC AHQ will distribute the official DSMB determinations to the site investigators/ participating sites for submission to applicable oversight bodies, including their respective IRBs, according to the local policies and procedures.

Documentation of DSMB outcomes will also be provided to MedImmune and the IUSCC DSMC Chair via the DSMC Compliance Auditor (see next section).

Investigators will conduct continuous review of data and subject safety. At any time during the conduct of the trial, if it is the opinion of the sponsor-investigator that the risks (or benefits) to the subject warrant early closure of the study, this decision should be made in writing to the IUSCC DSMC Chair and Compliance Officer. Alternatively, the IUSCC DSMC may initiate suspension or early closure of the study at any time based on its review of the DSMB study reports.

13.1.2 IUSCC Data and Safety Monitoring Committee (DSMC) Oversight

The IUSCC DSMC retains authority over this study and may request additional actions based on the study's DSMB reports; however, the IUSCC DSMC defers to the study-specific DSMB for routine review and decision making per the IUSCC DSMP.

The IUSCC DSMC will review the study-specific DSMB reports semi-annually.

When the study is due for DSMC review, the DSMC Compliance Auditor will request the most recent study summary reports, Big Ten CRC AHQ monthly meeting minutes, and DSMB Outcome Letter(s). The DSMC Chair will administratively review these documents and may request additional reports. If no issues were found or if issues have been resolved, the DSMC Chair may accept the DSMB's determination and allow the study to continue without doing a full DSMC review. For DSMB suspensions or other issues of concern, the DSMC Chair will review at the DSMC Monthly meeting and may refer to the DSMC Full Meeting as needed for further discussion.

Trials managed by Big Ten CRC AHQ are not routinely audited or monitored by IUSCC; however, the IUSCC DSMC retains the right to audit Big Ten CRC trials on a for cause basis.

IND Annual Reports
For trials with an IND held locally by the IU principal investigator or university, the IND Annual Report will be prepared and submitted to the IUSCC Compliance Officer. This report will be reviewed by the DSMC at the time of FDA submission.

13.2 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

13.2.1 Data Monitoring

Monitoring will be conducted in accordance with the IUSCC DSMP for High Risk Phase II Trials. Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For cause visits may occur as necessary. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by Big Ten CRC AHQ or its designee.

The trial sites may also be subject to quality assurance audit by MedImmune or its designee as well as inspection by appropriate regulatory agencies.

13.3 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to Big Ten CRC AHQ for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially

appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Case Report Forms and Submission

This study will utilize electronic case report forms (eCRFs) in an electronic data capture (eDC) system. The eDC system will be compliant with Good Clinical Practices and Federal Rules and Regulations, to include 21 CFR Part 11.

Generally, clinical data will be electronically captured in the eDC and correlative results will be captured in the eDC or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the eDC, according to study-specific objectives. Please see guidelines in the Documents/Info tab of the EDC for further details.

The completed dataset is housed at Big Ten CRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and Big Ten CRC AHQ. After the initial publication, the complete data set will be available to all Big Ten CRC institutions.

14.2 Record Retention

To enable evaluations and/or audits from Health Authorities/Big Ten CRC AHQ, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

14.3 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study team. Samples that are collected will be identified by a subject study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject study number.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, Big Ten CRC AHQ, MedImmune, IRB, or government agencies, like

the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

14.4 Changes to the Protocol and Informed Consent

Study procedures will not be changed without the mutual agreement of the sponsor-investigator, Big Ten CRC AHQ, and MedImmune.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by Big Ten CRC AHQ and must be approved by the Sponsor-Investigator and MedImmune in addition to each site's IRB, and if applicable, also the local regulatory authority. Local requirements must be followed.

If a protocol amendment requires a change to the informed consent form sites must notify their local IRB. Approval of the revised informed consent form by the local IRB is required before the revised form is used.

The local investigator is responsible for the distribution of amended documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

MedImmune's willingness to supply study drug is predicated upon the review of the protocol. Big Ten CRC AHQ agrees to provide written notice to MedImmune of any modifications to the protocol or informed consent.

15 ETHICS

15.1 Ethics Review

The final study protocol, including the final version of the informed consent form, must be approved or given a favorable opinion in writing by an IRB. The local investigator must submit written approval to the Big Ten CRC AHQ office before he or she can enroll any subject into the study.

The local investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB at least annually, as local regulations require.

Progress reports and notifications of serious adverse events will be provided to the IRB according to local regulations and guidelines.

The investigator is also responsible for providing the IRB with reports of any serious adverse events from any other study conducted with the investigational product, according to local policies. MedImmune will provide this information to the sponsor-investigator. These reports will be reviewed by the sponsor-investigator and will be forwarded to participating sites every 2 weeks for submission to their Institutional Review Boards per their guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH Good Clinical Practice, and applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed written informed consent form. A copy of the informed consent form must be given to the subject.

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