A Phase II study of Concurrent Chemoradiation plus Durvalumab (MEDI4736) followed by Surgery followed by Adjuvant Durvalumab (MEDI4736) in medically operable patients with surgically resectable Stage III (N2) Non-Small Cell Lung Cancer
A Hoosier Cancer Research Network Clinical Trial LUN 17-321

Sponsor Investigator
Greg Durm, MD
Department of Medicine, IU School of Medicine
IU Simon Cancer Center

Co-Investigators
Nasser Hanna, MD
Tim Lautenschlaeger, MD
Thomas Birdas, MD
John Heymach, MD
Mary Jo Fidler, MD
Vamsi Velcheti, MD

Statistician
Yong Zang, PhD

Trial Management Provided by
Hoosier Cancer Research Network, Inc.
7676 interactive way, Suite 120
Indianapolis 46278

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PROTOCOL SIGNATURE PAGE

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VERSION DATE: 14MAY2021

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, 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 institutional review board(s).

_____ _____
Signature of Site Investigator Date

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Site Investigator Name (printed)

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Site Investigator Title

_____
Name of Facility

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Location of Facility (City and State)

PLEASE COMPLETE AND EMAIL A COPY TO HCRN

SYNOPSIS

TITLE	A Phase II study of Concurrent Chemoradiation plus Durvalumab followed by Surgery followed by Adjuvant Durvalumab in medically operable patients with surgically resectable Stage III (N2) Non-Small Cell Lung Cancer: A Hoosier Cancer Research Network Clinical Trial LUN 17-321
PHASE	II
OBJECTIVES	**Primary Objective** • Estimate the pathological complete response rate at the time of surgery in patients with stage IIIA (N2) NSCLC treated with concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection followed by adjuvant Durvalumab **Secondary Objectives** • Estimate the pathological N0 rate at the time of surgery in patients with stage IIIA (N2) NSCLC treated with concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection • Assess the feasibility of incorporating Durvalumab concurrently with Carboplatin/Paclitaxel plus radiation prior to surgery • Assess the feasibility of giving adjuvant Durvalumab following concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation followed by surgical resection for patients with stage IIIA (N2) NSCLC. • Define the toxicity profile of concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy for patients with stage IIIA (N2) NSCLC • Define the toxicity profile of adjuvant Durvalumab following concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation followed by surgery in patients with stage IIIA (N2) NSCLC • Estimate the 1-year disease free survival (DFS) of patients treated with concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection followed by adjuvant Durvalumab

STUDY DESIGN	This is an open label, multi-institutional, single arm Phase II trial. All patients will be treated with: Carboplatin AUC 2 IV days 1, 8, 15, 22, 29 +/- 36 Paclitaxel 45 mg/m^2 IV. days 1, 8, 15, 22, 29, +/- 36 Durvalumab 750 mg IV days 1, 15, 29 Radiation 45-61.2 Gy All patients with non-PD after induction therapy who remain surgical candidates will undergo surgical resection 4-12 weeks following induction therapy. After surgical resection, all patients who remain eligible will be treated with adjuvant Durvalumab 1500 mg once every 4 weeks for 6 cycles beginning 4-12 weeks after surgical resection.
KEY ELIGIBILITY CRITERIA (See Section 3 for full eligibility criteria)	**Inclusion Criteria** 1. ECOG Performance Status of 0 or 1 within 28 days prior to registration. 2. Histological or cytological confirmation of NSCLC (Adenocarcinoma, Squamous Cell Carcinoma, Large Cell Carcinoma). A pathology report (from the last 6 months) confirming the diagnosis of NSCLC must be obtained and reviewed by the treating physician prior to registration to study. 3. Must have resectable and medically operable stage III (N2) NSCLC with biopsy-proven N2 disease. Subjects must be considered resectable or operable based on the judgment of the treating physician. Stage III (N2) defined as per the 8th edition TNM staging (T1a, T1b, T1c, T2a, T2b, T3 or T4)N2M0. 4. Cannot have contralateral neck or contralateral mediastinum nodal involvement. 5. Cannot have distant metastasis, defined as M0 in the TMN staging system. 6. Demonstrate adequate organ function within 28 days prior to registration. **Exclusion Criteria** 1. Persons who do not meet the Stage III (N2) NSCLC classification criteria outlined above. 2. Persons who have small cell carcinoma. 3. Prior therapy with a PD-1, PD-L1 (including Durvalumab), PD-L2 or CTLA-4 inhibitor or a lung cancer-specific vaccine therapy. 4. Active second cancers. 5. Interstitial lung disease or history of pneumonitis requiring treatment with corticosteroids.

	6. Diagnosis of immunodeficiency or is receiving chronic systemic corticosteroid therapy or other immunosuppressive therapy (excludes inhaled corticosteroids) within 7 days of first dose of study drug. Patients treated with "physiologic" doses of steroids (≤ Prednisone 10mg PO daily or its equivalent) will still be eligible for enrollment. 7. Known history of human immunodeficiency virus (HIV) infection or chronic hepatitis B or C.
STATISTICAL CONSIDERATIONS	Simon's two-stage optimal design for this single arm Phase II study will be used (Simon, 1989). The trial is designed to conclude that concurrent chemoradiation plus Durvalumab would worth further investigation if the pathological complete response rate is 40% or more. The therapy will be deemed not worthy of further investigation, if the pathological complete response rate is 20% or less, which is the historically observed rate and the null hypothesis that will be tested against a one-sided alternative. Under these assumptions, the maximum sample size is 25 evaluable patients, with 12 patients accrued in the first stage and 13 subjects accrued in the second stage. A patient who completes the follow up for pathological response would be considered evaluable. If not, the patient will not be evaluable and will be replaced. In the first stage, if among these 12 patients, there are 2 or fewer patients who have pathological complete responses, then the study will be stopped for lack of efficacy. Otherwise, 13 additional patients will be accrued for a total of 25. The concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy will be considered to be worthy of further investigation if 8 or more patients who have pathological complete responses are observed among the 25 patients.
TOTAL NUMBER OF SUBJECTS	N = 25
ESTIMATED ENROLLMENT PERIOD	Estimated 24 months
ESTIMATED STUDY DURATION	Estimated 36 months

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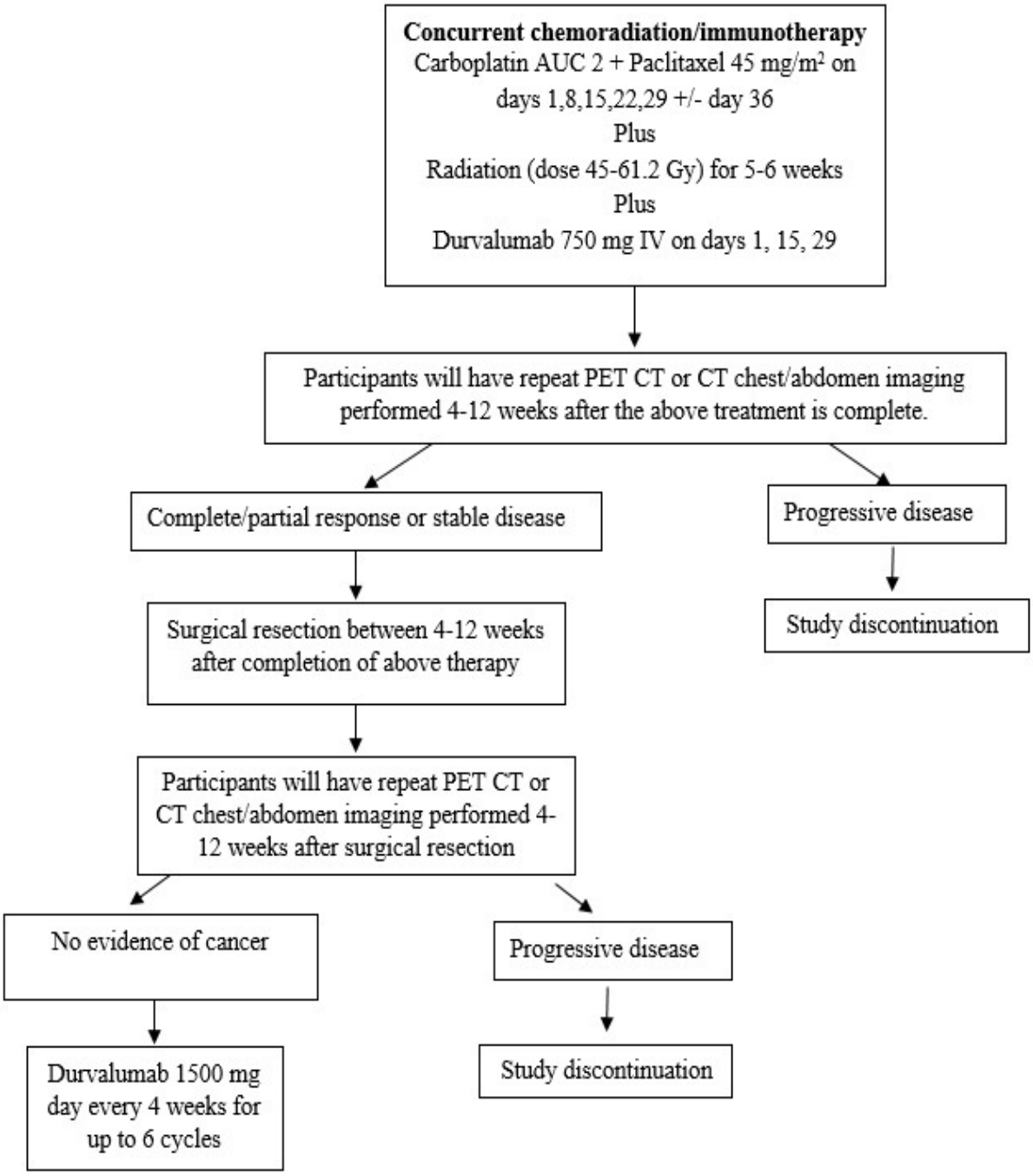
SCHEMA


Concurrent chemoradiation/immunotherapy
Carboplatin AUC 2 + Paclitaxel 45 mg/m² on days 1,8,15,22,29 +/- day 36
Plus
Radiation (dose 45-61.2 Gy) for 5-6 weeks
Plus
Durvalumab 750 mg IV on days 1, 15, 29
Participants will have repeat PET CT or CT chest/abdomen imaging performed 4-12 weeks after the above treatment is complete.
Complete/partial response or stable disease
Progressive disease
Study discontinuation
Surgical resection between 4-12 weeks after completion of above therapy
Participants will have repeat PET CT or CT chest/abdomen imaging performed 4-12 weeks after surgical resection
No evidence of cancer
Progressive disease
Study discontinuation
Durvalumab 1500 mg day every 4 weeks for up to 6 cycles

1. BACKGROUND AND RATIONALE

1.1 Stage IIIA Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the leading cause of cancer related deaths amongst men and women in the U.S. Non-small cell lung cancer (NSCLC) comprises 85% of lung cancers diagnosed. Stage IIIA NSCLC has a projected survival of 41% at 5 years [15], and the optimal treatment for medically operable patients with surgically resectable stage IIIA NSCLC remains undefined.

1.2 Current Standard of Care

The treatment for stage III NSCLC is varied and complex. Most patients with stage IIIA NSCLC are medically inoperable due to co-morbidities, most commonly cardiopulmonary compromise. Those who are medically operable frequently have surgically unresectable disease due to extent of nodal involvement or proximity to major structures, including the pulmonary artery, main stem bronchus, or superior vena cava. For patients with medically inoperable disease or surgically unresectable stage IIIA NSCLC, standard therapies include radiation, chemoradiation, and chemoradiation followed by Durvalumab.

1.2.1 Standard non-surgical management of stage III NSCLC

Until recently, the standard of care for the treatment of medically inoperable or surgically unresectable stage IIIA NSCLC in a fit patient was chemoradiation alone [1]. This remained a standard for nearly 2 decades. However, for fit patients eligible for treatment with Durvalumab, a new standard of care has been recently defined. The PACIFIC trial is a phase III study in which patients with inoperable or unresectable stage III NSCLC were randomized to Durvalumab consolidation therapy vs. placebo after completing standard chemoradiation [2]. Those in the treatment arm received Durvalumab consolidation therapy, dosed at 10 mg/kg IV every 2 weeks for up to 12 months, beginning 1-42 days after completing chemoradiation. Participants in the Durvalumab arm had increased progression free survival of 16.8 vs. 5.6 months in the placebo arm. Median time to death was prolonged in the treatment arm at 23.2 months vs. 14.6 months in the placebo arm. Median Progression free survival was superior in the Durvalumab arm (at 12 months, 55.9% in the Durvalumab group compared with 35.3% in the placebo arm, and at 18 months 44.2% compared with 27% respectively). Based upon this trial, the FDA granted approval for the use of Durvalumab following chemoradiation for patients with unresectable or inoperable Stage III NSCLC. However, it remains unknown if this is the optimal treatment for those with surgically resectable, medically operable stage IIIA disease.

1.2.2 Standard approaches to treatment for patients with medically operable, surgically resectable stage III NSCLC

Individuals who are medically operable and have surgically resectable disease may still be treated with non-surgical interventions only. Other patients will be considered for surgery upfront followed by chemotherapy with or without sequential radiation; neo-adjuvant chemotherapy followed by surgery; or neo-adjuvant chemoradiation followed by surgery.

1.2.3 Surgery followed by adjuvant therapy

The IALT trial evaluated survival in patients with stage I-III NSCLC treated with surgery alone vs. surgery followed by 4 cycles of adjuvant cisplatin-based chemotherapy [3]. Some patients also received sequential radiation after adjuvant chemotherapy was completed. Those in the chemotherapy arm were found to have increased survival at 5 years compared to those in the observation arm (44.5% vs. 40.4% respectively). The survival impact was greatest for those with stage IIIA disease. The ANITA trial was an open label, phase III randomized trial which compared overall survival of patients with stage IB-IIIA NSCLC treated with vinorelbine + cisplatin vs. observation after surgical resection [4]. Radiation was also permitted after completion of chemotherapy (or after surgery in the non-chemotherapy arm). Overall survival at the 5-year mark was improved by 8.6%, favoring those receiving chemotherapy. Once again, the largest gain in survival was seen in those with stage IIIA disease. The LACE meta-analysis provides further support for the use of cisplatin-based adjuvant chemotherapy, with the largest absolute improvement seen in those with stage IIIA disease [5].

1.2.4 Neo-adjuvant chemotherapy followed by surgery

The delivery of chemotherapy prior to surgery (neo-adjuvant approach) results in a higher likelihood of receiving systemic therapy when compared to delivering the treatment after surgery (adjuvant approach). Since many patients undergoing surgery are unable to receive adjuvant therapy due to prolonged recovery from surgery or other reasons, neo-adjuvant therapy has also been investigated in this patient population. Scagliotti, et al performed a phase III trial comparing surgery alone vs. neo-adjuvant cisplatin plus gemcitabine chemotherapy followed by surgery in Stage IB-IIIA NSCLC [6]. Median survival in the chemotherapy/surgery arm was 7.8 years compared with 4.8 years in the surgery alone arm. 3-year overall survival was also increased (67.6% vs. 59.8%). A meta-analysis evaluating platinum-based neo-adjuvant therapy in patients with stage I-III NSCLC further supports this approach [7]. The magnitude of gain appears to be similar between the neo-adjuvant and adjuvant approaches.

1.2.5 Neo-adjuvant chemoradiation followed by surgery

Another approach to the treatment of patients with medically operable, surgically resectable stage IIIA NSCLC is chemoradiation followed by surgery. This approach maximizes the use of local modalities of therapy (surgery and radiation) along with delivering systemic therapy. Optimal local control and systemic control are both necessary to maximize long-term outcomes. The largest study to date which evaluates the role of chemoradiation followed by surgery in patients with stage IIIA NSCLC was the Intergroup LUN 0139 trial reported by Albain et al [8]. Intergroup LUN 0139 was a Phase III randomized controlled multicenter cooperative group trial comparing concurrent chemoradiation with or without surgical resection in those with stage IIIA NSCLC. Participants were required to have Stage IIIA(pN2) disease, considered resectable from the time of diagnosis, have a predicted post resection FEV1 of > 800 cc, a KPS 90-100, or if KPS was 70-80 an albumin of 85% of normal with <10% weight loss over the past 3 months. Induction therapy consisted of cisplatin (50 mg/m2 on days 1, 8, 29, 36) with etoposide (50 mg/m2 on days 1-5 and 29-33), along with concurrent 45 Gy thoracic RT beginning day 1, in 1.8 Gy daily fractions. After completion of this therapy, their disease was re-evaluated with CT imaging, and if no progression occurred, those in Arm 1 underwent complete surgical resection, while those in the control arm continued radiation therapy to 61 Gy. Patients in both arms were permitted to receive 2 additional cycles of cisplatin plus etoposide.

Of the 429 patients who were enrolled and randomized to an arm, 202 were randomized to surgery and 194 to chemoradiation alone. Progression free survival was superior for those on the surgery arm (median 12.8 months) vs. chemoradiation alone arm (median 10.5 months). Overall survival was 23.6 months vs. 22.2 month, favoring surgery. There were more early deaths without progression in the surgery arm (17.8% vs. 9.8%), but more patients in the surgery arm were alive without progression of cancer (21.3% vs. 11.3%). 5-year survival was 27.2% in the surgery arm vs. 20.3% with chemoradiation alone. The 5-year survival rates for those achieving a pathologic complete response in the surgery arm was 41.9%. For those with a pathologic complete response in lymph nodes, the 5-year survival was 41%. For those with persistent nodal disease, the 5-year survival was 23.8%.

The results of the Intergroup 0139 study indicate that surgical resection can be curable in patients with stage IIIA NSCLC who undergo chemoradiation, even in those without a pathologic complete response, albeit at a lower cure rate than those with a pathologic complete response. A pathologic complete response can serve as an important surrogate for long-term survival in this patient population. Patient selection is important, however, when considering surgical resection after chemoradiation. For example, those patients with multi-nodal N2 disease or significant weight loss appear to have worse outcomes. In addition, those patients requiring a pneumonectomy after chemoradiation should be carefully selected to reduce the possibility of postoperative death.

1.3 The potential role of PD-1 or PD-L1 inhibitors in early stage NSCLC

The discovery of PD-1 and PD-L1 inhibitors has revolutionized the treatment of NSCLC. Several agents, including Nivolumab, Pembrolizumab, and Atezolizumab are FDA approved to treat patients in the advanced/metastatic setting based upon improved survival when compared with chemotherapy. Durvalumab, A PD-L1 inhibitor, is FDA approved as consolidation treatment in patients with stage III NSCLC undergoing chemoradiation in the non-surgical setting, heralding the emerging role of this class of agents to treat patients with earlier stage disease.

In 2017, investigators from Johns Hopkins and Memorial Sloan Kettering Cancer Center reported the results of a phase II study of neo-adjuvant Nivolumab followed by surgery for those with stage I-III NSCLC [9]. Eligible patients received Nivolumab, dosed 3 mg/kg, every 2 weeks for 2 treatments. Outcomes measured include safety, feasibility, radiologic/pathological responses to therapy, as well as immunologic, genomic, and pathological correlates of response in blood and tumor. Twenty-two patients were enrolled including 81% with Stage II or IIIA disease. One patient was deemed ineligible due to small cell histology. Only 1 patient experienced a grade 3 toxicity with nivolumab in the neo-adjuvant setting. There were no treatment related surgical delays, defined as per the feasibility portion as no more than 37 days of planned surgery delay. Twenty of 21 patients underwent a complete surgical resection of tumor. One patient was found to have tracheal invasion and was not resected. At a median of 12 months follow up, 80% who underwent resection were alive and disease free. Nine of 20 patients achieved a major pathological response defined as no evidence of cancer or >90% necrosis in the surgical specimen. This data suggests a potential role for the incorporation of PD-1 or PD-L1 blockade early in the course of therapy for those patients with stage II or III NSCLC.

At the American Society of Clinical Oncology (ASCO) meeting in 2018, Peters et al. reported data on the safety of adding nivolumab concurrently with chemoradiation. All patients were treated with concurrent chemoradiation, and nivolumab 360mg IV every 3 weeks was added at the beginning of radiation. At the time of the meeting, 58 patients were evaluable in the safety cohort (had received ≥1 dose of nivolumab). There were no unexpected adverse events. Six (10.3%) patients developed grade 3 pneumonitis and there were no grade 4 or 5 pneumonitis events [10]. While the efficacy data in this trial is not yet mature, this study provides evidence that concurrent chemoradiation + concurrent PD-1/PD-L1 inhibition is a safe and feasible approach. In comparison, in the Hoosier Oncology Group study of consolidation docetaxel after concurrent chemoradiation for stage III NSCLC, rates of grade 3 or higher pneumonitis were 9.6%. In the HCRN 14-179 study of consolidation Pembrolizumab after concurrent chemoradiation, the rate of grade 3 or higher pneumonitis was 6.5% and in the PACIFIC trial with consolidation Durvalumab, it was around 4% [11-13].

1.4 Rationale

Patients with stage III NSCLC continue to have a poor prognosis with surgery alone, surgery with chemotherapy, or chemoradiation alone. Trimodality therapy with chemoradiation and surgery has proven to cure some patients who were not cured with concurrent chemoradiation alone. Combining chemoradiation therapy followed by Durvalumab has also been shown to increase progression free survival compared to chemoradiation alone in patients with stage III NSCLC not undergoing surgical resection. Neo-adjuvant use of Nivolumab appears to result in a high pathological complete (or near complete) response rate for those undergoing surgery for stage II or III NSCLC. We, therefore, hypothesize that neoadjuvant Durvalumab will improve pathologic complete response rates when incorporated with chemoradiation prior to surgical resection. The current study will evaluate the feasibility, toxicity, and efficacy of incorporating Durvalumab with concurrent chemoradiation followed by surgery in patients with surgically resectable, medically operable stage IIIA NSCLC. This study will also evaluate the safety and feasibility of delivering up to 6 cycles of adjuvant Durvalumab following concurrent chemoradiaton/immunotherapy followed by surgery.

1.5 Durvalumab Information

1.5.1 Drug Information

Durvalumab is a human IgG1κ mAb selected from a panel of hybridomas secreting human antibodies recognizing human PD-L1. Durvalumab is composed of two identical heavy chains and two identical light chains, with an overall molecular weight of approximately 149 kDa. The antibody-coding deoxyribonucleic acid (DNA) sequence was recovered from a selected hybridoma and engineered by recombinant DNA technology to introduce a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to complement protein C1q and the fragment crystallisable gamma (Fcγ) receptors involved in triggering effector function. Functional binding properties of the modified antibody were confirmed. An expression plasmid was prepared for durvalumab production in Chinese hamster ovary (CHO) cells. Durvalumab is selective for human PD-L1 and blocks the binding of human PD-L1 to the human PD-1 and CD80 (B7.1) receptors (Durvalumab Investigator Brochure).

1.5.2 Rationale for Fixed Dosing

A population PK model was developed for durvalumab using monotherapy data as detailed in the durvalumab IB. Population PK analysis indicated only minor impact of body weight on PK of durvalumab (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg Q2W or 20 mg/kg Q4W) and fixed dosing (750 mg Q2W or 1500 mg Q4W) of durvalumab was evaluated by comparing predicted steady state PK exposures (AUCss,0-28, Cmax,ss, and Cmin,ss) using the population PK model. A fixed dose of 750 mg Q2W was selected to approximate 10 mg/kg Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 110 kg. Simulation results demonstrate that body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) regimens yield similar median steady-state exposures and associated variability, supporting the potential switch of durvalumab from weight-based to fixed dose. Similar considerations hold for the Q4W dosing regimens (20 mg/kg Q4W versus 1500 mg Q4W) (Durvalumab Investigator Brochure).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

Estimate the pathologic complete response rate in patients with stage IIIA NSCLC treated with concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgery followed by adjuvant Durvalumab.

2.1.2 Secondary Objectives

- Estimate the pathological N0 rate in patients with stage IIIA NSCLC treated with concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection.
- Assess the feasibility of incorporating Durvalumab concurrently with Carboplatin/Paclitaxel plus radiation prior to surgery
- Assess the feasibility of giving adjuvant Durvalumab following concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation followed by surgical resection for patients with stage IIIA NSCLC.
- Define the toxicity profile of concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy for patients with stage IIIA NSCLC
- Define the toxicity profile of adjuvant Durvalumab following concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation followed by surgery followed by adjuvant Durvalumab in patients with stage IIIA NSCLC
- Estimate the 1-yr DFS of patients treated with concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation followed by surgical resection followed by adjuvant Durvalumab

2.1.3 Correlative/Exploratory Objectives

- Explore the association between tissue PD-L1 and tumor mutational burden with pathologic complete response and N0 rates following resection
- Explore the association between tissue PD-L1 and tumor mutational burden with 1-yr PFS following concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection followed by adjuvant Durvalumab
- Explore frequency of circulating tumor DNA at time of diagnosis, following surgery, and following treatment with adjuvant Durvalumab

2.2 Endpoints

2.2.1 Primary Endpoint

- Pathologic complete response rate following concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection. This is defined as a lack of evidence of viable cancer in the surgical specimen at the time of surgery.

2.2.2 Secondary Endpoints

- Pathologic N0 rate following concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection. This is defined as a lack of evidence of viable cancer in the removed lymph nodes at the time of surgery.
- Feasibility of incorporating Durvalumab concurrently with Carboplatin/Paclitaxel + radiation prior to surgery. This will be defined as no grade 4 or 5 toxicities and no grade 3 toxicities not previously defined. It will also include the delivery of at least 2 of 3 planned doses of Durvalumab, the delivery of at least 4 planned doses of chemotherapy, the delivery of at least 45 Gy of radiation, and the ability to undergo surgery within a maximum of 12 weeks after finishing chemoradiation.
- Feasibility of giving adjuvant Durvalumab following concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation followed by surgical resection for patients with stage IIIA NSCLC. This will be defined as no grade 4 or 5 toxicities and no grade 3 toxicities not previously defined. It will also include the delivery of at least 2 of 6 planned doses of Durvalumab.
- Toxicities will be defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.
- Disease free survival will be defined as the time from surgical resection until the criteria for disease recurrence is met or death as a result of any cause. Disease recurrence is return of the cancer to where it started (local) or in another part of the body (distant).

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

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

1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status of 0 or 1 within 28 days prior to registration.

4. Histological or cytological confirmation of NSCLC (Adenocarcinoma, Squamous Cell Carcinoma, Large Cell Carcinoma). A pathology report (from the last 6 months) confirming the diagnosis of NSCLC must be obtained and reviewed by the treating physician prior to registration to study.

5. Must have resectable and medically operable stage III (N2) NSCLC with clinical or biopsy-proven N2 disease. If patients have clinical N2 disease they need to be biopsy-proven (with EBUS or mediastinoscopy) during screening and have confirmed prior to study enrollment). Subjects must be considered resectable and medically operable based on the judgment of the treating physician. Stage III (N2) defined as per the 7th edition of the TNM staging system (T1a, T1b, T1c, T2a, T2b, T3, or T4)N2M0.

6. Individuals cannot have contralateral neck or contralateral mediastinum nodal involvement.

7. Subjects must have a life expectancy of at least 12 weeks to qualify.

8. Individuals must not have distant metastasis, defined as M0 in the TMN staging system.

9. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 28 days prior to registration.

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	≥ 1.5 K/mm^3
Hemoglobin (Hgb)	≥ 9 g/dL (may be transfused)
Platelets	≥100,000/mcl
Renal	
Serum creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 x upper limit of normal (ULN) **OR** ≥ 40 mL/min for subjects with creatinine levels >1.5 x institutional ULN
Hepatic	
Bilirubin	≤ 1.5 × ULN **OR** Direct bilirubin of ≤ ULN for subjects with total bilirubin levels of >1.5x ULN
Aspartate aminotransferase (AST)	≤ 2.5 × ULN
Alanine aminotransferase (ALT)	≤ 2.5 × ULN

10. All CT or PET imaging studies must be completed within 6 weeks (42 days) prior to registration.

11. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to registration. **NOTE:** Women are considered of childbearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level greater than 40 mIU/mL.

12. Women of childbearing potential must be willing to abstain from heterosexual activity or use an effective method of contraception from the time of informed consent until 90 days after treatment discontinuation.

13. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving study drug and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 90 days after the last dose of investigational product.

14. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study.

3.2 Exclusion Criteria

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

1. History of a major surgical procedure (as defined by investigator) within 28 days prior to the first dose of study drug. **NOTE**: Local surgery for isolated lesions for palliative intent is acceptable.

2. History of another primary malignancy except for a) malignancy treated with curative intent and with no known active disease ≥ 5 years before the first dose of study drug, b) adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease, c) adequately treated carcinoma in situ without evidence of disease.

3. History of leptomeningeal disease.

4. Persons who have small cell carcinoma.

5. Persons who do not meet the Stage IIIA NSCLC classification criteria outlined above.

6. Presence of superior vena cava syndrome.

7. Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 90 days after the last dose of trial treatment.

8. Active central nervous system (CNS) metastases. Subjects must undergo a head computed tomography (CT) scan or brain MRI within 42 days prior to registration for protocol therapy to exclude brain metastases if symptomatic or without prior brain imaging.

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

10. Patients should not have received any prior therapy for the current diagnosis of NSCLC. Treatments done for previously diagnosed malignancies are permitted. Prior therapy with a PD-1, PD-L1 (including Durvalumab), PD-L2 or CTLA-4 inhibitor or a lung cancer-specific vaccine therapy are not permitted.

11. Presence of metastatic disease (stage IV NSCLC) is not allowed. Subjects must be evaluated with a CT or PET scan prior to registration for protocol therapy to exclude metastatic disease.

12. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    - Patients with vitiligo or alopecia
    - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    - Any chronic skin condition that does not require systemic therapy
    - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
    - Patients with celiac disease controlled by diet alone

13. Interstitial lung disease or history of pneumonitis requiring treatment with corticosteroids

14. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    - Steroids as premedication for hypersensitivity reactions (e.g., paclitaxel premedication and CT scan premedication)

15. History of psychiatric illness or social situations that would limit compliance with study requirements

16. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
    - Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the investigator.
    - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the investigator.

17. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the site investigator.

18. Clinically significant acute infection requiring systemic antibacterial, antifungal, or antiviral therapy including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Subjects with HIV/AIDS with adequate antiviral therapy to control viral load would be allowed. Subjects with viral hepatitis with controlled viral load would be allowed while on suppressive antiviral therapy. Testing not required.

19. Has received a live vaccine within 30 days prior to planned start of study therapy.
    NOTE: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

20. History of allograft or allogeneic bone marrow transplant.

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's 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 5 business days** of registration.

5. TREATMENT PLAN

This is an open label, multicenter single arm Phase II trial of concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection followed by adjuvant durvalumab in medically operable patients with surgically resectable Stage IIIA Non-Small Cell Lung Cancer. Those who receive concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy without progression of disease will continue to surgical resection. After surgical resection, if there is still no progression of disease on repeat imaging, then patients will receive adjuvant durvalumab every 4 weeks for up to 6 cycles.

5.1 Pre-medication and Hydration

Institutional guidelines may be used for pre-medication, hydration and treatment of infusion reactions during study treatment. A common regimen would include: Dexamethasone 12 mg, diphenhydramine 25-50mg and palonosetron 0.25 mg.

For subjects who experience a Grade 1 or Grade 2 infusion reaction, prior to subsequent infusions it is recommended that diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg should be administered at least 30 minutes before additional durvalumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

5.2 Neoadjuvant chemotherapy/radiation/immunotherapy

Drug	Dose[1]	Route	Schedule[2]	Sequence
Durvalumab	750 mg	Intravenously (IV) over 1 hour (± 10 minutes)	Days 1, 15, and 29	1st
Paclitaxel	45 mg/m^2	IV over 1 hour	Days 1, 8, 15, 22, 29, ± 36[3]	2nd
Carboplatin	AUC of 2	IV over 30 minutes	Days 1, 8, 15, 22, 29, ± 36[3]	3rd
Radiation	1.8-2.0 Gy per day for a total of 45-61.2 Gy over 5-6 weeks	Per institutional standards	5 days a week; excluding holidays	

[1] Body surface area (BSA) should be recalculated when weight changes by ≥ 10% according to the Mosteller formula.
[2] A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).
[3] Subjects receive chemotherapy throughout radiation and chemotherapy and course may be longer or shorter depending on overall radiation dose given.

5.2.1 Durvalumab

Durvalumab is available as a 50 mg/mL solution for intravenous solution in single-dose vials. The product will be diluted in an IV container made of polyvinyl chloride (PVC) or non-PVC materials containing 0.9% (w/v) sodium chloride or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1-15 mg/mL. Diluted solutions should be used immediately. If not used immediately, store the IV bag for up to 24 hours under refrigeration (2-8°C) or at room temperature (25°C) for up to 4 hours. Do not freeze or shake diluted solution.

Administer durvalumab as an intravenous infusion over 1 hour (± 10 minutes) through an IV line containing a sterile, low-protein binding 0.22 micron filter. Durvalumab to be infused first prior to paclitaxel and carboplatin. There should be a 15 minute delay after the durvalumab infusion prior to administering the paclitaxel. Do not administer other medications through the same infusion line. Monitor during infusion for infusion related reactions.

5.2.2 Paclitaxel

Please refer to the current package insert for complete prescribing and toxicity information. Institutional standards may be used for all aspects regarding administration of paclitaxel. Paclitaxel is available as a 6 mg/mL solution for intravenous solution as a multi-dose vial. Prepare the product per institutional standards by diluting to a final concentration of 0.3-1.2 mg/mL using non-PVC containers.

Administer paclitaxel after completion of durvalumab as an intravenous infusion over 1 hour through an IV line containing a sterile, low-protein binding 0.22 micron in-line filter (must use new filter for each medication).

Nab-paclitaxel may be utilized for subjects that do not tolerate paclitaxel. Please refer to package insert for complete prescribing and toxicity information. Institutional standards may be used for all aspects regarding administration of nab-paclitaxel.

5.2.3 Carboplatin

Please refer to the current package insert for complete prescribing and toxicity information. Institutional standards may be used for all aspects regarding administration of carboplatin. Carboplatin is available as a 10 mg/mL solution for intravenous solution as a multi-dose vial. Prepare the product per institutional standards by diluting to a final concentration greater than 0.5 mg/mL using PVC or non-PVC containers.

Administer carboplatin third after completion of durvalumab and paclitaxel as an intravenous infusion over 30 minutes.

5.2.4 Radiation Therapy

Treatment will be delivered using IMRT or 3DCRT using typically 6-10MV photons. Proton therapy is also allowed. 4D simulation and appropriate IGRT are encouraged. Radiation therapy must begin **within one week** of the first day of chemotherapy (or vice versa). Therapy will be 1.8-2 Gy per day; 5 days per week, excluding holidays. 45-61.2 Gy will be delivered. Interruptions in radiation treatment are strongly discouraged. Dose interruptions are allowed for grade 4 dysphagia, odynophagia, or esophagitis, or for grade 4 hematologic toxicities resulting in

chemotherapy delays/modifications, or for a decline in ECOG performance status to 2, 3, or 4. If an interruption of > 3 consecutive days is planned, the sponsor-investigator should be contacted via the Hoosier Cancer Research Network project manager. Radiation treatment plans will be collected for future analysis. These plans are not required prior to study enrollment or treatment but should be collected by the D30 Safety Visit. Please email Radiation therapy records (DICOM files for planning CT, RT plan, RT structure, RT dose) to projects@hoosiercancer.org including HCRN LU17-321 in the subject line.

5.3 Surgical Resection

Patients will undergo repeat imaging between 4 and 12 weeks after completing neoadjuvant therapy. Those without evidence of progressive disease and found to be a surgical candidate by a thoracic surgeon will undergo surgical resection between 4 and 12 weeks after neoadjuvant therapy. If there is progression of disease, the subject will be taken off study treatment and follow up schedule will be per Study Calendar in Section 7.

5.3.1 Surgical guidelines/extent of resection

Participants will undergo lobectomy, pneumonectomy, and/or thoracotomy per the discretion of the thoracic surgeon. The resection should be chosen with the goal of complete removal of the primary lesion with negative margins (R0). If positive margins (R1) or (R2), participants would still eligible to proceed to the adjuvant portion of the study. Lymph nodes that are visible and technically resectable should be removed, labeled, and sent to pathology for review. Mediastinal lymph nodes that are removed during a thoracotomy may include left side lesions 5-10L, and if possible 4L; right side lesions 4R, 7-10R, and if possible 2R.

4-12 weeks after undergoing surgical resection as outlined above, all subjects will be evaluated including imaging studies. If there is no progression of disease, participants will move on to the adjuvant portion of the study, Durvalumab, as outlined below. Adjuvant treatment will begin between 4 and 12 weeks after surgery. If there is progression of disease, then the patient will go off study treatment and follow up schedule will be per Study Calendar in Section 7.

5.4 Adjuvant Immunotherapy

Drug	Dose[1]	Route	Schedule[2]	Cycle Length
Durvalumab	1500 mg	IV	Day 1	4 weeks for 6 cycles

[1] Body surface area (BSA) should be recalculated when weight changes by ≥ 10% according to the Mosteller formula.
[2] A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

5.5 Concomitant Medications

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered more than 30 days after the last dose of trial treatment should be recorded for serious adverse events (SAE).

5.5.1 Allowed Concomitant Medications

All treatments that the site investigator considers necessary for a subject's welfare may be administered at the discretion of the site investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

5.5.2 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The site investigator should discuss any questions regarding this with HCRN who will then communicate with the sponsor-investigator and Bristol-Myers Squibb Clinical team regarding the situation. The final decision on any supportive therapy or vaccination rests with the site investigator and/or the subject's primary physician. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than Durvalumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids (>10 mg prednisone equivalent) for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered standard of care (e.g. as premedication for contrast allergy or for COPD exacerbation). Inhaled or topical steroids, and adrenal replacement doses of steroids (for example prednisone 10mg daily) are permitted while on study.
- Would advise patients avoid herbal or natural remedies with reported immune-modulating effects.

Subjects who, in the assessment by the site investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6 Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the site investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to Durvalumab.

5.7 Suggested Supportive Care Measures for the Management of Immune-Mediated Adverse Events (imAE)

Early recognition of signs and symptoms potentially related to an inflammatory or immune-mediated mechanism is important for proper management of toxicities. For guidance on identifying, evaluating, and treating imAE, see the Toxicity Management Guidelines in Appendix A.

ImAE observed with anti PD-L1/PD-1 agents such as include pneumonitis, hepatitis, diarrhea/colitis and intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), nephritis, rash/dermatitis, pancreatitis, myocarditis, myositis/polymyositis and rare/less frequent imAE including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome.

Other inflammatory responses that are rare with a potential immune-mediated etiology are also considered as imAE and include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered imAEs (Durvalumab IB).
For guidelines on the treatment of immune-mediated adverse events, please refer to the published ASCO guidelines [14].

5.8 Reproductive Information

Participants of childbearing potential who are sexually active and their partners must agree to abstain from heterosexual activity or to use 2 forms of effective methods of contraception beginning with time of consent, during the study treatment and for 90 days (female) and 90 days (male) after last dose of study treatment. Two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method. See below for options:

Acceptable non-hormonal birth control methods:

- Total sexual abstinence ie, refrain from any form of sexual intercourse in line with the patients' usual and/or preferred lifestyle. Abstinence must be for the total duration as described above. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- Intrauterine Device PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal methods:

- Etonogestrel implants (eg, Implanon®, Norplant®) PLUS male condom
- Normal and low dose combined oral pills PLUS male condom
- Hormonal shot or injection (eg, Depo-Provera) PLUS male condom
- Intrauterine system device (eg, levonorgestrel-releasing intrauterine system -
- Mirena®) PLUS male condom

5.9 Blood Donation

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

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 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 Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Carboplatin and Paclitaxel Toxicity Guidelines

- If paclitaxel or carboplatin are held for more than 2 weeks, then the applicable drug should be held permanently for the duration of concurrent therapy
- Renal Toxicity- Carboplatin doses should be recalculated if serum creatinine increases by 10% or more.

6.1.1 Hematology Toxicity

There are no dose adjustments. Please see table below for guidelines on when therapy should be held.

Toxicity NCI CTCAE Grade (CTCAE v3.0)	Paclitaxel Dose At Start of Subsequent Cycles of Therapy [a]	Carboplatin Dose at Start of Subsequent Cycles of Therapy [a]
Neutropenia		
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	Maintain dose level	Maintain dose level
3 (500-999/mm^3)	Hold therapy	Hold therapy
4 (< 500/mm^3)	Hold therapy	Hold therapy
Neutropenic fever	Hold therapy	Hold therapy
Thrombocytopenia		
1 (< LLN-75,000/mm^3)	Maintain dose level	Maintain dose level
2 (50,000- 74,999/mm^3)	Hold therapy	Hold therapy
3 (25,000- 49,999/mm^3)	Hold therapy	Hold therapy
4 (< 25,000/mm^3)	Hold therapy	Hold therapy
Other Hematologic toxicities	There will be no dose modifications for changes in leukopenia or lymphopenia.	

6.1.2 Non-hematologic Toxicity

There are no dose adjustments. Please see table below for guidelines on when therapy should be held.

Worst Toxicity NCI CTCAE Grade (CTCAE v3.0)[a]	Paclitaxel Dose At Start of Subsequent Cycles of Therapy[a]	Carboplatin Dose At Start of Subsequent Cycles of Therapy[b]
Nail changes (paronychia) Grade 2	Maintain dose level	Maintain dose level
Neuropathy ≤ Grade 1	Maintain dose level	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at full dose[e]	Maintain dose level
Grade 3	Discontinue therapy	Maintain dose level
Other non-hematologic toxicities[c] ≥ Grade 3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2

6.2 Durvalumab Toxicity Guidelines

There is no increase or decrease in durvalumab dosing. Please see Appendix A for toxicity management guidelines.

6.3 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined above, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Documented disease recurrence (local or distant).
- Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - In a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant
- Protocol therapy is interrupted for > 6 weeks.

6.4 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Study Evaluation Cycle = 28 days	Screen	Neoadjuvant Therapy Cycle 1 (C1)[11]						Surgical Resection	Adjuvant Therapy C1-C6	Safety Follow Up (+ 7 days)[12]	Long-Term Follow up (± 14 days)[13]
	-28 days	Day 1	Day 8	Day 15	Day 22	Day 29	Day ± 36		Day 1 ± 3 days	30 and 90 days post last dose	Every 3 months
REQUIRED ASSESSMENTS											
Informed Consent	X										
Medical History[1]	X										
Physical Exam[2]	X	X	X	X	X	X	X	X	X	D30	
Vital signs and ECOG Performance Status[3]	X	X	X	X	X	X	X	X	X	D30	
AEs & concomitant medications	X	X	X	X	X	X	X	X	X	X	
Radiation Treatment Plans[14]										D30	
LABORATORY ASSESSMENTS											
Complete Blood Cell Count with diff (CBC)	X	X[11]	X	X	X	X	X	X	X	D30	
Comprehensive Metabolic Profile (CMP)	X	X[11]	X	X	X	X	X	X	X	D30	
PT/INR and aPTT	X										
Thyroid Function Testing[4]	X							X	X[4]		
Pregnancy test (serum or urine) (WOCBP)[4]	X										
DISEASE ASSESSMENT											
CT of chest[5]	X						X[5]	X[5]	X[5]	D30	X[5]
CT or MRI of abdomen[5]	X						X[5]	X[5]	X[5]	D30	X[5]
CT head or MRI Brain[5]	X										
Bone or PET Scan[5]	X										
TREATMENT EXPOSURE											
Carboplatin[6]		X	X	X	X	X	X				
Paclitaxel[6]		X	X	X	X	X	X				
Durvalumab 750 mg[6]		X		X		X					
Radiation[6]		X	X	X	X	X					
Durvalumab 1500 mg[7]									X		

Study Evaluation Cycle = 28 days	Screen	Neoadjuvant Therapy Cycle 1 (C1)[13]						Surgical Resection	Adjuvant Therapy C1-C6	Safety Follow Up (+ 7 days)[14]	Long-Term Follow up (± 14 days)[15]
	-28 days	Day 1	Day 8	Day 15	Day 22	Day 29	Day ± 36		Day 1 ± 3 days	30 and 90 days post last dose	Every 3 months
SPECIMEN COLLECTION											
Archival Tumor Tissue or Fresh Tissue[8]	X							X[8]			
Plasma samples[9]		X						X[9]	C1D1	X[9]	
BANKING SAMPLES											
Tissue[10]	X										
Whole blood, serum and plasma[10]		X							C1D1	D30	
FOLLOW-UP											
Survival Status, Subsequent Therapy											X

CBC with differential and platelet to include: WBC, ANC, Hgb, Hct, PLT. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

Key to Footnotes

1. Medical History; other data to obtained during this assessment includes: diagnosis and staging to include pathology report and staging documentation, a smoking history questionnaire and trial awareness question. In addition, prior anti-cancer treatment should be documented including medications (chemotherapy, checkpoint inhibitors, etc) radiation or surgery.

2. Physical exam by a medical oncologist should be performed at screening and during treatment. A radiation oncologist will assess the subject prior to radiation to establish a radiation plan. A thoracic surgery consultation should be completed at screening and prior to surgery to determine whether subject is able to undergo surgical resection.

3. Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status.

4. Thyroid function testing will be performed at screening, after completion of neoadjuvant therapy/prior to surgical resection and then every other cycle of adjuvant therapy starting with C1D1. TSH, free or total T4 will be performed. Free versus total T3 at investigator's discretion. For women of childbearing potential (WOCBP): urine or serum βhCG if clinically appropriate. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Testing is required within 7 days prior to registration.

5. Tumor response assessment will consist of evaluation by CT scan of the chest and MRI or CT of abdomen at screening. PET-CT scan be used in place of these at the discretion of the treating physician. A bone scan or PET scan should be obtained at screening if any clinical or laboratory suspicion of metastatic bone involvement is identified. MRI or CT of the brain should be performed at screening for all patients to rule out the presence of metastatic disease. Post treatment imaging studies will be performed: (1) 4-12 weeks after completing neoadjuvant therapy (2) 4-12 weeks after surgical resection (3) prior to C4D1 of adjuvant therapy and (4) at completion of adjuvant therapy (D30 safety visit). This imaging should include Chest CT which includes the liver and adrenal glands or PET-CT at the discretion of the treating physician. Further abdominal and pelvic imaging is not mandatory but can be obtained if there is clinical suspicion of progression in these areas at the discretion of the treating physician. Radiology imaging window of ± 7 days. De-identified CT or PET/CT images obtained as part of routine imaging may be sent for exploratory radiomic analysis and central review of imaging response by RECIST v1.1. Please email Radiation therapy records (DICOM files for planning CT, RT plan, RT structure, RT dose) to projects@hoosiercancer.org including HCRN LU17-321 in the subject line.

6. Neoadjuvant therapy consists of carboplatin, paclitaxel, Durvalumab and radiation. Radiation therapy must begin within one week of the first day of chemotherapy (or vice versa). Therapy will be 1.8-2 Gy per day; 5 days per week, excluding holidays. 45-61.2 Gy will be delivered over a time period of 5-6 weeks, depending on the total Gy being received, without a break. Interruptions in radiation treatment are strongly discouraged. Dose interruptions are allowed for grade 4 dysphagia, odynophagia, or esophagitis, or for grade 4 hematologic toxicities resulting in chemotherapy delays/modifications, or for a decline in ECOG performance status to 2, 3, or 4. If an interruption of > 3 consecutive days is planned, the sponsor-investigator should be contacted via the Hoosier Cancer Research Network project manager.

7. All subjects will be evaluated including imaging studies 4-12 weeks after undergoing neoadjuvant therapy. If there is no progression of local or distant metastasis and the subject is deemed an appropriate surgical candidate by a thoracic surgeon, they will undergo surgical resection (should occur within 12 weeks after neoadjuvant therapy. After undergoing surgical resection, all subjects will be evaluated including imaging studies within 4-12 weeks after surgery. If there is no progression of local or distant metastasis, subjects will move on to the adjuvant portion of the study which consists of durvalumab Day 1 of every Cycle for up to 6 cycles. Cycle = 4 weeks.

8. Submission of unstained slides from an archived tumor block (within the last 6 months) for correlative analysis is required if available. Tissue should be identified before registration and submitted to Hoosier Cancer Research Network (HCRN) after the subject is successfully registered. A new biopsy is not required if archival tissue is not available. Analysis will include PD-L1 and tumor mutational burden. Submission of unstained slides from surgical sample after completion of neoadjuvant therapy is required if available. See Correlative Laboratory Manual (CLM) for additional details.

9. A blood sample for plasma will be collected (1) prior to treatment C1D1 of neoadjuvant chemoradiation, (2) at the time of re-evaluation following chemoradiation (when the patient gets either their PET/CT or CT chest and abdomen) +/- 7 days, (3) after surgery (any time in the window of 1 week postoperatively until 12 weeks prior to start of adjuvant durvalumab treatment, then (4) D30 and (5) D90 safety visits.

10. Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample. Whole blood for banking will be collected at Pre-Treatment Cycle 1 Day 1 of neoadjuvant chemoradiation. Serum and plasma for banking will be collected at Pre-Treatment Cycle 1 Day 1 prior to initiation of adjuvant Durvalumab, and at the 30-Day Safety Follow up visit. Subjects will be consented for optional storage of any remaining blood samples after protocol-specified studies are complete. These samples will be stored for future unspecified cancer-related research and are considered "banking samples". See CLM for collection, processing, labeling and shipping instructions.

11. If screening (baseline) CBC and CMP were performed within 7 days of Day 1 of treatment, these do not need to be repeated. All laboratory assessments should be done prior to treatment. A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc.

12. The safety follow-up visits should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or at discretion of site investigator) and should be performed 30 days and 90 days (±7 days) after the last dose of treatment. Subjects who have an ongoing Grade ≥ 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier. The Day 90 visit may be done via phone, email or other avenues as appropriate.

13. After completion of protocol therapy, subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed for overall survival until death, withdrawal of consent, or the end of the study (whichever occurs first). Radiographic disease assessment should be performed every 12 weeks for up to one year from the data of study enrollment.

14. Radiation treatment plans will be collected for future analysis. These plans are not required prior to study enrollment or treatment but should be collected by the D30 Safety Visit.

8. BIOSPECIMEN STUDIES AND PROCEDURES

Analyses as described may be performed based on availability of funding.

8.1 Tissue

8.1.1 Archival Tissue

Submission of unstained slides from an archived tumor block (within the last 6 months) to perform correlative analysis is **required if available**. Analysis will include PD-L1 testing by immunohistochemistry and tumor mutational burden. Patients without sufficient archival tissue will not be required to undergo repeat biopsy, and they will still be eligible for enrollment without tissue submission.

8.1.2 Tissue from Surgical Resection

Submission of unstained slides from surgical sample after completion of neoadjuvant therapy is **required if available**. These samples will be used to explore the relationship between multiple pathological, immunological, and genomic characteristics of the cancers *and clinical outcome* in these patients.

8.1.3 Analyses of Tissue Samples

Analyses of pre and post treatment FFPE tissue samples will be prioritized as specified below:

1. Pathology analyses
2. PD-L1 IHC analysis
3. Multiplex IF analysis
4. DNA extraction and WES RNA *isolation and* sequencing
5. Banking for unspecified cancer related research

8.2 Peripheral Blood Samples

8.2.1 Plasma

A blood sample for plasma will be collected prior to treatment C1D1 of neoadjuvant chemoradiation, at the time of re-evaluation following chemoradiation (when the patient gets either their PET/CT or CT chest and abdomen) +/- 7 days, after surgery (any time in the window of 1 week postoperatively until 12 weeks prior to start of adjuvant durvalumab treatment, then D30 and D90 safety visits. These samples will be used for ctDNA analysis.

8.3 Storage of Biospecimens

Any specimens remaining (leftover) once protocol described biospecimen-based studies are complete will be stored for future unspecified cancer related research. Permission for this will be obtained from subjects.

8.4 Banking Samples for Future Unspecified Research

Subject consent will be obtained to collect additional samples for future unspecified cancer related research studies. Hoosier Cancer Research Network (HCRN) 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, prior to starting adjuvant durvalumab, and at the 30-day Safety Follow-up visit.
- Pre- and Post-treatment serum: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1, prior to starting adjuvant durvalumab, and at the 30-day Safety Follow-up visit.
- Unstained slides: Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample.

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

8.5 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's sequence ID assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

9.1 Pathologic Complete Response Rate

Pathologic complete response rate is defined as a lack of evidence of viable cancer in the surgical specimen at the time of surgery.

9.2 Pathologic N0 Rate

Pathologic N0 rate is defined as a lack of evidence of viable cancer in the removed lymph nodes at the time of surgery.

9.3 Disease Free Survival

Disease free survival is defined as the time from surgical resection until the criteria for disease recurrence is met or death as a result of any cause.

9.3.1 Disease Recurrence

Disease recurrence is return of the cancer to where it started (local) or in another part of the body (distant).

10. DRUG INFORMATION

10.1 Carboplatin

Please see the package insert for complete details regarding this drug.

Carboplatin (Paraplatin) is a platinum coordination compound with a molecular weight of 371.25. Mechanism of action is by creating interstrand DNA crosslinks. Dosing is based on the formula: Total Dose (mg) = (target AUC) x (GFR + 25). For this trial, AUC=2.

10.1.2 Supplier/How Supplied

Carboplatin is commercially available and should be obtained through a 3rd party. Carboplatin injection comes in many doses: 50 mg/5 mL, 150 mg/15 mL, 450 mg/45 mL, and 600 mg/60 mL aqueous solution in multidose vials (white flip-off seals), and individually cartooned.

10.1.3 Administration

Administer IV over 30 minutes. Avoid using aluminum containing products that may come into contact with Carboplatin (as it can lead to precipitation and decreased potency).

10.1.4 Storage and Stability

Unopened vials of Carboplatin are stable until the date indicated on the package. Storage should be at 25°C (77°F), but excursions are permitted from 15°-30°C (59°- 86°F). This drug requires protection from light. PARAPLATIN (carboplatin) injection multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

10.1.5 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis. Those interacting with Carboplatin must wear gloves at all times to prevent contact with skin. If contact with skin occurs, the handler should wash the area immediately with soap and water.

10.1.6 Adverse Events

Please refer to the Carboplatin Investigator's Brochure for a complete list of adverse events.

Hematologic toxicity: dose limiting bone marrow suppression that can lead to thrombocytopenia, leukopenia, and anemia. These effects are typically more severe in those with renal impairment and poor performance status. *Gastrointestinal toxicity:* Nausea and vomiting are common GI related side effects that are typically amenable to treatment with anti-emetics. Other effects include diarrhea, constipation, and pain. *Neurologic toxicity:* Peripheral neuropathies is the most frequent neurologic reported side effect. *Nephrotoxicity:* Increases in Cr measurements and BUN have been reported in 6% and 14% of individuals receiving Carboplatin respectively. *Hepatotoxicity:* Abnormal LFTs can occur, and are usually mild and reversible in about 50% of cases. *Allergic Reactions:* 2% of patients receiving Carboplatin have experienced hypersensitivity reactions and include rash, hives, pruritus, erythema, bronchospasm, and rarely anaphylactic reactions. These can be treated with antihistamines, steroids, and epinephrine therapy. Injection site reactions, including redness, swelling, and pain, have been reported *Electrolyte disturbances:* Various decreased electrolyte values have been reported after undergoing therapy with Carboplatin. *Other adverse events:* Cardiovascular, respiratory,

genitourinary, and mucosal side effects have been noted in < 6% of individuals receiving Carboplatin therapy. Malaise, anorexia, hypertension, dehydration, and stomatitis have been reported as well.

10.2 Paclitaxel

Please see the package insert for complete details regarding this drug.

Paclitaxel (Taxol) is an insoluble, lipophilic compound with a molecular weight of 853.9.

10.2.1 Supplier/How Supplied

Paclitaxel is commercially available and should be obtained through a 3rd party. Paclitaxel is a clear, colorless to slightly yellow viscous solution and is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Paclitaxel is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials.

10.2.2 Storage and Stability

Vials should be stored in original cartons between 20°–25° C (68°–77° F). Needs to be protected from sunlight. Unopened vials of Paclitaxel are stable until the date indicated on the package. Freezing/refrigeration affects the stability of this product. However, if refrigerated it may precipitate, but will dissolve again at room temperature. Infusions are stable at ambient temperature (approximately 25° C) and lighting conditions for up to 27 hours.

10.2.3 Handling and Disposal

Paclitaxel must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Clinical supplies may not be used for any purpose other than that stated in the protocol. The site 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.

10.2.4 Administration

Paclitaxel should be diluted in .9% Sodium Chloride injection, 5% Dextrose injection, 5% Dextrose and .9% Sodium Chloride/Ringer's to a concentration of .3 to 1.2 mg/mL. Prepared solutions are stable at 25 C up to 27 hours. Should avoid plasticized PVC containers and administrations sets is not recommended.

10.2.5 Adverse Events

Please refer to the Paclitaxel insert for a complete list of all adverse events.

Hematologic: Bone marrow suppression limits the dosing of Paclitaxel. Common side effects include leukopenia/neutropenia, anemia, thrombocytopenia. Suppression of the immune system places patients at increased risk for infection. *Hypersensitivity reactions:* All patients should be premedicated prior to Paclitaxel therapy in order to reduce the risk of hypersensitivity reactions. 2% of patients have severe reactions, usually in the first 3 courses of therapy, with symptoms of hypertension, flushing, chest pain, dyspnea, and tachycardia. Minor reactions included symptoms such as dyspnea, hypotension, tachycardia, hypertension, flushing, rash. *Cardiovascular:*

Includes hypotension, bradycardia; significant events occur in 1% of patients and includes syncope, arrhythmias, hypertension, venous thrombosis. *Respiratory:* Respiratory failure, pleural effusions, interstitial pneumonia, PE, lung fibrosis have all been reported. *Neurologic:* Peripheral neuropathy and paresthesia's are the most common side effect neurologically. *Arthralgia/myalgia:* 60% of patients undergoing Paclitaxel therapy experience arthralgias/myalgias, usually occurring a few days after therapy and is usually transient. *Hepatic:* Elevated liver enzymes have been noted to occur on laboratory testing. *Gastrointestinal:* Diarrhea, nausea, vomiting, and mucositis are common side effects of Paclitaxel therapy. *Injection site reaction:* Extravasation reactions can occur and treatment at this time is unknown. Other injection site reactions include erythema, tenderness, swelling at the location. *Other adverse events:* Alopecia occurs in about 90% of patients undergoing this therapy. Other effects include edema, malaise, asthenia, vision changes, increased Creatinine have also been reported.

10.3 Durvalumab

Please refer to Investigator's Brochure (IB) for detailed information regarding this medication.

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-CD279) and CD80 (B7-1). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab 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.

10.3.1 Supplier/How Supplied

Durvalumab is manufactured by AstraZeneca/MedImmune. AstraZeneca/MedImmune will supply durvalumab at no charge to subjects participating in this clinical trial. Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure. Durvalumab must be used within the individually assigned expiry date on the label.

The site 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.

10.3.2 Preparation and Administration

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

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

A dose of 750 mg or 1500 mg (for patients >30 kg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-μm filter.

Add 15.0 mL of durvalumab (i.e., 750 mg of durvalumab) or 30.0 mL of durvalumab (i.e., 1500 mg of durvalumab) to the IV bag. The IV bag size should be selected such that final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

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

Standard infusion time is one hour ± 10 minutes, however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

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

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

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

10.3.3 Storage and Stability

Unopened vials of Durvalumab liquid Drug Product must be stored at 2°C to 8°C (36°F to 46°F).

10.3.4 Adverse Events

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

Immunotherapy adverse related reactions: Individuals receiving Durvalumab therapy are at increased risk of pneumonitis, hepatitis, colitis, development of DM I, thyroid dysfunction, adrenal insufficiency, hypophysitis/hypopituitarism. Other effects include an immunotherapy-induced rash, ITP, nephritis. Severe infections can also occur in those receiving Durvalumab therapy. In pregnant women, Durvalumab can cause fetal harm based on animal studies. *Infusion related reactions:* Severe infusion related reactions have occurred and those with Grade III or IV reactions should have Durvalumab discontinued permanently. *Other side effects:* Fatigue, peripheral edema, pyrexia, decreased appetite, diarrhea, constipation, nausea/vomiting, cough, and dyspnea have also been reported.

Risks with durvalumab include, but are not limited to, diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions and infections/serious infections.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated adverse events.

11. Adverse Events

The descriptions and grading scales found in the NCI CTCAE v5 will be utilized for AE assessment. A copy of the CTCAE v5 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in the Study Procedure Manual or in the EDC system (Documents and Information Tab).

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.
Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- 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 for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- 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 adverse events of special interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious. If the investigator has any questions in regards to an event being an imAE, the investigator should promptly contact the sponsor-investigator.

AESIs observed with durvalumab include:

- Diarrhea/Colitis and intestinal perforation
- Pneumonitis/ILD
- hepatitis/transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash/Dermatitis
- Nephritis/Blood creatinine increases
- Pancreatitis/serum lipase and amylase increases
- Myocarditis
- Myositis/Polymyositis
- Neuropathy/neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.
- In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

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

11.1.4 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.5 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.
- Asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event**.** The form may be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

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

Once the SAE has resolved (see resolution guidelines listed above), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting SAEs to AstraZeneca

HCRN will report all SAEs to AstraZeneca **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to AstraZeneca as it is received from site. AEMailboxClinicalTrialTCS@astrazeneca.com.

11.3 Overdose

An overdose is defined as a patient receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol. Any overdose of a study patient with durvalumab, with or without associated AEs/SAEs, is required to be reported **per SAE guidelines described above**. 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.

11.4 Hepatic Function Abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" **per SAE guidelines described above** unless a definitive

underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

11.5 Pregnancy

If a patient becomes pregnant during the course of the study, study treatment should be discontinued immediately. Pregnancy itself is not regarded as an AE unless there is a suspicion that durvalumab may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study. If any pregnancy occurs in the course of the study, guidelines above regarding reporting of SAEs should be utilized.

11.6 Paternal exposure

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

11.7 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.8 HCRN Responsibilities to FDA

For protocols exempt from the requirements of an IND, the above stated requirements are not applicable. HCRN will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

11.9 IND Safety Reports Unrelated to this Trial

AstraZeneca will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12 STATISTICAL METHODS

12.1 Study Design

Simon's two-stage optimal design will be used for this single-arm Phase II study with the primary endpoint of pathological complete response among patients with stage IIIA (N2) NSCLC treated with concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection followed by adjuvant Durvalumab.

The trial is designed to conclude that concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy would be worth further investigation if the pathological complete response rate is 40% or more. The therapy will be deemed not worthy of further investigation, if the pathological complete response rate is 20% or less, which is the historically observed rate and the null hypothesis that will be tested against a one-sided alternative. Under these assumptions, the maximum sample size is 25 evaluable patients, with 12 patients accrued in the first stage and 13 subjects accrued in the second stage. Given the rare disease of the study population, the trial will not be halt at the end of 1st stage while the interim analysis is performed. If deemed appropriate, DSMB can instruct the trial to pause.

In the first stage, if among these 12 patients, there are 2 or fewer patients who have pathological complete responses, then the study will be stopped for lack of efficacy. Otherwise, 13 additional patients will be accrued for a total of 25. The concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy will be considered to be worthy of further investigation if 8 or more patients who have pathological complete responses are observed among the 25 patients. This design yields a type I error rate of 10%. When the true pathological complete response rate is indeed 40%, the power of the study is 81.5%, the expected sample size is 17.7 and the probability of early stopping is 55.8%.

The sample size of 25 patients are patients who have evaluable pathological response. If not, such as the case when a patient may not come back for surgery after taking the study drugs, such patient will not be evaluable and will be replaced. If 10% of the enrolled patients are not evaluable, then the study would need to enroll about 28 patients.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

The primary endpoint is the pathologic complete response rate following concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection defined as a lack of evidence of viable cancer in the surgical specimen at the time of surgery.

12.2.2 Definition of Secondary Endpoints

In addition to the study of feasibility, the secondary endpoints include 1) the pathological N0 rate in patients with stage IIIA NSCLC treated with concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection, and 2) 1-yr DFS of patients treated with

concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection followed by adjuvant Durvalumab.

12.3 Sample Size and Accrual

This sample size of the trial is a maximum of 25 evaluable patients. The sample size justification and rationale are described in Section 12.1. It is possible that not all patients may be evaluable for the pathologic complete response. If a patient is not evaluable, then the patient will be replaced. If 10% of the enrolled patients are not evaluable, then about 28 patients will need to be enrolled to satisfy the sample size requirement of 25 evaluable patients. Suppose that the accrual rate is 3 patients per months, then the trial can finish the accrual within 10 months.

12.4 Assessment of Safety

All patients who receive one dose of treatment, regardless of whether they have surgery or not, will be evaluated for safety. The Cancer Therapy Evaluation program (CTEP) Active Version (Version 5) of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting.

12.5 Assessment of Efficacy

All patients who have received concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy followed by surgical resection will be evaluable for the primary endpoint of pathologic complete response. The secondary point of 1-year PFS will be analyzed for those who were treated at least one dose of concurrent Carboplatin/Paclitaxel/Durvalumab plus radiation therapy.

12.6 Data Analysis Plans

In general, 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.

12.6.1 Analysis Plans for Primary Objective

The pathological complete response rate will be summarized and 95% confident interval will be calculated after adjusting for the two-stage nature of the study design. The details of the statistical methods for the inference for a two-stage design with binary response can be found in the following two papers:

Jung SH and Kim KM. (2004). On the estimation of the binomial probability in multistage clinical trials. Statistics in Medicine 23, 881-896.

Koyama T and Chen H. (2008). Proper inference from Simon's two-stage designs. Statistics in Medicine 27, 3145-3154.

12.6.2 Analysis Plans for Secondary Objectives

The pathological N0 rate will be summarized and 95% confident interval will be calculated after adjusting for the two-stage nature of the study design. The details of the statistical methods for the inference for a two-stage design with binary response can be found in the following two papers:

Jung SH and Kim KM. (2004). On the estimation of the binomial probability in multistage clinical trials. Statistics in Medicine 23, 881-896.

Koyama T and Chen H. (2008). Proper inference from Simon's two-stage designs. Statistics in Medicine 27, 3145-3154.

The method of Kaplan-Meier will be used to estimate and plot the progression-free survival (defined as the time from registration until disease progression or death from any cause). Patients who are alive without progressive disease at the time of analysis cut-off time will be censored at the date they were last assessed for disease status. One-year PFS will be estimated by the Kaplan-Meier method.

12.6.3 Analysis Plans for Exploratory Objectives

Data analysis for the correlative/exploratory objectives are mainly descriptive and exploratory. The association between tissue PD-L1 and tumor mutational burden with pathologic complete response and N0 rates will be tabulated and analyzed by the logistic regression. The association between tissue PD-L1 and tumor mutational burden with DFS will be analyzed by the Cox regression. The frequency of circulating tumor DNA at time of diagnosis, following surgery, and following treatment with adjuvant Durvalumab will be summarized and tabulated.

12.6.4 Analysis Plans for Safety Data

The analysis of the safety data will be descriptions. The toxicity events will be summarized and tabulated by patients and by events episodes.

12.7 Interim Analysis/Criteria for Stopping Study

Because Simon's two-stage design will be used in this trial, a decision will be made at the end of the first stage based on the efficacy data, which serves effectively as an interim monitor for efficacy data. The stopping rule is described in Section 12.1.

Additionally, a safety rule will be implemented in the first stage of the trial (for the first 12 patients) as follows.

- If there is an event of death, the study will be placed on hold until further evaluation of the reason of the patient death. If it is determined that the patient death is unexpected and possibly related to durvalumab therapy (either in the induction phase or in the adjuvant phase), the study will be closed to further accrual. In the event the death is determined to be unlikely related to durvalumab in either the induction or adjuvant phase, the trial may continue to accrue.
- The study will be stopped to further accrual if there are 2 or more deaths, regardless of the attribution.
- The study will be stopped to further accrual if there are any unexpected, durvalumab-related grade 4 toxicity in the 1st stage of the study (12 patients).

When the study is determined to be stopped for further accrual, the study will be closed after the planned follow-up for the patients who have been already enrolled.

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with the Indiana University Melvin and Bren Simon Cancer Center's (IUSCC) DSMP for Moderate Risk Trials.

HCRN facilitated oversight activities for Moderate Risk Trials include:

- Review and processing of all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator.
- Investigators will conduct continuous review of data and patient safety. For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure), the sponsor investigator will notify HCRN 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.
- Notify participating sites of adverse events potentially requiring expedited reporting and subsequent DSMC recommendations for study modifications.
- Coordinate monthly 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. HCRN should maintain meeting minutes and attendance for submission to the DSMC upon request.
- Conduct data monitoring across all participating sites in accordance with the monitoring requirements set forth in the IUSCC DSMP.

13.2 Indiana University Data Safety Monitoring Committee

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study to assess toxicity, compliance, data integrity, and accrual per the Institutional DSMP. Trials managed by HCRN are not routinely audited or monitored by IUSCC; however, the IUSCC DSMC retains the right to audit HCRN trials on a for cause basis.

The IUSCC DSMC will review study data annually during the active treatment and safety follow-up portion of the trial, per the IUSCC DSMP.
In preparation for the IUSCC DSMC review, HCRN will provide the following:

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

Documentation of DSMC reviews will be provided to sponsor-investigator and HCRN. The IUSCC DSMC will notify the sponsor-investigator and other regulatory bodies, as appropriate, for issues of immediate concern. The sponsor-investigator will work with HCRN to address the DSMC's concerns as appropriate.

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 patient warrant early closure of the study, this recommendation should be made in writing to the DSMC Chair and Compliance Officer. Alternatively, the DSMC may initiate suspension or early closure of the study at any time based on its review of the study reports.

13.3 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.

Participating sites may also be subject to quality assurance audits by AstraZeneca or its designee as well as inspection by appropriate regulatory agencies.

13.3.1 Onsite Monitoring

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. Additional 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 HCRN or its designee.

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

13.4 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 HCRN 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 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform (EDC system), a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. Select data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in EDC system 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 system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all 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. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects 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 site personnel.
Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, AstraZeneca 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.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site 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, as local regulations require.

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

15.2 Ethical Conduct of the Study

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

15.3 Informed Consent Process

The site 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 site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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APPENDIX A: Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy – 17 November 2020

General Considerations Regarding Immune-Mediated Reactions

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

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., NCCN, ESMO) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.
Early identification and management of immune-mediated adverse events (imAEs) are essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse events. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, durvalumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents such as TNF inhibitors (e.g., infliximab) should be considered for events not responding to systemic steroids.
Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines.
With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.

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

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; ESMO European Society for Medical Oncology

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

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high-resolution CT scan. – Consider Pulmonary and Infectious Diseases consults.
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up, and then as clinically indicated.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider chest CT with contrast and repeat in 3-4 weeks. – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV once, may

			be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Consider, as necessary, discussing with study physician.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with study physician, as needed. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for *Clostridium difficile* toxin, etc.

		– Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1	No dose modifications.	**For Grade 1** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist,consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity 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 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consult a GI specialist for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressants such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider. [a] **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days.

	Grade 3 or 4	**Grade 3** • For patient treated with PDL-1 inhibitors, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper. Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days. • Permanently discontinue study drug for 1) Grade 3 colitis in patients treated with CTLA-4 inhibitors or 2) Any grade of intestinal perforation in any patient treated with ICI. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 2 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 2 days, continue steroids and promptly add further immunosuppressants (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**
Hepatitis (elevated LFTs)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**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).
	Grade 1	• No dose modifications. • If it worsens, then treat as Grade 2.	**For Grade 1** – Continue LFT monitoring per protocol.

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**	**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. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper. • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	**For Grade 2** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until LFT elevations improve or resolve. – If no resolution to Grade ≤1 in 1 to 2 days, consider discussing with study physician, as needed. – If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	Grade 3 or 4	**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 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	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an immunosuppressants (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform Hepatology Consult, abdominal workup, and imaging as appropriate.

		Grade ≤1 or baseline within 14 days • For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. **For Grade 4** Permanently discontinue study drug/study regimen.	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin**	**Any Elevations of AST, ALT, or TB as Described Below**	**General Guidance**	**For Any Elevations Described** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg. – For HCV+ patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with HBcAb+: Evaluate for both HBV and HCV as above.
		• No dose modifications.	

or signs of DILI/liver decompensation	Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline	• If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. • For all transaminase elevations , see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN . • If toxicity worsens, then treat as described for elevations in the rows below.If toxicity improves to AST or ALT ≤5.0×ULN , resume study drug/study regimen after completion of steroid taper. • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– 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 (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressants (e.g.,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult).[a] Discuss with study physician if mycophenolate mofetil is not available.

		Infliximab should NOT be used.
Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days	– 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 discussing with study physician, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an immunosuppressant (e.g.,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.**
Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above** **(except would recommend obtaining liver biopsy early)**

If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR):

- **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise**
- **For example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)**
- **For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**

Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Consult a 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, decreased urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consider using steroids in the absence of a clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade events.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup.When event returns to baseline, resume study drug/study

			regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Carefully monitor serum creatinine daily. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant in consultation with a nephrologist.
Rash or Dermatitis **(Including Pemphigoid)**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – **HOLD STUDY DRUG IF STEVENS-JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), OR OTHER SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED.** – **PERMANENTLY DISCONTINUE STUDY DRUG IF SJS, TEN, OR SCAR IS CONFIRMED.**
	Grade 1	No dose modifications.	**For Grade 1** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emolient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume	**For Grade 2** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid,

		drug/study regimen after completion of steroid taper.	consider discussing with study physician, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event persists for >1 week or recurs.
	Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper. • If toxicity worsens, then treat as Grade 4. **For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Consider consulting an endocrinologist for endocrine events. – Consider discussing with study physician, as needed. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections).

			– Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c).If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2, 3, or 4	• For Grade 2-4 endocrinopathies other than hypothyroidism and type 1 diabetes mellitus, consider holding study drug/study regimen dose until acute symptoms resolve.	**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt

		• Study drug/study regimen can be resumed once patient 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 if the patient is clinically stable as per investigator or treating physician's clinical judgement. • If toxicity worsens, then treat based on severity.	initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, and without corticosteroids. **Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis**. – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4** In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade**	**General Guidance**	**For Any Grade** – Consider Gastroenterology referral

	(Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)		
	Grade 1	No dose modifications.	**For Grade 1** – IV hydration – Manage as per amylase/lipase increased (asymptomatic)
	Grade 2, 3, or 4	**For Grade 2** Hold study drug/study regimen dose until resolution to Grade ≤1. **For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 2, 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Neurotoxicity (to include but not limited to non-infectious meningitis, non-infectious encephalitis, and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (Depending on the type of neurotoxicity, refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate. – **FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.**
	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. • Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days. • If toxicity worsens, then treat as Grade 3 or 4.	**For Grade 2** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care

		should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 1	No dose modifications.	**For Grade 1** – Consider discussing with the study physician, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist.
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	**For Grade 2** – Consider discussing with the study physician, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above.

	or if there are signs of respiratory insufficiency or autonomic instability.	– Consult a neurologist. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. o Avoid medications that can worsen myasthenia gravis. *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 IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 3 or 4** – Consider discussing with study physician, as needed. – Recommend hospitalization. – Monitor symptoms and consult a neurologist. *MYASTHENIA GRAVIS:*

		• 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.	○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ○ Avoid medications that can worsen myasthenia gravis. *GUILLAIN-BARRE:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**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 discussing with the study physician, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a

		cardiac biopsy, including any other diagnostic procedures. – 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	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** - 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	• 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 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**

		• If Grade 3-4, permanently discontinue study drug/study regimen.	
Myositis/ Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.

		– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1	• No dose modifications.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2	• Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
Grade 3 or 4	**For Grade 3**	**For Grade 3 or 4** – Monitor symptoms closely; recommend hospitalization.

	• Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4** • Permanently discontinue study drug/study regimen.	– Obtain Neurology consult – Consider discussing with the study physician, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.
[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.
[c]NCCN Clinical Practice Guidelines in Oncology "Management of Immunotherapy-Related Toxicities" Version 1.2020 – December 2019

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

Other–Immune-Mediated Reactions

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

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2** • The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. • Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard 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 famotidine, and IV glucocorticoid).

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

Non-Immune-Mediated Reactions

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

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.