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CANCER RESEARCH NETWORK

Induction durvalumab followed by chemoradiation and consolidation durvalumab (MEDI4736) for stage III non-small cell lung cancer

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PROTOCOL SIGNATURE PAGE

Induction durvalumab followed by chemoradiation and consolidation durvalumab for stage III non-small cell lung cancer

VERSION DATE: 09MAY2022

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

_____
Site Investigator Name (printed)

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Site Investigator Title

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Name of Facility

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Location of Facility (City and State)

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SYNOPSIS

TITLE	Induction durvalumab followed by chemoradiation and consolidation durvalumab for stage III non-small cell lung cancer
SHORT TITLE	Induction durvalumab for stage III NSCLC
PHASE	Feasibility
OBJECTIVES	Primary Objectives • 12-month progression-free survival from completion of chemoradiation (to be compared with PACIFIC trial 12month progression-free survival as historical control). Progression-free survival will be measured beginning then at the start of consolidation durvalumab. • Safety and feasibility Secondary Objective • Overall response rate Exploratory Objectives • Correlation of PFS and toxicity based upon tumor and immune cell PD-L1 status in baseline tumor biopsy prior to therapy; • Correlation of toxicity based upon type of chemotherapy administered; • Correlation of outcomes based upon tumor mutation burden in baseline tumor biopsy prior to therapy; • Assessment of immune response via peripheral blood immune monitoring through multiple timepoints of therapy; • Correlation of immune response with outcomes in terms of disease control and toxicity; • Correlation of tumor immune score via quantitative multiplex tumor biopsy assay with clinical outcomes; • Exploration of immune response signal to indicate further exploration of a treatment schedule in a larger trial; • Collection of microbiome samples to correlate with outcomes and toxicity

STUDY DESIGN	Single arm study of induction durvalumab (1500 mg IV) for 1 cycle (every 4 weeks), administered prior to starting concurrent definitive chemoradiation, followed by consolidation durvalumab (1500 mg IV every 4 weeks) for up to 12 cycles. The study will include an initial safety run-in portion. Patients in the safety run-in will be monitored through completion of induction durvalumab, chemoradiation, and 2 cycles of consolidation durvalumab for assessment of safety prior to completion of enrollment.
KEY ELIGIBILITY CRITERIA (See Section 3 for complete eligibility details)	Inclusion Criteria 1. Histologically confirmed stage III NSCLC per AJCC, 8th edition (not surgical candidates either due to medical inoperability or surgically unresectable disease), eligible for curative-intent concurrent chemoradiation. 2. Plan for treatment with concurrent chemoradiation and a dose of radiation ranging from 54-66Gy 3. Planned mean dose delivery to the lung <20 Gy 4. V20 < 35% 5. Eastern Cooperative Oncology Group performance status 0 or 1. 6. Women of childbearing potential must have a negative pregnancy test and must avoid becoming pregnant as outlined in Section 5.7. Men must avoid fathering a child as outlined in Section 5.7. 7. Adequate bone marrow, renal and hepatic function as defined by: □ Hgb: ≥ 9 g/dL □ WBC: ≥ 3,000/mm^3 □ Platelets: ≥ 100,000/mm^3 □ Total bilirubin: ≤ 1.5 x institutional upper limit of normal (ULN) □ AST (SGOT)/ALT (SGPT): ≤ 2.5 x institutional ULN

	8. Measurable disease by RECIST 1.1 criteria. Exclusion Criteria 1. No prior therapy for stage III NSCLC. 2. Prior exposure to anti-PD-1 or anti-PD-L1 antibodies 3. No history of pulmonary fibrosis, interstitial lung disease, or pneumonitis requiring steroids. 4. Active or prior documented autoimmune disease within the last 2 years. Patients with vitiligo, stable hypothyroidism, Grave's disease, or psoriasis not requiring systemic treatment are not excluded. 5. Active and ongoing steroid use, except for non-systemically absorbed treatments (such as inhaled or topical steroid therapy for asthma, COPD, allergic rhinitis). 6. Uncontrolled concurrent illness or active ongoing infection. 7. Active other malignancy, except for controlled basal cell or squamous cell skin cancer, in situ cervical or bladder cancer. 8. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and

	radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C. 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. 9. Body weight < 30 kg Specific to Consolidation Therapy 1. Patients must have recovered from toxicities associated with prior chemoradiation to CTCAE < Grade 2. 2. Patients must not have progressed following chemoradiation therapy, as measured on imaging per RECIST 1.1. 3. Confirmation of ECOG Performance Status of 0 or 1. 4. Any grade pneumonitis from prior chemoradiation will not be permitted.

STATISTICAL CONSIDERATIONS	In the PACIFIC study, 12-month progression-free survival was 55.9% (1). This study will be planned to detect a 14% improvement in 12month progression-free survival as a potential signal to move forward with further evaluation in a large randomized trial. Thus, 12-month progression-free survival of 69.9% would be felt to be clinically meaningful for further investigation. Assuming that 12-month PFS in the historical control group is 55.9%, with an 18-month accrual interval and additional 12month follow up after the accrual interval, the required sample size would be 49 patients, with a one-sided test given type I error 0.05 and power of 0.8. Accounting for a 10% dropout rate, a total of 54 patients would be enrolled in this study.
TOTAL NUMBER OF SUBJECTS	N = 54
ESTIMATED ENROLLMENT PERIOD	Estimated 18 months
ESTIMATED STUDY DURATION	Estimated 36 months

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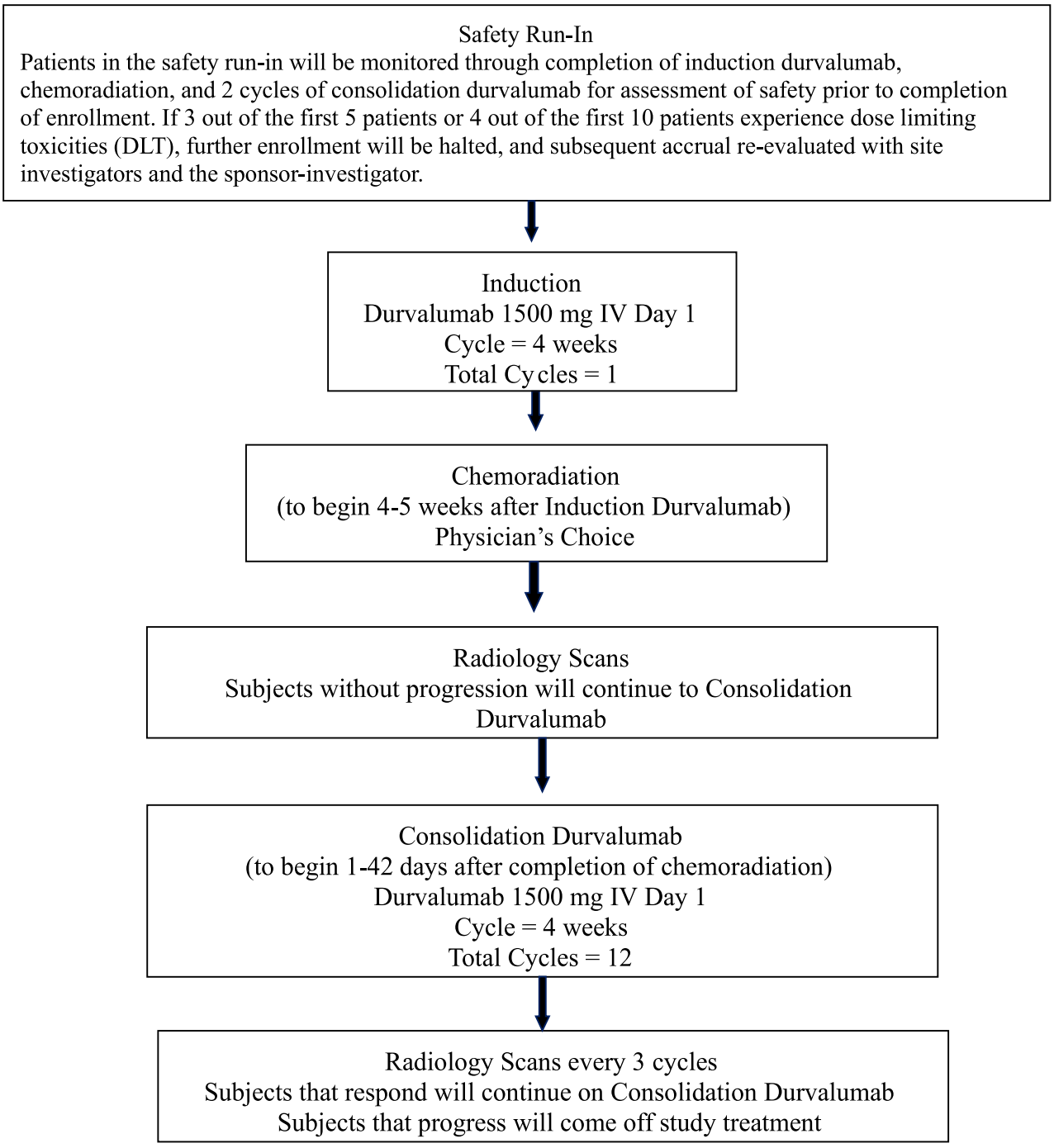
SCHEMA



1. BACKGROUND AND RATIONALE

1.1 Non-Small Cell Lung Cancer Background

Non-small cell lung cancer (NSCLC) is the most common cancer killer in the United States, and worldwide. Despite indications of benefit of low dose CT screening for lung cancer in certain high-risk populations, most patients with NSCLC are diagnosed at more advanced stages. The majority of patients with stage III NSCLC are not eligible for surgical resection, and despite curative-intent treatment with definitive chemoradiation, most will experience disease recurrence and will die.

In a randomized phase III trial evaluating the addition of consolidation durvalumab after completion of standard of care concurrent platinum-doublet chemotherapy with radiation for patients with stage III NSCLC, progression-free survival (PFS) was significantly improved with durvalumab compared with placebo (16.8 months vs 5.6 months; P<0.001). This benefit, including a benefit of 12-month and 18-month PFS, was demonstrated across all subgroups, and was independent of PD-L1 tumor expression prior to chemoradiation. Median time to death or development of metastasis was significantly improved with durvalumab compared with placebo (23.2 months vs 14.6 months), and fewer patients receiving durvalumab developed brain metastases (5.5% vs 11%). Objective response rate was significantly improved with durvalumab (28.4% vs 16%) (1). Overall survival was also significantly improved with durvalumab (hazard ratio for death, 0.68; median overall survival with durvalumab not reached, versus 28.7 months with placebo) (2). Despite prior concerns regarding potential increased risk of pneumonitis with checkpoint inhibition after radiation, no significant difference in grade 3 or 4 pneumonitis was seen with durvalumab, although an expected increase in immune-mediated adverse events was seen with durvalumab compared with placebo (24.2% vs 8.1%, respectively) (1).

Nivolumab has been evaluated as neoadjuvant therapy for resectable stage IB-IIIA NSCLC in a small feasibility study (3). Nivolumab, 3 mg/kg every 2 weeks, was administered for 2 doses prior to surgical resection in 22 patients. Twenty patients underwent surgical resection (1 patient withdrew without toxicity or disease progression; 1 patient had unresectable disease). Interestingly, nine patients (45%) exhibited major pathologic response (defined as <10% viable tumor cells within the resected specimen) with just the two doses of neoadjuvant nivolumab. In an interim report of short interval follow up (median postoperative follow up of 12 months), 80% (16 patients) were free of recurrence. Correlation was noted between tumor mutation burden and neoantigen loads and pathologic response, as well as influx of PD-1+ CD8+ T cells as assessed by multiplex immunohistochemistry assay (3). T cell receptor sequencing in peripheral blood demonstrated corresponding increases in T cell clones in the periphery compared with local tumor invasion (3). Surgery was not delayed in this patient population. Currently, multiple studies utilizing different checkpoint inhibitors are being evaluated in the neoadjuvant setting for resectable NSCLC (4).

1.2 Current Standard of Care, Stage III NSCLC

The current standard of care for patients with unresectable stage III NSCLC amenable for curative-intent therapy is combined modality chemoradiation, followed by consolidation durvalumab for 12 months, based upon the PACIFIC trial results (1). Despite the compelling survival advantage with the addition of consolidation durvalumab, over 22% of patients still experience new lesions and recurrent disease (2).

1.3 Durvalumab

The non-clinical and clinical experience is fully described in the most current version of the durvalumab Investigator's Brochure. Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (5). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (5). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

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

1.3.1 Overall risks of Checkpoint Blockade

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

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

1.3.1.1 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis pneumonitis/ILD, endocrinopathies, hypo- and hyper-thyroidism, type I diabetes mellitus (which may present as diabetic ketoacidosis), diabetes insipidus, hypophysitis and adrenal insufficiency, encephalitis, 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.

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

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 7% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated (Appendix A). A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

1.3.2 Rationale for Durvalumab Dosing

A durvalumab dose of 20 mg/kg Q4W is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (6).

1.3.2.1 PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 17 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PDL1. A low level of immunogenicity has been observed. No patients have experienced immunecomplex disease following exposure to durvalumab (For further information on immunogenicity, please see the current IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W) (Error! Reference source not found.). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W

regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

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

1.3.2.2 Clinical data

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

1.3.2.3 Rationale for Fixed Dosing

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

Similar findings have been reported by others (7, 8, 9, 10). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (8). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters (9).

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

1.4 Rationale

Given that checkpoint inhibition with nivolumab delivered for a defined interval in the small patient population with resectable NSCLC did not delay surgery, and induced a major pathologic response in 43% of patients (3), consideration of checkpoint inhibition as induction prior to definitive chemoradiation for patients with stage III NSCLC is intriguing. Despite previous concerns regarding potential risk for increased toxicity (particularly pneumonitis) with checkpoint inhibition after chemoradiation, consolidation durvalumab after definitive chemoradiation was demonstrated to be safe and feasible, with improvement in progression-free and overall survival. The addition of a checkpoint inhibitor, such as durvalumab, as induction therapy prior to definitive chemoradiation and consolidation checkpoint inhibition for stage III NSCLC, offers an intriguing question as to the potential for the further improvement of immune recognition and response.

We hypothesize that the addition of durvalumab as induction therapy prior to definitive chemoradiation, followed by consolidation durvalumab, as a "sandwich" approach to immunotherapy with chemoradiation, will improve efficacy in terms of 12-month progressionfree survival, for patients with stage III NSCLC, as compared with historical controls (using the PACIFIC study). In this study, we will utilize the monthly "flat dose" administration of durvalumab, 1500 mg intravenously every 4 weeks.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

- Estimate 12-month progression-free survival (PFS) after completion of chemoradiation in patients with Stage III non-small cell lung cancer (NSCLC), measured from the start of consolidation durvalumab. Compare with PACIFIC trial 12-month progression-free survival as historical control (which was measured from the start of consolidation durvalumab).
- Assess the safety and feasibility of induction durvalumab followed by chemoradiation and consolidation durvalumab for stage III NSCLC.

2.1.2 Secondary Objectives

- Estimate Objective response rate (ORR).

2.1.3 Correlative/Exploratory Objectives

- Correlation of outcomes and toxicity based upon tumor and immune cell PD-L1 status in baseline tumor biopsy prior to therapy.
- Correlation of toxicity based upon type of chemotherapy administered.
- Correlation of outcomes based upon tumor mutation burden in baseline tumor biopsy prior to therapy.
- Assessment of immune response via peripheral blood immune monitoring through multiple timepoints of therapy.
- Correlation of immune response with outcomes in terms of disease control and toxicity.

- Correlation of tumor immune score via quantitative multiplex tumor biopsy assay with clinical outcomes.
- Exploration of immune response signal to indicate further exploration of a treatment schedule in a larger trial.
- Collection of microbiome samples to correlate with outcomes and toxicity.

2.2 Endpoints

2.2.1 Primary Endpoints

- 12-month progression-free survival will be measured using imaging after completion of chemoradiation, prior to C1 consolidation durvalumab (1-42 days after completion of chemoradiation). This will be compared with PACIFIC trial 12-month progression-free survival as historical control.
- Toxicity will be measured by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.

2.2.2 Secondary Endpoints

- Objective response rate (ORR). ORR will be measured using two timepoints, per RECIST 1.1. "ORR1" will be assessed using baseline imaging in comparison to imaging obtained after completion of induction durvalumab and chemoradiation. "ORR2" will be assessed using imaging after completion of induction durvalumab and chemoradiation in comparison to imaging obtained while receiving, and after completion of, consolidation durvalumab.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subjects 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 prior to registration. 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.

4. Histological or cytological confirmation of stage III non-small cell lung cancer per AJCC, 8th edition, eligible for curative-intent concurrent chemoradiation. NOTE: subjects are not candidates for surgical resection either due to medical inoperability or surgically unresectable disease.

5. Measurable disease according to RECIST 1.1 criteria.

6. Plan for treatment with concurrent chemoradiation with a dose of radiation ranging from 54-66 Gy:
    - Planned mean dose delivery to the lung <20 Gy
    - V20 <35%

7. No prior therapy for stage III NSCLC.
8. Demonstrate adequate organ function as defined in the table below. All screening labs to be obtained within 14 days prior to registration.

System	Laboratory Value
Hematological	
Hemoglobin	≥ 9.0 g/dL
White blood cell (WBC)	≥ 3,000/mm^3
Absolute neutrophil count (ANC)	≥ 1,500/mm^3
Platelet count	≥ 100,000/mm^3
Renal	
Calculated creatinine clearance[1]	≥ 40 mL/min
Hepatic	
Bilirubin	≤ 1.5 x institutional upper limit of normal (ULN). [2]
Aspartate aminotransferase (AST)	≤ 2.5 x institutional ULN
Alanine aminotransferase (ALT)	≤ 2.5 x institutional ULN

1 Cockcroft-Gault formula will be used to calculate creatinine clearance

2 This will not apply to patients with Gilbert's syndrome. Patients with Gilbert's syndrome will be permitted to enroll.

9. Females of childbearing potential must have a negative serum pregnancy test within 24 hours of C1D1. NOTE: Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

10. Females of childbearing potential must be willing to abstain from heterosexual intercourse or to use contraception as outlined in Section 5.7.

11. Men who are sexually active with WOCBP must be willing to abstain from heterosexual intercourse or to use contraception as outlined in Section 5.7.

12. Life expectancy of at least 12 weeks per investigator discretion.

13. 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. Prior therapy for stage III NSCLC

2. Mixed histology with small cell lung cancer will not be allowed.

3. Sequential chemoradiation will not be permitted.

4. Induction and consolidation chemotherapy (separate from concurrent chemoradiation) will not be allowed.

5. Prior exposure to anti-PD-1 or anti-PD-L1 antibodies including durvalumab.

6. 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., CT scan premedication)

7. History of pulmonary fibrosis, interstitial lung disease, or pneumonitis requiring steroids.

8. Active or prior documented autoimmune disease within the last 2 years. Patients with vitiligo, stable hypothyroidism, Grave's disease, or psoriasis not requiring systemic treatment are not excluded.

9. Body weight < 30 kg

10. Active and ongoing steroid use, except for non-systemically absorbed treatments (such as inhaled or topical steroid therapy for asthma, COPD, allergic rhinitis).

11. Active infection requiring systemic therapy.

12. Uncontrolled current illness that in the opinion of the investigator renders the investigational treatment plan unsafe.

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

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

15. Active other malignancy; exceptions include basal cell or squamous cell skin cancer, in situ cervical or bladder cancer.

16. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C 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.

17. Treatment with any investigational drug within 30 days prior to registration.
18. History of organ transplantation (including allogeneic stem cell transplantation).

19. Other medical or psychiatric conditions that in the opinion of the site investigator would preclude safe participation in this protocol.

3.3 Eligibility Criteria for Consolidation Durvalumab

1. Patients must have recovered from toxicities associated with prior chemoradiation to CTCAE < Grade 2.

2. Patients must not have progressed following chemoradiation therapy, as measured on imaging per RECIST 1.1.

3. Confirmation of ECOG Performance Status of 0 or 1.

4. Any grade pneumonitis from prior chemoradiation will not be permitted.

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.

5. TREATMENT PLAN

This is a single arm study of induction durvalumab at 1500 mg intravenously (IV) on Day 1 of a four week cycle for 1 cycle, followed by concurrent definitive chemoradiation, followed by consolidation durvalumab at 1500 mg IV Day 1 of every 4 week cycle for up to 12 cycles.

Chemoradiation should begin no earlier than 4 weeks and no later than 5 weeks after the dose of induction durvalumab. Patients meeting required criteria for consolidation and without disease progression after chemoradiation should begin consolidation durvalumab within 1-42 days after

completion of chemoradiation. Subjects unable to start within the timeframes described should be discussed with the sponsor-investigator. Concurrent chemoradiation will be with platinumbased chemotherapy (cisplatin or carboplatin, with etoposide, taxane, or pemetrexed) selected at the treating physician's discretion. Patients receiving different chemotherapeutic agents will be analyzed together for toxicity, with exploratory analysis of toxicity related to different chemotherapeutic regimens. Radiation will be administered using standard fractionation at a dose of 54-66 Gy.

5.1 Induction Durvalumab Administration

Drug	Dose	Route	Schedule[2]	Cycle Length	Total # of Cycles
Durvalumab	1500 mg	Intravenously (IV) over 1 hour	Day 1	4 weeks	1
[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).					

5.1.1 Durvalumab

Durvalumab will be administered over 1 hour (± 15 minutes). Please refer to the current IB for more detailed information.

Patients will be monitored before, during and after the infusion with assessment of vital signs. Patients are monitored (pulse rate, blood pressure) every 30 minutes (with a window of - 5 minutes/+ 10 minutes), during the infusion period (including times where infusion rate is slowed or temporarily stopped). In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of durvalumab may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤ Grade 2 infusion related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion related reaction is ≥ Grade 3 or higher in severity, study drug will be discontinued.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary

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

5.2 Chemotherapy and Radiation Therapy Administration

5.2.1 Chemotherapy Administration

Concurrent chemoradiation will be with platinum-based chemotherapy (cisplatin or carboplatin, with etoposide, taxane, or pemetrexed) selected at the treating physician's discretion. The chemotherapy regimen used should be administered per institutional standards following the prescribing guidelines for each drug. Information regarding chemotherapy regimen used will be captured in the EDC system.

5.2.2 Radiation Therapy Administration

Treatment will be delivered using IMRT or 3DCRT using typically 6-10MV photons per institutional standards. 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 per institutional standard as this is a standard of care regimen for this patient population. 54-66 Gy will be delivered. Interruptions in radiation treatment are strongly discouraged. Dose interruptions are allowed, however, for toxicity management at treating investigator discretion to align with institutional standard of care.

5.3 Consolidation Durvalumab Administration

Drug	Dose	Route	Schedule[2]	Cycle Length	Total # of Cycles
Durvalumab	1500 mg	Intravenously (IV) over 1 hour	Day 1	4 weeks	12

[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).

5.4 Safety Run In-Portion

This study will include an initial safety run-in portion. The dose limiting toxicity (DLT) period is through completion of induction durvalumab, chemoradiation, and 2 cycles of consolidation durvalumab. Enrollment will pause after the first 5 patients are enrolled. If 3 out of the first 5 patients experience dose limiting toxicities during the DLT period, further enrollment will be halted, and subsequent accrual re-evaluated with site investigators and the sponsor-investigator. If stopping criteria are not met, enrollment will continue, and accrual will again pause after 10 total patients are enrolled.

If 4 out of the first 10 patients experience dose limiting toxicities (DLT) during the DLT period, further enrollment will be halted, and subsequent accrual re-evaluated with site investigators and the sponsor-investigator. If stopping criteria are not met, enrollment will then continue for the full planned cohort. Patients in the safety run-in phase will be analyzed for PFS and outcomes as members of the full study cohort.

Subjects in the safety run in group who do not remain on the study through completion of the DLT period for reasons other than DLT will be replaced with another subject.

5.4.1 Definition of Dose Limiting Toxicities

The DLT period is through completion of induction durvalumab, chemoradiation, and 2 cycles of consolidation durvalumab. NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used in grading adverse events. A DLT will be defined as:

- Any grade of febrile neutropenia regardless of duration or reversibility Any Grade 4 immune-mediated adverse event (imAE) Any grade of immune-mediated neurotoxicity.
- Grade ≥ 3 colitis
- Grade 3 non-infectious pneumonitis irrespective of duration
- Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Grade 3 imAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Grade 3 liver transaminase elevation with concurrent total bilirubin > 2 × ULN Grade ≥ 3 non-imAE, except for the exclusions listed below

The following conditions are excluded from the DLT definition:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days.
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days
- Transient asymptomatic laboratory abnormalities that do not require hospitalization

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 investigator considers necessary for a subject's welfare may be administered at the discretion of the 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), 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 AstraZeneca 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. FluMist®) 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 immunemodulating effects.
- Hematopoietic growth factor support will not be allowed during chemoradiation.

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 antiinflammatory 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.

Early recognition of signs and symptoms potentially related to an inflammatory or immunemediated 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 may 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].

5.7 Reproductive Information

Participants of childbearing potential who are sexually active and their partners must agree to abstain from heterosexual intercourse or to use 2 forms of effective methods of contraception beginning with time of consent (females) or prior to C1D1 treatment (males), during the study treatment and for 90 days after last dose of durvalumab (or timeframe outlined per package insert for chemotherapy or institutional guidelines for radiation). 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, postovulation 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 (IUD) PLUS male condom. IUD coils should be 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

Female subjects should not breastfeed during treatment and for at least 3 months after the last dose of durvalumab (or timeframe outlined per package insert for chemotherapy or institutional guidelines for radiation).

Male subjects should not donate sperm during treatment and for at least 3 months after the last dose of durvalumab (or timeframe outlined per package insert for chemotherapy or institutional guidelines for radiation).

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 Dose Delays/Dose Modifications

6.1.1 Induction Durvalumab

Dose reductions of durvalumab with induction therapy will not be permitted. See Appendix A for toxicity management guidelines.

6.1.2 Chemoradiation

Chemoradiation should not be initiated until any toxicity attributed to induction durvalumab has resolved to ≤ Grade 1. If initiation of chemoradiation is delayed ≥ 1 week beyond the planned initiation date secondary to toxicity from durvalumab induction therapy, the HCRN Project Manager and sponsor-investigator should be notified.

Dose reductions or delays of chemotherapy and/or radiation based upon toxicities from chemotherapy or radiation will be conducted per institutional standard of care at the discretion of the treating investigator.

Chemotherapy doses held during chemoradiation should not be added after completion of radiation.

6.1.3 Consolidation Durvalumab

Dose reductions of durvalumab during consolidation therapy will not be permitted. See Appendix A for toxicity management guidelines.

6.2 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 confirmed disease progression. In the absence of clinical deterioration, if disease progression is identified per RECIST 1.1, confirmatory scan should be performed no earlier than 4 weeks after the initial assessment of progressive disease. Study drug administration may continue between these assessment scans in the absence of prohibitive toxicity, and the patient must continue to meet eligibility criteria. Patients with rapid clinical deterioration or rapid disease progression will not be eligible to continue treatment and will be discontinued from therapy.
- Subjects who fall to ≤ 30 kg.
- 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
  - o 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.

6.3 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

Induction and Consolidation: Cycle = 28 days	Screen	Induction	Chemoradiation	Consolidation	Safety follow up visit[11]	Long-term Follow up[12]
		Cycle 1		Cycle 1-12	30 and 100 days post last dose	Every 3 months (±14days)
	-28 days	Day 1 ± 3	Day 1 ± 3	Day 1 ± 3		
REQUIRED ASSESSMENTS						
Informed Consent	X					
Medical History[1]	X					
Diagnosis and Staging[2]	X					
Physical Exam[3]	X	X	X[3]	X	D30	
Vital signs and ECOG Performance Status[4]	X	X	X[3]	X	D30	
ECG	X					
AEs & concomitant medications	X	X	X[3]	X	X	
LABORATORY ASSESSMENTS						
Complete Blood Cell Count with diff (CBC)	X	X[13]	X	X	D30	
Comprehensive Metabolic Profile (CMP)	X	X[13]	X	X	D30	
PT/INR and aPTT	X					
Thyroid Function Testing[5]	X			X[5]		
Pregnancy test (serum or urine) (WOCBP)[6]	X	X[6]		X[6]		
DISEASE ASSESSMENT						
CT of chest[7]	X			X[7]	X[7]	X[7]
CT or MRI of abdomen and pelvis[7]				X[7]	X[7]	X[7]
MRI or CT Brain[7]	X			as clinically indicated		
PET Scan[7]	X[7]			as clinically indicated		

TREATMENT EXPOSURE						
Durvalumab		X		X		
Chemoradiation per standard of care			X			
SPECIMEN COLLECTION						
Archival Tumor Tissue[8]	X					
Blood Samples[9]		C1D1		X9		
Stool Microbiome[10]		X10				
FOLLOW-UP						
Survival Status, Subsequent Therapy						X

Key to Footnotes

1: Medical History; other data to obtained during this assessment includes: (1) a smoking history questionnaire, (2) trial awareness question (3) documentation of prior anti-cancer treatment including medications (chemotherapy, checkpoint inhibitors, etc) radiation or surgery and (4) If prior genetic testing has been done those results should be made available.

2: Diagnosis and Staging to include pathology report and staging documentation. AJCC version 8 will be used for recording of staging.

3: Patients should have weekly physical exam and vital signs per good medical practice during chemoradiation. AEs and concomitant meds should be recorded weekly during chemoradiation.

4: Vital signs to include temperature, pulse, respirations, blood pressure, weight, and height (screening only) and ECOG performance status. Patients will be monitored before, during and after the durvalumab infusion with assessment of vital signs. Patients are monitored (pulse rate, blood pressure) every 30 minutes (- 5 minutes/+ 10 minutes), during the infusion period (including times where infusion rate is slowed or temporarily stopped).

5: 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. Thyroid Function testing should be performed at

screening, at start of consolidation durvalumab, then every 3 cycles during consolidation durvalumab. TSH will be obtained. T4 and T3 including free versus total testing is at the discretion of the site investigator.

6: For women of childbearing potential (WOCBP): urine or serum βhCG will be done at screening and within 24 hrs of 1st dose of study drug. During treatment with consolidation durvalumab, a pregnancy test should be performed every 4 weeks. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

7: Tumor assessments to be performed at (1) screening (PET scan may be within 42 days prior to C1D1) (2) within 0-24 days after completion of chemoradiation/prior to C1D1 of consolidation durvalumab, then every 3 months (about every 3 cycles/± 7 business days) during consolidation durvalumab. Screening tumor assessment will consist of evaluation by CT scans of chest (contrast enhanced), PET scan, and contrast-enhanced MRI or CT of the brain. Response assessment imaging will include CT scans of chest, abdomen, and pelvis (contrast enhanced). MRI or CT brain or PET scan after screening should be performed as clinically indicated. Imaging selected for each subject should remain the same throughout the study. Tumor imaging at treatment discontinuation/D30 safety follow up visit is at discretion of site investigator. If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF until PD or death is confirmed, or until another treatment is initiated. A window of 7 days may be applied to obtain scans.

8: Archival tissue is required if available and should be identified at screening and shipped prior to chemoradiation. PD-L1 testing may performed using either 22C3 or SP263 testing per the institution's standard of care. If not performed via the treating institution, PD-L1 testing to be performed through the Providence Cancer Institute, using in-house SP263 assay pending the availability of funding. Tumor Mutation Burden testing and multispectral IHC will also be performed pending the availability of funding.

9: Peripheral blood will be collected for serum, plasma, and peripheral blood mononuclear cells (PBMCs). Timepoints include (1) prior to Cycle 1 Day 1 (C1D1) induction durvalumab, (2) prior to C1D1 consolidation durvalumab, and at (3) 8 weeks after starting consolidation durvalumab (prior to Cycle 3 Day 1 consolidation durvalumab). Immune monitoring testing and ctDNA analysis will be collected. Analysis to be performed pending the availability of funding. Subjects will be consented for optional storage of any remaining tissue/blood samples collected prior to C1D1 treatment after protocol-specified studies are complete. These samples will be stored for future unspecified cancer-related research and are considered "banking samples".

10: Stool for microbiome analysis will be performed prior to treatment C1D1. Subjects will be provided a kit with detailed instructions regarding collection of the sample prior to the timepoint it is due. Analysis will be performed pending the availability of funding. Please see the CLM for additional details.

11: The safety follow-up visit 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 (± 7 days) and 100 days (±7 days) after the last dose of treatment. More frequent follow up for management of toxicity will be per institutional standard of care and the treating investigator. Subjects who have an ongoing Grade ≥ 2 or serious AE (SAE) at this visit will continue to be monitored by a member of the study team until the event is resolved, stabilized, determined to be irreversible by the site investigator or until a new anti-cancer treatment starts, whichever occurs earlier. The D100 evaluation may be completed via phone call.

12: After the D100 safety visit, subjects who discontinue treatment for any reason without documented disease progression will be followed for disease progression every 3 months up to 12 months after initiation of consolidation durvalumab. Once disease progression is documented, subjects will enter a survival follow up period every 6 months for 1 year from the time of documented progression or until 1 year after initiation of consolidation durvalumab. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. A window of ± 14 days will be applied to follow up.

13: 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.

8. BIOSPECIMEN STUDIES AND PROCEDURES

While anti-PD-1/L1 improves clinical outcomes for patients with many cancers, it appears that these responses are best in tumors with dense lymphocytic infiltration or PD-L1 positivity, arguing that improved outcome is associated with a pre-existing anti-cancer immune response (59). Based on this, we hypothesize that strategies which can convert "cold" tumors, lacking T cell infiltrates and PD-L1+ cells, into "hot" tumors with brisk T cell infiltrates, will increase response rate and overall survival.

This proposal seeks to perform Multiplex immunohistochemistry (mIHC) on pre-treatment biopsies of patients enrolled on this clinical trial. This will help us identify patients whose pretreatment tumors lack TIL and/or PD-L1+ cells and determine whether the tumor micro environment (TME) may be associated with clinical outcomes. Our group has applied mIHC to develop a next generation of immunoscore, termed the cumulative suppressive index (CSI). The CSI incorporates PD-L1 and FoxP3+ cells as well as their respective distance to CD8 T cells to provide a prognostic biomarker (10). We are currently evaluating whether it can also serve as a predictive biomarker. Recently, a similar approach has used distance measurements to evaluate PD-1+ cells in close proximity to PD-L1+ cells and showed a significant correlation with response to checkpoint blockade (11). The same report also identified that close proximity of IDO and HLA-DR expression was also predictive of increased overall survival. Patients positive for both multiplex IHC assessments had a significantly (P=0.0018) improved overall survival. We posit that these two predictive biomarkers represent a surrogate of a T cell immune response to the patient's cancer. Supporting this concept, a retrospective analysis of five clinical trials found that multiplex IHC was a better than gene expression profiling, tumor mutational burden or PD-L1 expression at predicting response to checkpoint blockade (12). On this basis we propose performing the CSI, as well as the PD-1/PD-L1 and IDO/HLA-DR proximity assays on biopsy samples from patients enrolled on this study.

Samples for immunological monitoring will include blood (including for circulating tumor DNA analysis), archival tumor tissue, and collecting peripheral blood mononuclear cells (PBMC) and serum. The main objectives of the monitoring will be to characterize circulating T-cell subsets and changes in the tumor microenvironment (TME) following treatment that may correlate with clinical responses.

Flow cytometry analysis with a panel of markers including CD3, CD4, CD8, CD25, CD127, CCR7, FoxP3, ICOS, and CD45RA will be performed. T cell sub-populations of interest include effector, regulatory T cell (T_{reg}), central memory, and effector memory cells. Other immunological measures may be evaluated including, but not limited to, immunohistochemistry analysis of biopsy samples and measurement of serum cytokine levels using multiplex ELISA (Luminex assay) to generate hypotheses for future studies and to gain insight into possible biomarkers of response.

8.1 Tissue

8.1.1 Archival Tissue

Archival tissue is required if available and may be submitted for PD-L1 testing (if not performed by 22C3 or SP263 assay at treating institution per standard of care). Tissue should be identified at screening and shipped prior to chemoradiation. Testing for tumor mutation burden will be performed. TMB is calculated as the number of somatic mutations per megabase of DNA across a 500-gene panel. Archival tissue will be stored for future multispectral immunohistochemistry evaluation. Analysis to be performed pending the availability of funding.

8.2 Peripheral Blood Samples

Analysis to be performed pending the availability of funding.

8.2.1 Serum

Specimens for serum will be collected prior to C1D1 induction durvalumab; prior to C1D1 consolidation durvalumab; and at 8 weeks after consolidation durvalumab (prior to Cycle 3) for immune monitoring analysis. All specimens should be collected prior to drug administration.

8.2.2 Peripheral Blood Mononuclear Cells (PBMCs)

Specimens for PBMCs will be collected prior to C1D1 induction durvalumab; prior to C1D1 consolidation durvalumab; and at 8 weeks after consolidation durvalumab (prior to Cycle 3) for immune monitoring analysis. All specimens should be collected prior to drug administration.

8.2.3 ctDNA

Specimens will be collected prior to C1D1 induction durvalumab; prior to C1D1 consolidation durvalumab; and at 8 weeks after consolidation durvalumab (prior to Cycle 3) for circulating tumor DNA analysis.

8.3 Microbiome

Microbiome stool specimens will be collected from each patient at screening or prior to C1D1 of induction durvalumab. Analysis to be performed pending the availability of funding.

8.4 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples collected for study-specific correlative research prior to C1D1 treatment. Hoosier Cancer Research Network (HCRN) will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

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

Disease response will be assessed as per the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 (see Eisenhauer EA et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Can, 2009.45:p.228-247).

Refer to the RECIST 1.1 publication for complete details on these criteria.

9.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.1 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

9.3 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as

reference to further characterize any objective tumor regression in the measurable dimension of the disease.

9.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.6 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis) NOTE: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.8 Definitions for Response Evaluation – RECIST 1.1

9.8.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

9.8.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

9.8.3 Duration of Response

Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

9.8.4 Duration of Overall Complete Response

The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

9.8.5 Objective Response Rate

Objective response rate (ORR). ORR will be measured using two timepoints, per RECIST 1.1. "ORR1" will be assessed using baseline imaging in comparison to imaging obtained after completion of induction durvalumab and chemoradiation. "ORR2" will be assessed using imaging after completion of induction durvalumab and chemoradiation in comparison to imaging obtained after completion of consolidation durvalumab.

9.8.7 Time to Progression

A measurement from the date of Cycle 1 Day 1 of induction durvalumab until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation or date of death.

9.8.8 Progression Free Survival

12-month progression-free survival will be measured using imaging prior to C1D1 consolidation durvalumab (between 1-42 days after completion of chemoradiation) as baseline. This timepoint is selected in order to compare with the PACIFIC trial 12-month progression-free survival as historical control. 12-month PFS will be defined as the time from the date of CT prior to beginning consolidation radiation until the date of objective disease progression or death (by any cause in the absence of progression), as measured for the 12-month period after initiation of consolidation durvalumab.

10 DRUG INFORMATION

10.1 Durvalumab

Please refer to Investigator's Brochure 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

[B7H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-CD279) and CD80 (B71). 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.

10.1.1 Supplier/How Supplied

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab to the investigator as a solution for infusion after dilution. 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 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) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10.0 mL. 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.

10.1.2 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 1500 mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22µm filter. Add 30.0 mL of durvalumab (i.e., 1500 mg of durvalumab) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

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

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

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

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. A durvalumab dose of 1500 mg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

Add 30.0 mL of durvalumab 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.

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (- 5 minutes/+ 10 minutes), using a 0.2- or 0.22-µm filter. Less than 55 minutes is considered a deviation.

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

The IV line will be flushed with a volume of IV solution (0.9% [w/v] sodium chloride injection 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

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The table below summarizes time allowances and temperatures.

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

10.1.3 Storage and Stability

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

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

10.1.4 Adverse Events

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

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.

Immunotherapy adverse related reactions: Individuals receiving Durvalumab therapy are at increased risk for immune related adverse events such as pneumonitis/interstitial lung disease, hepatitis/increases in transaminases, colitis and intestinal perforation, development of type I diabetes mellitus, thyroid dysfunction, adrenal insufficiency, hypophysitis/hypopituitarism. Other effects include an immunotherapy-induced rash, immune thrombocytopenia, nephritis, pancreatitis/increases in amylase and lipase, and myocarditis. Severe infections can also occur in those receiving Durvalumab therapy. 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.

10.2 Chemotherapy

Please refer to the current package insert for complete prescribing and toxicity information for each chemotherapy medication. Institutional guidelines may be used for preparation and administration of chemotherapy used. The chemotherapy utilized will be sourced commercially.

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 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

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.
- Development of a new cancer. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.
- 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 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.

11.1.4 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)

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

AESIs observed with durvalumab include:

- Diarrhea/Colitis and intestinal perforation
- Pneumonitis/ILD o If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix A) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc.) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans
  where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed. o The sponsor-investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.
- 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 immunemediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis.
- In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

11.1.6 Death

- 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).
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to HCRN as an SAE as described below. It should also be documented in the EDC system. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the EDC system. A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety.
- Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the EDC system. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

11.1.7 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 as a SAE to HCRN who will report to the sponsor-investigator. HCRN must report these to AstraZeneca Patient Safety as outlined in Section 11.2.2.2 within 7 calendar days. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab. The investigator will use clinical judgment to treat any overdose.

11.1.8 Hepatic function abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" as a SAE to HCRN who will report to the sponsor-investigator. HCRN must report these events to AstraZeneca Patient Safety within 7 calendar days, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

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

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

11.1.9 Pregnancy

11.1.9.1 Maternal exposure

If a patient becomes pregnant during the course of the study, durvalumab 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, then the site investigator or other site personnel should inform HCRN within 1 business day and HCRN will report to the sponsor-investigator. HCRN will work with the site investigator to ensure that all relevant information is provided within 1 to 5 calendar days. HCRN must report to AstraZeneca Patient Safety within 7 calendar days for pregnancies with SAEs and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

11.1.9.2 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 180 days after the last dose of durvalumab, should, if possible, be followed up and documented.

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.

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 followup 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. All SAE correspondence should be sent to AstraZeneca via the following address: AEMailboxClinicalTrialTCS@astrazeneca.com.

11.3 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.

11.4 HCRN Responsibilities to FDA

For protocols exempt from the requirements of an IND, 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.

11.5 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

This is a single arm study of induction durvalumab (1500 mg IV) for 1 cycle (every 4 weeks), administered prior to starting concurrent definitive chemoradiation, followed by consolidation durvalumab (1500 mg IV every 4 weeks) for up to 12 cycles.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

1. Estimate 12-month progression-free survival (PFS) in patients with Stage III non-small cell lung cancer (NSCLC). Compare with PACIFIC trial 12-month progression-free survival as historical control. In the PACIFIC study, 12-month progression-free survival was 55.9% and was measured using baseline imaging from the time of patient randomization after completion of chemoradiation (1-42 days after completion of chemoradiation). For this study, in order to allow for comparison with this historical control, 12-month PFS will be measured starting at imaging performed 1-42 days after completion of chemoradiation, prior to initiation of consolidation durvalumab.
2. Assess the safety and feasibility of induction durvalumab followed by chemoradiation and consolidation durvalumab for stage III NSCLC. Toxicity will be measured and recorded as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.

Patients receiving different chemotherapeutic agents will be analyzed together for toxicity, with exploratory analysis of toxicity related to different chemotherapeutic regimens.

12.2.2 Definition of Secondary Endpoints

1. Objective response rate (ORR). ORR will be measured using two timepoints, using RECIST 1.1. "ORR1" will be assessed after completion of induction and chemoradiation

in comparison with baseline imaging. "ORR2" will also be assessed comparing first imaging after completion of induction and chemoradiation to imaging after consolidation durvalumab.

12.2.3 Correlative/Exploratory Endpoints

Data analysis for the correlative/exploratory objectives are descriptive and exploratory. Refer to Sections 12.6.3 and 12.6.5, below, for details of analysis plan for the correlative and exploratory endpoints.

- Correlation of outcomes and toxicity based upon tumor and immune cell PD-L1 status in baseline tumor biopsy prior to therapy.
- Correlation of toxicity based upon type of chemotherapy administered.

Patients receiving different chemotherapeutic agents will be analyzed together for toxicity, with exploratory analysis of toxicity related to different chemotherapeutic regimens.

- Correlation of outcomes based upon tumor mutation burden in baseline tumor biopsy prior to therapy
- Assessment of immune response via peripheral blood immune monitoring through multiple timepoints of therapy
- Correlation of immune response with outcomes in terms of disease control and toxicity
- Correlation of tumor immune score via quantitative multiplex tumor biopsy assay with clinical outcomes
- Exploration of immune response signal to indicate further exploration of a treatment schedule in a larger trial
- Collection of microbiome samples to correlate with outcomes and toxicity

12.3 Sample Size and Accrual

This study will be planned to detect a 14% improvement in 12-month progression-free survival as a potential signal to move forward with further evaluation in a large randomized trial. Thus, 12-month progression-free survival of 69.9% would be felt to be clinically meaningful for further investigation.

Assuming that 12-month PFS in the historical control group is 55.9%, with an 18-month accrual interval and additional 12-month follow up after the accrual interval, the required sample size would be 49 patients, with a one-sided test given type I error 0.05 and power of 0.8. Accounting for a 10% dropout rate, a total of 54 patients would be enrolled in this study.

12.4 Assessment of Safety

All subjects receiving at least one dose of durvalumab will be evaluable for toxicity. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, will be used for toxicity grading. Please refer to the study calendar for the schedule of toxicity assessment.

12.5 Assessment of Efficacy

All subjects who have received at least one dose of consolidation durvalumab and have their disease re-evaluated will be evaluable for the primary endpoint of 12-month PFS. In order to compare with the PACIFIC study as historical control, 12-month PFS will be measured starting at imaging performed 1-42 days after completion of chemoradiation, prior to initiation of consolidation durvalumab. See Section 12.6.1 for details regarding statistical analysis of the primary objective.

12.6 Data Analysis Plans

12.6.1 Analysis Plans for Primary Objective

The progression-free survival analyses will be performed considering the risk of dying from another cause before experiencing progression related events using the competing risk egression method (de Glas et al., 2016). Cumulative incidence functions will be displayed and summarized for the median time to progression as well as percentage of progression patients at 12, 18, and 24 months. In addition, competing risk regression will be used to estimate sub distribution hazard ratios of the study arm versus historical control arm and 95% confidence intervals, adjusted for patient demographic, clinical, pathological, and tumor related factors. To compare the overall survival between groups, Kaplan-Meier survival curves will be displayed and summarized. Survival curves will be statistically compared using the log-rank test. If the proportional hazards assumption is met, survival curves will also be compared using proportional Cox regression, adjusting for risk factors.

12.6.2 Analysis Plans for Secondary Objectives

ORR between two time points will be compared, using Chi-square or Fisher exact test for independent samples, and McNemar's Chi-squared test for related or paired samples.

12.6.3 Analysis Plans for Exploratory Objectives

To assess the immune response via peripheral blood immune monitoring through multiple time points of therapy, the patterns of change will be described using descriptive statistics and plots of means (standard deviation) as well as quantiles over time. Additionally, longitudinal data analysis will be employed to calculate the trajectory of change between repeated measures. Various variance-covariance structures will be explored to obtain an efficient model. We will also perform repeated measures ANOVA to test for a time by intervention interaction.

To evaluate the association between outcomes and predictors, controlling for other risk factors, we will perform linear regression analysis for continuous outcome; logistic and ordinal logistic regression analyses for binary and ordinal outcomes, respectively.

12.6.4 Other Planned Analyses

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline, efficacy, and safety variables (i.e., treatment-related or serious adverse events), as appropriate. Frequency counts and percentage of subjects within each category will be provided for categorical data. Measures of central tendency (mean, median and mode), measures of variability and dispersion (standard deviation, range and quantiles) will be calculated for continuous

variables. Chi-square or Fisher exact test will be used to detect the difference of percentage between treatment arms. Kruskal-Wallis rank sum or ANOVA analyses will be performed to test the homogeneity of continuous variables between groups. All variables will be examined for normality and transformed as needed prior to analysis.

12.7 Criteria for Stopping Study

The study will include an initial safety run-in portion. Patients in the safety run-in will be monitored through completion of induction durvalumab, chemoradiation, and 2 cycles of consolidation durvalumab for assessment of safety prior to completion of enrollment.

If 3 out of the first 5 patients or 4 out of the first 10 patients experience dose limiting toxicities (DLT), further enrollment will be halted and subsequent accrual re-evaluated with investigators and sponsor-investigator. Patients in the safety run-in phase will be analyzed for PFS and outcomes as members of the full study cohort.

The stopping rule criterion was based on the sequential probability ratio test H0: DLT rate = 10% vs H1: DLT rate = 30%, given type I error of 0.05 and power 0.8.

Enrollment will thus first be paused after the first 5 patients are enrolled and complete the above safety window. If stopping criteria are not met, enrollment will then continue with another pause after 10 total patients are enrolled and complete the above safety window. If stopping criteria are not met, enrollment will then continue for the full planned cohort.

Patients in the safety run-in phase will be analyzed for PFS and outcomes as members of the full study cohort.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP) HCRN

oversight activities 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
- Submit data summary reports to the DSMB for review according to DSMB Charter

This study will have a Data and Safety Monitoring Board (DSMB). The DSMB is chaired by an independent medical oncologist external to this trial. The DSMB will provide a recommendation to the sponsor-investigator after all information is reviewed. This information will also be provided to HCRN who will distribute to the site investigator/participating sites for submission to their respective IRB according to the local IRB’s policies and procedures.

The DSMB review will include but is not limited to:

- Adverse event summary report
- Audit results if applicable

- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The DSMB will meet after the first 5 patients are enrolled and have completed 2 cycles of consolidation durvalumab, or after 3 patients of the first 5 in the safety run-in cohort have experienced DLT (whichever comes first), to review data for stopping rules as above. The DSMB will again meet after the first 10 patients are enrolled and have completed 2 cycles consolidation durvalumab, or after 4 patients of the first 10 in the safety run-in cohort have experienced DLT (whichever comes first), to review data for stopping rules as above. Additional DSMB meetings may be convened upon request of the sponsor-investigator, DSMB, or other applicable oversight body.

After the safety lead-in period, the next regular meeting will occur within 6 months of the 11th subject beginning study drug administration. The DSMB will continue to meet approximately every 6 months during the active study drug administration of the study. At the discretion of the DSMB, they may meet more frequently during the course of the study, as more data becomes available. The timing of the next scheduled meeting will be documented in the minutes from the prior meeting.

The DSMB will review the data regularly until at least 100 days after the last participant goes off study treatment. At this point, the DSMB will conduct reviews as needed until the study terminates.

13.2 Data Quality Oversight Activities

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

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For cause visits may occur as necessary. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by 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.

13.3 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the

requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to 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 – 28OCT2021

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 treatmentemergent 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

Relevant Society Guidelines for Management of imAEs

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

1. Brahmer JR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021;9:e002435
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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 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. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed. – 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 or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Consider, as necessary, discussing with Clinical study lead
	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 clinical study lead, 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 or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the 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.
	No dose modifications.	For Grade 1
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.
Grade 2		– If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.

		Hold study drug/study regimen until resolution to Grade ≤1 □ If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper (<10 mg prednisone, or equivalent).	– 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 or relevant practice guidelines. [a] Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay – Consider, as necessary, discussing with clinical study lead if no resolution to Grade ≤1 in 3 to 4 days.

	Grade 3 or 4	Grade 3 For 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 ently discontinue ug/study regimen. Perman study dr	– 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 or relevant practice guidelines). 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)	Gen ral 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 d se modifications. If it orsens, then consi ler holding thera y.	– For Grade 1 Continue LFT monitoring per protocol.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1.	– For Grade 2 Regular and frequent checking of LFTs (e.g., every 1 to 2 days)

Infliximab should not be used for management of immune-related hepatitis.	If toxicity improves to Grade ≤1 or baseline and there were no elevations in bilirubin, resume study drug/study regimen after completion of steroid taper < 10 mg prednisone or equivalent.	• Permanently discontinue study drug/study regimen for any case meeting Hy's law 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]	– If no resolution to Grade ≤1 in 1 to 2 days, consider discussing with clinical study lead, 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. – 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 or relevant practice guidelines). Discuss with clinical study lead if mycophenolate is not available. Infliximab should NOT be used. – Perform Hepatology Consult, abdominal workup, and imaging as appropriate.
PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients			
Grade 3 or 4	For Grade 3 Hold study drug/study regimen for elevations in transaminases ≤8 × ULN (and no elevations in bilirubin), or elevations in bilirubin ≤5 × ULN until resolution to Grade < 1 or baseline: • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline after completion of steroid taper (< 10 mg prednisone or equivalent). • Permanently discontinue study drug/study regimen for elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN. For Grade 4 Permanently discontinue study drug/study regimen.		
For Grade 3 or 4 – Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent.			

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 improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper (< 10 mg prednisone or equivalent).	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 drug/study regimen after completion of steroid taper (< 10 mg prednisone or equivalent).	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, consider discussing with clinical study lead, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – 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 (< 10 mg prednisone or equivalent). 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 clinical study lead.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	General Guidance	For Any Grade Consider – consulting an endocrinologist for – endocrine events. – Consider discussing with clinical study lead, as needed. Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.

		– 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).
Grade 2, 3, or 4		– 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.

		• For Grade 2-4 endocrinopathies other than hypothyroidism and type 1 diabetes mellitus, consider holding study drug/study regimen dose until acute symptoms resolve. • Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (< 10 mg prednisone or equivalent). • Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	– For Grade 2, 3, or 4 Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary – scan. For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., – hydrocortisone, sex hormones). Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and – without corticosteroids. Isolated type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, 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) Grade 1 Grade 2, 3, or 4	General Guidance No dose modifications. 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.	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
Acute Pancreatitis	Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	General Guidance	– For Any Grade Consider Gastroenterology referral
	Grade 2, 3, or 4	For Grade 2 Hold study drug/study regimen dose until resolution to Grade ≤1. If toxicity improves to Grade <1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). 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 GuillainBarre)	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.	– For Grade 2 Consider, as necessary, discussing with the clinical study lead. – 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).
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	Grade 3 or 4	For Grade 3 or 4 Permanently discontinue study drug/study regimen.	– For Grade 3 or 4 Consider, as necessary, discussing with clinical study lead. – 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).

	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 clinical study lead, 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 or if there are signs of respiratory insufficiency or autonomic instability.	For Grade 2 – Consider discussing with the clinical study lead, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).

MYASTHENIA GRAVIS:

- 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.
- 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.
- 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.
- Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers , calcium channel blockers, relaxants).

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.

	Grade 3 or 4	For Grade 3	For Grade 3 or 4

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

For Grade 4 Permanently discontinue study drug/study regimen.

- Consider discussing with clinical study lead, as needed.
- Recommend hospitalization.
- Monitor symptoms and consult a neurologist.

MYASTHENIA GRAVIS:

- Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist.
- Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG.
- If myasthenia gravislike 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(e.g. some antibiotics, beta blockers , calcium channel blockers, relaxants).

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Myocarditis	Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	General Guidance Discontinue drug permanently if biopsyproven 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 clinical study lead, as needed. − Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. − 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.
	Grade 2, 3 or 4 □		− Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)

		If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	– For Grade 2-4 Monitor symptoms daily, – hospitalize. Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic – procedures including a cardiac – biopsy. Supportive care (e.g., oxygen). If no improvement within 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 or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.
Myositis/ Polymyositis	Any Grade (Refer to NCI CTCAE applicable version in study protocol for 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 cooccur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. − Consider, as necessary, discussing with the clinical study lead. − 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 workup 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, antismooth 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 clinical study lead.

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

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

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 clinical study lead 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 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 clinical study lead."
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 standard, appropriate clinical practice guidelines and society guidelines.

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 clinical study lead."

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