# A Randomized, Phase II Study of Staggered, Chemo-Immunotherapy with Durvalumab, MEDI4736 Pemetrexed and Carboplatin (PC) for Metastatic Non-Squamous NSCLC

IRB 127115

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| **Drug Manufacturer** | AstraZeneca |
| **Drug Manufacturer Protocol ID** | ESR 18 14097 |
| **Investigational agent(s)** | Durvalumab |
| **Commercial agent(s)** | Pemetrexed<br>Carboplatin |
| **IND Number** | Exempt |
| **NCT Number** *(CT.gov)* | NCT04163432 |

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**Version 9: 17APR2025**

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## LIST OF ABBREVIATIONS

| Abbreviation or Term[1] | Definition/Explanation |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| ANOVA | Analysis of variance |
| APTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| AV | Atrioventricular |
| β-HCG | Beta-human chorionic gonadotropin |
| BID | Twice daily |
| BLQ | Below limit of quantification |
| BMI | Body mass index |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| $Ca^{++}$ | Calcium |
| CBC | Complete blood count |
| CFR | Code of Federal Regulations |
| CHF | Congestive heart failure |
| CI | Confidence interval |
| Cl- | Chloride |
| $CL_{cr}$ | Creatinine clearance |
| $C_{max}$ | Maximum observed concentration |
| $C_{min}$ | Trough observed concentration |
| CNS | Central nervous system |
| CR | Complete response |
| CRF | Case report form |
| CT | Computed tomography |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| CV | Coefficient of variation |
| CYP | Cytochrome P450 |
| D/C | Discontinue |

| Abbreviation or Term[1] | Definition/Explanation |
|---|---|
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| DLT | Dose Limiting Toxicity |
| ECG | Electrocardiogram |
| Eg | Exempli gratia (for example) |
| FACS | Fluorescence Activated Cell Sorting |
| FDA | Food and Drug Administration |
| FDG-PET | Fluorodeoxyglucose (FDG)-positron emission tomography (PET) |
| GCP | Good Clinical Practice |
| GFR | Glomerular filtration rate |
| GGT | Gamma glutamyl transferase |
| GLP | Good laboratory practice |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| $HCO_3^-$ | Bicarbonate |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| HR | Heart rate |
| hr | Hour or hours |
| $IC_{50}$ | Half maximal inhibitory concentration |
| i.e. | Id est (that is) |
| IEC | Independent ethics committee |
| IND | Investigational New Drug |
| INR | International normalized ratio |
| IRB | Institutional review board |
| IU | International unit |
| IV | Intravenous, intravenously |
| LDH | Lactate dehydrogenase |
| LLQ | Lower limit of quantitation |
| MedRA | Medical Dictionary for Drug Regulatory Activities |
| MRI | Magnetic resonance imaging |

| Abbreviation or Term[1] | Definition/Explanation |
|---|---|
| MRSD | Maximum recommended starting dose |
| MTD | Maximum tolerated dose |
| NOAEL | No-observed-adverse-effect level |
| NOEL | No-observed-effect-level |
| PD | Pharmacodynamic(s) |
| PFS | Progression Free Survival |
| PK | Pharmacokinetic(s) |
| PO | Per os (administered by mouth) |
| PR | Partial response |
| PT | Prothrombin time |
| PTT | Partial thromboplastin time |
| QC | Quality control |
| RBC | Red blood cell |
| QD | Once daily |
| QTc | QT interval corrected |
| QTcF | QT interval corrected using Fredericia equation |
| SAE | Serious adverse event |
| SD | Standard deviation or stable disease |
| $T_{1/2}$ | Terminal elimination half-life |
| $T_3$ | Triiodothyronine |
| $T_4$ | Thyroxine |
| $T_{max}$ | Time of maximum observed concentration |
| TID | Three times daily |
| TSH | Thyroid-stimulating hormone |
| ULN | Upper limit of normal |
| ULQ | Upper limit of quantitation |
| UV | Ultraviolet |
| WBC | White blood cell |
| WOCBP | Women of childbearing potential |
| WONCBP | Women of nonchildbearing potential |

[1] All of these abbreviations may or may not be used in protocol.

## PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

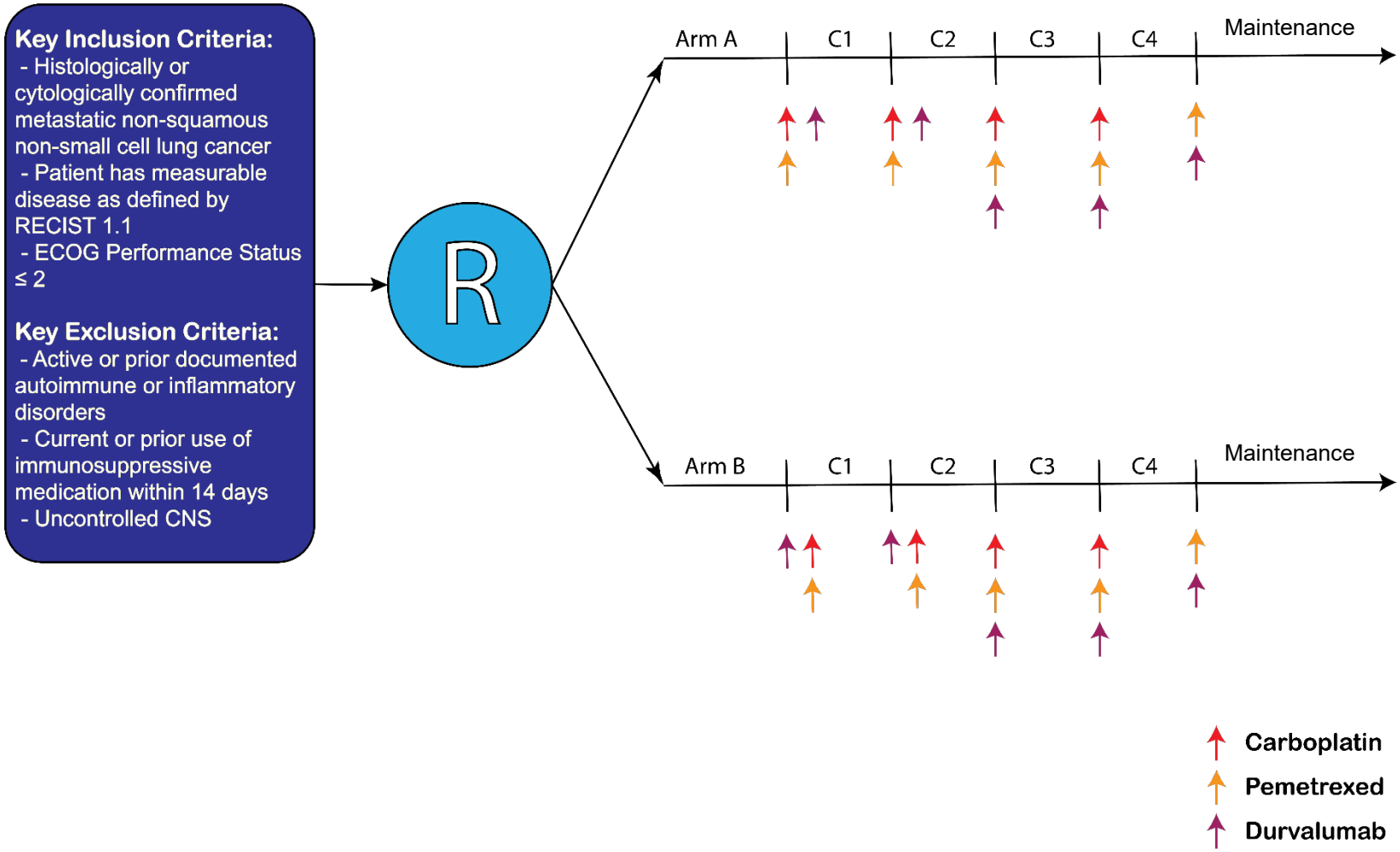
## STUDY SUMMARY

| | |
|---|---|
| Title | A Randomized, Phase II Study of Staggered, Chemo-Immunotherapy with Durvalumab, Pemetrexed and Carboplatin (PC) for Metastatic Non-Squamous NSCLC |
| Short Title | Staggered CI w Durvalumab, Pemetrexed & Carbo for Metastatic Non-squamous NSCLC |
| Protocol Identifiers (IRB – internal) | IRB# 127115 |
| IND number | Exempt |
| Phase | Phase II |
| Design | Open label, randomized, phase II trial. |
| Study Duration | Accrual is anticipated to complete within 18 months. Patients will remain on study until progression and then followed for survival. |
| Study Center(s) | The study will be conducted at a HCI and up to 3 additional sub-sites. |
| Objectives | **Primary Objective**<br>To assess the efficacy of two different staggered dosing schedules of durvalumab in combination with pemetrexed and carboplatin in patients with non-small cell lung cancer.<br>**Secondary Objectives**<br>• To assess the safety and feasibility of each arm of staggered dosing.<br>• To assess short and long term efficacy. |
| Number of Subjects | 84 patients (42 per arm) |
| Diagnosis and Main Eligibility Criteria | **Inclusion Criteria:**<br>• Metastatic non-squamous non-small cell lung cancer.<br>• Histologically or cytologically confirmed lung cancer.<br>• Chemo-immunotherapy naïve (including durvalumab).<br>• Measurable disease as defined by RECIST 1.1<br>• ECOG Performance Status ≤ 2.<br>**Exclusion Criteria:**<br>• EGFR and ALK mutated NSCLC<br>• Active or prior documented autoimmune or inflammatory disorders<br>• Current or prior use of immunosuppressive medication within 14 days of cycle one day one, |

| | |
|---|---|
| | • Active primary immunodeficiency<br>• Uncontrolled CNS metastases |
| Study Product, Dose, Route, Regimen | Durvalumab, pemetrexed, and carboplatin will be administered on two different staggered dosing regimens. They will be administered every 28 days for the first two cycles (cycles one and two), then every 21 days for two additional cycles (cycles three and four). Pemetrexed and durvalumab will be continued as maintenance therapy until treatment discontinuation criteria is met. |
| Duration of administration | Carboplatin will be administered for a total of four doses. Durvalumab and pemetrexed will be administered until treatment discontinuation criteria is met. |
| Reference therapy | Pemetrexed, carboplatin, and pembrolizumab |
| Statistical Methodology | The main assessments of the primary endpoints DCR, as well as the secondary endpoints RR, PFS, OS, specific adverse events, grade ≥3 adverse events, and serious adverse events and exploratory endpoints PROs, performance status, and genomic, proteomic, and immune markers, will be separately evaluated within each arm. In particular, rates or median times-to-event, as appropriate, along with 95% confidence intervals will be constructed within each arm. Additionally, comparisons of the primary and secondary endpoints will be examined in terms of estimated odds or hazard ratios, as appropriate, along with 95% confidence intervals. Both univariate and multivariable comparisons adjusted for performance status will be constructed. Multivariable estimates will be constructed in the context of logistic or Cox proportional hazards models. |

## SCHEMA

Figure 1: Study Schema



# 1 OBJECTIVES

## 1.1 Primary Objective

To assess the efficacy of two different staggered dosing schedules of durvalumab in combination with pemetrexed and carboplatin in patients with non-small cell lung cancer.

Primary Endpoint(s): the rate of clinical benefit will be described using RECIST 1.1 response criteria.

## 1.2 Secondary Objective(s)

- To assess the safety and feasibility of each arm of staggered dosing of durvalumab in combination with pemetrexed and carboplatin in patients with non-small cell lung cancer.

  Secondary Endpoint: The frequency of adverse events (AEs) and serious adverse events (SAEs) will be collected and assessed by CTCAE, version 5.0 for the duration of treatment.

- To assess short and long term efficacy of durvalumab in combination with pemetrexed and carboplatin in patients with non-small cell lung cancer.

  Secondary Endpoints:

  - Objective response rate will be assessed using RECIST 1.1 response criteria.
  - Progression free survival (PFS) will be assessed as the time between trial initiation and documented progression by either clinical progression or radiographic imaging.
  - Overall survival will be assessed as the time from trial initiation until death from any cause.

## 1.3 Exploratory Objective(s)

- To provide a platform of contemporary patients treated with chemo-immunotherapy to evaluate clinical and laboratory biomarkers of prognosis.

  Exploratory Endpoint: Patient Reported Outcomes (Pain, Fatigue, Anxiety, Depression, Physical), Blood-based genomic and proteomic testing (immune, nutrition, inflammation) and Physiologic function/reserve (steps, active minutes, sleep, performance status, 2 minute walk, etc.) through the protocol, "An Observational Study Assessing the Clinical Effectiveness of the VeriStrat® Test and Validating Immunotherapy Tests in Subjects with Non-Small Cell Lung Cancer," IRB 100314.

- To assess immune profile activation before and after immune therapy.

  Exploratory Endpoint: Lymphocyte detection, enumeration, and characterization; cytokine, chemokine, interferon assays; and flow cytometry.

- To assess patient reported outcomes and nutritional status during trial participation.

  Exploratory Endpoint: Questionnaires administered through the protocol, "Rethinking Measurement of Performance Status in Cancer Patients," IRB 112529.

# 2 BACKGROUND

## 2.1 Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death for both males and females in the United States and has a 5-year relative survival rate of 23% (1). The NCCN treatment guidelines recommend to identify and treat patients with actionable cancer mutations, such as ERK or ALK, as the first tier decision point. The second tier branch point of the treatment algorithm suggests to identify those with high PD-L1 biomarker for treatment with PD1 therapy. The remainder of patients receive either chemotherapy or chemoimmunotherapy for first line treatment (2). However, recent literature has demonstrated the benefit of incorporating immunotherapy despite PD-L1 expression.

## 2.2 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (3).

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD 1 receptor (CD279) is expressed on the surface of activated T cells (4). It has 2 known ligands: PD L1 (B7 H1; CD274) and PD L2 (B7 DC; CD273) (5). The PD 1 and PD L1/PD L2 belong to the family of immune checkpoint proteins that act as co inhibitory factors, which can halt or limit the development of T cell response. When PD L1 binds to PD 1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD L1 is constitutively expressed by B cells, dendritic cells, and macrophages. Importantly, PD L1 is commonly over expressed on tumor cells or on non-transformed cells in the tumor microenvironment (6). PD L1 expressed on the tumor cells binds to PD 1 receptors on the activated T cells leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD 1/PD L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

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

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti–PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti–PD-L1 antibody could be

used to therapeutically enhance antitumor immune response in cancer patients (7,8,9,10,11,12) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (13,14,15). In addition, high mutational burden (16,17) may contribute to the responses seen with immune therapy.

Nivolumab and pembrolizumab, two anti–PD-1 agents, and atezolizumab, an anti–PD-L1, agent have been granted approvals by agencies such as the US FDA and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, there are data from agents in the anti–PD-1/PD-L1class showing clinical activity in a wide range of tumor types.

### 2.2.1 Durvalumab background/non-clinical and clinical experience

Durvalumab is the fourth anti-PD drug approved for the treatment of advanced NSCLC. It has been approved for treatment of unresectable stage III where the overwhelming majority have metastatic cancer. It is used as a single agent after the completion of definitive chemoradiation and has been shown to increase the long-term survival. The median time to death or distant metastasis was 28.3 months in the durvalumab group and 16.2 months in the placebo group with hazard ratio of 0.53; 95% CI, 0.41 to 0.68. (18) At ASCO 2019, the OS rate was 57% at three years for patients receiving Durvalumab vs. 43.5% for placebo and the median OS has not yet been reached with the Durvalumab arm vs. 29.1 months for placebo.

In addition, Durvalumab has been studied in metastatic NSCLC. In the Mystic trial, Durvalumab +/- tremelimumab was compared to first line platinum-based chemotherapy. While it did not meet the primary endpoint of superior OS, durvalumab did show a strong trend toward OS with an HR of 0.76 (p=0.036) as a single agent compared to first line chemotherapy.

### 2.2.1 Durvalumab dose rationale

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 (19,20,21,22). 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 (23). 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 (21).

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.

## 2.3 Chemo-immunotherapy

The Keynote-189 trial defined chemo-immunotherapy as a new standard first-line treatment for metastatic non-squamous NSCLC patients without a targetable driver mutation (e.g., EGFR or ALK). It was a randomized phase III trial of carboplatin and pemetrexed with or without pembrolizumab regardless of PDL1 status (24). The trial demonstrated superior efficacy measures in response rate (47%, 19%), progression free survival (PFS) (HR 0.48 [95% CI 0.40-0.58], $P < .00001$; 8.8 months vs 4.9 months), progression free survival 2 (PFS2) ( HR 0.49 [95% CI 0.40-0.59], $P < .00001$; 17.0 mo vs 9.0 mo) and overall survival (OS) (HR 0.56 [95% CI 0.45-0.70], $P < 0.00001$; 22.0 mo vs 10.7 mo) (25,26). Despite the addition of immunotherapy to chemotherapy, there was no substantial difference in toxicity. Of interest, the majority of patients not receiving immunotherapy crossed over to immunotherapy (54% as of September 2018). Hence, patients receiving chemo-immunotherapy concurrently achieve a much greater benefit than those receiving chemo-immunotherapy sequentially.

The addition of immunotherapy to established chemotherapy regimens has shown synergistic action in many cancer types with extended efficacy endpoints (27,28,29). The synergy demonstrated by chemo-immunotherapy is hypothesized to stem from the genetic instability of cancer cells and resulting differences in tumor mutational burden. The higher the mutational burden, the more likely it is that a portion of these mutated genes will produce immunogenic neo-antigens. When chemotherapy administration causes tumor cell lysis, it is hypothesized that neoantigens, as well as stealth neoanitgens, are released leading to an augmentation of tumor antigen presentation through the major histocompatibility complex (MHC) class I resulting in a decrease in immune suppression and an increase in CD8+ T-cells and macrophages in the local tumor microenvironment (30).

Another possible mechanism of synergy between chemo-immunotherapy is platinum-based chemotherapy resistance arises by the alteration of PD-L1 expression in the tumor microenvironment. Extracellular PD-L1 expression has been found to increase after platinum-based therapy resulting in immune suppression (31,32,33,34). However, by incorporating immunotherapy with chemotherapy, an anti-PD-L1 agent may overcome this resistance by maintaining and enhancing the immune response. The synergistic effects of cytotoxic therapy may be elicited by either chemotherapy or radiation (35).

### 2.3.1 Staggered Dosing Rationale

While the concurrent administration of chemotherapy and immunotherapy has demonstrated substantial improvement in the treatment of NSCLC, it is not known whether it could be improved upon. When considering the mechanism of action of the agents involved, a less than ideal environment is present for the administration of

immunotherapy. It is well understood that the administration of systemic chemotherapies causes cytopenias. Specifically, the resulting leukopenia results in a diminished immune system leaving the individual susceptible to infection. Chemotherapy is also co-administered with corticosteroids to increase tolerance as prophylaxis against adverse reactions. Yet to deliver this comfort to the patient, corticosteroids must act as an immunosuppressant. (36) Despite these known hits to the immune system, the current standard of care is to administer immunotherapy on the same day of chemotherapy and corticosteroid administration.

It has been well documented that the benefit of chemotherapy lies not only in its cytotoxic effects but also in the off-target, downstream interaction with the immune system. (37,38,39,40,41) Evidence suggests that administering chemotherapy prior to immunotherapy can improve immunotherapy effectiveness by various mechanisms. (42) Yet, there are also reports of better chemotherapy response when administered after progression on anti-PD1 therapy. (43,44,45,46) It is not fully understood if in this complicated interplay results would differ if the immune system is primed prior to chemotherapy administration or stimulated after chemotherapy administration.

It is, therefore, reasonable to question the timing of immunotherapy delivery. (47) Therefore, we propose to administer chemo-immunotherapy in two separate staggered dosing regimens intended to distance the administration of immunotherapy from the mechanisms of immunosuppression. The chemo-immunotherapy arm will receive chemotherapy on day one and then immunotherapy on day eight. The immuno-chemotherapy arm will administer immunotherapy on day one and chemotherapy on day eight.

## 2.4 Study Hypothesis

Initial immune activation plays a critical role in the effectiveness of chemo-immunotherapy. The unprecedented efficacy of Keynote-189 may be due to any or many of several mechanisms, but since the majority of patients receive the same triplet of pemetrexed, carboplatin, and pembrolizumab, the early overlap of these agents creates a critical interaction. Yet, not all patients benefit from these therapies, so it would be important to understand whether this is due to host factors or tumor factors. Lastly, a paradox of concurrent chemo-immunotherapy is that the immunotherapy and chemotherapy may have opposing effects on the immune system. PD1-based immunotherapies are by design immune stimulatory while chemotherapy, and/or the steroids required to administer them safely, are immune suppressive.

This trial will evaluate two different schedules of concurrent chemoimmunotherapy while simultaneously measuring immune activation, immune resistance and host factors. Both arms will consist of concurrent chemoimmunotherapy with durvalumab, pemetrexed, and carboplatin, but in arm 1 the chemotherapy will precede the immunotherapy by a week and in arm 2 the immunotherapy will precede the chemotherapy by a week. Staggering these therapies still allows concurrent administration while allowing some degree of temporal isolation to better understand the contributions by chemotherapy and immunotherapy in this setting. Host and laboratory factors will be measured during treatment. We hypothesize that staggered dosing of immunotherapy in combination with chemotherapy can improve clinical benefit.

# 3 DRUG INFORMATION

## 3.1 Durvalumab

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks programmed cell death ligand 1 (PD-L1). It is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO cell suspension culture).

### 3.1.1 Mechanism of Action

PD-L1 expression can be found on a variety of cells throughout the body. It plays a vital role in the immune identification of self though the interaction with immune cells expressing PD-1. The interaction of PD-1 and its ligand blocks T-cell function and activation leading to a state T-cell exhaustion and immune suppression. However, malignant cells often utilize this pathway for immune evasion.

Durvalumab is a monoclonal anti-body that blocks the interaction of PD-L1 with PD-1. By inhibiting the signal of self-tolerance, the inhibition of immune response is lifted and T-cells are able to initiate tumor cell apoptosis.

### 3.1.2 Pharmacokinetics

The pharmacokinetics of durvalumab was studied in 1902 patients with doses ranging from 0.1 mg/kg (0.01 times the approved recommended dosage) to 20 mg/kg (2 times the approved recommended dosage) administered once every two, three, or four weeks.

PK exposure increased more than dose-proportionally at doses < 3 mg/kg (0.3 times the approved recommended dosage) and dose proportionally at doses ≥ to 3 mg/kg every 2 weeks. Steady state was achieved at approximately 16 weeks.

**Distribution**

The geometric mean (% coefficient of variation [CV%]) steady state volume of distribution was 5.6 (18%) L.

**Elimination**

Durvalumab clearance decreases over time, with a mean maximal reduction (CV%) from baseline values of approximately 23% (57%) resulting in a geometric mean (CV%) steady state clearance (CLss) of 8.2 mL/h (39%) at day 365; the decrease in CLss is not considered clinically relevant. The geometric mean (CV%) terminal half-life, based on baseline CL was approximately 18 (24%) days.

### 3.1.3 Clinical Experience

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1 as well as those directed against PD-1 or 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 normal 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 diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyperthyroidism

The efficacy of durvalumab was evaluated in the PACIFIC study (NCT02125461), a multicenter, randomized, double-blind, placebo-controlled study in patients with unresectable Stage III NSCLC who completed at least 2 cycles of concurrent platinum-based chemotherapy and definitive radiation within 42 days prior to initiation of the study drug and had a WHO performance status of 0 or 1. The study excluded patients who had progressed following concurrent chemoradiation, patients with active or prior documented autoimmune disease within 2 years of initiation of the study or patients with medical conditions that required systemic immunosuppression. Randomization was stratified by sex, age (< 65 years vs. ≥ 65 years), and smoking history (smoker vs. non-smoker). Patients were randomized 2:1 to receive durvalumab 10 mg/kg or placebo intravenously every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed RECIST 1.1-defined progression. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were progression-free survival (PFS) as assessed by a BICR RECIST 1.1 and overall survival (OS). Additional efficacy outcome measures included ORR assessed by BICR.

A total of 713 patients were randomized: 476 patients to the durvalumab arm and 237 to the placebo arm. The study population characteristics were: median age of 64 years (range: 23 to 90); 70% male; 69% White and 27% Asian; 16% current smokers, 75% former smokers, and 9% never smokers; 51% WHO performance status of 1; 53% with Stage IIIA and 45% were Stage IIIB; 46% with squamous and 54% with non-squamous histology. All patients received definitive radiotherapy as per protocol, of which 92% received a total radiation dose of 54 Gy to 66 Gy; 99% of patients received concomitant platinum-based chemotherapy (55% cisplatin-based, 42% carboplatin-based chemotherapy and 2% switched between cisplatin and carboplatin).

The pre-specified interim PFS analysis based on 371 events (81% of total planned events) demonstrated a statistically significant improvement in PFS in patients randomized to durvalumab compared to placebo. Preliminary results are presented in Table 1. OS data were not mature at the time of the interim PFS analysis. Please see the current IB for additional details regarding efficacy and toxicity data for Durvalumab.

**Table 1: Efficacy Results for the PACIFIC Study**

| **Endpoint** | **Durvalumab (N=476)** * | **Placebo (N=237)** * |
|---|---|---|
| **Progression-Free Survival (PFS)** † | | |
| Number (%) of patients with event | 214 (45%) | 157 (66%) |
| Median in months (95% CI) | 16.8 (13, 18.1) | 5.6 (4.6, 7.8) |
| Hazard Ratio (95% CI) ‡ § | 0.52 (0.42, 0.65) | |

| | | |
|---|---|---|
| p-value (log-rank) ‡ ¶ | < 0.0001 | |
| **Overall Response Rate (ORR)** | | |
| ORR(95% CI) | 26% (23, 31) | 14% (10, 19) |
| Complete Response | 1% | 0 |
| Partial Response | 25% | 14% |

* Among the ITT population, 7% in the DURVALUMAB arm and 10% in the placebo arm had non-measurable disease as assessed by BICR according to RECIST v1.1

† Blinded Independent Central Review

‡ Stratified by sex, age, and smoking history

§ Pike estimator

¶ Compared with allocated α of 0.0104 (Lan DeMets spending function approximating O'Brien Fleming boundary) for interim analysis

Durvalumab was discontinued due to adverse reactions in 15% of patients. The most common adverse reactions leading to durvalumab discontinuation were pneumonitis or radiation pneumonitis in 6% of patients. Serious adverse reactions occurred in 29% of patients receiving durvalumab. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonitis or radiation pneumonitis (7%) and pneumonia (6%). Fatal pneumonitis or radiation pneumonitis and fatal pneumonia occurred in < 2% of patients and were similar across arms. The most common adverse reactions (occurring in ≥ 20% of patients) were cough, fatigue, pneumonitis or radiation pneumonitis, upper respiratory tract infections, dyspnea, and rash.

Table 2 summarizes the adverse reactions that occurred in at least 10% of patients treated with durvalumab.

**Table 2: Adverse Reactions Occurring>10% Patients in the PACIFIC Study**

| | **durvalumab N=475** | | **Placebo* N=234** | |
|---|---|---|---|---|
| **Adverse Reaction** | **All Grades (%)** | **Grades 3-4 (%)** | **All Grades (%)** | **Grades 3-4 (%)** |
| **Respiratory, Thoracic, and Mediastinal Disorders** | | | | |
| Cough/Productive Cough | 40 | 0.6 | 30 | 0.4 |
| Pneumonitis†/Radiation Pneumonitis | 34 | 3.4 | 25 | 3.0 |
| Dyspnea‡ | 25 | 1.5 | 25 | 2.6 |
| **Gastrointestinal Disorders** | | | | |
| Diarrhea | 18 | 0.6 | 19 | 1.3 |

| | | | | |
|---|---|---|---|---|
| Abdominal pain§ | 10 | 0.4 | 6 | 0.4 |
| **Endocrine Disorders** | | | | |
| Hypothyroidism¶ | 12 | 0.2 | 1.7 | 0 |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Rash# | 23 | 0.6 | 12 | 0 |
| PruritusÞ | 12 | 0 | 6 | 0 |
| **General Disorders** | | | | |
| FatigueS | 34 | 0.8 | 32 | 1.3 |
| Pyrexia | 15 | 0.2 | 9 | 0 |
| **Infections** | | | | |
| Upper respiratory tract infectionsÀ | 26 | 0.4 | 19 | 0 |
| PneumoniaÈ | 17 | 7 | 12 | 6 |

* The PACIFIC study was not designed to demonstrate statistically significant difference in adverse reaction rates for durvalumab, as compared to placebo, for any specific adverse reaction listed in Table 4

† includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, pulmonary fibrosis

‡ includes dyspnea and exertional dyspnea

§ includes abdominal pain, abdominal pain lower, abdominal pain upper, and flank pain

¶ includes autoimmune hypothyroidism and hypothyroidism

# includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema, rash and dermatitis

Þ includes pruritus generalized and pruritus

S includes asthenia and fatigue

À includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis, and upper respiratory tract infection

È includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia klebsiella, pneumonia necrotising, pneumonia pneumococcal, and pneumonia streptococcal.

Other adverse reactions occurring in less than 10% of patients treated with durvalumab were dysphonia, dysuria, night sweats, peripheral edema, and increased susceptibility to infections.

Table 5 summarizes the laboratory abnormalities that occurred in at least 20% of patients treated with durvalumab.

**Table 3: Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients in the PACIFIC Study**

| | **Durvalumab** | **Placebo** |
|---|---|---|

| Laboratory Abnormality | All Grades* (%)† | Grade 3 or 4 (%) | All Grades* (%)† | Grade 3 or 4 (%) |
|---|---|---|---|---|
| **Chemistry** | | | | |
| Hyperglycemia | 52 | 8 | 51 | 8 |
| Hypocalcemia | 46 | 0.2 | 41 | 0 |
| Increased ALT | 39 | 2.3 | 22 | 0.4 |
| Increased AST | 36 | 2.8 | 21 | 0.4 |
| Hyponatremia | 33 | 3.6 | 30 | 3.1 |
| Hyperkalemia | 32 | 1.1 | 29 | 1.8 |
| Increased GGT | 24 | 3.4 | 22 | 1.7 |
| **Hematology** | | | | |
| Lymphopenia | 43 | 17 | 39 | 18 |

* Graded according to NCI CTCAE version 4.0
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: durvalumab (range: 464 to 470) and placebo (range: 224 to 228)

Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/interstitial lung disease (ILD), endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis (including pemphigoid, myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis).

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

In monotherapy clinical studies, AEs at an incidence of ≥ 20% include events such as fatigue and decreased appetite. Approximately 10% of participants discontinued the drug due to an AE.

Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, serious adverse events (SAEs), and Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 to 5 events reported across the durvalumab program.

### 3.2 Pemetrexed

Pemetrexed is a folate analog metabolic inhibitor that is the current standard of care chemotherapy course for non-squamous NSCLC patients. It is standardly used in the first-line setting conjunction with carboplatin for four cycles and then as maintenance for locally

advanced or metastatic patients whose disease has not progressed. However, it is not indicated for squamous NSCLC.

### 3.2.1 Mechanism of Action

Pemetrexed is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers such as the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, is thought to occur to a lesser extent, in normal tissues. Polyglutamated metabolites are thought to have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

### 3.2.2 Pharmacokinetics

The pharmacokinetics of pemetrexed administered as a single-agent in doses ranging from 0.2 to 838 mg/m$^2$ infused over a 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration ($C_{max}$) increase proportionally with dose. The pharmacokinetics of pemetrexed do not change over multiple treatment cycles.

**Distribution**

Pemetrexed has a steady-state volume of distribution of 16.1 liters. In vitro studies indicate that pemetrexed is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

**Metabolism and Excretion**

Pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. The clearance decreases, and exposure (AUC) increases, as renal function decreases. The total systemic clearance of pemetrexed is 91.8 mL/min and the elimination half-life of pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min).

The pharmacokinetics of pemetrexed in special populations were examined in about 400 patients in controlled and single arm studies.

*In vitro* studies indicate that pemetrexed is a substrate of OAT3 (organic anion transporter 3), a transporter that may play a role in active secretion of pemetrexed.

**Effect of Renal Insufficiency**

Pharmacokinetic analyses of pemetrexed included 127 patients with reduced renal function. Plasma clearance of pemetrexed decreases as renal function decreases, with a

resultant increase in systemic exposure. Patients with creatinine clearances of 45, 50, and 80 mL/min had 65%, 54%, and 13% increases, respectively in pemetrexed total systemic exposure (AUC) compared to patients with creatinine clearance of 100 mL/min.

### 3.2.3 Clinical Experience

A multi-center, randomized, open-label study in 1725 chemo-naive patients with Stage IIIb/IV NSCLC was conducted to compare the overall survival following treatment with pemetrexed in combination with cisplatin (PC) versus gemcitabine in combination with cisplatin (GC). Pemetrexed was administered intravenously over 10 minutes at a dose of 500 mg/m2 with cisplatin administered intravenously at a dose of 75 mg/m2 after Pemetrexed administration, on Day 1 of each 21-day cycle. Gemcitabine was administered at a dose of 1250 mg/m2 on Day 1 and Day 8, and cisplatin was administered intravenously at a dose of 75 mg/m2 after administration of gemcitabine, on Day 1 of each 21-day cycle. Treatment was administered up to a total of 6 cycles, and patients in both treatment arms received folic acid, vitamin $B_{12}$, and dexamethasone.

Patient demographics of the intent to treat (ITT) population are shown in Table 4. The demographics and disease characteristics were well balanced.

**Table 4: First-Line Therapy: Summary of Patient Characteristics in Study of NSCLC**

| **Patient Characteristic** | **Pemetrexed plus Cisplatin (PC) (N=862)** | **Gemcitabine plus Cisplatin (GC) (N=863)** |
|---|---|---|
| **Age (yrs)** | | |
| Median (range) | 61.1 (28.8-83.2) | 61.0 (26.4-79.4) |
| **Gender** | | |
| Male/Female | 70.2%/29.8% | 70.1%/29.9% |
| **Origin** | | |
| Caucasian | 669 (77.6%) | 680 (78.8%) |
| Hispanic | 27 (3.1%) | 23 (2.7%) |
| Asian | 146 (16.9%) | 141 (16.3%) |
| African descent | 18 (2.1%) | 18 (2.1%) |
| **Stage at Entry** | | |
| IIIb/IV | 23.8%/76.2% | 24.3%/75.7% |
| **Histology** | | |
| Nonsquamous NSCLC[a] | 618 (71.7%) | 634 (73.5%) |

| | | |
|---|---|---|
| Adenocarcinoma | 436 (50.6%) | 411 (47.6%) |
| Large cell | 76 (8.8%) | 77 (8.9%) |
| Other[b] | 106 (12.3%) | 146 (16.9%) |
| Squamous | 244 (28.3%) | 229 (26.5%) |
| **ECOG PS [c,d]** | | |
| 0/1 | 35.4%/64.6% | 35.6%/64.3% |
| **Smoking History[e]** | | |
| Ever/never smoker | 83.1%/16.9% | 83.9%/16.1% |

a Includes adenocarcinoma, large cell, and other histologies except those with squamous cell type.

b The subgroup of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma.

c Eastern Cooperative Oncology Group Performance Status.

d ECOG PS was not reported for all randomized patients. Percentages are representative of N=861 for the pemetrexed plus cisplatin arm, and N=861 for the gemcitabine plus cisplatin arm.

e Smoking history was collected for 88% of randomized patients (N=757 for the pemetrexed plus cisplatin arm and N=759 for the gemcitabine plus cisplatin arm).

Patients received a median of 5 cycles of treatment in both study arms. Patients treated with pemetrexed plus cisplatin received a relative dose intensity of 94.8% of the protocol-specified pemetrexed dose intensity and 95.0% of the protocol-specified cisplatin dose intensity. Patients treated with gemcitabine plus cisplatin received a relative dose intensity of 85.8% of the protocol-specified gemcitabine dose intensity and 93.5% of the protocol-specified cisplatin dose intensity.

The primary endpoint in this study was overall survival. The median survival time was 10.3 months in the pemetrexed plus cisplatin treatment arm and 10.3 months in the gemcitabine plus cisplatin arm, with an adjusted hazard ratio of 0.94.

**Table 5: First-Line Therapy: Efficacy in NSCLC – ITT Population**

| | **Pemetrexed plus Cisplatin (N=862)** | **Gemcitabine plus Cisplatin (N=863)** |
|---|---|---|
| Median overall survival (95% CI) | 10.3 mos (9.8-11.2) | 10.3 mos (9.6-10.9) |
| Adjusted hazard ratio (HR)[a,b] (95% CI) | 0.94 (0.84-1.05) | |
| Median progression-free survival (95% CI) | 4.8 mos (4.6-5.3) | 5.1 mos (4.6-5.5) |
| Adjusted hazard ratio (HR) [a,b] (95% CI) | 1.04 (0.94-1.15) | |
| Overall response rate (95% CI) | 27.1% (24.2-30.1) | 24.7% (21.8-27.6) |

a Adjusted for gender, stage, basis of diagnosis, and performance status.

b A HR that is less than 1.0 indicates that survival is better in the PC arm than in the GC arm. Alternatively, a HR that is greater than 1.0 indicates survival is better in the GC arm than in the PC arm.

Table 6 provides the frequency and severity of adverse reactions that have been reported in >5% of 839 patients with NSCLC who were randomized to study and received pemetrexed plus cisplatin and 830 patients with NSCLC who were randomized to study and received gemcitabine plus cisplatin. All patients received study therapy as initial treatment for locally advanced or metastatic NSCLC and patients in both treatment groups were fully supplemented with folic acid and vitamin $B_{12}$.

**Table 6: Adverse Reactions in Fully Supplemented Patients Receiving Pemetrexed plus Cisplatin in NSCLC[a]**

| Reaction[b] | Pemetrexed /cisplatin (N=839) | | Gemcitabine/cisplatin (N=830) | |
|---|---|---|---|---|
| | All Grades Toxicity (%) | Grade 3-4 Toxicity (%) | All Grades Toxicity (%) | Grade 3-4 Toxicity (%) |
| **All Adverse Reactions** | 90 | 37 | 91 | 53 |
| **Laboratory** | | | | |
| **Hematologic** | | | | |
| Anemia | 33 | 6 | 46 | 10 |
| Neutropenia | 29 | 15 | 38 | 27 |
| Leukopenia | 18 | 5 | 21 | 8 |
| Thrombocytopenia | 10 | 4 | 27 | 13 |
| **Renal** | | | | |
| Creatinine elevation | 10 | 1 | 7 | 1 |
| **Clinical** | | | | |
| **Constitutional Symptoms** | | | | |
| Fatigue | 43 | 7 | 45 | 5 |
| **Gastrointestinal** | | | | |
| Nausea | 56 | 7 | 53 | 4 |
| Vomiting | 40 | 6 | 36 | 6 |
| Anorexia | 27 | 2 | 24 | 1 |
| Constipation | 21 | 1 | 20 | 0 |

| | | | | |
|---|---|---|---|---|
| Stomatitis/Pharyngitis | 14 | 1 | 12 | 0 |
| Diarrhea | 12 | 1 | 13 | 2 |
| Dyspepsia/Heartburn | 5 | 0 | 6 | 0 |
| **Neurology** | | | | |
| Neuropathy-sensory | 9 | 0 | 12 | 1 |
| Taste disturbance | 8 | 0[c] | 9 | 0[c] |
| **Dermatology/Skin** | | | | |
| Alopecia | 12 | 0[c] | 21 | 1[c] |
| Rash/Desquamation | 7 | 0 | 8 | 1 |

a For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.
b Refer to NCI CTC Criteria version 2.0 for each Grade of toxicity.
c According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

**Continuation of Pemetrexed as Maintenance Following Pemetrexed Plus Platinum Induction Therapy**

A multi-center, randomized, double-blind, placebo-controlled study was conducted to evaluate continuation of pemetrexed in patients with Stage IIIb/IV nonsquamous NSCLC. Patients completing induction treatment of four cycles of Pemetrexed plus cisplatin with stable disease or better and PS 0/1 were randomized (2:1) to maintenance treatment with pemetrexed or placebo. Randomization was stratified by response to induction (complete response (CR)/partial response (PR) versus stable disease (SD)), disease stage (IIIb versus IV), and ECOG performance status (0 versus 1). Pemetrexed was administered intravenously over 10 minutes at a dose of 500 mg/m2 on Day 1 of each 21-day cycle and continued until disease progression. Patients in both study arms received folic acid, vitamin B12, and dexamethasone. The main efficacy outcome was investigator-assessed progression-free survival.

A total of 539 patients were randomized; all completed four cycles of pemetrexed and cisplatin induction prior to randomization. Of the randomized patients, 44% versus 42% achieved a complete or partial response to induction therapy and 53% versus 53% had stable disease after induction treatment in the pemetrexed or the placebo arms respectively.

Patient efficacy results are shown in Table 7.

**Table 7: Pemetrexed as Maintenance Therapy Following Pemetrexed Plus Cisplatin Induction Therapy: Summary of Patient Characteristics in Study of Nonsquamous NSCLC**

| Efficacy Parameter[a,b] | **Pemetrexed (N=359)** | **Placebo (N=180)** |
|---|---|---|
| Median overall survival[c] (95% CI) | 13.9 mos (12.8-16.0) | 11.0 mos (10.0-12.5) |
| Hazard ratio (HR)[c] (95% CI) | 0.78 (0.64-0.96) | |
| p-value | p=0.02 | |
| Median progression-free survival (95% CI) | 4.1 mos (3.2-4.6) | 2.8 mos (2.6-3.1) |
| Hazard ratio (HR)[c] (95% CI) | 0.62 (0.49-0.79) | |
| p-value | p<0.0001 | |

a PFS and OS were calculated from time of randomization, after completion of 4 cycles of pemetrexed plus cisplatin induction therapy.

b Values for PFS given based on investigator assessment.

c A hazard ratio of less than 1 indicates that the maintenance treatment with pemetrexed is associated with lower risk of progression or death compared to treatment with placebo.

Table 8 provides the frequency and severity of adverse reactions reported in >5% of the 438 patients with NSCLC who received pemetrexed maintenance and the 218 patients with NSCLC who received placebo following a platinum-based induction therapy.

All patients received study therapy immediately following 4 cycles of platinum-based treatment for locally advanced or metastatic NSCLC. Patients in both study arms were fully supplemented with folic acid and vitamin $B_{12}$.

**Table 8: Adverse Reactions in Patients Receiving Pemetrexed versus Placebo in NSCLC[a] Following Platinum-Based Induction Therapy**

| | **Pemetrexed (N=438)** | | **Placebo (N=218)** | |
|---|---|---|---|---|
| **Reaction[b]** | **All Grades Toxicity (%)** | **Grade 3-4 Toxicity (%)** | **All Grades Toxicity (%)** | **Grade 3-4 Toxicity (%)** |
| **All Adverse Reactions** | 66 | 16 | 37 | 4 |
| **Laboratory** | | | | |
| **Hematologic** | | | | |
| Anemia | 15 | 3 | 6 | 1 |
| Neutropenia | 6 | 3 | 0 | 0 |
| Leukopenia | 6 | 2 | 1 | 1 |

| | | | | |
|---|---|---|---|---|
| **Hepatic** | | | | |
| Increased ALT | 10 | 0 | 4 | 0 |
| Increased AST | 8 | 0 | 4 | 0 |
| **Clinical** | | | | |
| **Constitutional Symptoms** | | | | |
| Fatigue | 25 | 5 | 11 | 1 |
| **Gastrointestinal** | | | | |
| Nausea | 19 | 1 | 6 | 1 |
| Anorexia | 19 | 2 | 5 | 0 |
| Vomiting | 9 | 0 | 1 | 0 |
| Mucositis/stomatitis | 7 | 1 | 2 | 0 |
| Diarrhea | 5 | 1 | 3 | 0 |
| **Infection** | 5 | 2 | 2 | 0 |
| **Neurology** | | | | |
| Neuropathy-sensory | 9 | 1 | 4 | 0 |
| **Dermatology/Skin** | | | | |
| Rash/Desquamation | 10 | 0 | 3 | 0 |

a. For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.
b. Refer to NCI CTCAE Criteria version 3.0 for each Grade of toxicity.

## 3.3 Carboplatin

### 3.3.1 Mechanism of Action

Carboplatin, USP, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, USP, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin, USP and cisplatin induce equal numbers of drug-DNA cross-links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin, USP and cisplatin appear to be directly related to the difference in aquation rates.

### 3.3.2 Pharmacokinetics

In patients with creatinine clearances of about 60 mL/min or greater, plasma levels of intact carboplatin, USP decay in a biphasic manner after a 30-minute intravenous infusion of 300 mg/m2 to 500 mg/m2 of carboplatin, USP. The initial plasma half-life (alpha) was found to be 1.1 to 2 hours (N=6), and the post distribution plasma half-life (beta) was found to be 2.6 to 5.9 hours (N=6). The total body clearance, apparent volume of distribution and mean residence time for carboplatin, USP is 4.4 L/hour, 16 L and 3.5 hours, respectively. The Cmax values and areas under the plasma concentration vs time curves from 0 to infinity (AUC inf) increase linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, USP, therefore, exhibits linear pharmacokinetics over the dosing range studied (300 mg/m2 to 500 mg/m2).

Carboplatin, USP is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing species other than carboplatin, USP are present in plasma. However, platinum from carboplatin, USP becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days.

The major route of elimination of carboplatin, USP is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. All of the platinum in the 24-hour urine is present as carboplatin, USP. Only 3 to 5% of the administered platinum is excreted in the urine between 24 and 96 hours. There are insufficient data to determine whether biliary excretion occurs.

In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin, USP decrease as the creatinine clearance decreases. Carboplatin injection dosages should therefore be reduced in these patients.

The primary determinant of carboplatin injection clearance is glomerular filtration rate (GFR) and this parameter of renal function is often decreased in elderly patients. Dosing formulas incorporating estimates of GFR to provide predictable carboplatin injection plasma AUCs should be used in elderly patients to minimize the risk of toxicity.

### 3.3.3 Clinical Experience

Carboplatin is currently FDA approved for use in the following indications: initial treatment of advanced ovarian carcinoma and secondary treatment of advanced ovarian carcinoma. However, it is used for the treatment for a variety of malignancies and in many different settings due to its better tolerance and lower rate of toxicities over cisplatin. It is commonly used in combination with paclitaxel in patients with NSCLC.

In contrast to the adverse effect profile of cisplatin, the dose-limiting toxicity of carboplatin is myelosuppression. Myelosuppression caused by carboplatin is dose-related and reversible and is usually characterized by thrombocytopenia, leukopenia, and/or neutropenia. Anemia may be cumulative and may require transfusion support. Although usually reversible, these hematological effects have resulted in infectious or hemorrhagic complications in 5% of patients on carboplatin therapy. In one study, maximally tolerated doses were 600 mg/m$^2$, producing severe thrombocytopenia. With single-agent therapy, the nadir is usually 21 days. The risk of severe myelosuppression is increased in patients who have previously received cisplatin and/or radiation therapy.

Other risk factors include combination with other myelosuppressive agents, low initial blood cell counts, increasing age, renal impairment, poor performance status, or extensive prior chemotherapy

Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of carboplatin injection administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

A summary of commonly documented treatment related adverse events and their prevalence are provided in Table 9.

**Table 9: Common treatment related adverse events associated with carboplatin**

| Adverse Event | Prevalence |
|---|---|
| **Dermatologic** | |
| Alopecia | 2% to 50% |
| **Endocrine metabolic** | |
| Hypocalcemia | 29% to 31% |
| Hypokalemia | 20% to 28% |
| Hypomagnesemia | 29% to 43% |
| Hyponatremia | 29% to 47% |
| **Gastrointestinal** | |
| Abdominal pain | 17% |
| Diarrhea | 6% |
| Nausea | 75% to 80% |
| Vomiting | 65% to 81% |
| **Hematologic** | |
| Anemia | 21% to 90% |
| Leukopenia | 26% to 71% |
| Neutropenia | 16% to 67% |
| Thrombocytopenia | 35% to 62% |

| | |
|---|---|
| **Hepatic** | |
| Alkaline phosphatase raised | 24% to 37% |
| AST/SGOT level raised | 15% to 19% |
| **Renal** | |
| Blood urea abnormal | 14% to 22% |
| Serum creatinine raised | 6% to 10% |
| **Ophthalmic** | |
| Visual disturbance | 1% |
| **Other** | |
| Pain | 23% |
| Hypersensitivity reaction | 2% |

# 4 STUDY DESIGN

## 4.1 Description

This is a Phase II, open label, randomized study of durvalumab in combination with pemetrexed and carboplatin in eligible adult patients with locally advanced or metastatic non-small cell lung cancer. The study will focus on the efficacy of two alternative staggered dosing regimens.

## 4.2 Treatment Randomization

Once deemed eligible, patients will be randomized in a 1:1 ratio to each arm. Arm A will receive chemotherapy on day one and immunotherapy on day eight of a 28-day cycle for the first two cycles. Arm B will receive immunotherapy on day one and chemotherapy on day eight of a 28-day cycle for cycles one and two. After the first two cycles, patients on Arm A and Arm B will be administered chemotherapy and immunotherapy on day one of a 21 day cycle for cycles three and four. Upon completion of four cycles of chemo-immunotherapy, patients will go on to receive maintenance therapy with durvalumab and pemetrexed until treatment discontinuation criteria is met. Maintenance therapy will be administered on day one of a 21-day cycle.

**Figure 2: Arm A Chemo-Immuno Treatment Schedule**

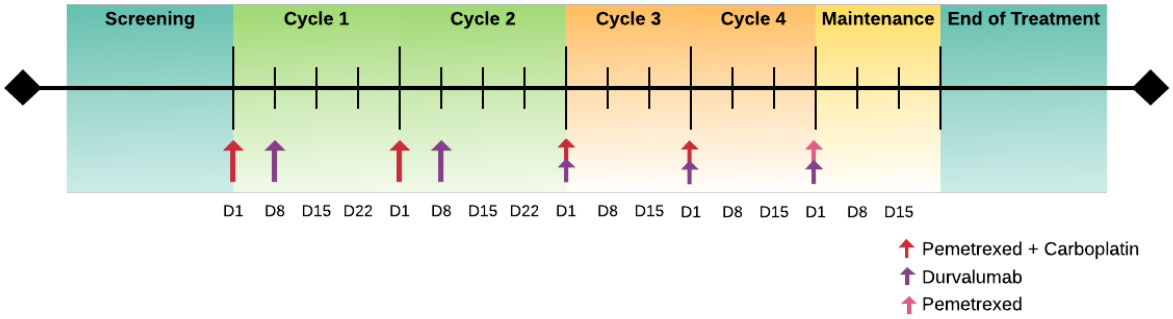
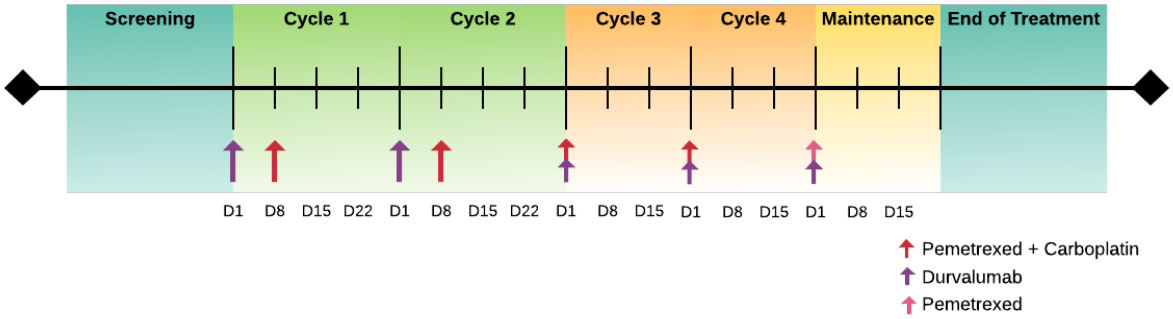



**Figure 3: Arm B Immuno-Chemo Treatment Schedule**




Patients will be stratified by performance status at the time of randomization. Ten patients with a performance status equal to 2 will be allowed on each arm. The remaining slots will enroll patients with a performance status ≤ 1.

## 4.3 Number of Patients

Approximately 84 patients (42 on each arm) will be enrolled in the study.

## 4.4 Number of Study Centers

This will be a multi-center trial with up to 3 additional investigational sites. This trial will be coordinated by the Huntsman Cancer Institute at the University of Utah.

## 4.5 Study Duration

Accrual is anticipated to complete within 18 months. Patients will remain on study until progression and then followed for survival.

# 5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with the enrolling investigator's signature in the patient research chart.

**Patient No. _____**

**Patient's Initials: (L,F,M) _____**

## 5.1 Inclusion Criteria

**Yes/No (Response of "no" = patient ineligible)**

**5.1.1** _____ Male or female subject aged ≥ 18 years.

**5.1.2** _____ Histologically or cytologically confirmed lung cancer.

**5.1.3** _____ Metastatic non-squamous non-small cell lung cancer.

**5.1.4** _____ Body weight >30kg

**5.1.5** _____ Patient has measurable disease as defined by RECIST 1.1 as assessed by either CT or MRI.

**5.1.6** _____ Chemoimmunotherapy naïve (including durvalumab).

**5.1.7** _____ ECOG Performance Status ≤ 2.

Note: If performance status = 2, ensure that there is a slot available prior to registration as only 20 PS = 2 patients will be enrolled on the protocol.

**5.1.8** _____ Must have a life expectancy of at least 12 weeks.

**5.1.9** _____ Adequate organ function as defined as:

- Hematologic:
    - White blood cell count > 2.0 k/uL
    - Platelet count ≥ 100,000/$mm^3$
    - Hemoglobin ≥ 9 g/dL
    - Absolute neutrophil count (ANC) ≥ 1,500/$mm^3$
- Hepatic:
    - Total Bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
        - Except for patients with Gilbert's syndrome.
    - AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN or ≤ 5 × institutional ULN if liver metastases are present
- Renal:

- eGFR ≥ 30 mL/min/1.73m2 or creatinine clearance ≥ 30 mL/min by Cockcroft-Gault:
  - Males: $\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}$
  - Females: $\left(\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}\right)\times 0.85$

**5.1.10** _____**For patients enrolled prior to amendment v18MAR2024:** Concurrent enrollment in the study, "Rethinking Measurement of Performance Status in Cancer Patients," IRB 112529 or the patient has declined participation

**5.1.11** _____ **For patients enrolled prior to amendment v18MAR2024:** Concurrent enrollment in the study, "An Observational Study Assessing the Clinical Effectiveness of the VeriStrat® Test and Validating Immunotherapy Tests in Subjects with Non-Small Cell Lung Cancer," IRB 100314 or the patient has declined participation.

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

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

**5.1.13** _____ Highly effective contraception for both male subjects with partners of childbearing potential and female subjects of childbearing potential throughout the study and for at least 90 days after the last dose of study therapy.

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

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

## 5.2 Exclusion Criteria

**Yes/No (Response of "yes" = patient ineligible)**

**5.2.1** _____ ALK or EGFR non-squamous non-small cell lung cancer.

**5.2.2** _____ Prior radiation therapy within 2 weeks prior to cycle one day one.

Exception: Prior palliative radiotherapy is permitted, provided it has been completed at least 2 days prior to study enrollment and no clinically significant toxicities are expected.

**5.2.3** _____ 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.

**5.2.4** _____ History of allogenic organ transplantation.

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

- Patients with vitiligo or alopecia
- Patients with endocrine disorders with controlled disease on hormone replacement therapy (e.g. adrenal, thyroid, or pituitary replacement therapy)
- Any chronic skin condition that does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the principal investigator
- Patients with celiac disease controlled by diet alone

**5.2.6** _____ Current or prior use of immunosuppressive medication within 14 days of cycle one day one, EXCEPT for the following permitted steroids:

- Intranasal, inhaled, topical steroids, eye drops, or local steroid injection (e.g., intra-articular injection);
- Systemic corticosteroids at physiologic doses ≤ 10mg/day of prednisone or equivalent;
- Steroids as premedication for hypersensitivity reactions (e.g., computed tomography (CT) scan premedication).
- Other immunosuppressive agents which, in the opinion of the investigator, are not expected to significantly impact study participation or the mechanism of action of the study therapy.

**5.2.7** _____ History of active primary immunodeficiency

**5.2.8** ____ Diagnosis of any other malignancy within 2 years prior to study enrollment, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the breast, bladder, or of the cervix, and low-grade (Gleason 6 or below) prostate cancer on surveillance with no plans for treatment intervention (e.g., surgery, radiation, or castration) or prostate cancer that has been adequately treated with prostatectomy or radiotherapy and currently with no evidence of disease or symptoms is allowed.

**5.2.9** _____ Uncontrolled CNS metastases. Subjects with previously treated brain metastases will be allowed if the brain metastases have been treated, toxicities have resolved to grade 1 or baseline and steroids are no longer required.

Note: Patients with asymptomatic brain metastasis are allowed if previous steroid treatment was discontinued for 5 half-lives.

**5.2.10** _____ History of leptomeningeal carcinomatosis

**5.2.11** _____ Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent

**5.2.12** _____ Known HIV infection that is not well controlled. All of the following criteria are required to define an HIV infection that is well controlled: undetectable viral RNA load 12 months, CD4+ count of ≥ 350 cells/uL, no history of AIDS-defining opportunistic infection within the past 12 months, and stable for at least 1 month on the same anti HIV medications.

**5.2.13** _____ Active tuberculosis infection (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice)

**5.2.14** _____ Known active hepatitis infection, positive hepatitis C virus (HCV) antibody, hepatitis B virus (HBV) surface antigen (HBsAg) or HBV core antibody (anti-HBc), at screening. Participants with a past or resolved HBV infection (defined as the presence of anti HBc and absence of HBsAg) are eligible. Participants positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

**5.2.15** _____ Participants co-infected with HBV and HCV, or co-infected with HBV and HDV, namely: HBV positive (presence of HBsAg and/or anti HBcAb with detectable HBV DNA); AND

a. HCV positive (presence of anti-HCV antibodies); OR

b. HDV positive (presence of anti-HDV antibodies).

**5.2.16** _____ Vaccination with a live vaccine within 30 days of cycle one day one and while on trial is prohibited except for administration of inactivated vaccines.

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

**5.2.18** _____ Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies, cisplatin, other platinum-containing compounds, or mannitol. (NCI CTCAE v5.0 Grade ≥ 3).

**5.2.19** _____ Subjects taking prohibited medications as described in Section 6.5.2. A washout period of prohibited medications for a period of at least 5 half-lives or as clinically indicated should occur prior to the start of treatment.

**5.2.20** _____ Participation in another clinical study with an investigational product during the last 2 weeks.

**5.2.21** _____ Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

**5.2.22** _____ Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.

- Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
- Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.

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

**5.2.24** _____ Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at approximately 5 minutes apart).

**5.2.25** _____ Patients who have received prior anti–PD-1, anti PD-L1 or anti CTLA-4.

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

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

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

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

**I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.**

| | | |
|---|---|---|
| **Investigator Signature** | **Date** | **Time** |

### 5.3 Recruitment Strategies

Potential patients will be identified by Investigators in the setting of their outpatient clinics.

## 6 TREATMENT PLAN

### 6.1 Dosing and Administration

The schedule of IP administration will be based on patient randomization. However, all medications will be administered at the same dose and rate across arms despite differing administration schedules. Do not co-administer drugs through the same infusion line.

#### 6.1.1 Durvalumab

Durvalumab will be administered first at a fixed dose of 1500 mg for patients who weight >30 kg. If a patient's weight falls to ≤ 30 kg, weight-based dosing at 20 mg/kg will be a utilized.

Durvalumab will be infused over 1 hour (± 15 minutes) through an IV administration set with a 0.2- or 0.22-µm filter. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 4 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.

#### 6.1.2 Pemetrexed and Carboplatin

As pemetrexed and carboplatin are primarily excreted renally, dosing will be adjusted for kidney function per institutional standards. Pemetrexed will be dosed after durvalumab and before carboplatin at 500 mg/m$^2$ for patients with a creatinine clearance ≥ 45 mL/min (by Cockcroft-Gault formula). If creatinine clearance is < 45 mL/min, pemetrexed may be dosed at 400 mg/m$^2$.

**Table 10: Pemetrexed Dosing by Creatinine Clearance**

| Creatinine Clearance | Pemetrexed Dose |
|---|---|
| ≥ 45 mL/min | 500 mg/m$^2$ |
| 44 mL/min – 30 mL/min | 400 mg/m$^2$ |

The total dose (in mg) of carboplatin will be calculated using the Calvert Formula utilizing a target AUC of 5 and a patient's glomerular filtration rate (GFR in mL/min).

$$Total\ Dose\ (mg) = (target\ AUC) \times (GFR + 25)$$

Pemetrexed will be administered as an intravenous infusion according to institutional practice.

Carboplatin will be administered as an intravenous infusion over 30 minutes (± 10 minutes). Intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Vitamin Supplementation

It is recommended that patients be instructed to initiate folic acid 400 mcg to 1000 mcg orally once daily 7 days before the first dose of pemetrexed. Folic acid should be continued during the full course of pemetrexed therapy and for 21 days after the last dose of pemetrexed.

All patients should also begin vitamin $B_{12}$ supplementation. It is recommended vitamin $B_{12}$ be administered 1 mg intramuscularly 1 week prior to the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin $B_{12}$ injections may be given the same day as pemetrexed administration.

Corticosteroids

Patients will be provided with dexamethasone as premedication prior to pemetrexed administration. Dexamethasone 4 mg will be administered by mouth twice daily the day before, the day of, and the day after pemetrexed administration.

### 6.1.3 Accountability and Compliance

All doses of durvalumab, pemetrexed, and carboplatin will be administered at the investigational site by well-trained medical staff. The start and stop times of the infusion, along with the total volume administered, will be recorded in the patients' medical records. Additionally, the start and stop times of any interruptions to infusions and/or changes in the rate of infusion will also need to be recorded in the patients' medical records. Any reasons that a dose other than the protocol-specified dose, infusion rate, or dosing schedule was administered should be clearly documented in the patient's research chart.

## 6.2 Durvalumab

### 6.2.1 How Supplied, Stored, Packaged, and Labeled

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

### 6.2.2 Preparation and Dispensing

Investigational study medication will be prepared and dispensed by properly trained and delegated individuals at the participating investigational site.

Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

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

A dose of 1500 mg (for patients >30 kg 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 0.22-µm 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.

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

## 6.3 Pemetrexed

### 6.3.1 How Supplied, Stored, Packaged, and Labeled

Pemetrexed is a white to either light-yellow or green-yellow lyophilized powder available in sterile, single-use vials containing 100 mg or 500 mg pemetrexed.

- NDC 67184-0503-1: single-use vial with blue cap individually packaged in a carton.
- NDC 67184-0504-1: single-use vial with blue cap individually packaged in a carton.

Pemetrexed should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) per USP Controlled Room Temperature.

Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C (36-46°F). When prepared as directed, reconstituted and infusion solutions of pemetrexed contain no antimicrobial preservatives. Discard unused portion. Pemetrexed is not light sensitive.

### 6.3.2 Preparation and Dispensing

Investigational study medication will be prepared and dispensed by properly trained and delegated individuals at the participating investigational site.

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions of pemetrexed. The use of gloves is recommended. If a solution of pemetrexed contacts the skin, wash the skin immediately and thoroughly with soap and water. If pemetrexed contacts the mucous membranes, flush thoroughly with water.

Pemetrexed is not a vesicant. There is no specific antidote for extravasation of pemetrexed. To date, there have been few reported cases of pemetrexed extravasation,

which were not assessed as serious by the investigator. Pemetrexed extravasation should be managed with local standard practice for extravasation as with other non-vesicants.

Preparation of pemetrexed:

1. Use aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.
2. Calculate the dose of pemetrexed and determine the number of vials needed. Vials contain either 100 mg or 500 mg of pemetrexed. The vials contain an excess of pemetrexed to facilitate delivery of label amount.
3. Reconstitute each 100-mg vial with 4.2 ml of 0.9% Sodium Chloride Injection (preservative free). Reconstitute each 500-mg vial with 20 mL of 0.9% Sodium Chloride Injection (preservative free). Reconstitution of either size vial gives a solution containing 25 mg/mL pemetrexed. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted pemetrexed solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.
4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter is observed, do not administer.
5. An appropriate quantity of the reconstituted Pemetrexed solution must be further diluted into a solution of 0.9% Sodium Chloride Injection (preservative free), so that the total volume of solution is 100 ml.
6. Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated. When prepared as directed, reconstitution and infusion solutions of pemetrexed contain no antimicrobial preservatives. Discard any unused portion.

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free). Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these should not be used. Co-administration of pemetrexed with other drugs and diluents has not been studied, and therefore is not recommended. Pemetrexed is compatible with standard polyvinyl chloride (PVC) administration sets and intravenous solution bags.

## 6.4 Carboplatin

### 6.4.1 How Supplied, Stored, Packaged, and Labeled

Carboplatin is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin, USP. Each mL contains 10 mg carboplatin, USP, 10 mg mannitol and water for injection, USP. Carboplatin, USP is a platinum coordination compound. The chemical name for carboplatin, USP is platinum, diammine [1,1-cyclobutane-

dicarboxylato (2-)-0,0']-, (SP-4-2), and carboplatin. Each mL of carboplatin injection contains 10 mg of carboplatin, USP in water for injection and is available as follows:

- NDC 57277-105-05 50 mg/5 mL vials (with blue flip-off seals), individually cartoned.
- NDC 57277-106-15 150 mg/15 mL vials (with royal blue flip-off seals), individually cartoned.
- NDC 57277-107-45 450 mg/45 mL vials (with yellow flip-off seals), individually cartoned.

Unopened vials of carboplatin injection are stable to the date indicated on the package when stored at 20°-25° C (68°to 77° F) and should be protected from light.

Carboplatin injection multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Solutions for infusion should be discarded 8 hours after preparation.

### 6.4.2 Preparation and Dispensing

Investigational study medication will be prepared and dispensed by properly trained and delegated individuals at the participating investigational site.

Caution should be exercised in handling and preparing carboplatin injection. Several guidelines on this subject have been published.

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing carboplatin injection. If carboplatin injection contacts the skin, immediately wash the skin thoroughly with soap and water. If carboplatin injection contacts mucous membranes, the membranes should be flushed immediately and thoroughly with water.

Aluminum reacts with carboplatin, causing precipitate formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin injection.

While carboplatin is a premixed aqueous solution of 10 mg/mL, it can be further diluted per institutional standards to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP.

When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin aqueous solutions be discarded 8 hours after dilution.

## 6.5 Concomitant Medications and Therapies

### 6.5.1 Radiotherapy

Palliative radiation therapy for a single site of bone or brain metastasis is allowed on the study. The radiation field must not affect any of the target lesions designated for disease assessment. Protocol treatment will be held during radiation therapy per investigator discretion. A wait period of 2 weeks following the conclusion of therapy is recommended.

### 6.5.2 Prohibited Concomitant Medications and Therapies

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the active treatment period. Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy.
- Other investigational agents.
- Radiation therapy (with the exception noted above in Section 6.5.1).
- Any live vaccine therapies for the prevention of infectious disease through 30 day after the last dose.
- Herbal remedies with immune-modulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).
- Monoclonal antibodies against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study.
- Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers.
    - The following are allowed exceptions:
        - Use of immunosuppressive medications for the management of IP-related AEs,
        - Short-term premedication for pemetrexed.
        - Use in patients with contrast allergies.
        - Use of inhaled, topical, and intranasal corticosteroids.
        - A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
- EGFR tyrosine kinase inhibitors

### 6.5.3 Cautionary Use of Other Medications

Caution should be used when administering NSAIDs concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of 2 days before, the day of, and 2 days following administration of pemetrexed.

In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

## 6.6 Criteria for discontinuation of treatment ("off treatment")

Patients may withdraw from treatment or the study overall at any time at their own request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety, behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures. In addition to the drug-specific discontinuation criteria listed in Dose Modification Section and the Dose Limiting Toxicity Section, the following will result in treatment discontinuation:

- Completion of planned study treatment
- Disease progression unless criteria listed in Section 10.6 are met.
- Unacceptable Toxicity
- Subject withdraws consent from the study treatment and/or study procedures.
- Non-compliance as defined as missing > 30% of required study drug treatment without necessity for AE management.
- Pregnancy
- Significant protocol violation
- Patient refused further treatment
- Study terminated by investigator sponsor
- Lost to follow-up
- Death

Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient who agrees

to a modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up.

Patients who permanently discontinue drug for reasons other than objective RECIST disease progression should continue to have RECIST scans performed per standard of care until RECIST 1.1-defined radiological PD plus an additional follow-up scan or death (whichever comes first) as defined the Schedule of Events

If a patient is discontinued for RECIST 1.1-defined progression, then the patient should have 1 additional follow-up scan performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD.

All patients will be followed for survival until the end of the study.

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in the Schedule of Events as an alternative.

## 6.7 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up, and evaluations should resume according to the protocol.

In order to support key end points of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, including those patients who withdrew consent or are classified as "lost to follow up."

- Lost to Follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status.
- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status.

## 6.8 Criteria for discontinuation of study ("off study")

Subjects will be taken off study for the following:

- Completed study follow-up period
- Screen failure

- Subject is lost to follow-up
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Participant requests to be withdrawn from study
- Death

### 6.9 Withdrawal of consent

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

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to all further participation in the study including any further follow up (e.g., survival contact telephone calls).

## 7 TOXICITIES AND DOSAGE MODIFICATION

In the event of study treatment toxicity, and per the Investigator’s discretion, dosing may be interrupted, delayed and/or reduced, as described in the Dose Modification Guidelines for each investigational product. In the event of multiple toxicities, treatment/dose modifications should be based on the worst toxicity observed (CTCAE v5.0) and/or the most conservative recommendation for any given toxicity. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom. Treatment/dose modifications may occur independently for each investigational product based on the observed toxicity.

All dose modifications must be clearly documented in the patient's medical chart. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator.

### 7.1 Dose Interruptions

Dose interruptions for study treatment-related AEs are allowed as per the dose modification recommendations. If toxicities require dose hold, all study drugs should be held and resumed concurrently. If a dose interruption for the management of treatment emergent adverse events of pemetrexed or carboplatin is >14 days, the medication should be discontinued. If a dose interruption of durvalumab lasts > 12 weeks, the patient should discontinue study therapy. Dosing may be delayed for 7 days to allow for holidays or patient preference.

### 7.2 Dose Reductions

In addition to dose interruption, the need for a dose reduction of the offending agent at the time of treatment resumption should also be considered based on the dose modification

recommendations. Dose reductions should proceed by decreasing the administered dose by one dose level. If more than two dose reductions are required for a single IP, it should be discontinued. Carboplatin and pemetrexed will be administered per SOC and may be individually discontinued and a patient may remain on durvalumab. However, if a patient must discontinue durvalumab for TRAEs, all study therapy should be discontinued and the patient should proceed to follow-up.

Once study treatment has been reduced for a given patient, all subsequent cycles should be administered at that dose level. Intra-patient dose re-escalation is not allowed.

Table 11 shows dose levels for pemetrexed and carboplatin. Listed percentages are a proportion of the original dose. Durvalumab will be administered at a fixed dose without the option for dose reduction.

**Table 11: Dose Level Reduction**

| Agent | Initial Dose | Level -1 | Level -2 |
|---|---|---|---|
| Pemetrexed | 100% | 75% | 50% |
| Carboplatin | 100% | 75% | 50% |

### 7.3 Adverse Event Management Guidelines

Adverse events attributed to either pemetrexed or carboplatin may warrant dose modifications. General treatment modifications for are provided in Table 12 for adverse events deem to be probably, possibly, or definitely related to either study medication.

**Table 12: Dose Modification Guidelines for Pemetrexed and Carboplatin**

| Adverse Event | Grade | Dose Modification |
|---|---|---|
| Thrombocytopenia or neutrophil count decrease | Grade ≥ 2 | • Hold study therapy and recheck counts in 7 days (± 2 days).<br>• If recovered grade ≤ 1 after holding treatment for 7 days (± 2 days), resume treatment at the same dose level. If not yet recovered, hold treatment and continue to recheck every 7 days (± 2 days).<br>• If counts take ≥ 14 days to recover to grade ≤ 1, reduce the dose of pemetrexed and carboplatin by one dose level upon treatment continuation. |
| Neutrophil Count Decrease | Grade ≥ 2 | • Hold study therapy and recheck counts in 7 days (± 2 days).<br>• If recovered grade ≤ 1 after holding treatment for 7 days (± 2 days), resume treatment at the same dose level. If not yet |

| | | |
|---|---|---|
| | | recovered, hold treatment and continue to recheck every 7 days (± 2 days).<br>• If counts take ≥ 14 days to recover to grade ≤ 1, reduce the dose of pemetrexed and carboplatin by one dose level upon treatment continuation. |
| Creatinine elevation | Grade 2 or creatinine clearance 44 mL/min to 30 mL/min | • Continue study therapy, decrease pemetrexed dose to 400 mg/m$^2$ if not previously done. |
| | Grade 3 or creatinine clearance < 30 mL/min | • Discontinue pemetrexed and carboplatin |
| Other non-hematologic events<br>• Except for:<br>o *Alopecia*<br>o *Fatigue*<br>o *Laboratory abnormalities responsive to oral supplementation or deemed by the investigator to be clinically insignificant* | Grade ≥ 3 | • Hold study therapy until resolution to a grade ≤ 1.<br>• Decrease the offending agent by one dose level. |

## 7.4 Immune-Mediated Adverse Events

Toxicity management guidelines (TMG) are located in the University of Utah's Electronic Research Intergrity and Compliance Administration system (ERICA) as a supplement to protocol. Drug administration modifications of durvalumab will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0. Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related.

In addition to the TMG criteria for permanent discontinuation of study regimen based on CTCAE grade/severity , permanently discontinue study regimen for the following conditions:

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

Whenever long-term steroid and other immunosuppressive medications are used to treat immune-related adverse events, consider the need for prophylactic antibiotics, antifungals, anti- *Pneumocystis jirovecii* pneumonia (PJP) treatment, gastrointestinal protection, and glucose monitoring.

It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. If not noted in these guidelines, general recommendations below should be followed.

## 7.5 Supportive Care

All supportive measures consistent with optimal patient care may be given throughout the study. Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the safety run-in observation period. These factors may be used at any time to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines. In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines.

Patients who enter the study on stable doses of erythropoietin or darbepoetin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician.

Patients should not donate blood during trial participation and for 90 days after the last dose of durvalumab.

## 7.6 Contraception

Appropriate methods of birth control is required when there is the risk of pregnancy. Women of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab).

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

Male subjects with partners of child bearing potential must practice reliable method of contraception approved by the investigator. Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab).

Highly effective methods of contraception, defined as methods that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in Table 14. Note that some contraception methods are not considered highly effective (e.g., male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

**Table 13: Highly effective methods of contraception**

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

a. This is also considered a hormonal method

## 8 SCHEDULE OF EVENTS

The Schedule of Events table provides an overview of the protocol visits and procedures. Refer to the Study Procedures section of the protocol for detailed information on each assessment required for compliance with the protocol. The Investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Events table in order to conduct evaluations or assessments required to protect the wellbeing of the patient. This Schedule of Events will be followed for the entire study.

**Table 14: Schedule of Events Arm A (Chemo-Immuno)**

| Protocol Activities | Screening | On-Treatment Period | | | | Post Treatment Period | |
|---|---|---|---|---|---|---|---|
| | | One Cycle = 28 days | | One Cycle = 21 days | | | |
| | | Cycle 1 & 2 Day 1 | Cycle 1 & 2 Day 8 | Cycle 3 & 4 Day 1 | Cycle 5 + Day 1 [1] | EOT [2] | Follow-up |
| Visit Window | (-28 days) | | (± 3 days) | (± 3 days) | (± 3 days) | | |
| Informed Consent | X | | | | | | |
| Demographics | X | | | | | | |
| Medical History [3] | X | | | | | | |
| Eligibility Criteria | X | | | | | | |
| Vital Signs [4] | X | X | X | X | X | X | |
| Physical Exam [5] | X | X | | X | X | X | |
| ECOG Score [6] | X | X | | X | X | X | |
| Hematology [7] | X | X | | X | X | X | |
| Chemistry [8] | X | X | | X | X | X | |
| Endocrine [9] | X | X | | X | X | X | |
| Pregnancy Test [10] | X | | | | | | |
| HIV and hepatitis serologies [11] | X | | | | | | |
| Blood for correlatives [12] | X | X | | | | X | |
| ECG [13] | X | As Clinically Indicated | | | | | |
| Disease Assessment [14] | X | | | X | X | X | |
| AE collection [15] | | ← X → | | | | | |
| Concomitant Medication Collection | ← X → | | | | | | |
| Durvalumab [16] | | | X | X | X | | |
| Pemetrexed | | X | | X | X | | |
| Carboplatin | | X | | X | | | |
| Long-Term Follow-Up [17] | | | | | | | X |

[1] Cycle 5+ will be considered the maintenance phase of treatment.

[2] End of treatment visit will occur at the time the decision is made to discontinue study therapy. If a patient discontinues therapy for any reason other than disease progression, disease assessments should continue on schedule.

[3] Medical history will be collected using Charlson Comorbidity Index (Appendix 2).

[4] Height is required only during screening.

[5] If necessary to facilitate scheduling, physical exam may occur one day prior to study treatment.

[6] See Appendix 1.

[7] CBC with differential and platelets. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit.

[8] Chemistry to include a complete metabolic panel (CMP), amylase, and lipase. Amylase and lipase should only be drawn at screening, cycle 2 day one, cycle 4 day one, and then every 3 cycles while on durvalumab monotherapy. Complete Metabolic Panel including: sodium, potassium, chloride, carbon dioxide, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, urea nitrogen, glucose, creatinine, calcium, protein, albumin, bilirubin, anion gap. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit.

[9] TSH is required at screening and every even cycle prior to durvalumab administration. ACTH, Free T3, and Free T4 should be drawn at screening and as clinically indicated during study therapy. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit.

[10] For women of childbearing potential, a negative pregnancy test by serum or urine must be obtained ≤ 7 days of cycle one day one.

[11] Only required for patients with a known history of HIV or hepatitis B or C to demonstrate eligibility.

[12] Correlative blood samples should be drawn at screening, cycle 2 day one, and at the end of treatment.

[13] Only preformed at screening and as clinically indicated while on study. A triplicate ECG (within 15 minutes at 5 minutes apart) should be completed at screening or as clinically indicated.

[14] Response assessment to be performed per SOC prior to cycle 3 day one (±7 days), prior to cycle 5 day 1, and then prior to day 1 every 4 cycles (±7 days) until disease progression. Response assessments will continue on follow-up every 12 weeks (±7 days) if a patient discontinues study treatment for any reason other (i.e., toxicity, patient preference, investigator decision) than disease progression.

[15] AEs will be collected from cycle one day one until 90 days after the last dose of durvalumab.

[16] The interventional products are to be administered in the order appearing on the calendar: Durvalumab, pemetrexed, and carboplatin.

[17] Patients will be contacted every three months (±7 days) during the first year and every six months (±14 days) during years 2-5 until death, end of the study or patient withdrawal of consent, whichever comes first. Survival status may be collected by public records, medical records, or by contacting the patient by phone. If patients discontinue for any reason other than disease progression, they will continue to have disease assessments every 12 weeks (± 7 days) until documented disease progression, either clinically or radiographically, or initiation of a different anticancer therapy.

## Table 15: Schedule of Events Arm B (Immuno-Chemo)

| Protocol Activities | Screening | On-Treatment Period | | | | Post Treatment Period | |
|---|---|---|---|---|---|---|---|
| | | One Cycle = 28 days | | One Cycle = 21 days | | | |
| | | Cycle 1 & 2 Day 1 | Cycle 1 & 2 Day 8 | Cycle 3 & 4 Day 1 | Cycle 5 + Day 1 [1] | EOT [2] | Follow-up |
| Visit Window | (-28 days) | | (± 3 days) | (± 3 days) | (± 3 days) | | |
| Informed Consent | X | | | | | | |
| Demographics | X | | | | | | |
| Medical History [3] | X | | | | | | |
| Eligibility Criteria | X | | | | | | |
| Vital Signs [4] | X | X | X | X | X | X | |
| Physical Exam [5] | X | X | | X | X | X | |
| ECOG Score [6] | X | X | | X | X | X | |
| Hematology [7] | X | X | | X | X | X | |
| Chemistry [8] | X | X | | X | X | X | |
| Endocrine [9] | X | X | | X | X | X | |
| Pregnancy Test [10] | X | | | | | | |
| HIV and hepatitis serologies [11] | X | | | | | | |
| Blood for correlatives [12] | X | X | | | | X | |
| ECG [13] | X | As Clinically Indicated | | | | | |
| Disease Assessment [14] | X | | | X | X | X | |
| AE collection [15] | | ← X → | | | | | |
| Concomitant Medication Collection | ← X → | | | | | | |
| Durvalumab [16] | | X | | X | X | | |
| Pemetrexed | | | X | X | X | | |
| Carboplatin | | | X | X | | | |
| Long-Term Follow-Up [17] | | | | | | | X |

[1] Cycle 5+ will be considered the maintenance phase of treatment.

[2] End of treatment visit will occur at the time the decision is made to discontinue study therapy. If a patient discontinues therapy for any reason other than disease progression, disease assessments should continue on schedule.

[3] Medical history will be collected using Charlson Comorbidiy Index (Appendix 2).

[4] Height is required only during screening.

[5] If necessary to facilitate scheduling, physical exam may occur one day prior to study treatment.

[6] See Appendix 1.

[7] CBC with differential and platelets. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit.

[8] Chemistry to include a complete metabolic panel (CMP), amylase, and lipase. Amylase and lipase should only be drawn at screening, cycle 2 day one, cycle 4 day one, and then every 3 cycles while on durvalumab monotherapy. Complete Metabolic Panel including: sodium, potassium, chloride, carbon dioxide, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, urea nitrogen, glucose, creatinine, calcium, protein, albumin, bilirubin, anion gap. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit.

[9] TSH is required at screening and every even cycle prior to durvalumab administration. ACTH, Free T3, and Free T4 should be drawn at screening and as clinically indicated during study therapy. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit.

[10] For women of childbearing potential, a negative pregnancy test by serum or urine must be obtained ≤ 7 days of cycle one day one.

[11] Only required for patients with a known history of HIV or hepatitis B or C to demonstrate eligibility.

[12] Correlative blood samples should be drawn at screening, cycle 2 day one, and at either the end of treatment visit or next SOC visit to the institution.

[13] Only preformed at screening and as clinically indicated while on study.

[14] [14] Response assessment to be performed per SOC prior to cycle 3 day one (±7 days), prior to cycle 5 day 1 (±7 days) and then- prior to treatment every 4 cycles. Response assessments will continue on follow-up every 12 weeks (±7 days) if a patient discontinues study treatment for any reason other than disease progression (i.e., toxicity, patient preference, investigator decision).

[15] AEs will be collected from cycle one day one until 90 days after the last dose of durvalumab.

[16] The interventional products are to be administered in the order appearing on the calendar: Durvalumab, pemetrexed, and carboplatin.

[17] Patients will be contacted every three months (±7 days) during the first year and every six months (±14 days) during years 2-5 until death, end of the study or patient withdrawal of consent, whichever comes first. Survival status may be collected by public records, medical records, or by contacting the patient by phone. If patients discontinue for any reason other than disease progression, they will continue to have disease assessments every 12 weeks (± 7 days) until documented disease progression, either clinically or radiographically, or initiation of a different anticancer therapy.

# 9 STUDY PROCEDURES

## 9.1 Screening

For screening procedures see the Schedule of Events and the Assessments Section. Screening activities may only begin after a subject has signed consent. All screening activities must take place within 28 days prior to cycle one day one, unless otherwise noted.

## 9.2 Treatment Period

Once a subject has completed screening, has been found to be eligible, and has been registered, treatment procedures may begin. The start of a new cycle of therapy may be delayed up to 7 days to allow for holidays or patient preference. See the Schedule of Events and the Assessments Section for treatment period procedures.

## 9.3 End of Treatment

Upon discontinuation of study treatment an End of Treatment visit will occur. The end of treatment visit should occur when the decision to discontinue treatment is made. If this visit overlaps with a regularly scheduled visit, only the procedures listed in the calendar for the EOT visit will be performed. For End of Treatment procedures see the Schedule of Events and the Assessments Section.

## 9.4 Long-Term Follow-Up

Patients that discontinue study treatment for any reason other than disease progression, must have disease assessments every 12 weeks (± 7 days) until disease progression or initiation of a different anticancer therapy.

Upon disease progression or initiation of a new anticancer therapy, patients will be followed for survival in long-term follow-up for a total of 5 years. Patients will be contacted every three months (±7 days) during the first year and every six months (±14 days) during years 2-5 until death, end of the study or patient withdrawal of consent, whichever comes first. Survival status may be collected by public records, medical records, or by contacting the patient by phone. All efforts should be made to contact the patient for these time points.

# 10 STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases the Investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

## 10.1 Physical Examinations and Vital Signs

Patients will have physical examinations to include major body systems, vital signs, assessment of ECOG performance status (see Appendix 1), weight and height (height will be measured at screening only) at the time points described in the Schedule of Events. If

necessary to facilitate scheduling, physical exam may occur one day prior to study treatment.

Vital signs, to include blood pressure, pulse rate and temperature will be also recorded at the time points described in the Schedule of Events. Vital signs should be taken prior to administration of any investigational products at the visit.

## 10.2 Adverse Events

Adverse events experienced during trial participation will be collected per the Schedule of Events and Adverse Events Section. Each study participant will be questioned about the occurrence of adverse events in a non-leading manner. Should the treating investigator feel that the adverse event is attributed to study therapy, then dose modification guidelines in the Section 7 will be followed.

## 10.3 12-Lead Electrocardiograms

All patients require a triplicate 12-lead ECG measurement at screening and a single 12-lead ECG measurement on trial according to the Schedule of Events. The parameters to be recorded are QT, QTc, PR, and QRS. A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. If the QTc is prolonged (>500 msec) then a triplicate ECG should be conducted within 15 minutes at approximately 5 minutes apart. If the mean QTc is >500 follow dose modification guidelines in Section 7.

## 10.4 Laboratory Assessments

Samples for all laboratory assessments will be drawn at the time points indicated in the Study Calendar and when clinically indicated. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit. All safety laboratory analyses will be performed by the local laboratory for each study center. All safety laboratory assessments must be reviewed by the treating investigator prior to study drug administration. When applicable, results from the pregnancy test must also be available for review prior to dosing.

**Table 16: Laboratory Assessments**

| **Laboratory Assessments** | |
|---|---|
| **CBC with Platelet Count and Differential (Hematology)** | • White Blood Cell Count<br>• Hemoglobin<br>• Platelets<br>• Absolute Neutrophil Count<br>• Absolute Lymphocytes |
| **Chemistry** | • Complete Metabolic Panel<br>o Sodium<br>o Potassium<br>o Chloride<br>o Carbon Dioxide<br>o Alkaline Phosphatase<br>o Aspartate Aminotransferase<br>o Alanine Aminotransferase |

| | |
|---|---|
| | ○ Urea Nitrogen<br>○ Glucose<br>○ Creatinine<br>○ Calcium<br>○ Protein<br>○ Albumin<br>○ Bilirubin<br>○ Anion Gap<br>• Amylase†<br>• Lipase† |
| **Endocrine** | • TSH<br>• ACTH*<br>• Free T3*<br>• Free T4* |
| **Pregnancy** | Beta-hCG Qualitative Urine or Serum |
| *ACTH, Free T3, and Free T4 should be drawn at screening and as clinically indicated during study therapy.<br>† Amylase and Lipase should only be drawn at screening, cycle 2 day 1, cycle 4 day 1, and every three months while on durvalumab therapy. | |

## 10.5 Tumor Response Assessment

The decision for body areas to be scanned will depend on the disease under study and the extent of disease. Tumor assessments must include all known or suspected disease sites. The minimum recommended body areas to be scanned are chest, abdomen, and pelvis. Antitumor activity will be assessed through radiological tumor assessments conducted at baseline (within 28 days prior to cycle one day one), prior to cycle 3 day one (±7 days), prior to cycle 5 day 1 (±7 days) and then prior to treatment every 4 cycles (±7 days) until disease progression or initiation of subsequent anti-cancer therapy. In addition, radiological tumor assessments will be conducted whenever disease progression is suspected (e.g., symptomatic deterioration) or when clinically indicated.

Brain CT or MRI scans are required at baseline for all patients with stable brain lesions and for those for whom Central Nervous System (CNS) involvement is suspected. If stable brain metastases are present at baseline, brain imaging should be repeated at each tumor assessment. Otherwise, brain imaging will be conducted post-baseline only when clinically indicated.

The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

## 10.6 Treatment after Radiographic Progression

If radiographic imaging shows disease progression per RECIST 1.1 Criteria, subjects may continue on study therapy if it is felt by the treating investigator to be of clinical benefit to the subject.

However, the following criteria must be met:

- No decline in ECOG performance status;
- Absence of clinical signs and symptoms (including worsening of laboratory values) from disease progression;
- Absence of rapid progression of disease by radiographic imaging;
- Absence of progressive tumor at critical anatomical sites (i.e. cord compression) requiring urgent alternative medical intervention.

Before continuation of treatment after initial PD, the subject must be re-consented via informed consent addendum and informed that, by continuing to receive investigational products, the subject may be foregoing approved or investigational therapies with possible clinical benefit(s). Subjects should continue to follow all assessments as outlined in the Schedule of Events.

Once radiographic progression has been documented, disease assessments should continue per the Schedule of Events to ensure the above criteria is consistently met. However, RECIST 1.1 assessments and measurements will no longer be required

### 10.7 Patient Reported Outcomes

All patient reported outcomes will be collected through concurrent enrollment in the study, "Rethinking Measurement of Performance Status in Cancer Patients," IRB 11252 unless the patient declines participation.

## 11 CRITERIA FOR EVALUATION AND ENDPOINT

### 11.1 Efficacy

Disease assessments will be measured by CT scans and evaluated using RECIST v1.1 criteria. The following definitions and criteria should be used for the baseline evaluations of existing disease, and for the ongoing evaluation of tumor responses.

**Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter (LD) ≥ 10 mm using CT, MRI, or caliper measurements or ≥20 mm with x-ray. A lymph node must be ≥15 mm in short axis when assessed by CT scan

**Non-measurable lesions** - all other lesions including small lesions (LD < 10 mm with CT, MRI, or caliper measurements or <20 mm with x-ray).

**Documentation of "Target" and "Non-Target" Lesions**

- All measurable lesions up to a maximum of two lesions per organ and five 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessments).

- A sum of the LD for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

**Response Criteria:**

| | **Evaluation of target lesions** |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions<br>(Must persist for a minimum of four weeks) |
| Partial Response (PR) | At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD<br>(Must persist for a minimum of four weeks) |
| Progressive Disease (PD) | At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions |
| Stable Disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started |

| | **Evaluation of non-target lesions** |
|---|---|
| Complete Response (CR) | Disappearance of all non-target lesions |
| Stable Disease (SD) | Persistence of one or more non-target lesion(s) |
| Progressive Disease (PD) | Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions |

**Evaluation of Best Overall Response**

The best overall response is the best response observed until progression/recurrence and is determined as indicated in the table below:

| **Target Lesions** | **Non-Target Lesions** | **Evaluation of New Lesions** | **Best Overall Response** |
|---|---|---|---|

| | | | |
|---|---|---|---|
| CR | CR | No | CR |
| CR | SD | No | PR |
| PR | Non-PD | No | PR |
| SD | Non-PD | No | SD |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

### 11.2 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

### 11.3 Interim analysis and stopping

An interim analysis after 50 patients have been randomized for harm and safety signals will be performed and results presented to the DSMC. Endpoints which will be examined for harm will include DCR, RR, PFS, and OS, and endpoints which will be examined for safety include grade ≥3 adverse events and serious adverse events. Harm and safety endpoints will be compared between arms in terms of odds or hazard ratio estimates, as appropriate, accompanied by 95% confidence intervals and p-values. Harm and safety endpoints will also be summarized separately within arms as rates or median time-to-event, as appropriate, along with 95% confidence intervals. These analyses will be provided to the PI, sponsor, and DSMC for their judgement on the trial's continuation. Notably, the trial will not be subject to binding stopping rules.

## 12 STATISTICAL CONSIDERATIONS

### 12.1 Statistical analyses

The primary and secondary goals of this study are to characterize the efficacy and toxicity of each arm of a randomized phase II trial (primary and secondary objectives).

The main assessments of the primary endpoints DCR, as well as the secondary endpoints RR, PFS, OS, specific adverse events, grade ≥3 adverse events, and serious adverse events and exploratory endpoints PROs, performance status, and genomic, proteomic, and immune markers, will be separately evaluated within each arm. In particular, rates or median times-to-event, as appropriate, along with 95% confidence intervals will be constructed within each arm. Additionally, comparisons of the primary and secondary endpoints will be examined in terms of estimated odds or hazard ratios, as appropriate, along with 95% confidence intervals. Both univariate and multivariable comparisons adjusted for

performance status will be constructed. Multivariable estimates will be constructed in the context of logistic or Cox proportional hazards models.

Assessments of time trends for secondary and exploratory endpoints, including PROs, nutritional and immune markers, and physical activity, will be conducted in the context of linear mixed effects models with fixed effects for time trend, as well as subject-level intercept and slope random effects, separately within each treatment arm.

## 12.2 Sample size determination

42 subjects per arm will ensure that rates (of DCR, RR, AEs, etc.) can be estimated via 95% confidence intervals with margins of error 0.15 or less. Rates of time-to-event outcomes (PFS) at 1 year can be estimated via 95% confidence intervals with margins of error 0.2 or less if at least 25 events are observed at 1 year.

## 12.3 Population for analyses

### 12.3.1 Evaluable for efficacy

Analysis of ORR, OS, and PFS will include all patients who have completed one cycle of study therapy.

### 12.3.2 Evaluable for toxicity

The toxicity analysis will include all patients who receive at least one dose of durvalumab, pemetrexed, and carboplatin.

## 12.4 Endpoints

### 12.4.1 Primary endpoint

The primary endpoint is the rate of clinical benefit defined as patients achieving stable disease, partial response, or complete response as defined by RECIST 1.1.

### 12.4.2 Secondary endpoint

- Safety and feasibility will be characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0), timing, seriousness, and relationship to study treatment. AEs will be tabulated. No statistical testing will be performed for AEs.
- Objective response rate (ORR) will be assessed by the number of patients obtaining a complete response plus the number of patients obtaining a partial response divided by the total number of response evaluable subjects. The ORR will be reported along with a 95% exact binomial confidence interval. No hypothesis testing will be performed for ORR.
- Progression free survival (PFS) will be assessed as the time between trial initiation and documented progression by either clinical progression, radiographic imaging. Kaplan-Meier methods will be used to analyze PFS. No hypothesis testing will be performed for PFS.

- Overall Survival (OS) will be assessed as the time between trial initiation and death of any cause. Patients will be censored at five years. Kaplan-Meier methods will be used to analyze OS. No hypothesis testing will be performed for OS.
- Questionnaires administered through the protocol, "Rethinking Measurement of Performance Status in Cancer Patients," IRB 112529
- Biomarker evaluation will be conducted through the protocol, "An Observational Study Assessing the Clinical Effectiveness of the VeriStrat® Test and Validating Immunotherapy Tests in Subjects with Non-Small Cell Lung Cancer," IRB 100314.

# 13 REGISTRATION GUIDELINES

**Study related screening procedures can only begin once the patient has signed a consent form.**

**Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.**

**Patients must be registered before receiving any study treatment and must being treatment within five working days after registration.**

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to CTORegistrations@hci.utah.edu.

# 14 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRFs should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

**Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.**

# 15 SPECIAL INSTRUCTIONS

## 15.1 Blood correlative studies

Up to 30 mLs of blood will be collected at the time-points indicated on the Schedule of Events. These samples will be used to identify predictive biomarkers with immunotherapy.

Testing may include, but is not limited to:

- Lymphocyte detection, enumeration, and characterization
- Cytokine/chemokine/interferon assays
- Flow Cytometry

Specimen collection and processing instructions can be found in the lab manual.

# 16 ETHICAL AND REGULATORY CONSIDERATIONS

## 16.1 Human Subject Protections

The study will be conducted in accordance with the appropriate FDA, IRB, ICH GCP, and other federal and local regulatory requirements, as applicable. Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB-approved version. All patients must be at least 18 years of age to participate.

## 16.2 Institutional Review

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other applicable patient-facing documents. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information.

The investigator or designee should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures. Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) to ensure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. The roles and responsibilities of the DSMC are set forth in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, significant revisions or amendments to the protocol, and approving cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This is a study classified as high risk per the NCI-approved DSM plan.

Each high-risk study will be assigned a physician member of the DSMC as medical monitor, or in rare cases, an external medical monitor. The medical monitor will be notified of all serious adverse events (SAEs). Specific notifications will also be issued when a dose-limiting toxicity is encountered and when the MTD dose is defined. Approval of the medical monitor is required for all dose escalations. All serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC monthly.

Each high-risk study will also be assigned a dedicated research compliance officer who will monitor the trial. Moderate-risk studies will be monitored by RCO personnel after the first patient is enrolled and then quarterly thereafter during active enrollment. The RCO monitor will review the study status and summarize enrollment, toxicities, SAEs, dose escalation, statistical endpoints (e.g., stopping rules), deviations, etc. for the full DSMC membership at the regularly scheduled meetings. Amendments that increase risk, change dosing, or impact study objectives will be reviewed by the DSMC and approved by the PRMC and IRB. High-risk trials will be formally reviewed by the DSMC after the first patient is enrolled and then quarterly thereafter.

An initial audit of high-risk studies will be conducted by the RCO approximately one year after enrollment begins and annually thereafter. Audits of high-risk studies may be conducted more frequently as requested by the DSMC, IRB, PRMC, RCO management, or the PI.

## 16.3 Adverse Events and Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for AE and SAE reporting.

### 16.3.1 Adverse Events (AEs)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Collection of adverse events will begin with the first dose of study therapy and end 90 days after the last dose of study drug (or until a new cancer treatment is initiated).

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded and followed as appropriate.

Adverse event should be evaluated to determine:

1. The severity grade based on CTCAE v5.0 (grade 1-5)
2. Its relationship to the study drug(s) (definite, probable, possible, unlikely, not related)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the study therapy is described in the Background and Rational (section 2) and in the investigator brochure or the current product insert will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

### 16.3.2 Abnormal Test Findings

Abnormal test finding, such as incidental image findings, should only be listed as an adverse event if it meets the following criteria:

- Is associated with accompanying symptoms; and/or
- Requires additional testing or intervention; and/or
- Leads to changes in study therapy dosing; and/or
- Leads to the addition or change of a concomitant medication or therapy; and/or
- Is considered an adverse event by the treating investigator.

An abnormal test considered to be an error should not be listed as an adverse event. Repeating a test due to an abnormal result in the absence of any of the criteria above does not require listing as an adverse event.

### 16.3.3 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Causes congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - Treatment on an emergency outpatient basis (< 24 hours) for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition

- The 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.

Collection of serious adverse events will begin with the first dose of study therapy and end 90 days after the last dose of durvalumab or until a new cancer treatment is initiated, whichever happens the soonest.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

### 16.3.4 Adverse Events of Special Interest (AESI)

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

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

AESIs observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis / transaminase increases
- Endocrinopathies (i.e., events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g., Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eyeskin, haematological and rheumatological events, vasculitis, non-infectious meningitis, and non-infectious encephalitis.

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

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

### 16.3.5 Deaths

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

- Death clearly resulting from disease progression should be documented in the patient's research chart and eCRF and reported as an SAE within 24 hours of notification.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE within 24 hours of notification.
    - 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.
- 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 included in the patient's research chart.

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 eCRF. 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.

### 16.3.6 Hepatic function abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor. The Sponsor must report these events to AstraZeneca Patient Safety using the designated Safety e-mailbox within 7 calendar days or sooner when required, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of

Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

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

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca/MedImmune. Please refer to the Toxicity Management Guidelines, for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

## 16.4 SAE Reporting Requirements

All serious adverse events should be reported as soon as possible but no later than one business day after the Investigator becomes aware. All SAEs must be reported via the HCI CTMS (OnCore) and submitted to HCI-RCO@utah.edu. The HCI Clinical Site Monitor will in turn, submit the report to the Medical Monitor. The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the monthly DSMC meeting.

At a minimum, initial SAE reports must include a description of the event, assessment of event causality, event grade, and the expectedness of the event. Although the Investigator may not know all the information at the time of the event, the available information should be reported. An SAE follow-up may be submitted at a later date once more information is known. It is required that follow-up reports be submitted until the SAE is resolved.

The HCI DSMC will notify all participating sites of all unexpected and related SAEs via the Research Compliance Office (RCO). The RCO will also notify all investigators at remote clinical sites participating in a multisite trial of any other safety updates, including external safety reports, manufacturer's reports, and updates to the investigator's brochure.

All SAEs have to be reported, whether or not considered causally related to the investigational product. The Sponsor is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

*Follow-Up Information*

It is recommended that follow-up reports be submitted as new information becomes available, however, a follow-up report should be submitted within 3 days of knowledge of event resolution. Follow-up information will be added to the SAE in OnCore and submitted to the DSMC via RCO.

AstraZeneca Notifications:

SAEs, whether related or not related to study drug, and pregnancies must be reported to AstraZeneca within 24 hours \ 1 Business Day of becoming aware of the event.

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to AstraZeneca using the same procedure used for transmitting the initial SAE report.

**SAE Email Address:** AEMailboxClinicalTrialTCS@astrazeneca.com

## 16.5 Overdose

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

Any overdose of a study patient with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor. The sponsor must report these to AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox within 7 calendar days or sooner when required. 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.

**Medication Error**

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

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient. The Sponsor must report to AstraZeneca Patient Safety using the designated Safety e-mailbox

## 16.6 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or with 3 months of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, and the sponsor as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

**Maternal exposure**

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic

pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

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

The sponsor will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days. The Sponsor must report to AstraZeneca Patient Safety using the designated Safety e-mailbox (see Section 10.5 for contact information) within 7 calendar days or sooner when required (see Section 10.5), for pregnancies with SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

**Paternal exposure**

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

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

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

## 16.7 Protocol Amendments

Any amendments or administrative changes to an IRB approved protocol will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial.

## 16.8 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The sponsor requires the **prompt reporting** to HCI RCO of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

## 16.9 FDA Annual Reporting

An annual progress report will not be submitted to the FDA because this trial does not hold an IND.

## 16.10 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Research Compliance Office.

## 16.11 Data Management

To accommodate evaluations, inspections, and/or audits from regulatory authorities, the Investigator must maintain all study records including subject identity, source documentation, original signed consent form, safety reporting forms, monitoring logs, IP accountability records, relevant correspondence (e.g., letters, emails, meeting minutes, etc.), and any other documents pertaining to the conduct of the study. The Investigator must also agree to the maintain source documents for a minimum of two years after regulatory approval of the investigational product per 21 CFR 312.57. For the duration of record maintenance, records must be stored in a secure location and protected from the elements. If for any reason the Investigator at another participating institution is no longer able to retain study records, the HCI Investigator Sponsor should be notified before any destruction so that the records can be transferred to an acceptable designee. Once retention requirements have been met, the participating site Investigator must get HCI Investigator Sponsor approval before the destruction of any records.

## 16.12 Record Keeping

Per 21 CFR 312.57, the Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

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## Appendix 1: ECOG Performance Status

| Score | Definition |
|---|---|
| 0 | Fully active, able to carry on all pre-disease activities without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work or office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hour |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |
| 5 | Dead |

Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5: 649–655.

# Appendix 2: Charlson Comorbidity Index

Date of Assessment: _____ Study Patient ID: _____

Study Patient Initials:_____

**Instructions**: Select one option per line.

| | None | Uncomplicated | End-organ Damage |
|---|---|---|---|
| Diabetes mellitus | | | |

| | None | Mild | Moderate/Severe |
|---|---|---|---|
| Liver disease | | | |

| | None | Leukemia, Lymphoma, or Localized Solid Tumor | Metastatic Solid Tumor |
|---|---|---|---|
| Malignancy – exclude basal cell carcinoma | | | |

| | Yes | No |
|---|---|---|
| HIV or AIDS | | |
| Moderate to severe chronic kidney disease | | |
| Congestive heart failure | | |
| Myocardial infarction | | |
| Chronic obstructive pulmonary disease (COPD) | | |
| Peripheral vascular disease | | |
| Cerebrovascular accident (CVA) or transient ischemic attack (TIA) | | |
| Dementia | | |
| Hemiplegia | | |
| Connective tissue disease | | |
| Peptic ulcer disease | | |

Investigator Signature _____