Cover Page for Clinical Trials Document posting

Official Title: S1400A, "A Phase II Study of MEDI4736 for Previously Treated Patients with Stage IV Squamous Cell Lung Cancer and no Matching Biomarkers (Lung-Map Sub-Study)"

NCT Number: 02766335

Version Date: 7/10/18

Description:

S1400 [NCT 02154490] is the parent study to **S1400A** [NCT 02766335].

The **S1400** Lung-MAP study is considered one study under one IND consisting of:

- S1400 Version Control Protocol
- S1400 Main Screening Protocol Component
- Multiple Sub-Studies (or sub-protocols) Components

Each component is contained in its own separate document.

S1400A is one of these components. Each "component" consists of the protocol document and its associated informed consent document(s). Since each screening and sub-study component operates independently from the other components contained in Lung-MAP, each has its own version date and NCT number. This is due to the complexity of the study and how it must be entered into different computer programs.

S1400A: (Non-Match sub-study): Anti-PD-L1 – MEDI4736

A BIOMARKER-DRIVEN MASTER PROTOCOL FOR PREVIOUSLY TREATED SQUAMOUS CELL LUNG CANCER

A PHASE II STUDY OF MEDI4736 FOR PREVIOUSLY TREATED PATIENTS WITH STAGE IV SQUAMOUS CELL LUNG CANCER AND NO MATCHING BIOMARKERS (LUNG-MAP SUB-STUDY)

NCT #02154490

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STUDY AGENTS:

Available from Pharmaceutical Collaborator:
MEDI4736 (NSC 778709) (IND-119672)

Available from Commercial Sources:
Docetaxel* (Taxotere®) (RP56976) (NSC 628503)

* Docetaxel is not a current study agent effective 5/26/15.

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available to the SWOG Workbench. Access this by using your active CTEP-IAM USER ID and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

CTSU sties should follow procedures outlined in the protocol for site registration. Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement:

For patient eligibility questions contact the SWOG Data Operations Center by phone or email:

206-652-2267
S1400question@crab.org

For treatment or toxicity related questions contact the Study PI of the Coordinating Group.

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help
Desk by phone or e-mail:

CTSU General Information Line:
888-823-5923
S1400contact@westat.com

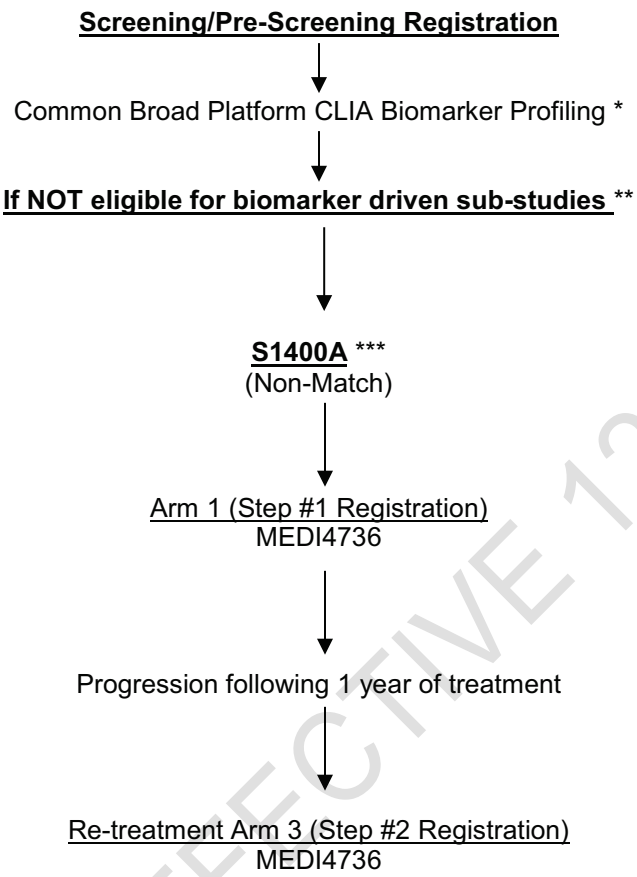
All calls and correspondence will be triaged to the appropriate CTSU representative.

For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website:

https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy

The CTSU Web site is located at https://www.ctsu.org

SCHEMA



* Archival formalin-fixed paraffin-embedded (FFPE) tumor, fresh core needle biopsy if needed

** Notification of sub-study assignment will be provided by the SWOG Statistical Center (see Section 11.0 in **S1400** for details).

*** Arm 2 Docetaxel has been removed from the schema as it is closed to accrual per Revision #2, Version Date 4/22/15.

1.0 OBJECTIVES

The design and objectives of **S1400A** have been modified to be different from the design and objectives for **S1400** Non-match studies as described in Sections 1.0 and Section 11.0 of **S1400**. Modifications to the original design of this study were deemed necessary based on emerging data regarding the availability of anti-PD1 therapy for second-line treatment of patients with squamous cell lung cancer which may render evaluation of OS as a primary endpoint non-feasible. The primary modifications include a change from the Phase II/III design employing Plan A for the Phase II component as specified in Section 11.0 of **S1400** to a single arm Phase II design. Changes to the design were made with no knowledge of the **S1400A** data. Details of the modified statistical design are included in **S1400A** Section 11.0.

1.1 Co-Primary Objectives

The co-primary objectives of **S1400A** are:

a. To assess the response rate (confirmed and unconfirmed, complete and partial) among patients treated with MEDI4736.

b. To assess the response rate (confirmed and unconfirmed, complete and partial) among PD-L1 positive patients treated with MEDI4736.

1.2 Secondary and Exploratory Objectives

a. To assess investigator-assessed progression-free survival (IA-PFS) among patients treated with MEDI4736.

b. To assess IA-PFS among PD-L1 positive patients treated with MEDI4736.

c. To assess overall survival (OS) in patients treated with MEDI4736.

d. To assess overall survival (OS) in PD-L1 positive patients treated with MEDI4736.

e. To evaluate the frequency and severity of toxicities associated with MEDI4736.

f. To assess immune-related IA-PFS using a modified response criteria adapted for immunotherapy (irRC-IA-PFS) in all patients and in the subset of patients determined to be PD-L1 positive treated with MEDI4736.

g. To compare IA-PFS, irRC-IA-PFS, OS, toxicity and response rates between patients randomized to MEDI4736 versus docetaxel.

1.3 Translational Medicine Objectives

a. To identify additional predictive or prognostic tumor/blood biomarkers beyond the chosen biomarker.

b. To identify potential resistance biomarkers at disease progression.

c. To establish a tissue/ blood repository from patients with refractory squamous cell cancer.

1.4 MEDI4736 Re-Treatment Objectives

Patients who complete a full year (12 months) of MEDI4736 may be re-treated following disease progression. The objectives for this portion of the trial are:

a) To evaluate response rates (confirmed and unconfirmed, complete and partial responses) among patients re-treated with MEDI4736.

b) To estimate median PFS from the date of re-treatment.

2.0 BACKGROUND

General Immune and PDL1 Introduction

The immune system is capable of identifying tumor-associated antigens and eliminating the cancerous cells expressing them. This process of tumor immune surveillance plays an important role in preventing and combating the growth of tumors. The process of immune surveillance is believed to result in a co-evolution of the tumor and immune response termed immunoediting, which is thought to follow three stages. *(1)* During the initial phase of elimination, the innate and adaptive immune systems detect and eliminate tumor cells. Elimination can result in complete clearance of tumor cells as is seen in rare cases of spontaneous regression of melanoma. *(2)* However, if elimination is incomplete, the immune system and tumor may enter a state of equilibrium. During this second phase of immunoediting, the immune response selectively eliminates susceptible tumor cells and may prevent tumor progression. As the equilibrium phase persists, the tumor may evolve mechanisms to avoid or attenuate the immune response. The emergence of tumor cells with reduced immunogenicity (IM) or enhanced immunosuppressive mechanisms leads to the escape phase of immunoediting. During escape, many factors may contribute to the failure of the immune system to control tumor growth including expression of T-cell inhibitory molecules, downregulation of tumor antigens, and presence of immunosuppressive regulatory T cells or immunosuppressive cytokines within the tumor microenvironment.

Enhancing the immune response may provide a means to regain control of tumors that have progressed to the escape phase during immunoediting. A number of mechanisms to stimulate the antitumor immune response have been successfully employed. Interleukin-2 (IL-2) and interferon (IFN) alpha have shown objective response rates (ORRs) of 12% to 23% in RCC, with durable complete responses (CRs) and partial responses (PRs) in some patients. *(3, 4)* High-dose IL-2 has also led to survival benefit, but only in patients with durable CRs (6%) in melanoma. *(5)* Recently sipuleucel-T, an immunotherapy consisting of activated autologous antigen-presenting cells, was granted United States Food and Drug Administration (US FDA) approval for treatment of metastatic hormone refractory prostate cancer. *(6)* Blockade of negative regulatory signals to T cells such as CTLA-4 and programmed death ligand 1 (PD-L1) has also shown promising clinical activity. Ipilimumab, which binds to CTLA-4 and prevents the interaction of CTLA-4 with cluster of differentiation 80 (CD80) and CD86, results in enhanced T-cell activation and proliferation. *(7)* Ipilimumab was granted US FDA approval in 2011 for the treatment of metastatic melanoma and is currently under investigation for several other malignancies.

PD-L1 (B7-H1, CD274) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. In normal tissue, PD-L1 is expressed on T cells, B cells, dendritic cells, macrophages, mesenchymal stem cells, bone marrow-derived mast cells, as well as various nonhematopoietic cells. *(8)* Its normal function is to regulate the balance between T-cell activation and tolerance through interaction with its two receptors, programmed death 1 (PD-1, CD279) and CD80 (B7-1). PD-L1 is also expressed by tumors and acts at multiple sites to help tumors evade detection and elimination by the host immune system. In the lymph nodes, PD-L1 on antigen presenting cells (APC) binding to PD-1 (CD279) or CD80 (B7-1) on activated T cells delivers an inhibitory signal to the T cell. *(9, 10)* Likewise, binding of CD80 on APCs to PD-L1 on T cells leads to inhibitory signaling in the T cell. These and bidirectional interactions between CD80 and PD-L1,

expressed on both APCs and T cells, lead to further inhibition of T-cell activation. These interactions result in reduced T-cell activation and fewer activated T cells in the circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target tumor cells, and protecting the tumor from immune elimination. *(11)*

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancer. In a number of these cancers, including lung, renal, pancreatic, and ovarian, the expression of PD-L1 is associated with reduced survival and unfavorable prognosis. *(12, 13, 14, 15, 16, 17, 18, 19)* In ovarian cancer, for example, the 5-year survival rate in patients with low levels of PD-L1 was 80.2%, compared to 52.6% in patients with high levels of PD-L1. *(20)* In lung cancer, only 20% of patients with tumors expressing PD-L1 survived for more than three years, compared to 49% of patients with tumors lacking PD-L1. *(21)* Based on these data, and on assessments of expression of PD-L1 on the surface of human tumors using proprietary immunohistochemistry methods for assessment, MEDI4736 has the potential to affect multiple types of solid tumors, including those with a high incidence rate and some less common types with limited treatment options and poor outcomes.

The levels of tumor-infiltrating lymphocytes, and more specifically cytotoxic T cells, have been correlated to improved prognosis in a number of cancers including colorectal, melanoma, and lung, suggesting that an antitumor immune response is beneficial to patients. (22*)* It has been shown in vitro that an antibody that blocks the interaction between PD-L1 and its receptors can relieve PD-L1-dependent immunosuppressive effects and enhance the cytotoxic activity of antitumor T cells. (23*)* Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of several preclinical studies using mouse tumor models support this hypothesis. In these studies, antibodies directed against PD-L1, or its receptor PD-1, showed antitumor activity. *(24, 25, 26, 27)*

Blocking PD-L1 is a similar approach to that taken by ipilimumab, but has some potential advantages. Firstly, the expression of CTLA-4 and its ligands is restricted to the hematopoietic system; thus the site of action for molecules targeting CTLA-4 is solely the peripheral lymphoid organs. In contrast, PD-L1 is expressed not only on cells of the hematopoietic system but also on a range of tumor types. Targeting of PD-L1 could therefore have additional effects within the tumor microenvironment. Secondly CTLA-4 plays an early and critical role in controlling T-cell activation. This is reflected in the phenotype of CTLA-4 knockout mice, which die at an age of between three and four weeks due to lymphoproliferative disease and tissue destruction. In contrast PD-L1, via binding to PD-1, acts later in the process of T-cell activation and is considered more dispensable for the control of initial T-cell activation. *(28)* This is reflected in the phenotype of PD-L1 knockout mice, which are viable and have normal T-cell numbers and activation levels, but which have increased T-cell activation in response to antigen and increased susceptibility in certain autoimmunity models. *(29, 30)* Similarly, PD-1 knockout mice show strain-specific phenotypes milder than those seen in CTLA-4 knockouts. *(31, 32)* Based on these data, inhibition of PD-L1 would be expected to have reduced toxicity relative to inhibition of CTLA-4. In support of this, recent Phase I clinical studies testing the tolerability of agents targeting PD-1 have shown a more favorable toxicity profile than ipilimumab. *(33, 34, 35)*

Product Derivation

MEDI4736 is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (MAb) directed against human PD-L1. MEDI4736 has an overall molecular weight of approximately 149 kDa, including N-linked oligosaccharides. The antibody is composed of 2 identical heavy chains of approximately 49,670 Da each, and 2 identical light chains of approximately 23,390 Da each. The fragment crystallizable (Fc) domain of MEDI4736 contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fcγ receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC). *(36)* Subsequent to this triple mutation, the anticipated lack of MEDI4736-mediated ADCC and

complement-dependent cytotoxicity were confirmed using cell-based functional assays. MEDI4736 is selective for recombinant PD-L1 and blocks the binding of recombinant PD-L1 to the PD-1 and CD80 receptors.

Summary of Clinical Experience

MEDI4736 has been given to humans as part of ongoing studies where it is given either as a single drug or in combination with other drugs. As of February 18, 2014, 221 subjects have been enrolled and treated in five ongoing clinical studies. The majority of the safety data currently available for MEDI4736 are based on the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors.

As of 18 February 2014, a total of 198 patients have entered into this study of which 177 had received MEDI4736 at 10 mg/kg given every 2 weeks (Q2W). This study has a dose escalation and a dose-expansion phase. The safety data were combined from all 177 subjects treated with the 10 mg/kg Q2W regimen of MEDI4736 (ie, data from subjects receiving 10 mg/kg Q2W from both dose escalation and dose expansion were combined). In addition, 21 subjects have been enrolled in the following dose-escalation cohorts: 4 subjects in each of the 0.1, 0.3, and 1 mg/kg Q2W cohorts; 3 subjects in the 3 mg/kg Q2W cohort, and 6 subjects in the 15 mg/kg Q3W cohort.

Focusing on the largest cohort (177 subjects treated with 10 mg/kg MEDI4736 Q2W), the most frequently reported (≥ 10% of subjects) treatment-emergent adverse events (TEAEs) regardless of grade or causality were fatigue, dyspnea, nausea, constipation, and decreased appetite. The majority of TEAEs were Grades 1 to 2 in severity and manageable by the general treatment guidelines as described in the current MEDI4736 study protocols.

Grade 3 or higher TEAEs were noted in 44/177 subjects (24.9%). These events occurring in more than 1 subject included dyspnea (9 subjects); dehydration (4 subjects); abdominal pain, fatigue, sepsis, increased aspartate aminotransferase, and increased gamma-glutamyltransferase (3 subjects); and hyperbilirubinemia, back pain, pulmonary embolism, respiratory failure, and hypotension (2 subjects each). In addition, the following 6 subjects had Grade 3 or higher TEAEs that are not yet coded (verbatim terms are shown): “progression of disease” (2 subjects), “abdominal pain due to progression of disease” (1 subject), “pain” (1 subject), “death due to progression of disease” (1 subject), and “death” (1 subject). The Grade 3 or higher TEAEs that were considered by the investigator to be related to MEDI4736 were increased aspartate aminotransferase (2 subjects), and hypothyroidism, vomiting, fatigue, infusion-related reaction, troponin, dehydration, and arthralgia (1 subject each).

Treatment-related, TEAEs were reported for 52/177 subjects (29.4%). The most frequently reported (2 or more subjects) treatment-related TEAEs (all grades) were fatigue (11.3%); nausea (5.6%); dyspnea (4.0%); diarrhea, vomiting, and pyrexia (3.4% each); myalgia (2.8%); hypothyroidism, decreased appetite, dizziness, cough, pruritus, and rash (2.3% each), abdominal pain, increased aspartate aminotransferase, and arthralgia (1.7% each); and asthenia, influenza-like illness, edema peripheral, increased alanine aminotransferase, headache, and dry skin (1.1% each). No dose-limiting toxicities (DLTs) have been reported.

The TEAEs reported for 2 or more subjects in any of the other Q2W cohorts were diarrhea (2/4 subjects in the 0.3 mg/kg cohort), nausea (2/4 subjects in the 1 mg/kg cohort), fatigue (2/4 subjects in the 0.3 mg/kg cohort), bronchitis (2/4 subjects in the 0.1 mg/kg cohort), arthralgia (2/4 subjects in the 0.3 mg/kg cohort), dizziness (2/4 subjects in the 1 m/kg cohort), dyspnea (2/4 subjects in the 0.3 mg/kg cohort), upper-airway cough syndrome (2/4 subjects in the 1 mg/kg cohort), rash (2/4 subjects in each of the 0.3 and 1 mg/kg cohorts), and hypertension (2/3 subjects in the 3 mg/kg cohort). The TEAEs reported for 2 or more subjects in the 15 mg/kg Q3W cohort were fatigue and cough (3/6 subjects each), and nausea and pyrexia (2/6 subjects each). No Grade 3 or higher events were reported for more than 1 subject in any of these cohorts. One Grade 3 or higher event

of fatigue in a subject in the 15 mg/kg Q3W cohort was considered by the investigator to be related to MEDI4736.

Treatment-emergent SAEs have been reported for 39 subjects treated with MEDI4736 10 mg/kg Q2W. The SAEs reported for 3 or more subjects were dyspnoea (2.8%), dehydration (2.3%), abdominal pain (1.7%) and sepsis (1.7%) Three (3) subjects at the 10mg/kg every 2 weeks dose schedule had treatment related SAEs that included the events of Grade 2 pneumonitis and pleural effusion (1 subject), another subject with Grade 3 arthralgia and one subject with Grade 2 right hand weakness and rule out cord compression.

In addition, treatment-emergent SAEs have been reported for 5 subjects in the Q2W dose escalation cohorts, and 2 subjects in the 15 mg/kg Q3W cohort as of 18 Feb 2014 as follows: NSCLC (1 subject in the 0.1 mg/kg Q2W cohort); abdominal pain, diarrhea, and pneumonia (1 subject each in the 0.3 mg/kg Q2W cohort); retroperitoneal hemorrhage (1 subject in the 3.0 mg/kg Q2W cohort); and increased blood creatinine, dehydration, and hyponatremia (1 subject each in the 1 mg/kg Q2W cohort), and pyrexia and malignant melanoma (1 subject each in the 15 mg/kg Q3W cohort). None of the SAEs in these cohorts were assessed by the investigator as related to MEDI4736. The Grade 3 or higher SAEs in these cohorts were retroperitoneal hemorrhage, hyponatremia, NSCLC, and malignant melanoma.

TEAEs resulting in discontinuation of MEDI4736 have been reported for 13 subjects treated with MEDI4736 10 mg/kg Q2W (subjects could have more than one TEAE resulting in discontinuation). The 18 TEAEs resulting in discontinuation of these 13 subjects were: dyspnea (4 subjects), respiratory failure (2 subjects), “progression of disease” (verbatim term, 2 subjects), and “abdominal pain due to progression of disease” (verbatim term), “pain” (verbatim term), atrial flutter, small intestinal obstruction, sepsis, urinary tract infection, dehydration, musculoskeletal chest pain, metastatic malignant melanoma, and pulmonary embolism (1 subject each). In addition, 1 subject in the 0.3 mg/kg Q2W cohort discontinued MEDI4736 treatment due to a TEAE of pneumonia. All were Grade 3 or higher with the exception of the event of pneumonia. None of the TEAEs resulting in discontinuation of MEDI4736 were considered related to MEDI4736 by the investigator.

Of the 198 subjects enrolled, 28 subjects have died (25 subjects treated with MEDI4736 10 mg/kg Q2W, and 1 subject in each of the 0.1, 0.3, and 3.0 mg/kg Q2W cohorts). No subjects died on treatment. None of the deaths were considered related to MEDI4736 by the investigator and all deaths were “due to disease” with the exception of 1 subject (cause of death was reported as “disease under treatment”).

Of the 177 subjects treated with MEDI4736 10 mg/kg Q2W, 77 have had at least one post-baseline disease assessment as of 18Feb2014. No subjects had complete response (CR). Four subjects (5.2%) had a best response of PR (unconfirmed): 1 subject with advanced cutaneous melanoma, 1 subject with squamous cell carcinoma of the head and neck (SCCHN), 1 subject with squamous NSCLC, and 1 subject with non-squamous NSCLC. In addition, 36 subjects (46.8%) had stable disease (SD), 20 subjects (26.0%) had confirmed progressive disease (PD), 14 subjects (18.2%) had unconfirmed PD, and 3 subjects (3.9%) were not evaluable.

Twelve of the 15 subjects in the 0.1, 0.3, 1.0 mg/kg, and 3.0 mg/kg Q2W dose-escalation cohorts had at least one post baseline disease assessment as of 18Feb2014. Two subjects in each of the 0.3 and 1.0 mg/kg cohorts had a best response of PR (3 confirmed and 1 unconfirmed) assessed by immune-related response criteria (irRC) (Wolchok et al, 2009). All 6 subjects in the 15 mg/kg Q3W cohort had at least one post-baseline disease assessment as of 18Feb2014. No subjects had CR or PR, 4 subjects had a best response of SD, 1 subject had confirmed PD, and 1 subject had unconfirmed PD.

The second study of MEDI4736 is a Phase I dose-escalation study of MEDI4736 in Japanese subjects with advanced solid tumors. Efficacy data are not yet available for this study. A total of 8

subjects have been enrolled. Dose escalation began with MEDI4736 1 mg/kg and proceeded to 3 mg/kg. Four subjects have been enrolled in each of the first 2 dose cohorts, for a total of 8 subjects.

Preliminary AE data as of 18Feb2014 are available for 8 subjects who have been treated with MEDI4736. Twenty-eight TEAEs have been reported among these subjects, all of which were Grade 1 or 2 (Table 5.3.1.3-2). The TEAEs reported for more than 1 subject were constipation, nausea, vomiting, and nasopharyngitis (each in 2 subjects). No DLTs have been reported in this study.

No SAEs have been reported in this study. No deaths have been reported and no subjects have discontinued treatment due to TEAEs.

Refer to the Investigator Brochure for additional information regarding studies of MEDI4736 in combination with other agents in lung cancer and other indications.

Based on an analysis of the dose-escalation data from the ongoing First Trial In Human (FTIH) study, a dose of 10 mg/kg every two weeks administered for up to a maximum of 12 months is recommended for further development. This dosing regimen is expected to have a high probability of ensuring a response in the majority of patients.

This recommendation is supported by multiple lines of evidence including: in-vitro data, nonclinical activity, clinical PK-PDx, clinical biomarkers, and clinical activity data collected from the FTIH study.

Based on the FTIH data, MEDI4736 exhibited non-linear (dose-dependent) PK consistent with target mediated drug disposition. A dose-dependent decrease in peripheral soluble PD-L1 was observed over the dose range of 0.1 to 10 mg/kg every two weeks; consistent with engagement of MEDI4736 with PD-L1.

Significant soluble PD-L1 (>90%) suppression at trough was observed with doses ≥0.3 mg/kg every two weeks. PK parameters such as dose-normalized area under the plasma drug concentration-time curve and t½ increased over the dose range of 0.1 to 10 mg/kg every two weeks and approached linearity at 3 mg/kg every two weeks; suggesting near complete target saturation (membrane bound and soluble PD-L1) with 3 mg/kg every two weeks. The expected mean trough concentration following 3 mg/kg every two weeks MEDI4736 is ~50 µg/mL.

Although clinical activity has been observed at lower doses, and DLTs have not been observed at the highest dose studied (10 mg/kg every two weeks), this dose/schedule is anticipated to maintain levels above a target trough concentration of 100 µg/mL (identified based on evaluation of non-clinical and clinical data).The proposed dosing regimen of 10 mg/kg every two weeks is expected to account for the variability in PK (~50%), PDx response and clinical activity (up to 100%) anticipated in a diverse cancer patient population, maintain sufficient PK exposure in case of an ADA impact and achieve PK exposure that yielded maximal anti-tumor activity in animal models. The target trough serum concentration of 100 µg/mL can be maintained in majority of patients with the 10 mg/kg every two weeks dosing regimen.

Data generated during the dose escalation phase of the FTIH study also suggest that higher doses (ie, 10 mg/kg every two weeks) may be associated with better clinical activity while still providing an acceptable safety profile. Dose-related changes in a variety of peripheral biomarkers have been observed over the dose range of 0.1 to 3 mg/kg every two weeks. Thus far, a low level of immunogenicity has been observed. Screening for ADA has detected 4 positive samples from 3 patients out of a total of 86 samples from 19 patients, with evidence for an impact on PK and target suppression in 1 individual.

Thus, the clinical activity observed coupled with the safety profile, translational science correlates, and non-clinical data supports further development with a dose of 10 mg/kg every two weeks.

Re-Treatment Rationale

Targeted therapies have significantly increased both the rate and durability of response in patients with biomarker-enriched subsets of cancers including advanced NSCLC (eg, gefitinib and erlotinib in EGFR mutation positive, and crizotinib in ALK translocation positive) as well as in metastatic or unresectable melanoma (vemurafenib and dabrafenib in BRAF V600E mutation, trametinib in both V600E and V600K) *(37, 38, 39, 40, 41)* Nevertheless, responses are mostly partial, and relapses are inevitable once resistance mechanisms emerge. Furthermore, the potential for tumor "addiction" and rapid clinical deterioration at the time of withdrawal and/or progression has been described. *(42, 43, 44, 45, 46)*

In contrast to targeted therapy, responses have been observed upon retreatment with immune-mediated therapy. Responses with immune-mediated therapy are no different than responses to initial treatment in terms of time to response, duration of response, or maintenance of response beyond treatment discontinuation *(47, 48)* Therefore, patients who achieve and maintain disease control (ie, complete response [CR], PR or SD) through to the end of the 12-month MEDI4736 treatment period may also restart treatment with MEDI4736 upon evidence of disease progression during follow-up (maximum of 12 months of further treatment).

HIV, HBV, and HCV Exclusion Rationale

Patients with known HIV/HBV/HCV infection will be excluded from this study. Immune checkpoint inhibition is a relatively new class of therapy. While HIV patients have been studied with anti-CTLA4 therapy, the unique interactions of PD-1/PD-L1 inhibitors and HIV may be difficult to predict and require further study. Since many of these patients may already be highly suppressed with antiretroviral therapy, standard assays may not be sensitive enough to detect a safety signal of increasing viral load. Thus, these patients may need to be studied in trials with access to such sensitive assays to better inform drug development in this particular population. The impact of PD-1/PD-L1 inhibition in HIV patients may be beneficial, which is of great interest in drug development in the field of chronic infections generally. We have elected not to complicate our trial with this added and important question at this time.

3.0 DRUG INFORMATION

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this sub-study, MEDI4736 is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 MEDI4736 (NSC 778709) (IND-119672)

a. PHARMACOLOGY

Mechanism of Action: MEDI4736 is a human monoclonal antibody of the IgG1κ subclass that inhibits binding of PD-L1 to PD-1 and CD80. In-vitro studies demonstrate that MEDI4736 relieves PD-L-1-mediated suppression of human T-cell activation. MEDI4736 does not trigger antibody- dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) in cell-based functional assays.

b. PHARMACOKINETICS

Following IV dosing of MEDI4736 in Study CD-ON-MEDI4736-1108

PK/pharmacodynamics data were available for 38 subjects in the dose-escalation (26 subjects) and dose-expansion (12 subjects) phases of Study CD-ON-MEDI4736-1108. Data were from IV infusions Q2W at 5 dose levels (4 subjects in each of the 0.1 and 0.3 mg/kg groups, 3 subjects in the 1 mg/kg group, 2 subjects in the 3 mg/kg group, 18 subjects in the 10 mg/kg group), and Q3W at 15 mg/kg in 6 subjects.

The Cmax increased in an approximately dose-proportional manner over the entire dose range of 0.1 to 15 mg/kg. The $AUC_{(0-14)}$ increased in a greater than dose-proportional manner from 0.1 mg/kg to 15 mg/kg Q3W and approached linearity at ≥ 3 mg/kg. These results suggest that MEDI4736 exhibits nonlinear PK likely due to saturable target-mediated CL; this is common for therapeutic antibodies targeting membrane-bound targets.

Exposures following multiple doses demonstrated accumulation consistent with the PK estimated from the first dose in each group.

Distribution: C_{max} 2.8 – 421 mcg/mL, $AUC_{(0-14)}$ 5.4 – 2373 d.mcg/mL

Metabolism & Elimination: half-life of about 21 days following 10 mg/kg Q2W IV administration.

c. ADVERSE EFFECTS

1. Adverse Events: The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 2833 patients. Below is the CAEPR for MEDI4736.

Version 2.2, April 5, 2018[1]

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
		Blood and lymphatic system disorders - Other (idiopathic thrombocytopenic purpura)[2]
		Thrombotic thrombocytopenic purpura[2]
CARDIAC DISORDERS		
		Myocarditis[2]
		Pericarditis[2]
ENDOCRINE DISORDERS		
		Adrenal insufficiency[2]
		Endocrine disorders - Other (diabetes mellitus type 1)[2]
		Hypopituitarism[2]
	Hyperthyroidism[2]	
	Hypothyroidism[2]	
EYE DISORDERS		
		Keratitis[2]
		Uveitis[2]
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
		Colitis[2]
	Diarrhea	
	Nausea	
		Pancreatitis[2]
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Edema limbs	
	Fatigue	
	Fever	
HEPATOBILIARY DISORDERS		
		Hepatobiliary disorders - Other (autoimmune hepatitis)[2]
IMMUNE SYSTEM DISORDERS		
		Immune system disorders - Other (immune related adverse events)[2]
		Immune system disorders - Other (sarcoidosis)

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Infusion related reaction
INFECTIONS AND INFESTATIONS		
	Infection[3]	
INVESTIGATIONS		
	Alanine aminotransferase increased[2]	
	Aspartate aminotransferase increased[2]	
	Creatinine increased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthritis[2]	
	Myalgia	
		Myositis[2]
		Musculoskeletal and connective tissue disorders - Other (polymyositis)[2]
NERVOUS SYSTEM DISORDERS		
		Guillain-Barre syndrome[2,4]
		Myasthenia gravis[2]
		Nervous system disorders - Other (aseptic meningitis)[2]
		Peripheral sensory neuropathy
RENAL AND URINARY DISORDERS		
	Dysuria	
		Renal and urinary disorders - Other (autoimmune nephritis)[2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough		
	Dyspnea	
	Pneumonitis[2]	
	Respiratory, thoracic and mediastinal disorders - Other (dysphonia)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Hyperhidrosis	

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Pruritus	
	Rash[2,5]	
		Skin and subcutaneous tissue disorders - Other (scleroderma)
		Skin and subcutaneous tissue disorders - Other (severe dermatitis)[2,6]
	Skin hypopigmentation	

NOTE: Cardiomyopathy, and graft versus host disease, while not observed on clinical trials of MEDI4736 (durvalumab) at this time, are known events with this class of agent (PD-L1 antagonist).

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Immune-mediated adverse reactions (irAEs) have been reported in patients receiving MEDI4736 (durvalumab). irAEs can involve any of the organs or systems in the body. Most irAEs were reversible and managed with interruptions of MEDI4736 (durvalumab), administration of corticosteroids and supportive care, however, these events can be serious and fatal.

[3] Infections includes infection in the lungs, upper respiratory tract, dental and oral soft tissues and other organs under the INFECTIONS AND INFESTATIONS SOC. Infections generally are mild (Gr 1-2) but severe infections including sepsis, necrotizing fasciitis, and osteomyelitis have been reported.

[4] Guillain-Barre Syndrome has been reported in patients receiving MEDI4736 (durvalumab) in combination with tremelimumab (CP-675,206) but can potentially occur after durvalumab monotherapy.

[5] Rash includes the terms: rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, and eczema.

[6] In rare cases, severe dermatitis has been reported to manifest as Stevens-Johnson syndrome, toxic epidermal necrolysis, or rashes complicated by dermal ulceration or necrotic, bullous, or hemorrhagic manifestations.

Adverse events reported on MEDI4736 (durvalumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MEDI4736 (durvalumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Disseminated intravascular coagulation
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (coronary artery disease); Pericardial effusion; Pericardial tamponade; Restrictive cardiomyopathy; Right ventricular dysfunction; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired
EYE DISORDERS - Eye disorders - Other (choroidal effusion with shut down of ciliary body)
GASTROINTESTINAL DISORDERS - Ascites; Constipation; Dental caries; Esophageal perforation; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Mucositis oral; Proctitis; Small intestinal obstruction; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema trunk; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic hemorrhage
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (drug-induced liver injury); Serum sickness
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Wound complication
INVESTIGATIONS - Blood bilirubin increased; CPK increased; GGT increased; Investigations - Other (electrocardiogram T wave inversion); Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Rhabdomyolysis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (brain metastasis swelling); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lung cyst); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare, tumor inflammation); Treatment related secondary malignancy; Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Dizziness; Edema cerebral; Headache; Nervous system disorders - Other (axonal neuropathy); Nervous system disorders - Other (hemiparesis); Paresthesia; Seizure
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin
VASCULAR DISORDERS - Hypertension

Note: MEDI4736 (durvalumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

For additional information on adverse events of special interest, see Section 18.1.

2. Pregnancy and Lactation: Nonclinical assessment of the potential reproductive and developmental toxicity of MEDI4736 has not been conducted at this time. It is not known whether MEDI4736 is excreted in breast milk. Nursing should be discontinued during and after MEDI4736 treatment as specified in the study protocol.

   Women of childbearing potential and non-sterilized males who are sexually active with a female partner should use highly effective contraceptive measures during and for at least 90 days after completion of treatment.

3. Drug Interactions: No formal drug-drug interaction studies have been conducted with MEDI4736. There are no known clinically significant interactions of MEDI4736 with other medicinal products.

d. DOSING & ADMINISTRATION

See Section 7.0, Treatment Plan.

Administration Instructions: MEDI4736 infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration. MEDI4736 will be administered as an IV infusion via an infusion pump intravenously over approximately 60 minutes. Doses of 10 mg/kg will be administered through an IV administration set with a 0.2-µm in-line filter. No incompatibilities between MEDI4736 and polyethylene, polypropylene, polyvinylchloride, or polyolefin copolymers have been observed. Flush the IV line with a volume of normal saline equal to the priming volume of the infusion set used at the completion of infusion to ensure the full dose is administered and document if the line was not flushed.

Since the compatibility of MEDI4736 with other IV medications and solutions, other than normal saline, is not known, the MEDI4736 solution should not be infused through an IV line in which other solutions or medications are being administered.

Monitoring of Dose Administration: Patients will be monitored during and after the infusion with assessment of vital signs.

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

e. HOW SUPPLIED

1. MEDI4736 is considered an investigational agent and will be supplied free of charge for this protocol by MedImmune, Inc. and distributed by the CTEP, DCTD, NCI.

2. Lyophilized powder formulation: MEDI4736 is formulated at 50 mg/mL in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02%

(weight/volume [w/v]) polysorbate 80, pH 6.0. The investigational product is supplied as a white to off-white lyophilized powder in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 200 mg (nominal) of active investigational product. MEDI4736 supplies will be shipped in tamper sealed kits containing 4 vials each. In the future, the packaging configuration will change to enable distribution quantities other than in multiples of 4.

f. STORAGE, PREPARATION & STABILITY

Storage

Unopened vials of MEDI4736 lyophilized drug product must be stored at 2°C to 8°C (36°F to 46°F). MEDI4736 vials should be stored in the original packaging. Do not freeze. Stability testing of the intact vials is on-going.

Total in-use storage time of MEDI4736 from reconstitution to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives and any unused portion must be discarded. Vials should not be shared between patients.

Product Preparation of MEDI4736

Sites should follow standard and local aseptic procedures and the clinical study protocol for all activities. All dispensing activities should be documented according to local procedures.

Study Drug Reconstitution

1. MEDI4736 requires reconstitution prior to use.

2. Calculate the amount of MEDI4736 needed for the subject to achieve the accurate dose (see below).

3. Calculate the number of MEDI4736 vials required. Each MEDI4736 vial should be reconstituted using aseptic techniques with 4 mL sterile water for injection (SWFI) to give a final concentration of 50 mg/mL.

4. Gently add SWFI to the side of the vial to minimize product foaming. Gently rotate and swirl for 5 minutes or until dissolution is complete. The vial should not be shaken or vigorously agitated.

5. Reconstituted MEDI4736 should stand undisturbed at room temperature for a minimum of 5 minutes or until the solution clarifies. The reconstituted solution should appear clear or slightly opalescent. A thin layer of bubbles on the liquid surface is considered normal.

   The reconstitution and extractable volumes for each vial are shown below:

Active drug	Volume of water for injections required for constitutions	Concentrate extractable volume	Concentrations
MEDI-4736, 200 mg	4 mL	4 mL	50 mg/mL

Preparation of Infusion Bags

Following reconstitution of the required number of vials necessary for the calculated dose, MEDI4736 must be further diluted prior to IV administration. Doses of 10 mg/kg will be administered using a 250 mL IV bag containing 0.9% (weight/volume) saline and delivered through an IV administration set with a 0.2-µm in-line filter.

Saline bags must be latex-free and can be made of polypropylene, polyethylene, polyolefin copolymers, or polyvinyl chloride.

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

The calculated volume of MEDI4736 is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Dose calculation
The volume of reconstituted MEDI4736 (mL) to add to the iv bag is calculated as follows:

10 mg/kg × Patient Weight (kg) ÷ MEDI4736 concentration (nominal 50 mg/mL)

Example: For a patient weighing 80 kg (rounded to nearest unit), dosed at 10 mg/kg, 16 mL [10 mg/kg × 80 kg divided by 50 mg/mL] of MEDI4736 is to be diluted in a 250 mL iv bag containing 0.9% (weight/volume) saline. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag and the diluted MEDI4736 is administered as described above.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: Study specific supplies will be provided to sites once a patient has been randomized. Starter supplies will not be provided. NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number (**S1400A**) must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 and a CV. If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Active CTEP-registered investigators and investigator-designated shipping designees

and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

2. Drug Handling and Accountability

a. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

3. Drug return and/or disposition instruction

a. All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

b. Drug expiration: Stability testing is ongoing. PMB will send a stock recovery letter when notified that the agent is no longer suitable for use.

4. Contact Information

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

4.0 STAGING CRITERIA

See Section 4.0 of **S1400** for staging criteria.

5.0 ELIGIBILITY CRITERIA

Patient must meet the eligibility criteria in Section 5.1, 5.2 and 5.3 of **S1400A** to be eligible for **S1400A**. If the patient does not meet the eligibility criteria listed in Section 5.1 and Section 5.2 of **S1400A**, submit the **S1400** Notice of Intention Not to Register form and follow patient per Section 7.4 of **S1400**. Patients proceeding to Retreatment Registration Step #2 must meet the eligibility criteria in Section 5.4 of **S1400A** to be eligible.

5.1 Registration Step #1 Disease Related Criteria

a. Patients must have been assigned to **S1400A**.

b. Patients must not have any prior exposure to immunotherapy such as, but not limited to anti-PD-1 or anti-PD-L1 antibodies. Prior exposure to the following is allowed: anti-CTLA-4 antibodies, live attenuated vaccines, anti-EGFR agents and GM-GSF.

c. Patients must not have received nitrosoureas or mitomycin-c within 42 days prior to sub-study registration.

d. Patients must not have any active or prior documented autoimmune or inflammatory disease (including inflammatory bowel disease, diverticulitis with the exception of diverticulosis, celiac disease, irritable bowel disease; Wegner syndrome; Hashimoto syndrome) within 3 years prior to sub-study registration. Patients with vitiligo, alopecia, Grave's disease, or psoriasis requiring systemic treatment within the past 3 years are not eligible.

e. Patients must not have any history of primary immunodeficiency.

5.2 Registration Step #1 Clinical/Laboratory Criteria

a. Patients must not have received any immunosuppressive medication within 28 days prior to sub-study registration and must not be planning to receive any such agents while on protocol treatment. However, intranasal and inhaled corticosteroids or systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent are allowed.

b. Patients must not have any prior Grade ≥ 3 immune-related adverse event (irAE) or any unresolved irAE > Grade 1.

c. Patients must not have any history of organ transplant that requires use of immunosuppressives.

d. Patients must not have any known allergy or reaction to any component of the MEDI4736 formulation.

e. Patients must not have a known history of tuberculosis.

f. Patients must not have received a live attenuated vaccination within 28 days prior to sub-study registration.

g. Patients must not have known HIV, Hepatitis B or Hepatitis C positivity. [*This criterion replaces common eligibility criteria in Section 5.3m and 5.3n*]

h. Patients must also be offered participation in banking for future use of specimens as described in Section 15.0.

5.3 Registration Step #1 - Common Eligibility Criteria for all Sub-Studies

The **S1400** Common Eligibility Criteria have been incorporated into Section 5.0 of each sub-study for ease of reference.

a. Patients whose biomarker profiling results indicate the presence of an EGFR mutation or EML4/ALK fusion are not eligible. Due to existence of approved therapies the biomarker exclusion rules are as follows:

Gene	Alteration type	Ineligible Alteration
EGFR	Substitution	L858R, T790M, A289V, G719A, S768I, G719C, R108K, G598V, R222C, L62R, L861Q, P596L, V774M
	Indel	non-frame shifting insertions or deletions between amino acids 740 and 780, in exons 19 and 20, transcript NM_005228
	Fusion	None
	Amplification	None
ALK	Substitution	None
	Indel	None
	Fusion	EML4-ALK, CLIP4-ALK, CLTC-ALK, KIF5B-ALK, NPM1-ALK, RANB2-ALK, STRN-ALK, TFG-ALK
	Amplification	None

b. Patients must have progressed per RECIST 1.1 (see Section 10.1) following the most recent line of therapy.

c. Patients must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 21 days prior to sub-study registration. Patients must have recovered (≤ Grade 1) from any side effects of prior therapy. Localized palliative radiation therapy is allowed for symptom management, provided treatment is completed ≥ 14 days prior to sub-study registration. All other types of radiation must be completed ≥ 28 days prior to sub-study registration.

d. Patients must have measurable disease (see **S1400** Section 10.1) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in **S1400** Section 10.1c. Measurable disease must be assessed within 28 days prior to sub-study registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to sub-study registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. Patients whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of the treating investigator) prior to registration. See **S1400A** Sections 15.0 and **S1400** Section 18.1c for guidelines and submission instructions for required central radiology review.

e. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to sub-study registration. Patient must not have leptomeningeal disease, spinal cord compression or brain metastases unless: (1) metastases have been locally treated and have remained clinically controlled and asymptomatic for at least 14 days following treatment, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 1 day prior to sub-study registration.

f. Patient must have fully recovered from the effects of surgery at least 14 days prior to sub-study registration.

g. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

h. Patients must have an ANC ≥ 1,500/mcl, platelet count ≥ 100,000 mcl, and hemoglobin ≥ 9 g/dL obtained within 28 days prior to sub-study registration.

i. Patients must have adequate hepatic function as defined by serum bilirubin ≤ Institutional Upper Limit of Normal (IULN) and either ALT or AST ≤ 2 x IULN within 28 days prior to sub-study registration (if both ALT and AST are done, both must be ≤ 2 IULN). For patients with liver metastases, bilirubin and either ALT or AST must be ≤ 5 x IULN (if both ALT and AST are done, both must be ≤ 5 x IULN).

j. Patients must have a serum creatinine ≤ the IULN OR measured or calculated creatinine clearance ≥ 50 mL/min using the following Cockroft-Gault Formula:

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{actual body weight in kg}^{\dagger})}{72 \times \text{serum creatinine}^{*}}$$

Multiply this number by 0.85 if the patient is a female. These tests must have been performed within 28 days prior to sub-study registration.

†The kilogram weight is the patient weight with an upper limit of 140% of the IBW.
*Actual lab serum creatinine value with a minimum of 0.8 mg/ dL.

k. Patients must have Zubrod performance status 0-1 (see **S1400** Section 10.4) documented within 28 days prior to sub-study registration.

l. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, and myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia (see **S1400** Section 18.1b).

m. [*This common eligibility criteria has been removed as it conflicts with the sub-study specific criteria in Section 5.2g. A place holder remains to keep consistency across all sub-studies*]

n. [*This common eligibility criteria has been removed as it conflicts with the sub-study specific criteria in Section 5.2g. A place holder remains to keep consistency across all sub-studies*]

o. Prestudy history and physical exam must be obtained within 28 days prior to sub-study registration.

p. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

q. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy

prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

r. As a part of the OPEN registration process (see **S1400** Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

s. Patients with impaired decision-making capacity are eligible as long as their neurological or psychological condition does not preclude their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator).

t. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

5.4 Registration Step #2 - MEDI4736 RE-TREATMENT

Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at **S1400**question@crab.org prior to registration.

Disease Related Criteria

a. Patient must have progressed following 12 months of treatment with MEDI4736. Patients who discontinue MEDI4736 prior to the completion of 12 months (for any reason) are not eligible.

Patients who have already completed two 12-month periods of treatment are not eligible.

b. Patients may have measurable or non-measurable disease (see **S1400** Section 10.1) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in **S1400** Section 10.1c. Measurable disease must be assessed within 28 days prior to re-treatment registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to re-treatment registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. Patients whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of the treating investigator) prior to RE-TREATMENT registration. See Sections 15.0 and **S1400** Section 18.1c for guidelines and submission instructions for required central radiology review.

c. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to RE-TREATMENT registration. Patient must not have leptomeningeal disease, spinal cord compression or brain metastases unless: (1) metastases have been locally and have remained clinically controlled and asymptomatic for at least 14 days following treatment and prior to RE-TREATMENT registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to RE-TREATMENT registration.

d. Patients must not have received any treatment after discontinuing MEDI4736 with the following exceptions. Localized palliative radiation therapy is allowed for symptom management, provided and treatment is completed ≥ 14 days prior to RE-TREATMENT registration. Local treatment for brain metastases as specified in section 5.4.c is allowed.

e. Patients must not have received any immunosuppressive medication within 28 days prior to RE-TREATMENT registration and must not be planning to receive any such agents while on protocol treatment. However, intranasal and inhaled corticosteroids or systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent are allowed.

f. Patients must not have any prior Grade ≥ 3 immune-related adverse event (irAE) or any unresolved irAE > Grade 1.

g. Patients must not have received a live attenuated vaccination within 28 days prior to RE-TREATMENT registration.

h. Patients must not have known HIV, Hepatitis B or Hepatitis C positivity.

i. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

j. Patients must have an ANC ≥ 1,500/mcl, platelet count ≥ 100,000 mcl, and hemoglobin ≥ 9 g/dL obtained within 28 days prior to RE-TREATMENT registration.

k. Patients must have adequate hepatic function as defined by serum bilirubin ≤ Institutional Upper Limit of Normal (IULN) and either ALT or AST ≤ 2 x IULN within 28 days prior to RE-TREATMENT registration (if both ALT and AST are done, both must be ≤ 2 IULN). For patients with liver metastases, bilirubin and either ALT or AST must be ≤ 5 x IULN (if both ALT and AST are done, both must be ≤ 5 x IULN).

l. Patients must have a serum creatinine ≤ the IULN OR measured or calculated creatinine clearance ≥ 50 mL/min using the following Cockroft-Gault Formula:

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{actual body weight in kg}^{\dagger})}{72 \times \text{serum creatinine}^{*}}$$

Multiply this number by 0.85 if the patient is a female. These tests must have been performed within 28 days prior to RE-TREATMENT registration.
†The kilogram weight is the patient weight with an upper limit of 140% of the IBW.
*Actual lab serum creatinine value with a minimum of 0.8 mg/dL.

m. Patients must have Zubrod performance status of 0-1 (see Section 10.4) documented within 28 days prior to RE-TREATMENT registration.

n. Prestudy history and physical exam must be obtained within 28 days prior to RE-TREATMENT registration.

o. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is

considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

p. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

q. Patients with impaired decision-making capacity are eligible as long as their neurological or psychological condition does not preclude their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator).

r. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

6.0 STRATIFICATION FACTORS

Prior to Revision #2, (Version Date 4/22/15) patients were stratified as follows below. As the design and objectives have been modified to a single arm study, randomization and stratification are no longer required.

6.1 Patients were randomized between MEDI4736 and docetaxel using block randomization.

6.2 Randomization was stratified by:

a. Zubrod Performance Status (0-1 vs. 2)

b. Gender (Male vs. Female)

c. Smoking Status (Current vs. Former/Never)

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Drs. Vassiliki Papadimitrakopoulou and Hossein Borghaei at **S1400A**MedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Pre-Medication and Supportive Care

Premedication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

Patients randomized to docetaxel should pre-medicate with dexamethasone beginning 24 hours prior to docetaxel administration. Dexamethasone may be administered per local institutional guidelines. Recommended dose listed below.

MEDI4736 specific pre-medication is not required for routine infusions. If during any infusion, a reaction occurs, pre-medication (e.g. acetaminophen) and/or antihistamine (e.g. diphenhydramine) may be used for subsequent infusions.

7.2 Treatment – Non-Match **S1400A**

Prior to Revision #2 (Version Date 4/22/15) patients were randomized into one of two treatment arms. As the design and objectives have been modified to a single arm, patients will be placed into Arm 1: MEDI4736. The information regarding the docetaxel treatment plan will remain within the section for the patients continuing to receive treatment per protocol.

a. **Arm 1: MEDI4736**

Agent	Dose	Route	Day	Schedule*	Duration
MEDI4736	10 mg/kg	IV over 60 min	1	Q 2 weeks	12 months

* NOTE: A cycle of treatment is 14 days. Disease assessment must occur every 6 weeks for the first year, then every 3 months. Treatment will continue for a maximum duration of 12 months or until any one of the criteria in Section 7.3 is met.

Patients will be weighed prior to initiation of a new cycle of treatment. Dose recalculation based on weight change must be done if the patient experiences 10% or more weight gain or weight loss from the last-dosing weight. Following preparation of the dose, the entire contents of the IV bag should be administered (see Section 3.1d).

b. **Arm 2: Docetaxel** (Closed to accrual per Revision #2, Version Date 4/22/15)

Agent	Dose	Route	Day	Schedule*
Dexamethasone	8 mg BID**	Oral, beginning 24 hours prior to docetaxel	0-2	Q 21 days
Docetaxel	75 mg/m^2	IV	1	Q 21 days

* NOTE: A cycle of treatment is 21 days. Disease assessment must occur after every 6 weeks. Treatment will continue until any one of the criteria in Section 7.3 is met.

** Dexamethasone may be administered per local institutional guidelines. Recommended dose listed above.

c. **Arm 3: MEDI4736 - Retreatment**

Agent	Dose	Route	Day	Schedule*	Duration
MEDI4736	10 mg/kg	IV over 60 min	1	Q 2 weeks	12 months

* NOTE: A cycle of treatment is 14 days. Disease assessment must occur every 6 weeks for the first year, then every 3 months. Treatment will continue for a maximum duration of 12 months or until any one of the criteria in Section 7.3 is met.

Patients will be weighed prior to initiation of a new cycle of treatment. Dose recalculation based on weight change must be done if the patient experiences 10% or more weight gain or weight loss from the last-dosing weight. Following preparation of the dose, the entire contents of the IV bag should be administered (see Section 3.1d).

7.3 Criteria for Removal from Protocol Treatment

a. Progression of disease as defined in Section 10.2d in **S1400**. However, the patient may continue protocol treatment with MEDI4736 as long as in the opinion of the treating investigator the patient is continuing to clinically benefit from treatment. Patients with progression of disease that is confirmed by a second determination of progression at least 4 weeks from the first documentation of progression must be removed from protocol treatment.

b. Completion of 12 months of treatment on MEDI4736. For patients assigned to Arm 1, MEDI4736: Upon evidence of progression following discontinuation of 12 months of treatment, patients may restart treatment with Arm 3, MEDI4736 for up to 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Patients will only be able to restart treatment once; thus a maximum of two 12-month periods will be allowed.

c. Symptomatic deterioration (as defined in Section 10.2e of **S1400**).

d. Unacceptable toxicity.

e. Treatment delay for any reason > 28 days (or as noted in Section 8.0)

f. The patient may withdraw from this study at any time for any reason.

7.4 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.5 Follow-Up Period

All patients will be followed until death or 3 years after initial sub-study registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized **for SAE reporting only**. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov) All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

a. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

b. Reductions are based on the dose given in the preceding reporting period and are based on toxicities observed since the prior toxicity evaluation.

c. Once dose is reduced, patients will continue at the new dose. No dose re-escalations are allowed.

d. A maximum of two dose reductions are allowed on docetaxel arm only. No dose reductions are allowed on MEDI4736 arm.

e. The maximum dose delay for any reason is 28 days.

8.3 Dose Modifications – MEDI4736

DRUG	DOSE LEVEL*	DOSE
MEDI4736	Full	10 mg/kg

* Dose reduction of MEDI4736 is not allowed. Dose interruptions and discontinuations are allowed to manage toxicity. See below.

Based on the mechanism of action of MEDI4736 leading to T-cell activation and proliferation, there is the possibility of observing immune related adverse events (irAEs) during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab and nivolumab including immune-mediated enterocolitis, dermatitis, hepatitis, pneumonitis, neuropathies, and endocrinopathies. Patients will be monitored for signs and symptoms of irAEs. In absence of alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, pneumonitis, neuropathies, and endocrinopathy will be considered to be immune related.

a. Dose Modification and Management Guidelines for Immune-Related Adverse Events of MEDI4736

Toxicity	Dose Modification	Toxicity Management
Immune-Related Adverse Events (irAEs) For toxicities not noted below		
In addition to the criteria for permanent discontinuation of study drug/regimen based on CTCAE grade/severity (table below) , permanently discontinue study drug/study regimen for the following conditions: Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/regimen **Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.**		
Grade 1	No dose modification	It is recommended that management of irAEs follow these guidelines. - Thoroughly evaluated patients to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.) - In the absence of a clear alternative etiology, all events should be considered potentially immune related. - Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events - For persistent (> 3 or 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone PO 1-2mg/kg/day or IV equivalent - If symptoms recur or worsen during corticosteroid tapering (> 28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering (≥ 28 days) at a slower rate - More potent immunosuppressives such as TNF inhibitors (e.g.infliximab)– (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. - Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient - Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled , 2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.
Grade 2	Hold MEDI4736 until resolution to ≤ Grade 1 and 5-7 days have passed after completion of steroid taper then resume MEDI4736 administration at next scheduled dose.	
≥ Grade 3	Discontinue MEDI4736 and remove from protocol therapy. Note: For ≥ Grade asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen	
Pneumonitis/ILD		
Any Grade		- Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.

Toxicity	Dose Modification	Toxicity Management
Grade 1	No dose modification However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	(Radiographic Changes Only) – Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated – Consider pulmonary and infectious disease consult
Grade 2	Hold MEDI4736 until resolution to ≤ Grade 1 and 5-7 days have passed after completion of steroid taper then resume MEDI4736 administration at next scheduled dose. - If toxicity worsens then treat as ≥ Grade 3 - If toxicity improves to baseline then the decision to reinitiate study drug/regimen at next scheduled treatment date will be based upon treating physician's clinical judgment.	– Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (e.g., prednisone 1-2 mg/kg/day or IV equivalent) – Reimaging as clinically indicated – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started – If still no improvement within 3-5 days despite IV methylprednisone at 2-4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5 mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections) – Consider pulmonary and infectious disease consult – Consider as necessary after discussing with Study Chair
≥ Grade 3	Permanently discontinue MEDI4736 and remove from protocol therapy.	– Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Obtain pulmonary and infectious disease consult – Hospitalize the patient – Supportive Care (oxygen, etc.) – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections

Toxicity	Dose Modification	Toxicity Management
Diarrhea/ Enterocolitis		
Any Grade		- Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) - Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event - Use analgesics carefully; they can mask symptoms of perforation and peritonitis
Grade 1	No dose modification	- Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
Grade 2	Hold MEDI4736 until resolution to ≤ Grade 1 and 5-7 days have passed after completion of steroid taper then, resume MEDI4736 administration at next scheduled dose.	- Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide - Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. - If still no improvement within 3-5 days despite 2-4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks). **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab - Consult study physician if no resolution to ≤ Grade 1 in 3-4 days - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)
≥ Grade 3	Permanently discontinue MEDI4736 and remove from protocol therapy.	- Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent - Monitor stool frequency and volume and maintain hydration - Urgent GI consult and imaging and/or colonoscopy as appropriate - If still no improvement within 3-5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5 mg/kg once every 2 weeks). - Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. - Once improving, gradually taper steroids over ≥28 day and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)

Toxicity	Dose Modification	Toxicity Management
Hepatitis (Elevated LFTs)		
Any Grade		- Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin - Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)
Grade 1 (Based on ULN regardless of baseline LFT)	No dose modification	- Continue LFT monitoring per protocol
Grade 2 (Based on ULN regardless of baseline LFT)	Hold MEDI4736 until resolution to ≤ Grade 1 and 5-7 days have passed after completion of steroid taper then resume MEDI4736 administration at next scheduled dose.	- Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. - If no resolution to ≤ Grade 1 in 1-2 days, discuss with study physician. - If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day or IV equivalent. - If still no improvement within 3-5 days despite 1-2 mg/kg/day of prednisone or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started. - If still no improvement within 3-5 days despite 2-4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil) . Discuss with Study Chair if mycophenolate mofetil is not available. **Infliximab should NOT be used**. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections.
Grade 3 (Based on ULN regardless of baseline LFT)	For elevated transaminases, ≤8x ULN or bilirubin ≤5x ULN, hold MEDI4736 until resolution to ≤ Grade 1 or baseline. Resume MEDI4736 administration at next scheduled dose. If resolution to ≤ Grade 1 or baseline does not occur within 14 days, permanently discontinue MEDI4736. For elevated transaminases >8× ULN or bilirubin >5x ULN, permanently discontinue MEDI4736. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause	- Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent - If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent , promptly start treatment with immunosuppressive therapy (mycophenolate mofetil) Discuss with study physician if mycophenolate is not available. Infliximab should NOT be used. - Hepatology consult, abdominal workup, and imaging as appropriate. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections.

Toxicity	Dose Modification	Toxicity Management
Hepatitis (Elevated LFTs)		
Grade 4 (Based on ULN regardless of baseline LFT)	Permanently discontinue MEDI4736.	

Toxicity	Dose Modification	Toxicity Management
Nephrits or Renal Dysfunction (Elevated Serum Creatinine)		
Any Grade		– Consult with Nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.) – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.) – Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) , in order to prevent potential progression to higher grade event
Grade 1	No dose modification	– Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity , treat as Grade 2 or Grade 3 or 4 – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc
Grade 2	Hold MEDI4736 until resolution to ≤ Grade 1 or baseline then resume MEDI4736 administration at next scheduled dose.	– Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult Nephrologist and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started. – Once improving gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections. – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
≥ Grade 3	Permanently discontinue MEDI4736 and remove from protocol therapy.	– Carefully monitor serum creatinine on daily basis – Consult Nephrologist and consider renal biopsy if clinically indicated – Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. – Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections).
Rash(excluding Bullous skin formations)		
Any Grade		Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY CHAIR SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****
Grade 1	No dose modification	Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)

Rash (excluding Bullous skin formations) (contd.)		
Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold MEDI4736 until resolution to ≤ Grade 1 or baseline and 5-7 days have passed after completion of steroid taper, resume MEDI4736 administration at next scheduled dose.	– Obtain dermatology consult – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent – Consider skin biopsy if persistent for >1-2 weeks or recurs
Grade 3	Hold MEDI4736 until resolution to ≤ Grade 1 or baseline; resume MEDI4736 administration at next scheduled dose.	– Consult dermatology – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Consider hospitalization – Monitor extent of rash [Rule of Nines] – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections) – Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled , 2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.
Grade 4	Permanently discontinue MEDI4736 and remove from protocol therapy.	
Endocrinopathy (e.g., hyper-thyroidism, hypo-thyroidism, hypo-pituitarism, adrenal insufficiency, etc.)		
Any Grade		– Consult Endocrinologist – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) – Monitor and evaluate thyroid function tests: TSH, free T_3 and free $T_4$and other relevant endocrine labs depending on suspected endocrinopathy. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing

Toxicity	Dose Modification	Toxicity Management
Endocrinopathy (e.g., hyper-thyroidism, hypo-thyroidism, hypo-pituitarism, adrenal insufficiency, etc.) (contd.)		
Grade 1	No dose modification	(including those with asymptomatic TSH elevation) – Monitor patient with appropriate endocrine function tests – If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.
Grade 2	For Grade 2 endocinopathy other than hypothyroidism, hold MEDI4736 until patient is clinically stable, resume MEDI4736 administration at next scheduled dose. Otherwise, hold MEDI4736 until resolution to ≤ Grade 1 or baseline and 5-7 days have passed after completion of steroid taper; resume MEDI4736 administration at next scheduled dose.	(including those with symptomatic endocrinopathy) – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids – Initiate hormone replacement as needed for management – Evaluate endocrine function, and as clinically indicated, consider pituitary scan – For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g., 1-2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. Levothyroxine, hydrocortisone, or sex hormones). - – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.
≥ Grade 3	For Grade 3 endocrinopathy other than hypothyroidism, hold MEDI4736 until resolution to ≤ Grade 1 or baseline; resume MEDI4736 administration at next scheduled dose.	– Consult endocrinologist – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity – Once improving, gradually taper immunosuppressive steroids over ≥4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections) – Discuss with Study Chair

Toxicity	Dose Modification	Toxicity Management
Immune Mediated Neurotoxicity (except Myasthenia Gravis and Guillain-Barre)		
Any Grade		– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.) – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) – Symptomatic treatment with neurological consult as appropriate
Grade 1	No dose modification	
Grade 2	Hold MEDI4736 until resolution to ≤ Grade 1 and 5-7 days have passed after completion of steroid taper resume MEDI4736 administration at next scheduled dose.	– Discuss with the study chair – Consider Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) – Promptly start systemic prednisone 1-2 mg/kg/day or IV equivalent – If no improvement within 3-5 days despite 1-2 mg/kg/day prednisone or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)
Grade 3	Hold MEDI4736 until resolution to ≤ Grade 1; resume MEDI4736 administration at next scheduled dose.	– Discuss with Study Chair – Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) – Once stable, gradually taper steroids over ≥4 weeks
Grade 4	Permanently discontinue MEDI4736 and remove from protocol therapy.	

Toxicity	Dose Modification	Toxicity Management
Immune-Mediated Peripheral Neuromotor Syndromes, such as Guillain-Barre and Myasthenia Gravis		
Any Grade		– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability – Evaluate patients to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in subjects with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations,and "repetitive stimulation" if myasthenia is suspected)are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation – Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
Grade 1	No dose modification	- Discuss with the study chair - Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above - Consider a neurology consult unless the symptoms are very minor and stable

Toxicity	Dose Modification	Toxicity Management
Immune-Mediated Peripheral Neuromotor Syndromes, such as Guillain-Barre and Myasthenia Gravis (contd.)		
Grade 2	Hold MEDI4736 until resolution to ≤ Grade 1; resume MEDI4736 administration at next scheduled dose. If there are signs of respiratory insufficiency or autonomic instability permanently discontinue MEDI4736 and remove from protocol therapy	– Discuss with the study chair – Monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain a Neurology Consult – Manage sensory neuropathy/neuropathic pain with appropriate medications (e.g., gabapentin, duloxetine, etc.) <u>MYASTHENIA GRAVIS</u> o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. <u>GUILLAIN-BARRE</u>*:* o Importantly the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
Grade 3	Hold MEDI4736 until resolution to ≤ Grade 1; resume MEDI4736 administration at next scheduled dose. If there are signs of respiratory insufficiency or autonomic instability permanently discontinue MEDI4736 and remove from protocol therapy.	– Discuss with study chair – Recommend hospitalization – Monitor symptoms and obtain neurological consult <u>MYASTHENIA GRAVIS</u> o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapharesis or IVIG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. <u>GUILLAIN-BARRE:</u> o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
Grade 4	Permanently discontinue MEDI4736 and remove from protocol therapy.	

Toxicity	Dose Modification	Toxicity Management
Cardiac toxicities (including arrhythmia, conduction disorder heart failure, IV dysfunction, Myocarditis)		
Any Grade	**General Guidance for Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial workup should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory workup as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) – **Discontinue protocol therapy permanently upon diagnosis of myocarditis, regardless of grade**	
Grade 1 (asymptomatic with laboratory (e.g., BNP, EKG, Troponin) and etiology is unclear)	No dose modifications required unless clinical suspicion for myocarditis is high in which case suspected, hold protocol therapy during workup. - If myocarditis is excluded, resume after complete resolution to Grade 0. - If myocarditis is diagnosed, permanently discontinue protocol therapy.	**For Grade 1 (no definitive findings):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory workup as clinically indicated. – Consider using steroids if clinical suspicion is high.

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

b. Dose Modification and Management Guidelines for Infusion-Related Reactions of MEDI4736

Toxicity	Dose Modification	Toxicity Management
Infusion- Related Reactions		
Any Grade	No dose modification	Management per institutional standard at the discretion of investigator Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
≤ Grade2	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate	Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator Consider premedication per institutional standard prior to subsequent doses
≥ Grade 3	Permanently discontinue MEDI4736 and remove from protocol therapy.	Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

c. Modification and Management Guidelines for Non-Immune Mediated Reactions of MEDI4736

Non-Immune Mediated Reactions		
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant	Treat accordingly as per institutional standard
Grade 1	No dose modification	
Grade 2	Hold MEDI4736 until resolution to ≤ Grade 1; resume MEDI4736 administration at next scheduled dose.	
Non-Immune Mediated Reactions (contd.)		
Grade 3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline. For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume MEDI4736 administration at next scheduled dose. Otherwise, permanently discontinue MEDI4736 and remove from protocol therapy.	Treat accordingly as per institutional standard
Grade 4	Permanently discontinue MEDI4736 and remove from protocol therapy.	

8.4 Dose Modifications – Docetaxel (NOTE: Arm 2 Closed to accrual per Revision #2, Version Date 4/22/15)

DRUG	DOSE LEVEL*	DOSE
Docetaxel	Full	75 mg/m^2
	-1 Level	55 mg/m^2
	-2 Level	35 mg/m^2

*Only two docetaxel dose reductions are allowed.

Dose Modifications for Docetaxel

Hematological Toxicity	
Grade 4 Febrile Neutropenia	Hold docetaxel until recovery to ≤ Grade 1. Then resume docetaxel administration with one dose level reduction.
Grade 4 Neutropenia	Must undergo a dose reduction for subsequent cycles regardless of the duration of the neutropenia with a maximum of two dose reductions.
Grade 4 Thrombocytopenia	Hold docetaxel until recovery to ≤ Grade 1. Then resume docetaxel administration with one dose level reduction.
Hepatic Toxicity	
Grade ≥ 3	Hold docetaxel up to two weeks. If recovered to ≤ Grade 1, resume treatment at one level dose reduction. Otherwise, remove from protocol treatment.
Grade 2	Reduce docetaxel at a one level dose reduction.
Non-Hematological Toxicity	
Grade 4 Vomiting	If occurs despite antiemetic prophylaxis, restart treatment after recovery to ≤ Grade 1 at a one level dose reduction.
Grade ≥ 3 Diarrhea	If occurs despite antidiarrheal treatment, restart treatment after recovery to ≤ Grade 1 at a one level dose reduction.
Non-Hematological Toxicity (contd.)	
Grade 2 Peripheral Neuropathy	One dose level reduction.
Grade 3 Peripheral Neuropathy	Remove from protocol treatment.
Grade 3 Fluid Retention	Hold docetaxel until recovery to ≤ Grade 1, then restart treatment at a one level dose reduction.
Grade ≥ 3 Stomatitis	Restart treatment after recovery to ≤ Grade 1 at a one level dose reduction.
For All Other Non-Hematological Toxicities	**Actions**
Grade ≥ 3	Hold docetaxel until recovery to ≤ Grade 1, then restart treatment at a one level dose reduction.

a. Hypersensitivity Reactions

No dose reductions will be made for any hypersensitivity reactions.
If, despite dexamethasone pre-treatment, the patient experiences a hypersensitivity reaction, treatment should be as indicated in the following table.

Hypersensitivity Reactions	
Grade 1:	• Consider decreasing the rate of infusion until recovery to < Grade 1. • Then, resume infusion at the initial planned rate.
Grade 2:	• Stop docetaxel infusion and give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV. • Resume docetaxel infusion after recovery < Grade 1; depending on the physician's assessment of the patient, docetaxel infusion should be resumed at a slower rate (e.g., infuse at an 8-hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, then finally, resume at the hour infusion rate). • Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, (e.g., infuse at an 8-hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, than at a 2-hour rate for 5 minutes, and finally, administer at the 1-hour infusion rate).
Grade ≥ 3	• REMOVE FROM PROTOCOL TREATMENT

In case of late occurring hypersensitivity symptoms, e.g., appearance within 1 week of treatment of a localized or generalized pruritis, symptomatic treatment may be given (e.g., oral antihistamine). Additional oral or IV premedication with antihistamine may also be given for the next cycle of treatment depending on the intensity of the reaction observed.

b. Fluid Retention

If symptomatic, patients developing fluid retention may be treated with diuretics at the treating investigator's discretion. Spironolactone at a starting dose of 25 mg TID plus furosemide 20-40 mg PRN is recommended.

c. Hepatic Dysfunction

Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions:

Dose Modifications for Abnormal Liver Function

Bilirubin	Alkaline Phosphatase	AST or ALT	Action
> IULN or	> 2.5 x IULN or	> 1.5 x IULN	Wait ≤ 2 weeks. If recovered*, retreatment should be at one level dose reduction. If not, remove from protocol treatment.

* Bilirubin ≤ IULN AND alkaline phosphatase ≤ 2.5 x IULN, AND AST or ALT ≤ 1.5 x IULN.

Note: A maximum of two dose reductions per patient are allowed.
IULN = institutional upper limit of normal.

d. Stomatitis

If stomatitis is present on Day 1 of any cycle, treatment should be withheld until the stomatitis has resolved.

e. Other Non-hematological Toxicities

Manage toxicities ≤ Grade 2 symptomatically, if possible, and retreat without dose reduction.

If toxicities ≥ Grade 3, drug should be held until resolution to ≤ Grade 1, then reinstituted, if medically appropriate, with a one level dose reduction.

Unacceptable toxicity from docetaxel is defined as one or more of the following:

Grade ≥ 3 nonhematologic toxicity (excluding nausea and vomiting) despite 2 prior dose reductions

Severe fluid retention not responsive to symptomatic therapy or dose reduction

Grade 4 vomiting despite antiemetics and dose reductions

Grade 4 hematologic toxicity despite two prior dose reductions. However, Grade 4 neutropenia must be either > 7 days in duration or must be accompanied by fever (single elevation in oral temperature > 38.5°C) requiring parenteral antibiotics or with documented infection to be considered an unacceptable toxicity (despite two prior dose reductions).

8.5 Dose Modification Contacts

For treatment or dose modification questions, please contact Drs. Vassiliki Papadimitrakopoulou and Hossein Borghaei at **S1400A**MedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

8.6 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Coordinator and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Arm 1 MEDI4736

		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Subsequent Cycles β		Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14		
PHYSICAL																	
History & Physical Exam	X			X		X		X		X		X		X		X	
Weight & Performance Status	X			X		X		X		X		X		X		X	
Vital Signs £	X	X		X		X		X		X		X		X			
Disease Assessment Ω	X							X						X		X	
Toxicity Notation				X		X		X		X		X		X		X	
Smoking Status Assessment	X															X	
LABORATORY																	
CBC/Diff/Platelets/Hgb	X€			X		X		X		X		X		X		X	
Serum Bilirubin	X€			X		X		X		X		X		X		X	
ALT or AST	X€			X		X		X		X		X		X		X	
Serum Creatinine/Calc CrCl	X€			X		X		X		X		X		X		X	
TSH/Free T3/T4 π	X€					X				X				X		X	
LDH ¥	X€																
Albumin ¥	X€																
X-RAYS AND SCANS																	
CT or MRI for Disease Assessment Ω	X							X						X		X	
Brain CT/MRI	X																
EKG	X									X©							
Image Submission Σ	X							X						X		X	
SPECIMEN SUBMISSION																	
Tissue for Banking																	X§
Blood for Banking ƒ	X			X				X		X							X
Whole Blood-PAXgene	X													X¿			

Calendar continued on next page. Click here for footnotes.

REQUIRED STUDIES	PRE-STUDY	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Subsequent Cycles β		Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14		
TREATMENT																	
Arm 1: (14 day cycle)																	
MEDI4736		X		X		X		X		X		X		X			

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

Footnotes for Calendar 9.1 (MEDI4736):

Ω CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.2c of **S1400**) must be repeated every 6 weeks (± 7 day window) for the first year, then every 3 months until disease progression. Disease progression must be confirmed by a second consecutive determination of progression at least 28 days from the date of initial documentation of progression (see Section 10.0).

Σ Submit scans as outlined in Section 14.0 and Section 15.0 of **S1400A**.

£ Vital signs (Temperature, Blood Pressure, Pulse, and Respiratory Rate) are to be performed pre-study and pre-infusion, during, and post-infusion at every cycle. Vital signs are to be reported on the **S1400A** Onstudy and **S1400A** Treatment forms.

© EKG are to be performed per local institutional guidelines with a recommendation of every 8 weeks.

β During continued treatment, items marked under physical and laboratory should be performed at every subsequent cycle unless otherwise noted. Disease assessments are to take place every 6 weeks for the first year, then every 3 months. Assessments will follow Best Practices for SWOG Studies: https://swog.org/Members/Download/QA/Best%20Practices%20upddate.pdf, however the disease assessment window is ± 7 days. Treatment and evaluation will continue until any of the criteria in Section 7.3 is met.

Δ After off treatment prior to progression, patients should be followed by repeating indicated tests every 3 months for the first year, then every 6 months for up to 3 years from date of sub-study registration. Patients who complete a year of MEDI4736 may be eligible for re-treatment following progression.

√ After off treatment after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at end of year 3 from date of sub-study study registration. Patients who complete a year of MEDI4736 may be eligible for re-treatment following progression.

§ With patient's consent, an additional research biopsy within 1 month after the time of first progression among patients who had a response to MEDI4736 (in the opinion of the treating physician) must be collected (see Section 15.0 of **S1400A**.

ƒ With patient's consent, additional research blood draws will be collected (see Section 15.0 of **S1400A**).

π TSH/Free T3/T4 are required at pre-study and if clinically indicated must be repeated every 4 weeks throughout treatment, then every 8 weeks prior to progression, or more often as clinically indicated.

¥ Results of these tests do not determine eligibility but are recommended prior to sub-study registration.

¿ With patient's consent, Whole Blood in a PAXgene tube must be collected at pre-study, Week 13 and 25 (see Section 15.0 of **S1400A**).

€ If these tests are obtained within 14 days prior to treatment as part of standard of care, tests need not be repeated.

9.2 Arm 2 Docetaxel

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Subsequent Cycles β			Off Tx Follow-Up Prior to Prog Δ	Off Tx Follow-Up After Prog √
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15		
PHYSICAL																		
History & Physical Exam	X				X			X			X			X			X	
Weight & Performance Status	X				X			X			X			X			X	
Vital Signs £	X				X			X			X			X				
Disease Assessment Ω	X							X						X			X	
Toxicity Notation					X			X			X			X			X	
Smoking Status Assessment	X																X	
LABORATORY																		
CBC/Diff/Platelets/Hgb	X				X			X			X			X			X	
Serum Bilirubin	X				X			X			X			X			X	
ALT or AST	X				X			X			X			X			X	
Serum Creatinine/Calc CrCl	X				X			X			X			X			X	
TSH/Free T3/T4 π	X							X						X			X	
LDH ¥	X																	
Albumin ¥	X																	
X-RAYS AND SCANS																		
CT or MRI for Disease Assessment Ω	X							X						X			X	
Brain CT/MRI	X																	
EKG	X							X©										
Image Submission Σ	X							X						X			X	
SPECIMEN SUBMISSION																		
Blood for Banking *f*	X				X			X			X							X

Calendar continued on next page. Click here for footnotes.

REQUIRED STUDIES	PRE-STUDY	Cycle 1 Wk 1	Wk 2	Wk 3	Cycle 2 Wk 4	Wk 5	Wk 6	Cycle 3 Wk 7	Wk 8	Wk 9	Cycle 4 Wk 10	Wk 11	Wk 12	Subsequent Cycles β Wk 13	Wk 14	Wk 15	Off Tx Follow-Up Prior to Prog Δ	Off Tx Follow-Up After Prog √
TREATMENT																		
Arm 2: (21 day cycle)																		
Docetaxel		X			X			X			X			X				
Dexamethasone		X			X			X			X			X				

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

Footnotes for Calendar 9.2 (Docetaxel):

Ω CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.2c of **S1400**) must be repeated every 6 weeks (± 7 day window) while on treatment until disease progression. Disease progression must be confirmed by a second consecutive determination of progression at least 28 days from the date of initial documentation of progression (see Section 10.0).

Σ Submit scans as outlined in Section 14.0 and Section 15.0 of **S1400** and **S1400A**.

£ Vital signs (Temperature, Blood Pressure, Pulse, and Respiratory Rate) are to be performed pre-infusion, during, and post-infusion at baseline and every cycle.

© EKG are to be performed per local institutional guidelines with a recommendation of every 8 weeks.

β During continued treatment, items marked under physical and laboratory should be performed at every subsequent cycle. Disease assessments are to take place every 6 weeks. Assessments will follow Best Practices for SWOG Studies: https://swog.org/Members/Download/QA/Best%20Practices%20upddate.pdf, however the disease assessment window is ± 7 days. Treatment and evaluation will continue until any of the criteria in Section 7.3 are met.

Δ After off treatment prior to progression, patients should be followed by repeating indicated tests every 3 months for the first year, then every 6 months for up to 3 years from date of sub-study registration.

√ After off treatment and after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at end of year 3 from date of sub-study study registration.

ƒ With patients consent, additional research blood draws must be collected (see Section 15.0 of **S1400A**).

π TSH/Free T3/T4 are required at pre-study and must be repeated every 6 weeks until disease progression.

¥ Results of these tests do not determine eligibility but are recommended prior to sub-study registration.

9.3 Arm 3 MEDI4736 - Retreatment

		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Subsequent Cycles β		Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14		
PHYSICAL																	
History & Physical Exam	X			X		X		X		X		X		X		X	
Weight & Performance Status	X			X		X		X		X		X		X		X	
Vital Signs £	X	X		X		X		X		X		X		X			
Disease Assessment Ω	X							X						X		X	
Toxicity Notation				X		X		X		X		X		X		X	
LABORATORY																	
CBC/Diff/Platelets/Hgb	X€			X		X		X		X		X		X		X	
Serum Bilirubin	X€			X		X		X		X		X		X		X	
ALT or AST	X€			X		X		X		X		X		X		X	
Serum Creatinine/Calc CrCl	X€			X		X		X		X		X		X		X	
TSH/Free T3/T4 π	X€					X				X				X		X	
LDH ¥	X€																
Albumin ¥	X€																
X-RAYS AND SCANS																	
CT or MRI for Disease Assessment Ω	X							X						X		X	
Brain CT/MRI	X																
EKG	X									X©							
Image Submission Σ	X							X						X		X	
SPECIMEN SUBMISSION																	
Whole Blood-PAXgene	X													X¿			

Calendar continued on next page. Click here for footnotes.

REQUIRED STUDIES	PRE-STUDY	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Subsequent Cycles β		Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14		
TREATMENT																	
Arm 3: (14 day cycle)																	
MEDI4736		X		X		X		X		X		X		X			

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

Footnotes for Calendar 9.3 (MEDI4736 - Retreatment):

Ω CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.2c of **S1400**) must be repeated every 6 weeks (± 7 day window) for the first year, then every 3 months until disease progression. Disease progression must be confirmed by a second consecutive determination of progression at least 28 days from the date of initial documentation of progression (see Section 10.0).

Σ Submit scans as outlined in Section 14.0 and Section 15.0 of **S1400A**.

£ Vital signs (Temperature, Blood Pressure, Pulse, and Respiratory Rate) are to be performed pre-study and pre-infusion, during, and post-infusion at every cycle. Vital signs are to be reported on the **S1400A** Onstudy and **S1400A** Treatment forms.

© EKG are to be performed per local institutional guidelines with a recommendation of every 8 weeks.

β During continued treatment, items marked under physical and laboratory should be performed at every subsequent cycle unless otherwise noted. Disease assessments are to take place every 6 weeks for the first year, then every 3 months. Assessments will follow Best Practices for SWOG Studies: https://swog.org/Members/Download/QA/Best%20Practices%20upddate.pdf, however the disease assessment window is ± 7 days.
Treatment and evaluation will continue until any of the criteria in Section 7.3 is met.

Δ After off treatment prior to progression, patients should be followed by repeating indicated tests every 3 months for the first year, then every 6 months for up to 3 years from date of sub-study registration.

√ After off treatment after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at end of year 3 from date of sub-study study registration.

π TSH/Free T3/T4 are required at pre-study and if clinically indicated must be repeated every 4 weeks throughout treatment, then every 8 weeks prior to progression, or more often as clinically indicated.

¥ Results of these tests do not determine eligibility but are recommended prior to sub-study registration.

¿ With patient's consent, Whole Blood in a PAXgene tube must be collected at pre-study, Week 13 and 25 (see Section 15.0 of **S1400A**).

€ If these tests are obtained within 14 days prior to treatment as part of standard of care, tests need not be repeated.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

See **S1400** Section 10.0 for criteria for evaluation and endpoint analysis. In addition, for patients randomized to MEDI4736, progression will be evaluated using an alternative system for immune related response criteria (irRC) defined here as irRC Progression.

10.1 irRC Progression

irRC progression is defined by progression outlined in **S1400** Section 10.2d except that progression determined by appearance of new lesions or by a 20% increase in the sum of diameters must be confirmed by a second consecutive determination of progression at least 28 days from the date of initial documentation of progression.

10.2 irRC Investigator-Assessed Progression-Free Survival (irRC-IA-PFS)

From date of sub-study registration to date of first documentation of irRC-progression assessed by local review or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of irRC-progression are censored at date of last contact. For patients with a missing scan (or consecutive missing scans) whose subsequent scan(s) that determine irRC-progression, the date of irRC-progression will be the expected date of the first missing scan (as defined by the disease assessment schedule) or the date of the first scan documenting potential irRC progression, whichever is earliest.

11.0 STATISTICAL CONSIDERATIONS

Modifications to the original design of this study were deemed necessary based on emerging data regarding the availability of anti-PD1 therapy for second-line treatment of patients with squamous cell lung cancer which may render randomization of patients to docetaxel as second line standard of care non-feasible. The primary modifications include a change from the Phase II/III design employing Plan A for the Phase II component as specified in Section 11.0 of **S1400** to a single arm Phase II design. Changes to the design were made with no knowledge of the **S1400A** data.

The primary definition of investigator-assessed progression-free survival (IA-PFS) and response will be defined by RECIST 1.1 for this study. However, IA-PFS will also be assessed using a modified response criteria adapted for immunotherapy in this sub-study (immune-related response criteria IA-PFS [irRC-IA-PFS]). See Section 10.0 of **S1400A** for the definition of this outcome. This section includes details specific to **S1400A**.

11.1 Primary Objective

The primary objectives of this study are to assess the response rate (confirmed and unconfirmed, complete and partial) among all patients and the subset of PD-L1 positive patients treated with MEDI4736.

11.2 Secondary Objectives

Secondary objectives include an evaluation of IA-PFS, OS, and toxicities in all patients and an evaluation of IA-PFS and OS in the subset determined to be PD-L1 positive. Exploratory objectives include an assessment of iRC-IA-PFS in all patients and in the subset of PD-L1 positive patients treated with MEDI4736. In addition IA-PFS, OS, irRC-IA-PFS, response, and toxicity will be compared between MEDI4736 versus docetaxel in the subset of patients enrolled during the randomized portion of the study.

11.3 Sample Size, Power Justification, and Analysis Plan for Primary Objective

The sample size for patients treated with MEDI4736 is 100 patients including at least 30 PD-L1 positive patients.

Response rates will be estimated by proportions counting patients with unknown response status as non-responders. With 100 patients, the response rate with MEDI4736 can be estimated to within 10% with 95% confidence. With 30 PD-L1 patients, the response rate in this subset can be estimated to within 18% with 95% confidence. Confidence intervals excluding a 10% response rate in both the overall and within the PD-L1 positive will be considered promising evidence of an improved response rate with MEDI4736 over docetaxel. Therefore the approximate lower bound for a promising response rate would be 20% or greater among all patients and 28% among PD-L1 positive patients.

11.4 Analysis Plan for Secondary and Exploratory Objectives

Two sets of analyses will be conducted on the **S1400A** data. The so-called Single Arm Analyses will be performed on all patients on the MEDI4736 arm, enrolled both under the randomized and single arm designs of the study. The so-called Randomized Study Analyses will be performed on the subset of patients accrued under the randomized design of the study.

Single Arm Analyses

Approximately 100 patients and 30 PD-L1 positive patients treated with MEDI4736 will be available for the Single Arm Analyses.

Survival times (IA-PFS, OS, and irRC-IA-PFS) will be estimated using the method of Kaplan-Meier. Ninety-five percent confidence intervals for the medians will be estimated using the Brookmeyer-Crowley method. In addition, survival percentages at 6 months and 12 months will also be assessed. Assuming complete follow-up, 100 patients treated with MEDI4736 and 30 PD-L1 positive patients will be sufficient to estimate survival endpoints at these time points to within 10% and 18%, respectively with 95% confidence.

The frequency and severity of toxicities for MEDI4736 will be evaluated. With 100 patients, the frequency of toxicities can be estimated to within 10% with 95% confidence. Any toxicity with at least 5% prevalence has at least a 99% likelihood of being observed.

With 100 patients accrued over 14-15 months, and an additional 6 months of follow-up, this design has 85% power to rule out a median IA-PFS of 4 months or less in favor of 6 months or more with 5% type I error. The observation of a median IA-PFS of at least 5.2 months may be considered promising evidence to rule out a median PFS of 4 months or less in patients treated with MEDI4736. The null hypothesis of 4 months was chosen to encode the clinically significant benchmark (based on 3-month median IA-PFS with docetaxel) as utilized in the randomized design specified in Section 11.0 of S1400.

With 30 patients, this design has 80% power to rule out a median IA-PFS of 4 months or less in favor of 8 months or more with 5% type I error. The observation of a median IA-PFS of at least 6.5 months may be considered promising evidence to rule out a median PFS of 4 months or less in PD-L1 positive patients treated with MEDI4736. The null hypothesis of 4 months was chosen for the PD-L1 positive subgroup as there has been no published data supporting a difference in prognosis for PD-L1 positive versus PD-L1 negative patients.

Randomized Study Analyses

It is expected that 76 patients accrued over 11 months, with equal numbers per treatment arm, will be available for the Randomized Study Analyses. With the modification in design to **S1400A**, the exact sample size for these comparisons may differ from expected. It follows that if the sample size is smaller than estimated, these analyses may be underpowered and a lack of statistical association may not reflect a true lack of benefit

IA-PFS, irRC-IA-PFS and OS will be compared between treatment arms using a 1-sided 0.10 level stratified log-rank test (stratifying on randomization stratification factors). It is assumed that the median with docetaxel will be 3 and 8 months respectively for IA-PFS/irRC-IA-PFS and OS. The analysis of OS will occur upon the observation of 55 deaths, and the analysis of PFS will occur upon the observation of 66 PFS events, which will occur approximately 15 and 9 months respectively after completion of accrual to the randomized portion of the study. This design has 90% power to detect a 2-fold increase in median OS and 94% power to detect a 2-fold increase in median IA-PFS and irRC-IA-PFS.

Response rates and the frequency of toxicities will be compared using a 1-sided 0.10 level Fisher's exact test. This design has at least 85% power to detect a difference in rates of 25% between the treatment arms.

11.5 Accrual Information

The total expected accrual to **S1400A** is approximately 140 patients to achieve 100 patients assigned to MEDI4736. It is expected that approximately 76 patients will be accrued under the randomized study design (with 38 patients per arm) and approximately 62 will be accrued under the single arm design.

The anticipated accrual duration is 14-15 months from study activation. The minimum follow-up duration for this study is 6 months; therefore the anticipated timing of the final analysis is 20-21 months from study activation.

The accrual rate and duration estimate is based on the assumption that 60% of patients will be assigned to **S1400A**, a linear ramp up over the first year of study, a 70% screen success rate, accounting for the time between screening and sub-study registration and that the **S1400** accrual rate by one year is on track with 625 patient accruals per year.

It is estimated that 90% of the 100 patients (90 patients) will have sufficient tissue and have consented for future testing for PD-L1 expression. The estimated rate of PD-L1 positivity is approximately 33%. Therefore the sample size for the PD-L1 is based on 33% of 90 patients being determined to be PD-L1 positive.

11.6 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG. Group members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

This section does not apply to this sub-study.

13.0 REGISTRATION GUIDELINES

See Section 13.0 of **S1400** for registration guidelines.

13.1 Registration Timing

Patients must plan to begin treatment within 7 working days after Step 1: sub-study registration and Step 2: re-treatment registration.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3 for details.

14.3 Data Submission Procedures

a. All participating institutions must submit data electronically via the Web using Medidata Rave® at the following url:
https://login.imedidata.com/selectlogin

1. If prompted, select the 'CTEP-IAM IdP' link.
2. Enter your valid and active CTEP-IAM user ID and password. This is the same account used for the CTSU members' web site and OPEN.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU) please refer to the CTSU Participation Table on Page 5 of **S1400**.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION STEP 1, SUBMIT:

S1400A Onstudy Form

Smoking Status Assessment Form

Baseline Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at baseline (NOTE: Upload reports via the Source Documentation: Baseline form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease at baseline as specified in Section 15.4.

b. WITHIN 7 DAYS OF REGISTRATION STEP 2, SUBMIT

S1400A Re-Treatment Eligibility Verification Form

Baseline Tumor Assessment Form (RECIST 1.1)

Submit radiology reports from all scans performed to assess disease at baseline (NOTE: Upload reports via the Source Documentation Baseline form found in the Re-treatment folder in Rave®)

c. IF PATIENT CONSENTS, SUBMIT SPECIMENS:

Specimens as specified in Section 15.0.

d. IMMEDIATELY AFTER EACH CYCLE (Arm 1, MEDI4736: 1 Cycle = 14 days, Arm 2, Docetaxel: 1 Cycle = 21 days, Arm 3, RETREATMENT MEDI4736: 1 Cycle = 14 days) OF TREATMENT, SUBMIT**:**

S1400A Treatment Form

S1400A Adverse Event Form

S1400A Laboratory Values Form.

e. WITHIN 7 DAYS AFTER EVERY DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION [see **S1400A** Section 9.0 for Disease Assessment Schedule]), SUBMIT:

Follow-Up Tumor Assessment Form (RECIST 1.1) documenting results of assessment

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in Section 15.4.

For patients on Arm 3 who enroll to be re-treated with MEDI4736, these documents must be submitted **after every disease assessment until a second progression**.

f. WITHIN 7 DAYS OF DISCONTINUATION OF TREATMENT OR RE-TREATMENT, SUBMIT:

Off Treatment Notice documenting reasons for off treatment

S1400A Treatment Form

S1400A Adverse Event Form

S1400A Laboratory Values Form.

Smoking Status Assessment Form (not required during Re-Treatment)

g. ONCE OFF TREATMENT SUBMIT EVERY 6 MONTHS FOR THE FIRST 2 YEARS FROM **S1400A** STEP 1 REGISTRATION, THEN AT THE END OF YEAR 3 SUBMIT:

Advanced NSCLC Follow-Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported).

h. WITHIN 7 DAYS OF PROGRESSION/RELAPSE, SUBMIT:

Site(s) of Progression or Relapse Form

Follow-Up Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in Section 15.4.

i. WITHIN 28 DAYS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information. In addition, if the patient was still on protocol treatment, submit materials specified in Section 14.4e or if patient was no longer on treatment, submit a final Advanced NSCLC Follow-Up Form.

15.0 SPECIAL INSTRUCTIONS

15.1 SWOG Specimen Tracking System (STS)

See **S1400** Section 15.1 for SWOG Specimen Tracking System (STS) instructions.

15.2 Correlative Studies and Banking (Optional for Patients)

Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) are considered optional for the patient:

a. With patient's consent, specimens must be collected and submitted as follows:

1. Peripheral Blood:

Specimens must be collected at the following times:

Arm 1: MEDI4736
- Baseline (see Section 15.3 of **S1400**)
  If a patient provided blood at pre-screening/screening (see Section 15.3 of **S1400**) and registration to **S1400** was within 42 days from sub-study registration, then that blood specimen can count as pre-study blood
- Weeks 3, 7, 9 Patients that go off treatment are not required to continue to submit specimens.
- First Progression after study treatment

Arm 2: Docetaxel
- Screening/Pre-Screening (see Section 15.3 of **S1400**)
- Weeks 4, 7, 10
- First Progression after study treatment

Approximately 8-10 mL of blood must be collected in EDTA tubes. Blood should be processed within one hour after venipuncture. If immediate processing within this time frame is not possible, EDTA tubes that are not processed immediately should be refrigerated at 4˚C. The approximate time from collection to processing should be recorded as part of the patient's source documentation. EDTA tubes must be centrifuged at 800 g for 10 minutes at 4˚C for the collection of plasma. Plasma must be transferred to one 15 ml centrifuge tube and spun again at 800g for an additional 10 minutes. Plasma must then be pipetted into 1 ml coded cryovials at 0.5 ml aliquots. Plasma must be clear before freezing; no cells or debris should be present. Each buffy coat layer (the gray-white layer at the interface of blood cells and plasma, approximately 1 ml) from the blood tube must each be transferred into appropriately labeled 2-ml cryovials. Samples must be placed immediately in a -80˚C freezer to ensure long-term viability.

2. Whole Blood- RNA PAXgene Tube

Specimens must be collected at the following times for patients assigned to Arm1, MEDI4736 and Arm 3, MEDI4736 Re-Treatment:

- Baseline
- Weeks 13 and 25

Specimen Collection

Approximately 2.5 mL of blood must be collected in an RNA PAXgene tube. The PAXgene tube should be the last tube drawn or if it is the only tube to be drawn, blood should be drawn into a "discard tube" prior to drawing into the PAXgene tube. Gently invert 8 to 10 times. Allow the specimen to sit upright at room temperature for a minimum of 2 hours, then freeze the tubes upright at -20ºC or colder within 3 hours of collection. The approximate time from collection to freezer should be recorded as part of the patient's source documentation. Specimens must be shipped frozen on dry ice.

3. New Biopsy of Tumor at Time of Progression among responders to Arm 1, MEDI4736:

A new biopsy is strongly requested from patients who responded protocol treatment, Arm 1 to MEDI4736 in the opinion of the treating physician and then experienced disease progression for molecular analysis of molecular characteristics associated with mechanisms of resistance. Patients that progress on Arm 3, Re-Treatment are not required to submit a new biopsy. New biopsy should be either bronchoscopy/surgical biopsy or CT guided biopsy. The biopsy should be performed within one month after progression and should be processed as FFPE material. The minimum requirement is a block or 12 unstained sections.

b. Specimen Submission

Samples for multiple patients can be shipped in batches, at least every 3 months if not more frequently, to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201.

Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp).

c. Specimen collection kits are not being provided for this submission; sites must use institutional supplies.

15.3 PD-L1 IHC Testing

With patient's consent, tissue will be sent from the SWOG Specimen Repository to Clarient Inc. for PD-L1 Testing (see Section 18.2 for details).

15.4 Radiology Review (Required)

CT, PET/CT, and/or MRI images must be locally read and interpreted by the local site radiology service. Imaging exams must then be submitted to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD Imaging Submission procedures for central data collection and quality control (QC) check as well as retrospective central review.

a. CT, PET/CT, and/or MRI images must be submitted to IROC Ohio for central review at the following timepoints:

- Baseline
- Every 6 weeks for the first year, then every 3 months until progression

All study participants must have a CT (or MR or PET/CT) exam prior to sub-study entry. Participants must then undergo additional imaging every 6 weeks for the first year, then every 3 months until progression of disease. The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams (see Section 10.1c). Each exam should be performed per Section 18.1c. IROC will perform a QC of the imaging exams.

Clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinical appropriate considerations.

Central review of scans will not be triggered if the study will not be submitted to the FDA for FDA approval of the investigational therapy. Central review of scans will be triggered only if deemed necessary for FDA evaluation. A detailed description of the central radiology PFS review, including image acquisition parameters and image submission instructions, can be found in Section 18.1c.

b. TRIAD Digital Image Submission

TRIAD is the secure electronic image upload application utilized for IROC Services of this trial. TRIAD de-identifies and validates the images as they are transferred.

1. TRIAD Access Requirements:

TRIAD will be the sole means of image transfer to the IROC Ohio. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging.

- Site staff who submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP-IAM account (see Section 13.2).

- To submit images, the site user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

2. TRIAD Installations:

After a user receives a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

Questions regarding image submissions, including TRIAD, should be directed to SWOG1400@irocohio.org or call IROC Ohio at 614-293-2929.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See Section 18.2 of **S1400A** for information on adverse events of special interest.

b. Reporting method

This study requires that expedited adverse event reporting use the NCI's Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808 or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1 or 16.2, as applicable.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent(s) used in Arm 1 of this study is MEDI4736. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] MEDI4736 Arm 1:

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events (if applicable) are found in the Section 16.1f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a non-CTEP-IND:**

1) **Group-specific instructions.**

Supporting Documentation Submission - Within 5 **calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- Autopsy report (if applicable)
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

2) The adverse events listed below are considered to be adverse events of special interest (AESIs) and require expedited reporting for this trial:

- ≥ Grade 1 pneumonitis
- ≥ Grade 2 AST or ALT if after evaluation it meets Hy's Law
- ≥ Grade 2 bilirubin
- Any Grade Infusion Reactions
- Any Grade Hypersensitivity Reactions

3) For study arm 1, the adverse event listed below does **not** require expedited reporting via CTEP-AERS: *Grade 4* ***neutropenia***

g. **Expedited reporting for <u>commercial</u> agents**

Commercial reporting requirements are provided in Table 16.2. The commercial agent(s) used in Arm 2 of this study is docetaxel. If there is any question about the reportability of an adverse event, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients on study arm 2 who have received the commercial drug(s) listed in Section 16.1g above within 30 days of the last administration of the commercial agent(s).

17.0 ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via NCI CTEP-AERS within 10 calendar days of learning of the event[b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. Reporting Secondary Malignancy, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

   For more information see:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

   *Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

17.0 BIBLIOGRAPH

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18.0 APPENDIX

18.1 MEDI4736 Background of Adverse Events of Special Interest (AESIs)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of these investigational products.

The adverse events listed below are considered to be AESI and require expedited reporting for this trial. See Section 16.1 for Adverse Event Reporting Requirements. Guidelines for management of these AEs are outlined in Section 8.3.

Pneumonitis
Adverse events of pneumonitis are of interest for the sponsor, as pneumonitis has been observed with other anti-PD-1 and anti-PD-L1 mAbs, and with MEDI4736.

Guidelines for the management of patients with irAEs including pneumonitis are described in Section 8.3.

Infusion reactions
Adverse events of infusion reactions (also termed infusion-related reactions) are of special interest to the sponsor and are defined, for the purpose of this protocol, as all AEs occurring from the start of investigational product infusion up to 48 hours after the infusion start time.

Hypersensitivity Reactions
Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy. (*35*) As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the mAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnoea, cyanosis, respiratory failure, urticaria, pruritis, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness. Infusion of biological products is commonly associated with infusion-related reactions.

Anaphylaxis and infusion-related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion-related reactions are commonly observed during or shortly after the first time exposure to therapeutic mAbs delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike infusion related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic skin and/or mucosal reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to investigational products, and consider the above mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of investigational product are to be judged by the investigator at his/her own discretion. For the investigator's convenience and in order to facilitate consistency in judgments refer to the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis. http://www.niaid.nih.gov/topics/foodallergy/Pages/default.aspx

Hepatic function abnormalities (hepatotoxicity)

Hepatic function abnormality meeting the definition of Hy's law (ie, any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN) is considered an AESI. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (eg, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

Gastrointestinal Disorders

Diarrhea, colitis, and enterocolitis are irAEs that have been reported with MEDI4736. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed.

18.2 PD-L1 IHC Testing

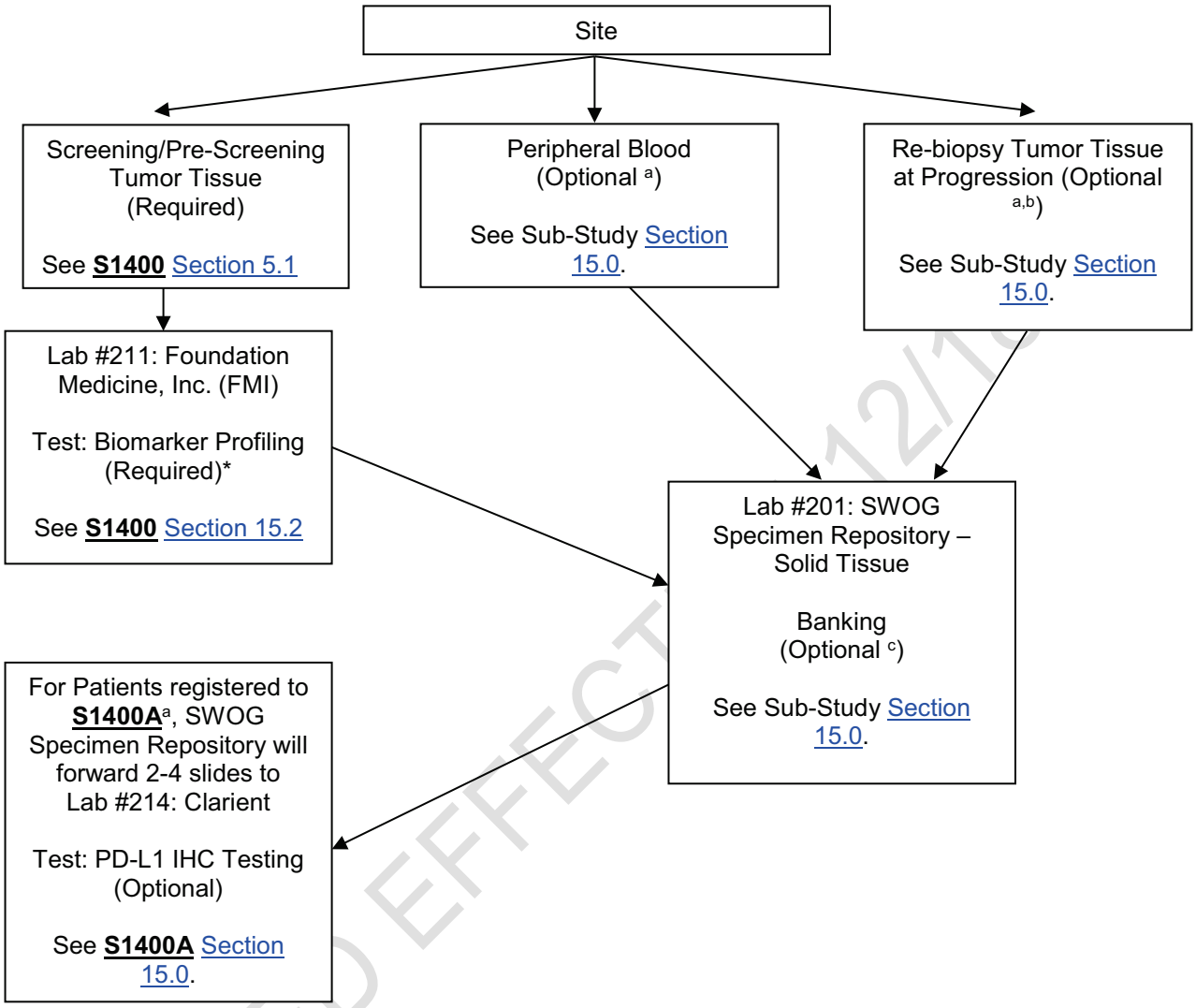
PD-L1 IHC testing will be performed on tumor specimens from patients registered to **S1400A** who consented to future testing in **S1400**. Tumor specimens will be shipped from the SWOG specimen repository at Nationwide to Clarient on a bi-weekly basis. The SWOG statistical center will provide Nationwide with the list of patient specimens to ship to Clarient. All specimens must be entered and tracked using the online SWOG Specimen Tracking System (STS). Shipments to Clarient will be accompanied by pathology report, SWOG patient ID, specimen ID, sample collection date, and sample type.

Assay Description
Medimmune has developed a technically validated immunohistochemistry (IHC)-based assay for PD-L1 determination in partnership with Ventana Medical Systems Inc. a CAP-accredited/CLIA-certified laboratory (Tucson, AZ).

Laboratory
Clarient will serve as the central laboratory for testing PD-L1 expression in patients who register to **S1400A** and have consented to additional testing beyond NGS.

Specimen Requirements
The preferred thickness is 4 micron unstained tissue sections; although 5 micron unstained tissue sections are allowable. For patients with tumor blocks at Nationwide, Nationwide will prepare 4 micron unstained slides. At least 100 tumor cells is defined to be sufficient viable tumor tissue for PD-L1 IHC testing. Fine needle aspirates are not acceptable. A minimum of 2 and preferably 4 unstained tissue sections along with a hematoxilyn-eosin (H&E)-stained slide or Aperio H&E-stained image will be sent to Clarient for PD-L1 IHC testing for consented patients with sufficient tissue.

Specimen Flow Diagram



a With patient's consent.

b Among patients who initially responded to protocol treatment.

c With patient's consent, any remaining tissue will be sent to the SWOG Specimen Repository Solid Tissue, Myeloma and Lymphoma Division, Lab #201, for future exploratory analysis.