SWOG CANCER RESEARCH NETWORK

Version Date: October 21,2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Mariah Norman, Protocol Coordinator (E-mail: mnorman@swog.org)

RE: Lung-MAP: Revision for **S1400F**

REVISION #32

IRB Review Requirements
(√) Expedited review allowed

Status Change
(√) IRB Review only

Protocol changes
(√) Dose Modification changes
(√) Informed Consent changes
(√) Patient notification not required
(√) Editorial / Administrative changes
(√) Dose Modification

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB*:* Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #32

This revision has been prepared for **S1400F** to: (1) Incorporate updated standard template language into the protocol; (2) Modify eligibility criteria to clarify the requirement for squamous patients only; and (3) Provide updated dose modifications.

1. S1400VCP – Version Control Protocol has been updated.

Protocol Changes

2. The version date has been updated.

3. Throughout the protocol, formatting, typographical errors, pagination, and cross-references have been corrected as needed.

4. **Title Page:** The statement under the NCT number has been changed to “this is an FDA registration study”

5. **Schema:** Clarified patients must have pure squamous cell lung cancer

6. **Table of Contents:** The page numbers have been updated.

7. **Section 5.1b, Sub-Study Specific Disease Related Criteria:** This criterion has been added to clarify that patients must have “histologically or cytologically confirmed Stage IV or recurrent pure squamous cell lung cancer”.

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

In partnership with nstitute NCI Community Oncology Research Program

8. **Section 8.3a, Dose Interruptions – MEDI4736 (Durvalumab) or in Combination with Tremelimumab:** This section has been updated to reflect current guidelines.

- Throughout this section the term "discuss with" has been changed to "consider discussing with". In some instances, "consult" has been changed to "consider consulting".
- Immune-Related Adverse Events (irAEs) for toxicities not noted below: The note to "For ≥ Grade 3 asymptomatic amylase or lipase levels…" have been removed.
- Pneumonitis/ Interstitial Lung Disease ILD: ILD have been clarified as Interstitial Lung Disease.
- Diarrhea/Enterocolitis: "Enterocolitis" has been updated to "Colitis". "≥ Grade 3" has been changed to "Grade 3" and the interruption for this toxicity has been updated. The toxicity of ≥ Grade 4 and its applicable interruption has been added.
- Hepatitis (Elevated LFTs) – Hepatitis: This table has been added to address toxicities of Hepatitis where transaminase rise is not isolated but occurs in a setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR).
- Rash (excluding Bullous skin formations): The statement regarding patients with endocrinopathies has been removed.
- Endocrinopathy: Type 1 diabetes mellitus has been added to the list of endocrinopathy examples. Toxicity management for all Grades has been revised to include additional guidelines.
- Immune Mediated Neurotoxicity: Grade 3 and Grade 4 toxicity guidelines have been added.
- Immune Mediated Peripheral Neuromotor Syndromes, such as Guillain-Barre and Myasthenia Gravis: For Grade 1 the statement "unless the symptoms are very minor and stable" following "obtain neurology consult" was removed.
- Myositis/ Polymyositis ("Poly/myositis"): This table has been added with guidelines for myositis/ polymyositis.

Model Consent Form Changes

1. The version date has been updated. No additional changes were made to the consent.

This memorandum serves to notify the NCI, CIRB and SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Natasha Leighl, BSc, MMSc, MD
Naiyer Rizvi, MD
AstraZeneca

S1400F: (Non-Match sub-study): Anti-PD-1/PD-L1 Resistant – MEDI4736 (Durvalumab) plus Tremelimumab

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

A MASTER PROTOCOL TO EVALUATE BIOMARKER-DRIVEN THERAPIES AND IMMUNOTHERAPIES IN PREVIOUSLY-TREATED NON-SMALL CELL LUNG CANCER

A PHASE II STUDY OF MEDI4736 (DURVALUMAB) PLUS TREMELIMUMAB AS THERAPY FOR PATIENTS WITH PREVIOUSLY TREATED ANTI-PD-1/PD-L1 RESISTANT STAGE IV SQUAMOUS CELL LUNG CANCER (LUNG-MAP NON-MATCH SUB-STUDY)

NCT # 03373760

This is an FDA registration study. There will be additional centralized and on-site monitoring conducted in addition to routine audits. Sites must also maintain a study specific Trial Master File for this study.

Lung-MAP and its sub-studies are being conducted under SWOG IND 119672 and CIRB. The Lung-MAP Study is considered a single study under one IND, consisting of the Screening Protocol and multiple sub-studies. Each sub-study protocol operates independently and has its own version date. However, for regulatory purposes, all Lung-MAP sub-study protocols should be processed as a single study for Continuing Review.

SUB-STUDY CHAIRS:

Natasha Leighl, BSc, MMSc, M.D.
(Medical Oncology)
NCTN Group: CCTG
Univ. Health Network-Princess Margaret Hospital
610 University Avenue
Toronto, Ontario, Canada M5G 2M9
Phone: 416/946-4645
FAX: 416/946-6546
E-mail: Natasha.leighl@uhn.ca

Naiyer Rizvi, M.D.
(Medical Oncology)
NCTN Group: SWOG
Columbia University Medical Ctr
Division of Hematology-Oncology
177 Fort Washington Ave, Ste 6GN435
New York, NY 10032
Phone: 646/317-6344
FAX: 212/305-3035
E-mail: nar2144@cumc.columbia.edu

STUDY AGENTS:

Available from Pharmaceutical Collaborator:
SWOG Held IND:
MEDI4736 (Durvalumab) (NSC 778709) (IND-119672)
Tremelimumab (NSC 744483) (IND-119672)

BIOSTATISTICIANS:

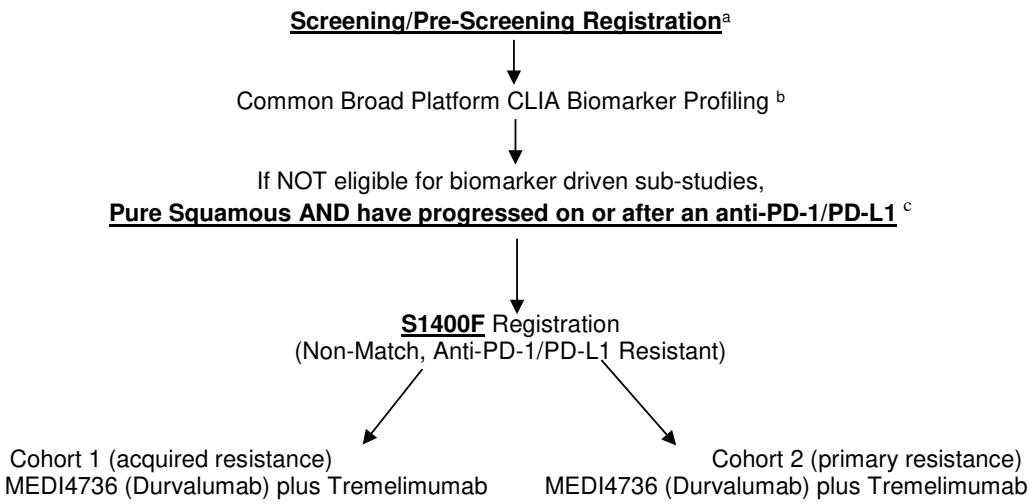
Mary Redman, Ph.D.
Katherine Minichiello, M.S.
Jieling Miao, M.S.
James Moon, M.S.
SWOG Statistics & Data Management Center
1100 Fairview Ave N, M3-C102
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: mredman@fredhutch.org
E-mail: kgriffin@fredhutch.org
E-mail: jmiao@fredhutch.org
E-mail: jmoon@fredhutch.org

TABLE OF CONTENTS

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	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 on the SWOG Workbench via the SWOG website (www.swog.org).
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.		
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center by phone or email: 206/652-2267 LUNGMAPquestion@crab.org **For treatment or toxicity related questions** contact the S1400FMedicalQuery@swog.org.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line: 1-888-823-5923 S1400contact@westat.com All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

SCHEMA



[a] Patients may have screened/pre-screened on **S1400** or **LUNGMAP**
NOTE: At the time of **LUNGMAP** activation, **S1400** screening will close to accrual. Please see the Lung-MAP protocol training webpage for additional information (https://www.swog.org/required-lung-map-s1400-training).

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

[c] Notification of sub-study assignment will be provided by the SWOG Statistics and Data Management Center (see Section 11.0 in S1400 or LUNGMAP for details).

1.0 OBJECTIVES

The design and objectives for **S1400** Non-match studies are described in Sections 1.0 and Section 11.0 of **S1400**. This study will enroll patients into two parallel and independently evaluated cohorts; patients will be defined as either acquired (Cohort 1) or primary (Cohort 2) resistance. See Section 6.0 for the definition of the cohorts.

The objectives within each cohort are:

1.1 Primary Objective

To evaluate the objective response rate (confirmed and unconfirmed, complete and partial) by RECIST 1.1 among patients treated with MEDI4736 (Durvalumab) plus tremelimumab.

1.2 Secondary and Exploratory Objectives

a. To estimate the duration of response (DoR) among patients who achieve a complete response (CR) or partial response (PR) (confirmed and unconfirmed) by RECIST 1.1.

b. To estimate the duration of response (DoR) per immune-related response criteria among patients who achieve a complete response (CR) or partial response (PR) (confirmed and unconfirmed) by RECIST 1.1

c. To evaluate overall survival (OS) among patients treated with MEDI4736 (Durvalumab) plus tremelimumab

d. To evaluate investigator-assessed progression-free survival (IA-PFS) among patients treated with MEDI4736 (Durvalumab) plus tremelimumab.

e. To evaluate IA-PFS assessed by immune-related response criteria (irRC-IA-PFS) as defined in Section 10.1 among patients treated with MEDI4736 (Durvalumab) plus tremelimumab.

f. To evaluate the frequency and severity of toxicities associated with MEDI4736 (Durvalumab) plus tremelimumab.

1.3 Translational Medicine Objectives

a. To explore the association of potential predictive markers identified in **S1400A**, with response and progression-free survival (PFS).

b. To explore the association of PD-L1 expression status with response and PFS.

c. To contribute to an ongoing serum and tumor bank in **S1400** or **LUNGMAP**.

2.0 BACKGROUND

Lung cancer remains the leading cause of cancer, cancer-related death and economic burden from cancer worldwide. Therapeutic progress in squamous lung carcinoma, particularly in the area of targeted therapy, has lagged behind the progress made in lung adenocarcinoma, with chemotherapy as the only standard until recently. The **S1400** study is designed to advance development of targeted therapies in squamous carcinoma with genomic alterations, with enrollment into biomarker-driven sub-studies of novel agents. In addition, **S1400** provides

therapeutic opportunities for the broader population of squamous carcinoma patients not eligible for biomarker-driven studies through non-match sub-studies, to date focusing on immune checkpoint inhibitors.

After **S1400** was developed and began accrual, the standard of care for platinum-treated advanced lung cancer patients with squamous carcinoma evolved from docetaxel chemotherapy to PD-1 checkpoint inhibitor therapy. Several Phase III randomized trials have demonstrated improved survival, progression-free survival, response and even quality of life with the use of PD-1 checkpoint inhibitors compared to docetaxel in advanced pre-treated non-small cell lung cancer. Nivolumab improved survival (HR 0.59, 95% CI 0.44-0.79, p<0.001; median 9.2 versus 6.0 months), PFS (HR 0.62, 95% CI 0.47 – 0.81, p<0.001, median 3.5 versus 2.8 months) and, response (20% versus 9%, p=0.008) and quality of life compared to docetaxel in patients with advanced squamous carcinoma. *(1)* Longer duration of response (median not reached versus 8 months with chemotherapy) and significantly fewer Grade 3 or 4 treatment-related AEs (7 versus 55%) were also seen in the nivolumab arm. *(2)* Nivolumab has also been approved for use in non-squamous lung cancer based on a similar trial demonstrating improved survival, response rate and less toxicity compared to docetaxel. *(3)* Pembrolizumab, another PD-1 checkpoint inhibitor, also demonstrated significantly better survival, PFS and response compared to docetaxel in pretreated non-small cell lung cancer patients with PD-L1 tumor expression (including 21% squamous carcinoma patients). *(4)*

Despite the progress of immune checkpoint inhibition in this population, a significant number of patients will not derive long-term benefit from second-line therapy with single agent PD-1 or PD-L1 inhibitors. For this group, the next step in therapy is undefined. Many will receive docetaxel as subsequent therapy, with significant treatment-associated toxicity, response rate in the range of 10% and median survival time of 6 months or less. Better options are needed for this newly emerging population, and whether this group has the potential to benefit from further immune targeted therapy is unknown.

Both PD-1 and CTLA-4 checkpoint inhibitors have demonstrated clinical activity across a range of tumor types, including melanoma, prostate cancer and lung cancer, both small cell and non-small cell subtypes. While both CTLA-4 and PD-1 checkpoint receptors are negative regulators of T cell activation and function, they use distinct mechanisms to block T cell activity. CTLA-4 inhibition impairs T-cell activation, while PD-1 inhibition results in T cell effector dysfunction. Blockade of one T-cell checkpoint may lead to reliance on other immune mechanisms, potentially making cells more sensitive to alternate checkpoint inhibitors. Preclinical studies suggest synergistic anti-cancer activity between PD-1 and CTLA-4 receptor inhibitors.

In a relevant mouse model of melanoma, single blockade of either CTLA-4 or PD-1 enhanced the infiltration of activated T-cells into tumors, but the T-cells accumulated high levels of unblocked negative co-receptors that eventually limited their expansion. Blocking CTLA-4, PD-1 and PD-L1 simultaneously allowed T-cells to continue to survive and proliferate, and resulted in enhanced infiltration, activation and cytokine production, thereby reducing tumor-induced immune suppression and promoting tumor rejection. *(5)* In a study by Curran et al, vaccination with irradiated B16 melanoma cells expressing the Flt3-ligand (Fvax) combined with antibody blockade of the negative T-cell co-stimulatory receptor CTLA-4 promoted rejection of pre-implanted tumors. However, despite CTLA-4 blockade, T-cell proliferation and cytokine production can be inhibited by the interaction of PD-1 with its ligands PD-L1 and PD-L2 or by the interaction of PD-L1 with B7-1. The study showed that the combination of CTLA-4 and PD-1 blockade was more than twice as effective as either agent alone in promoting the rejection of B16 melanomas in conjunction with Fvax. *(6)*

In clinical studies, combination of PD-1 and CTLA-4 inhibitors has led to exciting response data although greater toxicity. Larkin *et al* compared combination nivolumab/ipilimumab with either

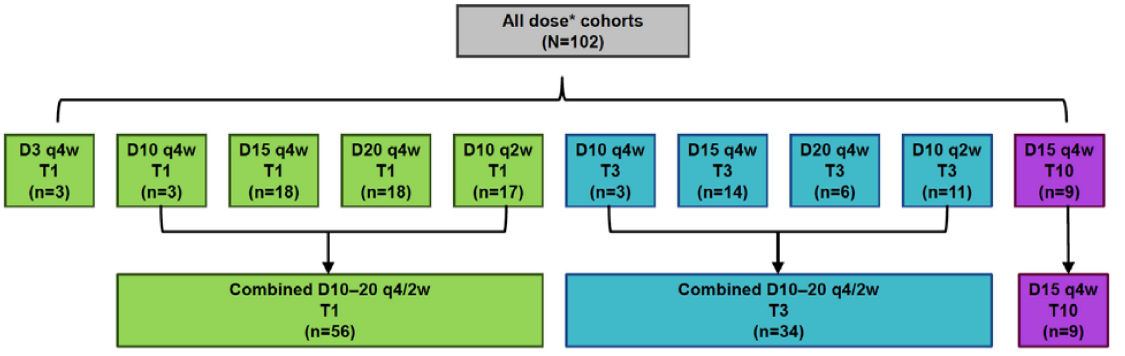
agent alone (1:1:1 randomization) as first-line therapy in advanced melanoma. Those receiving combination therapy had the longest PFS (median 11.5 v. 2.9 months with ipilimumab, HR 0.42, 99.5% CI 0.31-0.47, p<0.001; 6.9 months with nivolumab), as well as the highest response rate (57.6%). Patients with PD-L1- expressing tumors had similar PFS with either nivolumab or combination therapy (14.0 months median), although combination therapy yielded a higher response rate (72.1%, 57.5% nivolumab, 21.3% ipilimumab). However in the group with PD-L1 negative tumors, the combination yielded the best PFS (median 11.2 v. 5.3 months in the nivolumab arm), and response rate (54.8%, 41.3% nivolumab, 17.8% ipilimumab). Treatment-related Grade 3 or 4 AEs occurred more commonly in the combination arm (55%) compared to nivolumab alone (16.3%) or ipilimumab (27.3%). The most common severe events in the combination arm were diarrhea (44%), fatigue (35%) and pruritus (33%). Investigators deemed the safety profile of the combination greater than either single agent but still manageable. *(7)*

A recent report from a Phase I/II study of nivolumab plus ipilimumab in small cell lung cancer suggests higher response rates with combination therapy, 32.6% versus 18% with nivolumab alone. *(8)* Other reports of significant activity with combination therapy have also emerged from early phase trials in NSCLC, including a Phase I combination study of tremelimumab with MEDI4736 (Durvalumab) (PD-L1 inhibitor), demonstrating a 33% response rate in those with PD-L1 expressing tumors and a 27% response rate in those with PD-L1 negative tumors. *(9)*

Based on these data, a trial examining whether the addition of CTLA-4 blockade to PD-L1 blockade would improve outcome in the growing population of advanced squamous patients that progress on second-line PD-1 checkpoint inhibitor therapy would be appropriate. MEDI4736 (Durvalumab) is a human IgG1 monoclonal antibody that inhibits PD-L1 binding without induction of antibody-dependent cellular nor complement-dependent cytotoxicity, has shown clinical activity and safety across a range of solid tumors, including NSCLC. Tremelimumab, an IgG2 monoclonal antibody targeting CTLA-4 (CD152), has also shown activity across solid tumors including mesothelioma with manageable toxicity. A Phase I combination study of these two agents, both being developed by AstraZeneca, has been completed demonstrating efficacy and manageable toxicity at the recommended Phase III dose. (10)

Clinical Summary

Study D4190C00006, a Phase Ib dose-escalation and dose-expansion study of MEDI4736 (Durvalumab) in combination with tremelimumab in patients with advanced NSCLC, included patients with ECOG performance status of 0-1, and no more than three prior lines of metastic therapy. Two dosing schedules were evaluated using Q4W and alternative Q2W dosing. As of 6/1/15, a total of 102 patients have been treated in the study across 5 US centers with a median follow-up of 18.8 weeks (range 2-68). Dosing cohorts are detailed below:



D=MEDI4736 (Durvalumab); T=Tremelimumab; q#w=every # weeks; D#, T#= # mg/kg of each drug

As of 6/1/15, adverse events deemed related to protocol therapy led to treatment discontinuation in 28% of patients (29/102). Three treatment-related deaths occurred, include a case of polymositis (D10/T1), pericardial effusion (D20/T1) and myasthenia gravis/neuromuscular disorder (D20/T3). Adverse events were considered related to treatment in 82 patients (80%) and are presented in the table below. The majority of these events were <Grade 3 with Grade ≥3 events reported in 43 patients (42%). (11) Grade 1 and 2 AEs have been managed clinically without requiring dose modifications or delays. Grade 3 treatment-related AEs have been manageable and reversible with standard toxicity management guidelines, including steroids, with the exception of Patient 2000062006 who experienced myasthenia gravis and polymyositis.

Event, n (%)	D10–20 q4/2w + T1* (n=56)	D10–20 q4/2w + T3 (n=34)	D15 q4w + T10 (n=9)	All cohorts (N=102)
Related AE	41 (73)	32 (94)	8 (89)	82 (80)
Related Grade 3/4 AE	17 (30)	19 (56)	7 (78)	43 (42)
Related death†	2 (4)	1 (3)	0	3 (3)
Related SAE	12 (21)	18 (53)	7 (78)	37 (36)
Related AE leading to discontinuation	9 (16)	15 (44)	5 (56)	29 (28)

Selected treatment-related AEs of interest		Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3
Clinical conditions	Diarrhea	13 (23)	4 (7)	16 (47)	6 (18)	4 (44)	1 (11)	33 (32)	11 (11)
	Colitis	2 (4)	1 (2)	8 (24)	6 (18)	2 (22)	2 (22)	12 (12)	9 (9)
	Enteritis	1 (2)	1 (2)	0	0	0	0	1 (1)	1 (1)
	Pruritus	11 (20)	0	7 (21)	0	3 (33)	0	21 (21)	0
	Rash	6 (11)	0	7 (21)	0	2 (22)	0	15 (15)	0
	Hypothyroidism	5 (9)	1 (2)	4 (12)	0	1 (11)	0	10 (10)	1 (1)
	Pneumonitis	0	0	3 (9)	2 (6)	2 (22)	2 (22)	5 (5)	4 (4)
Investigations	Amylase increased	9 (16)	1 (2)	5 (15)	2 (6)	2 (22)	0	17 (17)	3 (3)
	Lipase increased	7 (13)	5 (9)	4 (12)	2 (6)	1 (11)	1 (11)	12 (12)	8 (8)
	ALT increased	6 (11)	2 (4)	4 (12)	1 (3)	0	0	10 (10)	3 (3)
	AST increased	4 (7)	3 (5)	3 (9)	1 (3)	0	0	7 (7)	4 (4)

Data cut-off: June 1, 2015. *Excludes D3 q4w T1 cohort (n=3).
†These patients also had Grade 3/4 AEs. Deaths: D10/T1 = polymyositis, D20/T1 = pericardial effusion, D20/T3 = neuromuscular disorder
AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; D, durvalumab; q#w, every # weeks; SAE, serious adverse event; T, tremelimumab.

As of 2/20/15, MEDI4736 (Durvalumab) PK (n = 55) and tremelimumab PK (n = 26) data were available from 10 cohorts following MEDI4736 (Durvalumab) every 4 weeks (Q4W) or Q2W dosing in combination with tremelimumab Q4W regimens. An approximately dose-proportional increase in PK exposure (C_{max} and area under the concentration-time curve from 0 to 28 days [AUC_{0-28}]) of both MEDI4736 (Durvalumab) and tremelimumab was observed. While steady state PK parameters were based on a limited number of patients, the observed PK exposures of MEDI4736 (Durvalumab) and tremelimumab in combination were consistent with monotherapy data of each agent, indicating no PK interaction.

As of 2/20/15, ADA data were available from 60 patients for MEDI4736 (Durvalumab) and 53 patients for tremelimumab in Study D4190C00006. Four of 60 patients were ADA positive for anti-MEDI4736 (Durvalumab) antibodies and 1 of 53 for anti-tremelimumab antibodies post treatment. There was no clear relationship between ADA and safety, efficacy nor dose of either agent.

Efficacy updates are available from the 2015 Annual Meeting of the Society for Immunotherapy of Cancer (data cut-off 6/1/15). *(12)* Of 84 response evaluable patients, 21 (25%) had confirmed or unconfirmed response to therapy. In those with PD-L1 expression in ≥ 25% of cells, responses were seen in 35% (7/20). In those with PD-L1 expression in 1-24% of cells, responses were seen in 22% and in those with PD-L1 negative tumors, responses were seen in 33% (9/27). Median time

to response was 7.1 weeks (range 5.0 -37.4), with a median duration of 16.7 weeks (0.1-49.1). At data cut-off on 6/1/15, responses were ongoing in 14 of 21 patients (66%).

The dose recommended for Phase III was MEDI4736 (Durvalumab) 20 mg/kg q4weeks plus tremelimumab 1 mg/kg q4weeks, based on aggregate safety, PK, PD and efficacy data. No dose-limiting toxicities were reported. Efficacy data suggested that the 20 mg/kg MEDI4736 (Durvalumab) + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. The response rate in all patients treated with tremelimumab 1 mg/kg was 28% (11/39), similar to the 25% overall response rate across doses. In those with ≥ 25% PD-L1+ tumors, responses were seen in 3/9 (33%), 1-24% PD-L1 positive tumors, the response rate was 26% (6/23) and in those with PD-L1 negative tumors, half experienced tumor response (6/12).

Fixed dosing for MEDI4736 (Durvalumab) and tremelimumab has been recommended by AstraZeneca for patients with >30 kg body weight. This is based on population PK models for each agent indicating similar steady stage PK concentrations with less inter-subject variability with fixed dosing regimens. Based on an average body weight of 75 kg, the fixed dose of MEDI4736 (Durvalumab) 1500 mg q4weeks is recommended (equivalent to 20 mg/kg q4weeks). Similarly, 75 mg q4weeks of tremelimumab (equivalent to 1 mg/kg q4 weeks) is recommended.

Four cycles of combination MEDI4736 (Durvalumab)/tremelimumab are proposed, followed by MEDI4736 (Durvalumab) monotherapy until disease progression. This is based on melanoma data suggesting that patients responding to CTLA-4 inhibitor ipilimumab appear to derive long-term benefit with 22% of patients alive at 3 years. Other PD-1 targeting agents have been developed with protocol-mandated drug discontinuation after a specified treatment period. Despite stopping drug, ongoing prolonged responses have been described across multiple studies of multiple PD-1/PD-L1 inhibitors, including combination nivolumab and ipilimumab. (13)

Sub-study **S1400I** tests whether combination CTLA-4 and PD-1 checkpoint inhibition will improve outcomes compared to PD-1 checkpoint inhibition alone in unmatched squamous patients as second-line therapy. By contrast, in the current sub-study **S1400F**, we hypothesize that a subgroup of patients that do not respond to single PD-1 checkpoint inhibition may benefit from combination checkpoint blockade, specifically the addition of a CTLA-4 inhibitor to ongoing PD-1 inhibitor therapy. Given the growing population of patients that will develop cancer progression during PD-1 checkpoint blockade monotherapy, the proposed study design of adding CTLA-4 inhibition in this population to ongoing PD-1 inhibition is novel and appropriate. As outlined in Section 3.1, the combination of MEDI4736 (Durvalumab) and tremelimumab has shown activity and manageable toxicity, and is worthy of further study in this setting. It will also offer an opportunity to explore potential markers of benefit and/or toxicity.

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-CTLA-4 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

Investigator Brochures

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

For this sub-study, MEDI4736 (Durvalumab) and tremelimumab are investigational and are 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, requests may be submitted to the CTSU website by completing the CTSU Request for Clinical Brochure.

3.1 MEDI4736 (Durvalumab) – Liquid (NSC 778709) (IND-119672)

a. PHARMACOLOGY

Mechanism of Action: MEDI4736 (Durvalumab) 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 (Durvalumab) relieves PD-L1-mediated suppression of human T-cell activation. MEDI4736 (Durvalumab) 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 (Durvalumab) monotherapy in Study CD-ON-MEDI4736-1108

PK/pharmacodynamics data were available for 977 patients treated with durvalumab 0.1 to 10mg/kg Q2W, 15 mg/kg Q3W or 20 mg/kg Q4W.

The C_{max} increased in an approximately dose-proportional manner within the dosage range. The $AUC_{(0-14)}$ increased dose-proportionally at doses of 3 to 20 mg/kg and more than dose proportionally at doses < 3 mg/kg. These results suggest that MEDI4736 (Durvalumab) exhibits nonlinear PK likely due to saturable target-mediated CL; this is common for therapeutic antibodies targeting membrane-bound targets. Steady state was achieved at approximately Week 16.

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. Frequency is provided based on 2833 patients. Below is the CAEPR for MEDI4736 (Durvalumab).

Version 2.4, April 17, 2019[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 insipidus)
		Endocrine disorders - Other (diabetes mellitus type 1)[2]
	Hyperthyroidism[2]	
		Hypopituitarism[2]
	Hypothyroidism[2]	
EYE DISORDERS		
		Keratitis[2]
		Uveitis[2]
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
		Colitis[2]
	Diarrhea	
		Gastrointestinal disorders -Other - (gastrointestinal perforation)[2,3]
	Nausea	
		Pancreatitis[2]
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Edema limbs	
	Fatigue	
	Fever	

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
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)
INFECTIONS AND INFESTATIONS		
	Infection[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Infusion related reaction
INVESTIGATIONS		
	Alanine aminotransferase increased[2]	
	Aspartate aminotransferase increased[2]	
	Creatinine increased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthritis[2]	
		Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]
	Myalgia	
		Myositis[2]
NERVOUS SYSTEM DISORDERS		
		Guillain-Barre syndrome[2,5]
		Myasthenia gravis[2]
		Nervous system disorders - Other (aseptic meningitis)[2]

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		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	
	Pruritus	
	Rash[2,6]	
		Skin and subcutaneous tissue disorders - Other (scleroderma)
		Skin and subcutaneous tissue disorders - Other (severe dermatitis)[2,7]
	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] Gastrointestinal perforations have been observed only in patients receiving MEDI4736 (durvalumab) in combination with tremelimumab (CP-675,206).

[4] 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.

[5] 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.

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

[7] 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 manifectations.

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; 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; Electrocardiogram T wave abnormal; GGT increased; 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 Appendix 18.1.

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

   Females of childbearing potential and nonsterilized males who are sexually active with a female partner should use highly effective contraceptive measures during and for 180 days after the last dose of investigational agent.

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

d. DOSING & ADMINISTRATION

See Section 7.0, Treatment Plan.

Administration Instructions: Durvalumab (MEDI4736) is administered intravenously into a peripheral or central vein using an IV bag containing 0.9% sodium chloride or 5% dextrose and a 0.2- or 0.22-µm in-line filter. Standard infusion time is 60 minutes (± 5 minutes). Less than 55 minutes is considered a deviation. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. Flush the IV line with a volume of normal saline or dextrose infusion solutions 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.

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 (Durvalumab) is considered an investigational agent and will be supplied free of charge for this protocol by AstraZeneca, Inc. and distributed by the CTEP, DCTD, NCI.

2. MEDI4736 (Durvalumab) 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 vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL.

f. STORAGE, PREPARATION & STABILITY

Storage and Stability

Unopened vials of MEDI4736 (Durvalumab) liquid drug product must be stored at 2°C to 8°C (36°F to 46°F). MEDI4736 (Durvalumab) vials should be stored in the original packaging. Do not freeze.

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

If a storage temperature excursion is identified, promptly return (tremelimumab or MEDI4736) to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Preparation of MEDI4736 (Durvalumab)

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.

Withdraw the required volume of durvalumab (MEDI4736) from the vial(s) and further dilute in an IV bag containing 0.9 % sodium chloride or 5% dextrose to obtain a final concentration of 1 to 20 mg/mL. The IV bag should be administered with a 0.2 or 0.22 µm in-line filter. No incompatibilities have between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Mix the bag gently by inverting to ensure a homogeneous mixture.

3.2 Tremelimumab (NSC 744483) (IND 119672)

a. PHARMACOLOGY

Mechanism of Action: Tremelimumab is a human immunoglobulin (Ig)G2 monoclonal antibody (mAb). Tremelimumab binds to human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), a cell surface receptor that is expressed primarily on activated T cells. Binding of CTLA-4 to its target ligands (B7.1 and B7.2) provides a negative regulatory signal, which limits T-cell activation. Tremelimumab antagonizes binding of CTLA-4 to B7 ligands and enhances human T-cell activation. It is expected that treatment with tremelimumab will lead to activation of the human immune system and increase antitumor immunity in subjects with solid tumors.

b. PHARMACOKINETICS

1. Absorption: Tremelimumab is administered by intravenous (IV) infusion. To date, the absorption of tremelimumab following extravascular administration has not been studied.

2. Distribution: Following an IV infusion, tremelimumab exhibits a biphasic pharmacokinetics with the mean systemic exposure parameters (maximum concertation [Cmax] and area under the plasma concentration-time curve [AUC]) increase in an approximately dose-proportional manner.

   Tremelimumab mean volume of distribution at steady state (Vss) is 81.2mL/kg. This is typical of mAbs with limited distribution. To date, the human tissue distribution of tremelimumab has not been studied.

3. Metabolism: Tremelimumab is likely to be cleared from circulation by endothelial cell uptake and proteolysis.

4. Elimination: The mean clearance for tremelimumab is 0.132 mL/hour/kg and the terminal-phase half-life is 22.1 days. Since mAbs are not primarily cleared via hepatic/renal pathways, no impact of renal/hepatic functions is expected on tremelimumab elimination.

c. ADVERSE EFFECTS

1. Adverse Effects:

   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. *Frequency is provided based on 1642 patients.* Below is the CAEPR for tremelimumab (CP-675,206).

Version 2.1, March 25, 2019[1]

Adverse Events with Possible Relationship to Tremelimumab (CP-675,206) (CTCAE 5.0 Term) [n= 1642]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia[2]	
CARDIAC DISORDERS		
		Myocarditis[3]
ENDOCRINE DISORDERS		
	Adrenal insufficiency[2]	
	Endocrine disorders - Other (thyroiditis)[2]	
	Hyperthyroidism[2]	
	Hypophysitis[2]	
	Hypothyroidism[2]	
EYE DISORDERS		
	Uveitis	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis[2]	
Diarrhea		
		Enterocolitis[2]

		Gastrointestinal disorders - Other (intestinal perforation)[2]
	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		
		Anaphylaxis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction	
INVESTIGATIONS		
	Alanine aminotransferase increased[2]	
	Aspartate aminotransferase increased[2]	
	Lipase increased[2]	
	Lymphocyte count decreased[2]	
	Neutrophil count decreased[2]	
	Platelet count decreased[2]	
	Serum amylase increased[2]	
	White blood cell decreased[2]	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Dehydration	
	Hypokalemia	
		Metabolism and nutrition disorders - Other (diabetes mellitus)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthritis[2]	
		Musculoskeletal and connective tissue disorders - Other (Sjogren's syndrome)
NERVOUS SYSTEM DISORDERS		
		Guillain-Barre syndrome[2]
	Headache[2]	

		Myasthenia gravis[2,4]
		Nervous system disorders - Other (encephalitis)[2]
	Peripheral motor neuropathy[2]	
	Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS		
	Acute kidney injury	
		Nephrotic syndrome[2]
	Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Pneumonitis[2]	
	Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Dry skin[2]	
Pruritus		
Rash maculo-papular[2]		
		Skin and subcutaneous tissue disorders - Other (cutaneous scleroderma-like syndrome)
		Skin and subcutaneous tissue disorders - Other (Grover's disease)
	Skin hypopigmentation	
	Urticaria[2]	
VASCULAR DISORDERS		
		Vascular disorders - Other (giant cell temporal arteritis)[2]

[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-related adverse events may occur in any organs including but not limited to the events listed in CAEPR table.

[3] Myocarditis has been reported with other anti-CTLA4 agents; however, it has not yet been observed in clinical trials of tremelimumab (CP-675,206).

[4] Myasthenia gravis was observed in trials of tremelimumab in combination with durvalumab.

Adverse events reported on tremelimumab (CP-675,206) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that tremelimumab (CP-675,206) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Eosinophilia
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Endocrine disorders - Other (Graves' disease with ophthalmopathy)
GASTROINTESTINAL DISORDERS - Constipation; Dyspepsia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Ileus; Mucositis oral; Rectal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Pain; Sudden death NOS
INFECTIONS AND INFESTATIONS - Conjunctivitis; Infections and infestations - Other (oral herpes); Lung infection; Sepsis
INVESTIGATIONS - GGT increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Generalized muscle weakness; Myalgia
NERVOUS SYSTEM DISORDERS - Dizziness; Syncope
PSYCHIATRIC DISORDERS - Confusion; Depression; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (asthma)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Rash acneiform
VASCULAR DISORDERS - Flushing; Hypertension; Thromboembolic event; Vascular disorders - Other (hemorrhage); Vasculitis

Note: Tremelimumab (CP-675,206) 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.

2. Pregnancy and Lactation: In an embryo-fetal toxicity study in primates, tremelimumab did not result maternal toxicity, developmental toxicity, or teratogenicity.

   The effects of tremelimumab on a pregnant woman or human fetus have not been studied, and information on the safety for women of childbearing potential or for pregnant women cannot be derived from the existing clinical data. Guidance on contraception and on avoidance of egg or sperm collection is provided in the Investigator's Brochure.

   The levels of tremelimumab in breast milk have not been analyzed. Since tremelimumab is a mAb of the IgG2a type and it could potentially be secreted in breast milk, breastfeeding should be avoided.

3. Drug Interactions: To date, no formal drug-drug interaction studies have been conducted with tremelimumab. In renal cell carcinoma studies, acute renal failure has been reported with the combination of tremelimumab and

sunitinib. It is unknown whether a similar reaction will be observed when tremelimumab is combined with other tyrosine kinase inhibitors.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

Tremelimumab is administered intravenously into a peripheral or central vein using an IV bag containing 0.9% sodium chloride or 5% dextrose and a 0.2 or 0.22-µm in-line filter. Standard infusion time is 60 minutes (± 5 minutes). Less than 55 minutes is considered a deviation. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Flush the IV line at the completion of the infusion with a volume of diluent equal to the priming volume of the infusion set used to ensure the full dose is administered and document if the line was not flushed.

MonitoringofDoseAdministration: 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. Tremelimumab is supplied free of charge by AstraZeneca, Inc. and distributed by the CTEP, DCTD, NCI

2. Tremelimumab is formulated at 20 mg/mL in 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, 0.27 mM disodium edetate dihydrate (EDTA), pH 5.5. It is provided in a 20-mL clear glass vials with an elastomeric stopper and aluminum seal. Each vial contains 400 mg (nominal) of active investigational product.

f. STORAGE, PREPARATION & STABILITY

Storage and Stability:

Store unopened tremelimumab vials refrigerated at 2°C to 8°C (36°F to 46°F). Tremelimumab vials should be stored in original packaging. Do not freeze.

Total time from needle puncture of the tremelimumab vial to the start of administration should not exceed:
4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F)

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration. In the event that either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials.

Tremelimumab does not contain preservatives, and any unused portion must be discarded.

If a storage temperature excursion is identified, promptly return (tremelimumab or MEDI4736) to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Preparation of Tremelimumab:

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.

Withdraw the required volume of tremelimumab from the vial(s) and further dilute in an IV bag containing 0.9% sodium chloride or 5% dextrose to obtain a final concentration of 0.10 to 10 mg/mL. The IV bag should be administered with a 0.2 or 0.22 µm in-line filter. Infusion bags must be latex-free and can be made of polyvinyl chloride (PVC) or polyolefins (e.g., polyethylene), manufactured with bis (2-ethylhexyl) phthalate (DEHP) or DEHP free.

3.3 DRUG ORDERING & ACCOUNTABILITY

a. Drug ordering: Sites may order initial agent supplies when a subject has been registered. Starter supplies will not be provided. NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). 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 participating investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

1. 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.

2. Drug Return and/or Disposition Instruction

a. Drug Returns: All unused drug supplies must 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.

c. Contact Information:

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

4.0 STAGING CRITERIA

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

5.0 ELIGIBILITY CRITERIA

Patient must meet the eligibility criteria in Section 5.0 of **S1400F** to be eligible for **S1400F**. If the patient does not meet the eligibility criteria listed in Section 5.1 and Section 5.2 of **S1400F**, submit the **S1400** Notice of Intention Not to Register form and follow patient per Section 7.4 of **S1400** or **LUNGMAP**. Any potential eligibility issues should be addressed to the SWOG Statistics and Data Management Center in Seattle at LUNGMAPquestion@crab.org prior to registration. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7, 14, 16, 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Sub-Study Specific Disease Related Criteria

a. Patients must have been assigned to **S1400F**.

b. Patients must have a histologically or cytologically confirmed Stage IV or recurrent pure squamous cell lung cancer.

c. Patients must have progressed during or after prior platinum-based chemotherapy. For patients whose only prior platinum-based chemotherapy regimen was for Stage I-III disease (i.e. patient has not received any platinum-based chemotherapy for Stage IV or recurrent disease), disease progression on platinum-based chemotherapy must have occurred within one year from the last date that patient received that therapy.

Patients must also have experienced disease progression during or after anti-PD-1 or anti-PD-L1 antibody monotherapy as their most recent line of treatment. Prior PD-1/PD-L1 combination therapy is not permitted. [*This criterion replaces common eligibility criteria in Section 5.3b.]*.

d. Prior exposure to CTLA-4 inhibitors (ipilimumab and tremelimumab) is not permitted. Prior exposure to the following is allowed: attenuated vaccines, anti-EGFR agents, and GM- CSF.

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

f. Patients must not have any 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, immune-mediated alopecia, Grave's disease, or psoriasis requiring systemic treatment within the past 2 years are not eligible. Patients with hypothyroidism (e.g. post Hashimoto syndrome) who are stable on hormone replacement therapy are eligible.

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

5.2 Sub-Study Specific 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 these medications while on protocol therapy. Systemic corticosteroids must be stopped at least 24 hours prior to sub-study registration. However, intranasal and inhaled corticosteroids as well as topical steroids are allowed at any time before and during protocol therapy.

b. Patients must not have experienced a Grade 3 or worse immune-related adverse event (irAE) (except asymptomatic nonbullous/nonexfoliative rash) or any unresolved irAE Grade 2, nor have experienced a toxicity that led to permanent discontinuation of prior anti-PD-1/PD-L1 immunotherapy.

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 (Durvalumab) and/or tremelimumab formulation.

e. Patients must not have clinical signs or symptoms of active tuberculosis infection.

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, or a known positive test for Hepatitis B virus surface antigen (HBV sAg), or Hepatitis C virus ribonucleic acid (HCV antibody) indicating current acute or chronic infection. Patients with a positive hepatitis C antibody with a negative viral load are allowed. *[This criterion replaces common eligibility criteria in Section 5.3n and 5.3m.]*

h. Patients must have Lipase, Amylase, TSH with reflex Free T3/Free T4 (if TSH is out of normal range) and an EKG obtained within 7 days prior to sub-study registration. Additional timepoints are noted in Section 9.0 Study Calendar.

i. Patients must also be offered participation in banking and in the correlative studies for collection and future use of specimens as described in **S1400F** Section 15.0.

5.3 Common Eligibility Criteria for all Sub-Studies

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. [*This common eligibility criteria has been removed as it conflicts with the sub-study specific criteria in Section 5.1b. A place holder remains to keep consistency across all sub-studies.]*

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. Patients must not have received any radiation therapy within 14

days prior to sub-study registration. (See Section 5.3e for criteria regarding therapy for CNS metastases).

d. Patients must have measurable disease (see **S1400** or **LUNGMAP** 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** or **LUNGMAP** 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 **S1400F** Section 15.0 and **S1400** or **LUNGMAP** Appendix 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 prior to registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours 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. This specimen must have been drawn and proceesed within 28 days prior to sub-study registration:

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

Multiply this number by 0.85 if the patient is a female.

† 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** or **LUNGMAP** 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** or **LUNGMAP** Section 18).

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** or **LUNGMAP** 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.

6.0 STRATIFICATION FACTORS

Patients will be stratified into two cohorts based on their response to anti-PD-1/PD-L1 therapy 24 weeks after initiation. Patients must have progressed on or after anti-PD-1 or anti-PD-L1 treatment. The two cohorts are defined as:

Cohort 1 (acquired resistance):
Patients with a history of 24 weeks or more of disease control (complete response, partial response or stable disease) after initiation of anti-PD-1/PD-L1 (single agent therapy) that have subsequently progressed (after 24 weeks);

Cohort 2 (primary resistance):
Patients with a history of disease progression within (<) 24 weeks of initiation of single agent anti-PD-1/PDL-1 therapy.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Drs. Natasha Leighl and Naiyer Rizvi at **S1400F**MedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

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.

Protocol treatment 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.

Intranasal and inhaled corticosteroids are allowed during protocol therapy. Corticosteroids to manage immune-related adverse events during protocol therapy will be permitted.

Small volume, low dose palliative radiotherapy (≤ 20 Gy) for painful bone metastases is permitted, provided that no target lesions are encompassed, and the patient does not have progression as defined in Section 10.0. Delaying the next dose of protocol therapy by up to one week is permitted.

7.2 Treatment – MEDI4736 (Durvalumab) plus Tremelimumab

MEDI4736 (Durvalumab)
plus tremelimumab for 4 cycles followed by MEDI4736 (Durvalumab) alone

Agent	Dose	Route	Day	Schedule*	Duration
Tremelimumab	75 mg	IV over 60 minutes	1	Q 28 days for up to 4 doses	
Durvalumab (MEDI4736)	1500 mg	IV over 60 minutes	1	Q 28 days until Disease progression	

* NOTE: One cycle is defined as 28 days. MEDI4736 (Durvalumab) and tremelimumab will be administered on Day 1 of Cycles 1-4. Note that tremelimumab must be administered first. For Cycle 1 MEDI4736 (Durvalumab) is to start 1 hour after the end of tremelimumab infusion to allow for an observation period. If no clinically significant

infusion reaction is observed after Cycle 1, subsequent infusion observation periods can be at the investigator's discretion. MEDI4736 (Durvalumab) alone will be administered on Day 1 of Cycle 5 and subsequent cycles until disease progression.

Weight-based dosing of MEDI4736 (durvalumab) 20 mg/kg and tremelimumab 1mg/kg should be utilized for patients ≤ 30 kg. The corresponding volume of MEDI4736 (durvalumab) and tremelimumab should be rounded to the nearest tenth mL (0.1 mL). Fixed dose level should be resumed when patient weight is > 30 kg.

Vital signs (Temperature, Blood Pressure, Pulse, and Respiratory Rate) are to be performed pre-study and at three timepoints during each cycle (1. pre-infusion, 2. between tremelimumab and MEDI4736 (Durvalumab) dosing for the first four cycles and during MEDI4736 (Durvalumab) infusion for subsequent cycles, and 3. post-infusion).

7.3 Criteria for Removal from Protocol Treatment

a. Progression of disease as defined in Section 10.2d in **S1400** or **LUNGMAP**. However, the patient may continue protocol treatment until irRC progression if the patient is continuing to clinically benefit in the opinion of the treating investigator and the patient is not exposed to unreasonable risk (including absence of symptoms and signs indicating clinically significant progressive disease; no decline in Zubrod performance status; absence of symptomatic rapid disease progression requiring urgent medical intervention [e.g.,symptomatic pleural effusion, spinal cord compression]). Patients must sign the **S1400F** Consent Addendum for post-progression treatment. Sites must obtain consent prior the start of the subsequent cycle.

   Patients with irRC progression of disease (as defined in Section 10.1 in **S1400F**) 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. Symptomatic deterioration (as defined in Section 10.2e of **S1400** or **LUNGMAP**).

c. Unacceptable toxicity.

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

e. 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

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

Note: Patients who enroll on a new sub-study following progression must continue follow-up on this sub-study, in addition to follow-up on the new sub-study.

8.0 TOXICITIES TO BE MONITORED AND DOSE INTERRUPTIONS

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. No dose reductions are allowed on MEDI4736 (Durvalumab) and tremelimumab.

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

c. Dose interruptions and discontinuations are allowed to manage toxicity.

d. Treatment with MEDI4736 (Durvalumab) may continue if tremelimumab is discontinued after consultation with the Study Chairs, Drs. Natasha Leighl and Naiyer Rizvi at S1400FMedicalQuery@swog.org.

8.3 Dose Interruptions – MEDI4736 (Durvalumab) or in Combination with Tremelimumab

Based on the mechanism of action of MEDI4736 (Durvalumab) or in combination with tremelimumab 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 Interruptions and Management Guidelines for Immune-Related Adverse Events

Toxicity	Dose Interruptions	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 28 days** after last dose of study drug/regimen • **Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.**		

Toxicity	Dose Interruptions	Toxicity Management
Grade 1	No dose modifications	It is recommended that management of irAEs follow these guidelines. – Thoroughly evaluate 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 PO 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 tumor 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 protocol therapy until resolution to ≤ Grade 1 and after completion of steroid taper then resume protocol therapy administration at next scheduled dose.	
≥ Grade 3	Discontinue protocol therapy and remove from protocol therapy.	

Toxicity	Dose Interruptions	Toxicity Management
Pneumonitis/ Interstitial Lung Disease (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.
Grade 1	No dose modifications 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 workup and then as clinically indicated – Consider Pulmonary and Infectious disease consult
Grade 2	Hold protocol therapy until resolution to ≤ Grade 1 and after completion of steroid taper then resume protocol therapy administration at next scheduled dose. - If toxicity worsens then treat as ≥ Grade 3	– Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (e.g., prednisone 1-2 mg/kg/day PO or IV equivalent) – Reimaging as clinically indicated – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started – If still no improvement within 3-5 days despite IV methylprednisolone 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 ≥28 days 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

Toxicity	Dose Interruptions	Toxicity Management
≥ Grade 3	Permanently discontinue protocol therapy and remove from protocol therapy.	– Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Obtain Pulmonary and iInfectious disease consult; consider, as necessary, discussing with study physician. – 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 Interruptions	Toxicity Management
Diarrhea/ Colitis		
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 modifications	– 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 protocol therapy until resolution to ≤ Grade 1 and after completion of steroid taper then, resume protocol therapy 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 PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/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 – Consider consulting 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	Hold protocol therapy until resolution to ≤ Grade 1 and after completion of steroid taper then, resume protocol therapy administration at next scheduled dose. If resolution to ≤ Grade 1 does not occur within 14 days, permanently discontinue 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)
≥ Grade 4	Permanently discontinue protocol therapy and remove from protocol therapy.	

Toxicity	Dose Interruptions	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 modifications	– Continue LFT monitoring per protocol
Grade 2 (Based on ULN regardless of baseline LFT)	Hold protocol therapy until resolution to ≤ Grade 1 or baseline and after completion of steroid taper then resume protocol therapy 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, consider discussing with study physician. – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day PO or IV equivalent. – If still no improvement within 3-5 days despite 1-2 mg/kg/day of prednisone PO 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 (i.e.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 protocol therapy until resolution to ≤ Grade 1 or baseline and after completion of steroid taper. Resume protocol therapy administration at next scheduled dose. If resolution to ≤ Grade 1 or baseline does not occur within 14 days, permanently discontinue protocol therapy. For elevated transaminases > 8× ULN or bilirubin >5x ULN, permanently discontinue protocol therapy. Permanently	– 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 (i.e.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 Interruptions	Toxicity Management
Hepatitis (Elevated LFTs)		
	discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause.	
Grade 4 (Based on ULN regardless of baseline LFT)	Permanently discontinue protocol therapy.	

Toxicity	Dose Interruptions	Toxicity Management
Hepatitis (Elevated LFTs) - Hepatitis		Infliximab should not be used for management of immune-related hepatitis
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - **Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise** - **Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise** - **Grade 3-4: Permanently discontinue study drug/study regimen**		
Any Grade		– Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
Grade 2	Hold protocol therapy until resolution to ≤ Grade 1 or baseline and after completion of steroid taper then resume protocol therapy	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician.

Toxicity	Dose Interruptions	Toxicity Management
Hepatitis (Elevated LFTs) - Hepatitis		Infliximab should not be used for management of immune-related hepatitis
	administration at next scheduled dose.	– If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
Grade 3	Hold protocol therapy until resolution to ≤ Grade 1 and after completion of steroid taper then, resume protocol therapy administration at next scheduled dose. If resolution to ≤ Grade 1 does not occur within 14 days, permanently discontinue protocol therapy Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. Infliximab should NOT be used. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections
Grade 4	Permanently discontinue protocol therapy.	

Toxicity	Dose Interruptions	Toxicity Management
Nephritis 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.) – Thoroughly evaluate 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 modifications	– 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 protocol therapy until resolution to ≤ Grade 1 or baseline and after completion of steroid taper then resume protocol therapy 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 PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or PO 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 ≥ 28 days 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 protocol therapy 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 PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO 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 ≥ 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 Interruptions**	**Toxicity Management**
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 modifications	Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold protocol therapy until resolution to ≤ Grade 1 or baseline and after completion of steroid taper, resume protocol therapy 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, consider discussing with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent – Consider skin biopsy if persistent for >1-2 weeks or recurs
Grade 3	Hold protocol therapy until resolution to ≤ Grade 1 or baseline; resume protocol therapy 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)
Grade 4	Permanently discontinue protocol therapy and remove from protocol therapy.	

Toxicity	Dose Interruptions	Toxicity Management
Endocrinopathy (e.g., hyper-thyroidism, hypo-thyroidism, hypo-pituitarism, Type 1 diabetes mellitus hypophysitis, adrenal insufficiency, etc.)		
Any Grade		– Consider consult an Endocrinologist for endocrine events – Consider discussing with study physician – 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, polydipsia, polyuria, hypotension and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
Grade 1	No dose modifications	(including those with asymptomatic TSH elevation) – Monitor patient with appropriate endocrine function tests – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5X 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 and Type 1 diabetes mellitus, hold protocol therapy until patient is clinically stable, and after completion of steroid taper, resume protocol therapy administration at next scheduled dose. Patients with endocrinopathies who may require	(including those with symptomatic endocrinopathy) – EvaluateConsult endocrinologist to guide evaluation of endocrine function, and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except for those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., levothyroxine, hydrocortisone, or sex hormones). - – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.

Toxicity	Dose Interruptions	Toxicity Management
Endocrinopathy (e.g., hyper-thyroidism, hypo-thyroidism, hypo-pituitarism, Type 1 diabetes mellitus hypophysitis, adrenal insufficiency, etc.)		
	prolonged or continued steroid replacement can be retreated with protocol therapy 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.	– Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once the patient ispatients on steroids are improving, gradually taper steroids immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
≥ Grade 3	For Grade 3/4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold protocol patient is clinically stable and after completion of steroid taper, resume protocol therapy administration at next scheduled dose. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement.	– Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).

Toxicity	Dose Interruptions	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 modifications	
Grade 2	Hold protocol therapy until resolution to ≤ Grade 1 and after completion of steroid taper then resume protocol therapy administration at next scheduled dose.	– Consider discussing 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 PO or IV equivalent – If no improvement within 3-5 days despite 1-2 mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)
Grade 3	Hold protocol therapy until resolution to ≤ Grade 1 and after completion of steroid taper then resume protocol therapy administration at next scheduled dose.	– Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.
Grade 4	Permanently discontinue protocol therapy and remove from protocol therapy.	

Toxicity	Dose Interruptions	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 modifications	– Consider discussing with the study chair – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain neurology consult
Grade 2	Hold protocol therapy until resolution to ≤ Grade 1; resume protocol therapy administration at next scheduled dose. If there are signs of respiratory insufficiency or autonomic instability permanently discontinue protocol therapy and remove	– Consider discussing 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

Toxicity	Dose Interruptions	Toxicity Management
Immune Mediated Peripheral Neuromotor Syndromes, such as Guillain-Barre and Myasthenia Gravis		
	from protocol therapy.	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. GUILLAIN-BARRE*:* 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 protocol therapy until resolution to ≤ Grade 1; resume protocol therapy administration at next scheduled dose. If there are signs of respiratory insufficiency or autonomic instability permanently discontinue protocol therapy and remove from protocol therapy.	- Consider discussing with study chair - Recommend hospitalization - Monitor symptoms and obtain neurological consult MYASTHENIA GRAVIS o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapharesis or IVIG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. GUILLAIN-BARRE: o 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 protocol therapy 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]

Toxicity	Dose Interruptions	Toxicity Management
Myositis/Polymyositis ("Poly/myositis")		
Any Grade		– Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously

Toxicity	Dose Interruptions	Toxicity Management
Myositis/Polymyositis ("Poly/myositis")		
		unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1	No dose modifications	– Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2	Hold protocol therapy until resolution to ≤ Grade 1; resume protocol therapy administration at next scheduled dose.	– Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is not rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of 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

Toxicity	Dose Interruptions	Toxicity Management
Myositis/Polymyositis ("Poly/myositis")		
		NCCN guidelines for treatment of cancer-related infections
Grade 3	Hold protocol therapy until resolution to ≤ Grade 1; resume protocol therapy administration at next scheduled dose.	– Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of 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. – Consider whether patient may require IV IG, plasmapheresis. – 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
Grade 4	Permanently discontinue protocol therapy and remove from protocol therapy.	

b. Dose Interruptions and Management Guidelines for Infusion-Related Reactions

Toxicity	Dose Interruptions	Toxicity Management
Infusion- Related Reactions		
Any Grade	No dose modifications	– 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.)
≤ Grade 2	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 – Steroids should not be used for routine premedication of ≤Grade 2 infusion reactions
≥ Grade 3	Permanently discontinue protocol therapy 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. Dose Interruptions and Management Guidelines for Non-Immune Mediated Reactions

Toxicity	Dose Interruptions	Toxicity Management
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 modifications	
Grade 2	Hold protocol therapy until resolution to ≤ Grade 1; resume protocol therapy administration at next scheduled dose.	
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 protocol treatment administration. Otherwise, permanently discontinue protocol treatment.	Treat accordingly as per institutional standard
Grade 4	Permanently discontinue protocol treatment.	

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact Drs. Natasha Leighl and Naiyer Rizvi at S1400FMedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.

8.5 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 MEDI4736 (Durvalumab) plus Tremelimumab

REQUIRED STUDIES	PRE-STUDY	Cycle 1 Wk 1	Cycle 2 Wk 5	Cycle 2 Wk 7	Cycle 3 Wk 9	Cycle 4 Wk 13	Cycle 5 Wk 17	Cycle 5 Wk 19	Cycle 6 Wk 21	Cycle 7 Wk 25	Subsequent Cycles β	At Off TX	Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
PHYSICAL														
History & Physical Exam	X		X		X	X	X		X	X	X	X	X	
Weight & Performance Status	X		X		X	X	X		X	X	X	X	X	
Vital Signs £	X£	X£	X£		X£	X£	X£		X£	X£	X£			
Disease Assessment Ω	X			XΩ		XΩ		XΩ		XΩ	XΩ		XΩ	
Toxicity Notation		X	X		X	X	X		X	X	X	X	Xđ	Xđ
Smoking Status Assessment	X											X		
LABORATORY														
CBC/Diff/Platelets/Hgb	X	X€	X		X	X	X		X	X	X	X	Xđ	Xđ
Serum Bilirubin	X	X€	X		X	X	X		X	X	X	X	Xđ	Xđ
ALT or AST	X	X€	X		X	X	X		X	X	X	X	Xđ	Xđ
Serum Creatinine/Calc CrCl	X	X€	X		X	X	X		X	X	X	X	Xđ	Xđ
Lipase π	X	X€	X		X	X	X		X	X	Xπ	X	Xπ	Xđ
Amylase π	X	X€	X		X	X	X		X	X	Xπ	X	Xπ	Xđ
TSH w/ reflex Free T3/Free T4 π	X	X€	X		X	X	X		X	X	Xπ	X	Xπ	Xđ
Albumin ¥	X													
X-RAYS AND SCANS														
CT or MRI for Disease Assessment Ω	X			XΩ		XΩ		XΩ		XΩ	XΩ		XΩ	
Brain CT/MRI	X					X♦				X♦	X♦		X♦	
EKG ©	X													
Image Submission Σ	X			X		X		X		X	X		X	
SPECIMEN SUBMISSION														
Tissue for Banking	X‡													X§
Blood for Banking ƒ	X		X		X	X								Xð

Calendar continued on next page. Click here for footnotes.

REQUIRED STUDIES	PRE-STUDY	Cycle 1 Wk 1	Cycle 2 Wk 5	Cycle 2 Wk 7	Cycle 3 Wk 9	Cycle 4 Wk 13	Cycle 5 Wk 17	Cycle 5 Wk 19	Cycle 6 Wk 21	Cycle 7 Wlk 25	Subsequent Cycles β	At Off TX	Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
TREATMENT														
28 day cycle														
Tremelimumab *		X	X		X	X								
MEDI4736 (Durvalumab) *		X	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.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

Click here for footnotes.

Footnotes for Calendar (Durvalumab [MEDI4736] plus Tremelimumab)**:**

Ω CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.3 of **S1400F**) must be repeated every 6 weeks (± 7 day window) until disease progression, regardless of treatment delays. The 6 weeks should start from Cycle 1 Day 1. If the patient remains on treatment following RECIST 1.1 progression, irRC disease progression is to 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).

♦ Only if patient has brain metastases at baseline. Scans must use the same modality as baseline and be repeated every 12 weeks (+/- 7 days) until disease progression.

Σ Submit scans as outlined in Section 14.0 and Section 15.0 of **S1400F**.

£ Vital signs (Temperature, Blood Pressure, Pulse, and Respiratory Rate) are to be performed pre-study and at three timepoints at every cycle: pre-infusion, between tremelimumab and MEDI4736 (Durvalumab) dosing, and post-infusion. Vital signs are to be reported on the **S1400F** Onstudy and **S1400F** Treatment forms.

© EKG to be performed at pre-study within 7 days prior to sub-study registration, then as clinically required throughout treatment.

β During continued treatment, items marked under physical and laboratory should be performed at the beginning of every subsequent cycle unless otherwise noted. Disease assessments and image submission are to take place every 6 weeks (± 7 days).

Δ After off treatment prior to progression, patients should be followed by repeating indicated studies every 3 months or more often as clinically indicated for the first year, then every 6 months for up to 3 years from date of sub-study registration. Disease assessment should continue every 6 weeks until 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 registration.

ǂ With patient's consent, an additional research biopsy prior to treatment must be collected. Patients who provided fresh biopsy during screening may use that leftover tissue if they received no intervening treatment (see Section 15.0 of **S1400F**).

§ With patient's consent, an additional research biopsy within 1 month after the time of first progression (irRC-Progression defined in Section 10 of **S1400F**) among patients who had a response to treatment (in the opinion of the treating physician) must be collected (see Section 15.0 of **S1400F**).

ƒ With patient's consent, additional research blood draws will be collected (see Section 15.0 of **S1400F**).

π Lipase, Amylase, and TSH/Reflex T3/T4 are required at pre-study within 7 days prior to sub-study registration. TSH/Reflex T3/T4 must be repeated every 4 weeks throughout treatment, then as clinically required until disease progression, as defined in Section 10.0 of **S1400F**. Lipase and Amylase must be repeated every 4 weeks throughout treatment, if clinically indicated, then as clinically required until disease progression, as defined in Section 10.0 of **S1400F**.

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

€ If the pre-study tests are obtained within 14 days prior to treatment, tests need not be repeated on Cycle 1 Day 1.

* MEDI4736 (Durvalumab) and Tremelimumab will be administered on Day 1 of Cycles 1-4. Note that tremelimumab must be administered first. MEDI4736 (Durvalumab) only will be administered on Day 1 of Cycle 5 and subsequent cycles until one of the criterion from Section 7.3 is met.

ȸ Assessments should continue until resolution of all acute adverse events.

ð Blood for Banking specimen must be collected at first progression (irRC-Progression defined in Section 10.0 of **S1400F**) after study treatment (see Section 15.0 of **S1400F**).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of Lesions

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. It is strongly recommended that CT slice of 0.5 cm be used. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm)

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. It is no longer necessary to distinguish between spiral and conventional CT.

2. Body scans should be performed with breath-hold scanning techniques, if possible.

3. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with stand-alone CT. *The slice thickness of 0.5 cm or less is highly recommended*. If CT scans have slice thickness > 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

4. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

5. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

6. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0 cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as *target* lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as *non-target* lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, all potential sites of metastases should be evaluated at each time point rather than following only sites of disease identified at baseline. It is acceptable to image only the areas of the body most likely to be involved with metastatic disease for the tumor type (chest, abdomen, pelvis, and/or bone scan are typical), with the addition of any areas with suspected involvement based upon clinical symptoms. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR)**: Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR)**: Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable**: Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see 10.2e).

Notes on progression and new lesions:

1. For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled

assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2. FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.
    - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.
    - No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

3. A previous abnormal target lymph node that became normal and subsequently enlarged in size meeting the criteria for a pathologic and measurable lymph node (a short axis of ≥ 1.5 cm) should be added to the sum of diameters to determine if criteria for progression are met based on target lesions.

4. A previously abnormal non-target lymph node that became normal and subsequently recurred must meet the criteria for progression based on non-target lesions to be considered progression.

A normal lymph node at baseline (<1.0 cm) that subsequently becomes pathologic is considered a new lesion and should be considered progression.

If a single pathologic lymph node is driving the progression event, continuation of treatment/follow-up and confirmation by a subsequent exam should be contemplated. If it becomes clear that the new lymph node has not resolved, or has increased in size, the date of progression would be the date the new lymph node was first documented.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**: Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).
2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.
3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not

progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.
6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.
7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.
8. Lymph nodes are considered one organ. Only two lymph nodes should be selected as target lesions. Other involved lymph nodes should be assessed and followed as non-target lesions.
9. "Paired" organs, i.e. lungs, kidneys and ovaries, are considered one organ.
10. Pleural-based lung lesions are considered part of the lung in determining target lesions (a maximum of two lung lesions should be selected), whereas pleural effusions/thickening can be reported as a separate site.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Time to Death

From date of sub-study registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.6 irRC-Progression

irRC-progression is defined by progression per RECIST 1.1 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.

10.7 Investigator-Assessed Progression-Free Survival

From date of sub-study registration to date of first documentation of 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 progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

10.8 Progression-Free Survival by Central Review

From date of sub-study registration to date of first documentation of progression assessed by central review or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

10.9 Duration of Response (DoR)

From date of first documentation of response (CR or PR) to date of first documentation of progression assessed by local review or symptomatic deterioration (as defined above), or death due to any cause among patients who achieve a response (CR or PR). Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

10.10 irRC Investigator-Assessed Duration of Response (irRC-IA-DoR)

From date of first documentation of response (CR or PR) to date of first documentation of irRC-progression assessed by local review or symptomatic deterioration, or death due to any cause. Patients last known to be alive without report of irRC-progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan(s) 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

This study will enroll patients into two parallel and independently evaluated cohorts; patients will be defined as either acquired (Cohort 1) or primary (Cohort 2) resistance. See Section 6.0 for the definition of the cohorts. Both cohorts have separate accrual goals and analysis plans. This study is employing Design #2 for non-match therapies. A complete description of the statistical design and analysis plan is included this section and in Section 11.2a of **S1400**. This section includes details specific to **S1400F.**

The objectives will be addressed in each cohort separately.

11.1 Primary Objective

The primary objective within each cohort is to assess the response rate (confirmed and unconfirmed, complete and partial) among patients treated with MEDI4736 (Durvalumab) plus tremelimumab.

11.2 Secondary Objectives

Secondary objectives include an evaluation of IA-PFS, OS, DoR, and toxicities.

11.3 Sample Size with Power Justification

The accrual goals for this study are to accrue up to 60 eligible patients per cohort and the same design assumptions apply to both cohorts. A design with 82% power and 1-sided 0.05 level type I error would require 60 patients to rule out an ORR of 5% or less if the true ORR is 15% or greater. If the true ORR is 20%, this design has 96% power. The observation of at least 6 responses of the 60 patients (10%) would be considered evidence to rule out an ORR of 5%. Assuming 90% of accrued patients will satisfy eligibility, **the total accrual goal is 66 patients/cohort (132 total).**

11.4 Analysis Plan

The evaluation within each cohort will include two interim analyses. The interim analyses within each cohort are as follows:

Interim 1: The first interim analysis will take place when 20 patients are evaluable for response. This interim analysis will only evaluate early stopping for futility. If no responses are observed, this will be considered evidence of futility and the recommendation will be to close the cohort for lack of evidence of efficacy of the regimen.

In addition to evaluating early stopping for futility, this analysis will evaluate the safety/tolerability of the regimen. All grade 4 hematologic and grade 3 or worse non-hematologic will be evaluated with a particular focus on diarrhea, colitis, transaminitis and lipase levels, and other immune-related adverse events (pneumonitis and other immune events). These toxicities will be evaluated by the **S1400F** Study Chairs, the **S1400** Study Chairs, and the study pharmaceutical collaborator. With 20 patients evaluable for toxicities, any toxicity with at least 10% prevalence has at least an 88% chance of being observed.

Interim 2: The second interim analysis will take place when 40 patients are evaluable for response. This interim analysis will also only evaluate early stopping for futility. If 3 or fewer responses are observed, this will be considered evidence of futility and the recommendation will be to close the cohort for lack of evidence of efficacy of the regimen.

Final Analysis: If a cohort is not closed to accrual at the first or second interim analysis, the cohort will proceed to full accrual of 60 evaluable patients. If the cohort continues to full accrual, the observation of at least 6 responses will be considered evidence to rule out the null hypothesis of a 5% response rate.

Summary of analyses:

Analysis	Sample Size	Futility	Continue/Positive
1st interim	20 patients	No responses	1+ response (5% RR)
2nd interim	40 patients	≤3 responses	4+ responses (10% RR)
Final	60 patients	≤5 responses	6+ responses (10% RR)

Evaluability for response: Evaluability for response is defined based on RECIST 1.1 and accrual to each cohort is to remain open while patients are being evaluated for response. However, within a cohort, if 20 or more eligible patients for the first interim analysis or 40 or more eligible patients for the second interim analysis, have made it to their second disease assessment and the required number of responses to continue past that interim analysis has not been observed, then the accrual to the cohort will be placed in temporary closure until the response status for all patients in the interim analysis set is known.

The following table describes the likelihood of stopping at the interim analyses under a response rate of 5%, 10%, 15%, and 20% and the probability of a rejecting the null.

RR	Probability of stopping Interim 1	Interim 2	Average sample size	Expected number of responses	Probability reject null
5%	36%	51%	36	2	5.6%
10%	12%	31%	49	5	46.8%
15%	4%	11%	56	8	82.2%
20%	1%	2%	59	12	96.5%

Response rates and associated confidence intervals will be calculated. Survival, IA-PFS, irRC-IA-PFS, and DoR will be estimated using the method of Kaplan-Meier. The Brookmeyer-Crowley method will be used to calculate confidence intervals for median OS, IA-PFS, and DoR. With 60 patients, ORR and toxicity rates can be estimated within 13% with 95% confidence. Any toxicity with at least 5% prevalence has at least a 95% chance of being observed.

With 60 patients, OS and PFS rates at landmark times can be estimated within 13% with 95% confidence. The analysis of PFS and OS will occur approximately 6 months after completion of accrual when at least 41 OS events have been observed (but not prior to 6 months after completion of accrual). It is estimated that the null rate (with docetaxel) in the population would be a median of 5 months (or a 6-month OS of 44%) for OS and of interest would be an improvement to a median of 9 months (a 6-month OS rate of 63%). With 60 patients accrued over 18-22 months and an additional 6 months of follow-up, the expected number of OS events is 41 events (under the alternative). The estimated number of PFS events at this time is at least 50 (under an alternative median PFS of 5 months). With 41 OS events, this study has 90% power to rule out a median OS of 5 months if the true median OS is 9 months or greater at the 1-sided 5% level. The observation of a 6-month OS rate of 55% or greater would be considered evidence to rule out the null rate.

The null median OS of 5 months was estimated by simulation under the assumption of exponential survival post progression on nivolumab and based on the data presented on the Checkmate 017 study which had a median PFS of 3.5 months with nivolumab and median OS of 9.2 months with nivolumab.

11.5 Accrual Information

The estimated average monthly accrual rate to **S1400F** is 3-4 patients with acquired resistance (Cohort 1) and 4-6 patients with primary resistance (Cohort 2). The estimated duration of accrual for Cohort 1 is 16-23 months and for Cohort 2 is 11-16 months, provided there are no halts in accrual. The accrual duration within a cohort may be different if accrual is temporarily halted for an interim analysis or closed for futility at an interim analysis. See the **S1400** main protocol for a description of the accrual rate assumptions/justification.

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 Statistics and Data Management Center, and will meet at the Group's bi-annual meetings as necessary.

12.0 DISCIPLINE REVIEW

This section does not apply to this sub-study.

13.0 REGISTRATION GUIDELINES

See Section 13.0 of **S1400** or **LUNGMAP** for registration guidelines. NOTE: At the time of **LUNGMAP** activation, **S1400** screening will close to accrual. Please see the Lung-MAP protocol training webpage for additional information (https://www.swog.org/required-lung-map-s1400-training).

13.1 Registration Timing

Patients must plan to begin treatment within 10 calendar days after sub-study 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. Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster ill be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members’ website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

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** or **LUNGMAP**.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF **S1400F** REGISTRATION, SUBMIT:

S1400F Onstudy Form
S1400F Eligibility Criteria 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 15.5.

b. IF PATIENT CONSENTS, SUBMIT SPECIMENS:

Specimens as specified in Section 15.0 of **S1400F**.

c. WITHIN 7 DAYS AFTER EACH CYCLE (CYCLE = 28 DAYS) OF TREATMENT, SUBMIT:

S1400F Treatment Form

S1400F Adverse Event Form

S1400F Laboratory Values Form

For Cycle 1 only: submit the **S1400F** Pre-Treatment Laboratory Values Form.

*For the last cycle of treatment, include all adverse events occurring within 30 days after last treatment.

d. WITHIN 14 DAYS AFTER EVERY DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION [see **S1400F** 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 **S1400F** Section 15.5.

e. WITHIN 7 DAYS OF DISCONTINUATION OF TREATMENT SUBMIT:

Off Treatment Notice documenting reasons for off treatment

Smoking Status Assessment Form

Forms specified in 14.4.c.

f. ONCE OFF TREATMENT SUBMIT EVERY 6 MONTHS FOR THE FIRST 2 YEARS FROM **S1400F** 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).

Note: Patients who enroll on a new sub-study following progression must continue follow-up on this sub-study, in addition to follow-up on the new sub-study.

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

Site(s) of Progression or Relapse Form

Follow-Up Tumor Assessment Form (RECIST 1.1)

S1400F Consent Addendum Form*

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 15.5.

* If patient will be provided the **S1400F** Consent Addendum to continue protocol treatment after RECIST 1.1 progression, please submit the **S1400F** Consent Addendum Form, available via the "Add Event" dropdown on the main patient page.See Section 7.3a.

h. WITHIN 28 DAYS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information and **S1400F** End of Study Form. 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.

i. WITHIN 28 DAYS OF CONSENT WITHDRAWAL, LOST TO FOLLOW-UP OR MAXIMUM FOLLOW-UP OF 3 YEARS, SUBMIT:

S1400F End of Study Form

S1400F Lost to Follow-Up form (lost to follow-up only)

15.0 SPECIAL INSTRUCTIONS

15.1 SWOG Specimen Tracking System (STS)

See **S1400** or **LUNGMAP** 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 Biospecimen Bank – 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:

- Pre-study (after consenting and prior to treatment initiation on sub-study)
  Note: If a patient provided blood at pre-screening or screening (see Section 15.3 of **S1400** or **LUNGMAP**) and registration to the sub-study is within 42 days from registration to **S1400** or **LUNGMAP** , then no additional pre-study blood specimen is required.

- Weeks 5, 9 and 13
  Note: Patients that go off treatment are not required to continue to submit specimens.

- First progression (irRC-Progression defined in Section 10 of **S1400F**) after study treatment

Collect approximately 8-10 mL of blood in EDTA tubes. Blood should be processed within one hour after venipuncture. If immediate processing within this time frame is not possible, then refrigerate (4°C) blood in EDTA tubes. 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 x g for 10 minutes at 4°C for the collection of plasma. [Note: Sites that do not have a refrigerated centrifuge should spin at room temperature and ensure specimens are placed on ice (regular, not dry) immediately after being drawn and process rapidly.] Using a pipette, transfer the plasma to a 15-mL centrifuge tube. Remove the buffy coat layer (thin white or gray layer of cells between the plasma and red blood cells) and split between two appropriately labeled 2-mL cryovials.

Spin the plasma in the 15-mL centrifuge tube at 800 x g for an additional 10 minutes. Avoiding any pelleted material, pipette the plasma into labeled cryovials at 0.5 ml aliquots. Plasma must be clear before freezing; no cells or debris should be present.

Plasma and buffy coat vials must be placed upright in a -80˚C freezer immediately after processing to ensure long-term viability.

Frozen plasma and buffy coat specimens should be shipped to the SWOG Biospecimen Bank on dry ice.

2. New Biopsy of Tumor prior to treatment:

A new biopsy must be collected from patients prior to starting protocol treatment. The biopsy will be used to identify possible mechanism of resistance to immunotherapies to develop future novel combinations. (See Appendix 18.2) The new biopsy should be either bronchoscopy/surgical biopsy or CT guided biopsy. Patients who provided fresh biopsy during screening may use that leftover tissue if they received no intervening treatment.

Specimens should be collected at the following time point: prior to the start of protocol treatment.

Process the biopsy as FFPE material. The minimum requirement is a block or 5-10 unstained, charged, and unbaked 4-5 micron sections.

FFPE specimens (block or slides) should be shipped to the SWOG Biospecimen Bank at ambient temperature.

3. New Biopsy of Tumor at Time of Progression among responders to MEDI4736 (Durvalumab) plus tremelimumab:

A new biopsy must be collected from patients who responded to protocol treatment (in the opinion of the treating physician) and then experienced disease progression. Biopsies will be used for molecular analysis of molecular characteristics associated with mechanisms of resistance. New biopsy should be either bronchoscopy/surgical biopsy or CT guided biopsy.

Specimens should be collected at the following time point: within one month after progression.

Process the biopsy as FFPE material. The minimum requirement is a block or 12 unstained, charged, and unbaked 4-5 micron sections.

FFPE specimens (block or slides) should be shipped to the SWOG Biospecimen Bank at ambient temperature.

b. Specimen Submission and Labeling

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

For additional information about labeling and shipping instructions for frozen plasma and buffy coat specimens, refer to the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures).

1. Liquid specimens must be labeled with the following:
   - SWOG patient number
   - Patient initials
   - Collection date (date the specimen was collected from the patient)
   - Specimen type (e.g. blood, serum, etc.)

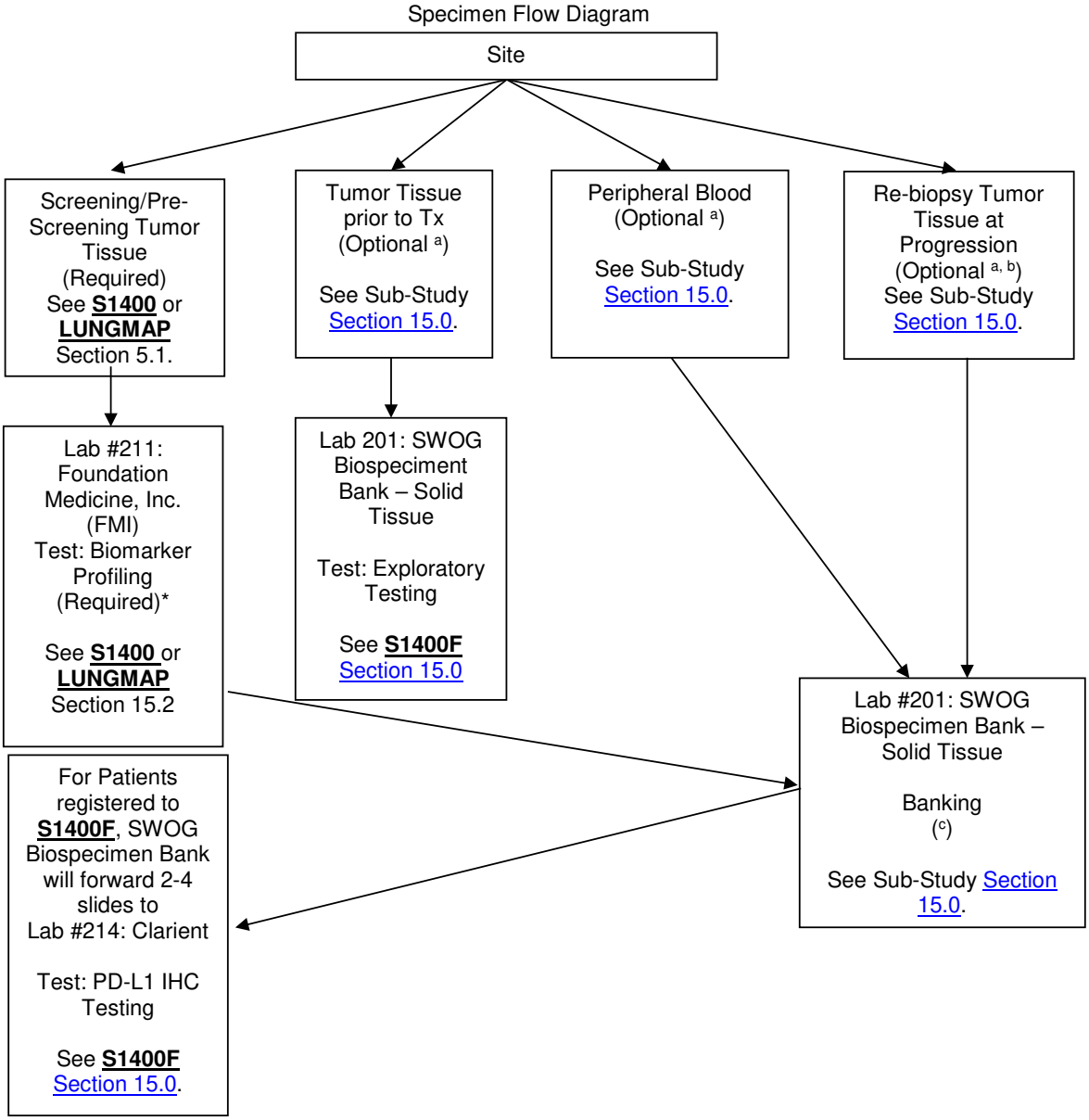
2. Solid tissue specimens must be labeled with the following:
    - SWOG patient number
    - Patient initials
    - Collection date, or procedure date
    - Site of collection (e.g., Lymph node, left breast, liver, etc.)
    - Specify whether tissue is from primary (P) or metastatic (M)
    - Surgical Pathology ID # (Accession#) and block number (e.g., A2, 3E, 2-1, B, etc.) must be on both the specimen label and the pathology report in order for the Bank to adequately match the specimen with any findings in the pathology report.

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

15.3 PD-L1 IHC Testing

Tissue remaining after the screening NGS testing will be sent from the SWOG Biospecimen Bank to Clarient Inc. for PD-L1 Testing (see Appendix 18.3 for details). The specimen will be kept until there are no additional sub-studies for the patient to enroll in or the tissue is used up, whichever happens first. If the patient consented to future testing in **S1400** or **LUNGMAP**, any leftover tissue will remain at the SWOG Biospecimen Bank for future exploratory analysis.

15.4 Specimen Flow Diagram



15.5 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 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 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 **S1400** or **LUNGMAP** Appendix 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 **S1400** or **LUNGMAP** Appendix 18.1c.

b. TRIAD Digital Image Submission

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes 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 14.3).

- 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/

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

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 Appendix 18.2 of **S1400F** for information on adverse events of special interest.

b. Reporting method

This study requires that expedited adverse event reporting use the Cancer Therapy Evaluate Program Adverse Event Reporting System (CTEP-AERS). The CTEP's guidelines for CTEP-AERS can be found at https://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located 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.

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 this study MEDI4736 (Durvalumab) and tremelimumab. [Please note – For this sub-study the post dosage expedited reporting requirement window has been extended to **90** days rather than the normal 30 day requirement or until the initiation of alternative anticancer therapy]. 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 90 Days of the Last Administration of the Investigational Agent/Intervention[1] MEDI4736 (Durvalumab) and tremelimumab:

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: 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

May 5, 2011

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 Statistics and Data Management 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:

   - Any Grade Diarrhea / Colitis
   - Any Grade Pneumonitis / ILD
   - Any Grade ALT/AST increases / hepatitis / hepatotoxicity
   - Any Grade Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
   - Any Grade Endocrinopathies (i.e. events of hypophysitis, hypopituitarism adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism and type I diabetes mellitus)
   - Any Grade Rash / Dermatitis
   - Any Grade Nephritis / Blood creatinine increases
   - Any Grade Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)
   - Any Grade Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis.

g. 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. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

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.

h. Reporting Pregnancy, Pregnancy Loss, 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. **Pregnancy Loss** Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions** SOC.

A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal** Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth. A neonatal death should be

reported expeditiously as **Grade 4 "Death neonatal"** under the **General disorders and administration** SOC.

Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death.

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 301-897-7404. 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 BIBLIOGRAPHY

1 Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med 373:123-135, 2015. [PMID: 26028407].

2 Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med 373:123-135, 2015. [PMID: 26028407].

3 Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med, 373:1627-1639, 2015. [PMID: 26412456].

4 Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): randomized controlled trial. Lancet Oncol 2015. [PMID: 26712084].

5 Drake CG. Combination immunotherapy approaches. Annals of Oncology;23 (Supplement 8): 41-46, 2012. [PMCID: PMC3845488].

6. Curran MA, Montalvo W, Yagita H et al. PD-1 and CTLA-4 combination blockade expands infiltrating T-cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci USA; 107: 4275–4280, 2010. [PMID: 20160101].

7 Larkin et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med; 373:23-34, DOI: 10.1056/NEJMoa1504030, 2015. [PMID: 26398076].

8 Antonia SJ, Bendell JC, Taylor MH, et al. Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032. J Clin Oncol 33, 2015. [(suppl, abstr 7503) http://meetinglibrary.asco.org/content/146138-156].

9 Antonia S, Goldberg S, Balmanoukian A, et al. A Phase 1 open-label study to evaluate the safety and tolerability of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in combination with tremelimumab in patients with advanced non-small cell lung cancer (NSCLC). Presented at ESMO 2014. Poster 1327P, Abstract 5924. http://annonc.oxfordjournals.org/content/25/suppl_4/iv466.3.

10 Rizvi N, Chaft J, Balmanoukian A, et al. Tumor Response from Durvalumab (MEDI4736) + Tremelimumab Treatment in Patients with Advanced Non-small Cell Lung Cancer is observed regardless of PD-L1 Status. *Journal for ImmunoTherapy of Cancer*, **3**(Suppl 2):P193, 2015. Abstract, http://www.immunotherapyofcancer.org/content/3/S2/P193.

11 Antonia Goldberg, balmanoukian et al. Phase Ib study of MEDI4736, a programmed cell death ligand-1 (PD-L1) antibody, in combination with tremelimumab, a cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody, in patients (pts) with advanced NSCLC. 2015 asco annual meeting abstr 3014; J Clin Oncol 33, 2015. [(suppl abstr 3014) http://meetinglibrary.asco.org/content/147703-156].

12 Rizvi N, Chaft J, Balmanoukian A, et al. Tumor Response from Durvalumab (MEDI4736) + Tremelimumab Treatment in Patients with Advanced Non-small Cell Lung Cancer is observed regardless of PD-L1 Status. *Journal for ImmunoTherapy of Cancer*, **3**(Suppl 2):P193, 2015. Abstract, http://www.immunotherapyofcancer.org/content/3/S2/P193.

13 Herbst RS, Gordon MS, Fine GD, et al. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advance or metastatic tumors. J Clin Oncol., 2013. [(suppl; abstr 3000), http://meetinglibrary.asco.org/content/115865-132].

18.0 APPENDIX

18.1 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 of the Investigational Product 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 this investigational product.

AESIs for MEDI4736 (durvalumab) in combination with tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the treating Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Chair.
AESIs observed with MEDI4736 (durvalumab) and tremelimumab are listed in Section 16.1f2.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.
Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in Section 8.3. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in Section 8.3. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered.

18.2 Biomarker Analysis of Immunotherapy Resistance

Background: Although immunotherapies have proven efficacy in NSCLC patients, the majority of patients do not respond or relapse after an initial response. Obtaining biopsies prior to the start of the combination of durvalumab and tremelimumab will allow possible mechanisms of resistance to be identified. Such identification could provide rationale for development of novel combinations to overcome resistance to immunotherapies.

Objective: To obtain fresh biopsies prior to the start of MEDI4736 (Durvalumab) and tremelimumab in patients that previously received immunotherapies.

Laboratory: Specimens will be shipped to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201 and stored until a laboratory has been identified to perform the analysis.

Specimen Requirements:

A new biopsy is required from patients who consent to have an optional biopsy to collect a sample of tissue prior to starting protocol treatment. The biopsy will be used to identify possible mechanism of resistance to immunotherapies to develop future novel combinations. The new biopsy should be either bronchoscopy/surgical biopsy or CT guided biopsy. The biopsy should be performed prior to the start of protocol treatment and should be processed as FFPE material. The minimum requirement is a 5-10 unstained, charged, and unbaked 4-5 micron sections.

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

18.3 PD-L1 IHC Testing

PD-L1 expression localization within the tumor microenvironment will be assessed in patients registered to **S1400F**. Tumor specimens will be shipped from the SWOG Biospecimen Bank at Nationwide Children's Hospital to Clarient about every 3 months. The SWOG Statistics and Data Mangaement Center will provide the SWOG Biospecimen Bank with the list of patient specimens to ship to Clarient.

Objective
To identify PD-L1 status in tumor samples from patients who have progressed on an anti-PD-1/PD-L1 and enrolled onto the **S1400F** sub-study.

Assay Description
AstraZeneca 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 **S1400F**.

Lab #214: Clarient

Specimen Requirements
For the PD-L1 IHC testing, no on-site processing of specimens will be required prior to shipment to the SWOG Biospecimen Bank. Tissue sample collected for **S1400** or **LUNGMAP** biomarker profiling will be used. The preferred thickness is 4 micron unstained tissue sections; although 5 micron unstained tissue sections are allowable. For patients with tumor blocks at SWOG Biospecimen Bank, SWOG Biospecimen Bank will prepare 4 micron, unstained slides. At least 100 tumor cells are defined to be sufficient viable tumor tissue for PD-L1 IHC testing. Fine needle aspirates are not acceptable. A minimum of 2 (preferably 4) unstained tissue sections along with a hematoxylin-eosin (H&E)-stained slide or Aperio H&E-stained image will be sent to Clarient for PD-L1 IHC testing from consented patients with sufficient tissue.

18.4 Instructions for the SWOG Biospecimen Bank

Frozen Plasma and Buffy Coat
The SWOG Biospecimen Bank will receive frozen plasma and buffy coat at up to 5 time points per patient. Upon receipt, the Bank will accession, barcode, and bank specimens in a -80°C freezer.

Formalin-fixed Paraffin-Embedded (FFPE) Tissue
The SWOG Biospecimen Bank will receive FFPE specimens as either blocks or slides/sections at up to 2 time points per patient. Upon receipt, the Bank will accession, barcode, and bank specimens at ambient temperature.

At the end of the study, the Bank will receive notification from the SWOG Statistics and Data Management Center (SDMC) to distribute specimens for testing. The SDMC will create three pull lists for Nationwide informing them which samples are:

- leftover tissue from patients biopsied at screening
- patients who consented to a biopsy prior to treatment
- patients who consented to a biopsy at progression

Tumor Tissue for PD-L1 IHC Testing
The SWOG Biospecimen Bank will send FFPE slides from consented patients for PD-L1 IHC testing at Clarient. About every 3 months, the Bank will receive notification from the SWOG Statistics and Data Management Center to distribute specimens for testing.

The Bank will send 2-4 unstained slides. If an FFPE tissue block was received, then the SWOG Biospecimen Bank will process 2-4 unstained slides (4 micron, charged) and an H&E-stained slide. The unstained slides will be shipped to Clarient for testing, and the H&E slides will be scanned to a 40x digital image.

Tumor Tissue for Immunotherapy Resistance Analysis
The SWOG Biospecimen Bank will send FFPE slides from consented patients for immunotherapy resistance analysis.

The Bank will send 5-10 unstained slides. If an FFPE tissue block was received, then the SWOG Biospecimen Bank will process up to 10 unstained slides (4 micron, charged, unbaked) to send for testing.