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S1800A: (Non-Match Immunotherapy Combination Sub-Study)

SWOG CANCER RESEARCH NETWORK

LUNGMAP, A MASTER PROTOCOL TO EVALUATE BIOMARKER-DRIVEN THERAPIES AND IMMUNOTHERAPIES IN PREVIOUSLY TREATED NON-SMALL CELL LUNG CANCER (LUNG-MAP SCREENING STUDY)

S1800A, A PHASE II RANDOMIZED STUDY OF RAMUCIRUMAB PLUS PEMBROLIZUMAB (MK-3475) VERSUS STANDARD OF CARE FOR PATIENTS PREVIOUSLY TREATED WITH IMMUNOTHERAPY FOR STAGE IV OR RECURRENT NON-SMALL CELL LUNG CANCER (LUNG-MAP NON-MATCHED SUB-STUDY)

NCT #03971474

This is an FDA Registration Trial. Additional site requirements include:

- **maintenance of a Trial Master File (https://www.swog.org/sites/default/files/docs/2017-10/Guidance%20on%20FDA%20Inspection.pdf)**
- **completion of a protocol specific Delegation of Task Log (DTL) (see Section 13.2)**
- **additional monitoring (see LUNGMAP Appendix 18.2)**

LUNGMAP and its sub-studies are being conducted under SWOG IND 143217 and CIRB. The LUNGMAP 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 LUNGMAP sub-study protocols should be processed as a single study for Continuing Review.

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AGENTS:
NCI Supplied Investigational Agents:
Ramucirumab (NSC 749128)
Pembrolizumab (MK-3475) (NSC 776864)

Commercially Available Agents:
Docetaxel (NSC 628503)
Gemcitabine hydrochloride (NSC 613327)
Pemetrexed (NSC 698307)

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TABLE OF CONTENTS

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Investigational Drug questions: Requests for Investigator's Brochures:	See Protocol Section 3.0
Temperature Excursion Reports:	See Protocol Section 3.4f for ramucirumab CTMM@lilly.com See Protocol Section 3.5f for pembrolizumab
Specimen Tracking System (STS) Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench:	technicalquestion@crab.org
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Cancer Therapy and Evaluation Program – Identity and Access Management (CTEP-IAM):	To review CTEP-IAM account (new requests, reset passwords): https://ctepcore.nci.nih.gov/iam/index.jsp
Access to iMedidata Rave or Delegation of Task Log (DTL):	See Protocol Section 14.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Questions related to Oncology Patient Enrollment Network (OPEN):	See **LUNGMAP** Protocol Section 13.2 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Patient Transfers:	patienttransfer@crab.org
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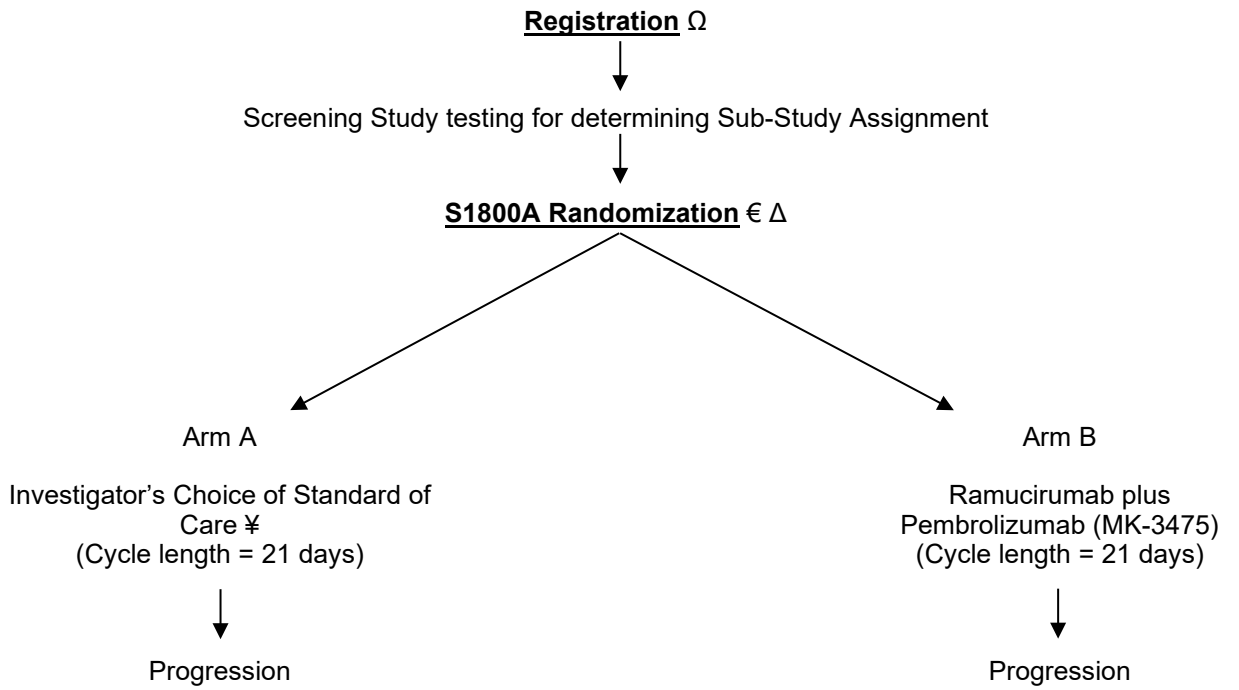
Adverse Event Reporting questions:	See Protocol Section 8.7 E-mail: adr@swog.org
Source Documentation Portal – Central Monitoring:	centralmonitorquestion@crab.org

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

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 > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to 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 CRA 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 in with a CTEP-IAM username and password.		
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center (SDMC) by phone or email: 206/652-2267 LUNGMAPQuestion@crab.org **For treatment or toxicity related questions** contact S1800AMedicalQuery@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: 888-823-5923 S1400contact@westat.com All calls and correspondence will be triaged to the appropriate CTSU representative.		

SCHEMA



Ω See **LUNGMAP** Section 5.1 for registration information. Note: Patients may have been enrolled on the legacy **S1400** screening/pre-screening study.

€ Notification of sub-study assignment will be provided by the SWOG Statistics and Data Management Center (SDMC) (see **LUNGMAP** Section 11.0 for details).

Δ See Section 11.0 for a more detailed statistical design.

¥ This is the Investigator's Choice of Standard of Care as outlined in Section 7.2a.

1.0 OBJECTIVES

1.1 Primary Objective

To compare overall survival between patients previously treated with platinum-based chemotherapy and immunotherapy for Stage IV or recurrent non-small cell lung cancer randomized to ramucirumab and pembrolizumab (MK-3475) versus standard of care (SoC).

1.2 Secondary Objectives

a. To compare response rates between the arms, including complete response (CR) and partial response (PR) (confirmed and unconfirmed).

b. To compare the disease control rate (CR, PR, confirmed and unconfirmed and SD)

c. To evaluate the duration of response (DoR) among responders within each arm.

d. To evaluate the frequency and severity of toxicities within each arm.

e. To compare IA-PFS between the arms.

f. To evaluate the clinical outcomes (OS, IA-PFS, response) by randomization stratification factors (See Section 6.0) by comparing outcomes within the ramucirumab and pembrolizumab (MK-3475) arm, performing a sub-group analysis of the arms, and by evaluating an interaction between the factors and treatment arm.

1.3 Translational Medicine Objectives

a. To evaluate if PD-L1 expression levels are associated with clinical outcomes (OS, IA-PFS, and response).

b. To evaluate if tumor mutation burden (TMB) as determined by the FMI Foundation One panel is associated with clinical outcomes.

c. To collect, process, and bank cell-free (cfDNA) at baseline and progression for future development of a proposal to evaluate comprehensive next-generation sequencing of circulating tumor DNA (ctDNA).

Note: The proposal to use these specimens would be submitted as an amendment to CTEP for approval prior to SDMC reviewing the results.

d. To establish a tissue/blood repository to pursue future studies.

2.0 BACKGROUND

2.1 Lung-MAP

The Lung-MAP study is an umbrella protocol which contains a screening component and multiple independently conducted and analyzed treatment sub-studies for patients with previously treated stage IV or recurrent NSCLC. This protocol is specifically designed for patients not eligible for one of the biomarker-driven sub-studies in Lung-MAP who have previously received (and progressed during or following) both platinum-based chemotherapy and immune checkpoint inhibitor therapy.

2.2 General Background

The therapeutic landscape in metastatic NSCLC has dramatically changed with approvals of immunotherapy agents in both treatment-naïve and previously treated cancer and irrespective of histology. *(1, 2, 3, 4, 5)* Tumors may modulate and evade the host immune response through several mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T-cell checkpoint regulators such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death-1 (PD-1, CD279) are cell surface molecules that play a critical role in down-regulating T-cell activation and proliferation. T-cell checkpoint inhibitors' anti-tumor activity depends on disruption of immune tolerance to tumor cell antigens. Following on the success of CTLA-4 and anti-PD-1 pathway-targeted agents in several cancers, the field of tumor immunotherapy is rapidly expanding with several new promising approaches. Overall, enhancement of the magnitude and potency of tumor antigen-specific adaptive cellular responses by CD8 and CD4 T cells is now considered a major goal in cancer immunotherapy. Knowing that single-agent immunotherapies have already demonstrated activity, it is plausible, that combination therapies could lead to a greater depth of response, and an increase in overall survival (OS) as has been noted with the combination of anti-PD-1 and anti-CTLA-4 in subjects with previously untreated NSCLC. (*6*) In addition, the biggest current need is for those patients with primary or acquired resistance.

2.3 Study Design

We now understand that the kinetics of immune-mediated anti-tumor activity may be delayed compared to that of cytotoxic chemotherapy or targeted therapy. Immunotherapy mediates tumor regression indirectly through activation of immune responses and/or inhibition of suppressive immune elements. This may result in delayed tumor regression, with some patients even experiencing the progression of existing disease or the appearance of new lesions prior to eventual disease regression. Furthermore, many immunotherapy agents do not impact PFS, but are associated with significant improvements in overall survival. *(7)*

Knowing that single-agent immunotherapies have already demonstrated activity, it is plausible that combination therapies could lead to a greater depth of response, and/or an increase in overall survival (OS) as has been noted with the combination of anti-PD-1 and anti-CTLA-4 in subjects with previously untreated NSCLC. *(8)*

2.4 Ramucirumab and Pembrolizumab (MK-3475)

An immunosuppressive tumor microenvironment exists within lung tumors. Vascular Endothelial Growth Factor (VEGF) has been shown to modulate the tumor immune microenvironment. CD25+ FOXP3+ CD4+ T cells (Treg) play an important role in developing immune tolerance within tumors. VEGF impedes T cell extravasation by limiting T cell adhesion to the luminal surfaces of blood vessels, inhibits the proliferation and cytotoxicity of cytotoxic T lymphocytes (CTLs), and stimulates the proliferation of T regulatory (Treg) cells. *(9)* VEGF also induces programmed death ligand 1 (PDL1) expression on dendritic cells. VEGFR2 has been shown to be expressed by FOXP3 high Treg and exists in peripheral blood mononuclear cells and lymphocytes within malignant effusions. Therefore, inhibition of VEGFR may inhibit the immunosuppressive function of Treg. *(10)* VEGFR2 has also been shown to reduce tumor induced Treg proliferation. *(11)* In a transgenic breast cancer model, VEGFR inhibition led to modulation of cytokines related to tumor cell infiltration. In addition, VEGFR2 inhibition decreased infiltration of suppressive immune cells while increasing mature dendritic cells. *(12)* VEGF has a systemic effect on myeloid-derived suppressor cells (MDSCs) and suppresses dendritic cell maturation. VEGF drives the recruitment and infiltration of angiogenic and immune-suppressive MDSCs and macrophages. MDSCs and macrophages then produce reactive oxygen species, nitric oxide, and arginase to suppress T cell proliferation, viability, and activity. High levels of VEGF have been associated with the accumulation of immature myeloid DC in cancer patients. *(13)* By contrast, inhibition of VEGF restores many of these

phenotypes. *(14)* Sunitinib is a multi-kinase inhibitor that has multiple targets including VEGFR and c-kit. Treatment with sunitinib led to a 50% reduction in the peripheral blood levels of MDSC in renal cell cancer patients. The decline was associated with improved Th1 lymphocyte function and decreased numbers of Tregs. *(15)* Furthermore, the simultaneous blockade of PD1 and VEGFR2 synergistically inhibited tumor growth by reducing tumor neovascularization and resulted in upregulation of proinflammatory cytokines. *(16)*

Ramucirumab is a human IgG1 monoclonal antibody that targets the extracellular domain of vascular endothelial growth factor receptor 2 (VEGFR2), blocking VEGF binding and receptor activation. *(17)* In a Phase III trial in patients with advanced NSCLC, the combination of ramucirumab and docetaxel demonstrated improved overall response rate (ORR), progression free survival and overall survival compared to docetaxel alone. *(18)* Such benefit was also seen in patients who progressed rapidly on first-line therapy who historically would have a poor prognosis in the second line setting in a post-hoc analysis. *(19)* In advanced renal cell carcinoma, the combination of axitinib and pembrolizumab (MK-3475) resulted in a 71% ORR. *(20)* In an early Phase I a/b trial, 27 NSCLC patients who previously progressed on chemotherapy received the combination of ramucirumab and pembrolizumab (MK-3475), which demonstrated a 30% ORR with 77% of evaluable patients experiencing some tumor shrinkage. *(21)* The doublet demonstrated encouraging antitumor activity independent of PD-L1 and histology, numerically better than anti-PD-1 monotherapy. In an updated presentation at ASCO 2018 by Roy Herbst et al, data in the NSCLC cohort was reported by PDL1 status. *(22)* Overall response rate was 18% in PDL1 <1% and 45% in ≥1% with duration of response not reached in either group, and disease control rate was 82% versus 91% in PDL1 <1% and ≥1%, respectively. For patients with PDL1 <1%, progression free survival (PFS) was 9.7 months and overall survival (OS) was 17 months. For those with PDL1 ≥1%, PFS was 6.9 months and OS was not reached. Toxicity in the NSCLC subgroup showed 26% with grade 3/4 adverse events, 7% with hypertension, 4% with fatigue, 4 % with infusion reaction and 4% with proteinuria. Dual blockade with ramucirumab and pembrolizumab (MK-3475) may lead to improved tumor responses and prolonged survival in patients with metastatic lung cancer. In addition, a study evaluating maintenance nivolumab with or without bevacizumab following first-line platinum-based doublet chemotherapy was evaluated in patients with advanced NSCLC. the median OS survival was not reached in either arm. In the combination arm, median PFS was 37.1 weeks, while nivolumab alone resulted in median PFS of 16 weeks for squamous cell carcinoma and 21.4 weeks for nonsquamous NSCLC. *(23)* The combination was well tolerated. The preclinical rationale in addition to early clinical data support the evaluation of this combination.

2.5 PD-L1 Test

Testing for Programmed death-ligand 1 (PD-L1) expression by Immunohistochemistry (IHC) was performed on all fresh tumor biopsies and archival tumor materials on LUNGMAP screening protocol, prior to LUNGMAP Revision #4. This was done by Foundation Medicine utilizing the 22C3 pharmDx (Dako) antibody which is already FDA approved and a reliable biomarker for selection of patients that are more likely to benefit from checkpoint inhibitor therapy.

2.6 Circulating tumor DNA (ctDNA)

In addition, the detection rates of mutations observed in ctDNA isolated from patient plasma at baseline and progression will be evaluated in comparison to mutations observed in tumor tissue. It is expected that mutations identified in plasma will be synonymous with those detected in tissue, with the following exceptions: a subset of patients may have insufficient amounts of ctDNA in circulation for detection, and secondly, a subset of patients may have additional mutations detected in plasma that are associated with metastases and not present in the original tissue biopsy. The overarching goal of the Lung-MAP liquid biopsy program, planned across multiple sub-studies, is to assess whether positive

identification of mutations in ctDNA can be utilized for molecular assignment. In this sub-study, the primary objective is to correlate detection frequencies between tissue and plasma.

2.7 Inclusion of Women and Minorities and Planned Enrollment Report

This study was designed to include women and minorities but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	1	3	0	0	4
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	5	6	0	0	11
White	55	69	1	2	127
More Than One Race	0	0	0	0	0
Total	61	80	1	2	144

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator's Brochures, please refer to SWOG Policy 15. For **S1800A**, the investigational drugs are ramucirumab (Arm B only) and pembrolizumab (MK-3475) and are being provided under an IND held by SWOG. [Note: Ramucirumab will be supplied for both Arm A (Investigator's Choice of Standard of Care) and Arm B (Investigational Combination).] of 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 Docetaxel (Taxotere®) (NSC-628503)
[Commercially Available Drug]

a. PHARMACOLOGY

Mechanism of Action: Docetaxel promotes the assembly of microtubules and stabilizes their formation by inhibiting depolymerization. This stabilization creates a microtubule which is non-functional. Cell death is promoted by the disruption of normal cell shape, motility, attachment, and intracellular transport. Docetaxel is cytotoxic predominately in the S-phase of the cell cycle.

b. PHARMACOKINETICS

1. Absorption: Intravenous administration of docetaxel results in 100% bioavailability. Area under the curve (AUC) of docetaxel was dose

proportional following doses of 70 mg/m^2 to 115 mg/m^2 with infusion times of 1 to 2 hours.

2. Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. In vitro studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins.

3. Metabolism: Docetaxel is primarily metabolized in the liver by cytochrome P450 3A4 and 3A5 isoenzymes (CYP3A4/5).

4. Elimination: Docetaxel elimination follows a three-compartment model with an initial distribution half-life of 3 to 5 minutes, an intermediate elimination half-life of 36 to 60 minutes, and a terminal half-life of 10 to 18 hours. Mean total body clearance was 21 L/h/m^2.Approximately 6% of unchanged drug is eliminated by the kidney in 24 hours, with the majority (80%) of excretion occurring in feces at 7 days.

c. ADVERSE EFFECTS

1. Possible Side Effects of Docetaxel: The most common adverse effects occurring in > 20% of people receiving docetaxel include: fluid retention, alopecia, nail disorders, skin reactions (rash, pruritis), nausea, vomiting, diarrhea, constipation, mucositis, infections, anemia, asthenia, neutropenia, neuropathy, fever, amenorrhea, erythema of the extremities with edema, pain and lacrimation with or without conjunctivitis.

   Adverse effects occurring in ≤ 20% of people receiving docetaxel include: cutaneous skin reactions, abdominal pain, thrombocytopenia, febrile neutropenia, hepatotoxicity, venous thromboembolism, pulmonary embolism, myalgia, anorexia, dysgeusia, dyspnea, and cardiac dysrhythmias.

   Rare (< 3%) but potentially serious adverse effects include: hypersensitivity reactions (rash/erythema, hypotension, wheezing, shortness of breath, swelling of the face or throat), acute myeloid leukemia, and interstitial lung disease or pneumonia.

   Patients receiving docetaxel infusions may experience alcohol intoxication from the ethanol included in the formulation.

   Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

2. Pregnancy and Lactation: Pregnancy Category D. Excretion in breast milk is unknown and breast feeding is not recommended during treatment.

3. Drug Interactions: Cytochrome P450 3A4/5 inducers, inhibitors, or substrates may alter docetaxel metabolism. In patients receiving treatment with docetaxel, close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A inhibitor cannot be avoided. Patients should use caution with sleep aids or narcotic analgesics due to possible additive sedation from the alcohol present in the docetaxel formulation. Due to potential drug interactions, a complete patient medication list, including docetaxel,

should be screened prior to initiation of and during treatment with docetaxel.

d. DOSING & ADMINISTRATION

See treatment plan in Section 7.0.

e. HOW SUPPLIED

Docetaxel is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert.

3.2 Gemcitabine hydrochloride (Gemzar®) (NSC-613327)
[Commercially Available Drug]

a. PHARMACOLOGY

Mechanism of Action: Gemcitabine (2'-Deoxy-2', 2'-difluorocytidine monohydrochloride), like cytarabine, is a nucleoside analog of deoxycytidine. This antimetabolite, a pyrimidine analog inhibiting both DNA and RNA viruses, is cell-cycle-specific in blocking the cells at the G1/S and is retained in human tumor cells for long periods. Studies suggest that gemcitabine is activated by deoxycytidine kinase. Deoxycytidine has been shown to reverse the growth inhibitory activity of gemcitabine.

b. PHARMACOKINETICS

1. Distribution: Gemcitabine plasma protein binding is negligible. The volume of distribution is increased with the infusion length. In a pharmacokinetics study of patients with various solid tumors, the volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes. For long infusions (70 to 285 minutes), the volume of distribution rose to 370 L/ m^2.

2. Metabolism: Gemcitabine is metabolized intracellularly to form active gemcitabine di- and tri-phosphates. The gemcitabine di- and tri-phosphates do not appear to circulate in plasma in measurable amounts. Gemcitabine is metabolized by the liver to form the inactive uracil derivative, 2'-deoxy-2',2'-difluorouridine (dFdU). The inactive metabolite does not appear to accumulate with weekly dosing; however, it is excreted by the kidneys and may accumulate in patients with decreased renal function.

3. Elimination: Following a single 1,000 mg/m^2/30 min [^{14}C]-gemcitabine infusion, 92% to 98% of the dose was recovered within 1 week after gemcitabine administration. Urinary excretion of the parent drug and the dFdU metabolite accounted for 99% of the excreted dose, and less than 1% of the dose was excreted in feces. The renal clearance of gemcitabine is less than 10%; therefore, the parent drug appears to be almost completely metabolized to the inactive dFdU.

Clearance of gemcitabine is affected by age and gender and is lower in women and the elderly. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Studies showed

that gemcitabine half-life for short infusions ranged from 42 to 94 minutes, for long infusions it varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The terminal phase half-life for the active metabolite, gemcitabine triphosphate, in mononuclear cells ranges from 1.7-19.4 hours.

c. ADVERSE EFFECTS

1. Possible Side Effects of Gemcitabine:

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in >20% to 100% of subjects treated with gemcitabine include: flu-like symptoms, nausea, vomiting, rash, alopecia, infection, myelosuppression including anemia, leukopenia, neutropenia, and thrombocytopenia, muscle weakness, hematuria, paresthesia, sensory neuropathy, fatigue, somnolence, hearing loss, peripheral edema.

Adverse effects reported in 4% to 20% of subjects include: diarrhea, constipation, stomatitis, dyspnea, capillary leak syndrome, posterior reversible encephalopathy syndrome (PRES).

Adverse effects reported in 3% or less of subjects include: arrhythmias, supraventricular arrhythmias, congestive heart failure, myocardial infarction, desquamation and bullous skin eruptions, gangrene, cerebrovascular accident, hepatic failure, adult respiratory distress syndrome (ARDS), anaphylaxis, renal failure, pulmonary fibrosis, pulmonary edema, and, Interstitial, pneumonitis.

2. Pregnancy and Lactation: Category D. Gemcitabine may cause fetal harm when administered to a pregnant woman. This agent has produced teratogenic effects in mice and rabbits when administered at a dose of < 2 mg/m^2. Adverse effects included decreased fetal viability, weight and morphologic defects. There is no data on gemcitabine administration during human pregnancy, and it is not currently known if metabolites are excreted in human milk. However, many drugs are excreted in human milk, and there is a potential for adverse effects in nursing infants. Therefore, the use of gemcitabine should be avoided in pregnant or nursing women because of the potential hazard to the fetus or infant.

3. Drug Interactions: Per gemcitabine package insert, no formal drug interaction studies have been performed to date. When gemcitabine was administered with carboplatin or paclitaxel there was minimal or no effect on the pharmacokinetics of the studied drugs.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Gemcitabine is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert.

3.3 Pemetrexed (Alimta®) (NSC 698037)
[Commercially Available Drug]

NOTE: Pemetrexed is not FDA-approved for squamous cell NSCLC and should not be used to treat patients with squamous cell NSCLC.

a. PHARMACOLOGY

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

b. PHARMACOKINETICS

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

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

3. Metabolism: Pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration.

4. Elimination: The clearance of pemetrexed decreases, and exposure (AUC) increases, as renal function decreases. The total systemic clearance of pemetrexed is 91.8 mL/min and the elimination half-life of pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min).

c. ADVERSE EFFECTS

1. Possible Side Effects of Pemetrexed: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in > 20% of subjects treated with pemetrexed include: anemia, fatigue, constipation, nausea, vomiting, mucositis/stomatitis, thrombocytopenia, bleeding, infection, neutropenia, and desquamation.

Adverse effects reported in 4% to 20% of subjects include: diarrhea, edema, increased serum creatinine, increased serum ALT, increased serum AST, interstitial pneumonitis, pulmonary fibrosis, pruritus, rash, and erythema multiforme.

Serious adverse effects reported in ≤ 3% of subjects include: bowel obstruction, neuropathy, alopecia, and thrombosis/embolism.

2. Pregnancy and Lactation: Pregnancy Category D. Pemetrexed can cause fetal harm when administered to a pregnant woman. Pemetrexed administered intraperitoneally to mice during organogenesis was embryotoxic, fetotoxic and teratogenic in mice at greater than 1/833rd the recommended human dose. If pemetrexed is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant. Women should be advised to use effective contraceptive measures to prevent pregnancy during treatment with pemetrexed. Due to the potential for serious adverse reactions in the nursing infant, a decision should be made to discontinue pemetrexed or to discontinue breast-feeding during therapy, taking into account the benefits of treatment to the mother.

3. Drug Interactions: Although ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed, it can be administered with pemetrexed in patients with normal renal function (creatinine clearance ≥80 mL/min). No dose adjustment of pemetrexed is needed with concomitant non-steroidal anti-inflammatory drugs (NSAIDs) in patients with normal renal function. Caution should be used when administering NSAIDs concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of 2 days before, the day of, and 2 days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

Due to potential drug interactions, a complete patient medication list, including pemetrexed, should be screened prior to initiation of and during treatment with pemetrexed. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Pemetrexed is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert.

3.4 Ramucirumab (Cyramza™, IMC-1121B, LY3009806) (NSC 749128, IND 143217) [Investigational Drug]

Ramucirumab will be supplied for both Arm A (Investigator's Choice of Standard of Care) and Arm B (Investigational Combination). See Section 3.4e for additional details.

a. PHARMACOLOGY

Mechanism of Action: Ramucirumab is a recombinant human IgG1 monoclonal antibody that specifically binds to vascular endothelial growth factor receptor 2 (VEGFR2). The binding of ramucirumab to VEGFR2 prevents its interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D) and as a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2 and its downstream intracellular signaling components, including Erk1/Erk2, neutralizing ligand-induced proliferation and migration of human endothelial cells. Ramucirumab inhibited angiogenesis in an *in vivo* animal model.

b. PHARMACOKINETICS

4. Absorption: Ramucirumab is given via intravenous infusion.

5. Distribution: In population pharmacokinetic models involving 2,820 patients, the mean volume of distribution (Vd) of ramucirumab at steady state was 4.47 L.

6. Metabolism: As a monoclonal antibody, ramucirumab is largely confined to the extracellular space, and elimination is primarily by catabolism.

7. Elimination: The mean clearance of ramucirumab was 0.0132 L/hour. The mean terminal half-life was 10.2 days.

c. ADVERSE EFFECTS

1. Adverse Effects: The below summary is based on patients receiving single-agent ramucirumab for gastric cancer (N=236). The type and frequency of adverse events observed vary when ramucirumab is administered in combination with other antineoplastic agents. Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

2.

Version: April 2022

Adverse Events with Possible Relationship to Ramucirumab		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia* Neutropenia	
CARDIAC DISORDERS		
	Hypertension*	Arterial thromboembolic events (myocardial infarction, cardiac arrest, cerebrovascular accidents, and cerebral ischemia)
GASTROINTESTINAL DISORDERS		
Abdominal pain*	Diarrhea*	Intestinal obstruction Gastrointestinal perforation
METABOLISM AND NUTRITION DISORDERS		
	Hypokalemia* Hyponatremia*	
NERVOUS SYSTEM DISORDERS		
	Headache*	
RENAL AND URINARY DISORDERS		
	Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Epistaxis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Rash	

* Serious events reported

Important adverse events, including serious adverse events, observed with ramucirumab across clinical trials and disease states: hemorrhage, infusion related reactions, gastrointestinal hemorrhage, impaired wound healing, Posterior Reversible Encephalopathy Syndrome (PRES), nephrotic syndrome, thyroid dysfunction, and worsening of pre-existing hepatic impairment.

3. Pregnancy and Lactation:

There are no available data on ramucirumab use in pregnant women. Based on its mechanism of action, ramucirumab can cause fetal harm. Avoid the use of ramucirumab in pregnant women and advise a pregnant

woman of the potential risk to a fetus. Animal models link angiogenesis, VEGF and VEGF Receptor 2 to critical aspects of female reproduction, embryofetal development, and postnatal development. Contraception should be used during treatment and for at least three months after the last dose of ramucirumab. Based on animal models, ramucirumab may potentially impair female fertility.

Studies have not been conducted to assess ramucirumab's impact on milk production, its presence in breast milk, or its effects on the breast-fed child. Ramucirumab is excreted in human milk and, due to potential risks to the nursing infant, do not breastfeed during treatment with ramucirumab and avoid breastfeeding for 2 months after the last dose of ramucirumab.

4. Drug Interactions: No clinically meaningful changes in the exposure of either ramucirumab or its concomitant drugs in the currently approved combinations, including paclitaxel, docetaxel, irinotecan (or its active metabolite, SN-38), and erlotinib were observed in patients with solid tumors. Studies indicate that it is unlikely for drug-drug interactions with concomitant administration of ramucirumab and durvalumab.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

Ramucirumab is administered through a separate infusion line. The use of a protein sparing 0.22 micron in-line filter is recommended. The line should be flushed with sterile sodium chloride (0.9%) solution for injection at the end of the infusion. Do not administer as an intravenous push or bolus.

e. HOW SUPPLIED

1. Ramucirumab will be supplied free of charge. It will be provided by Eli Lilly and Company and distributed by CTEP PMB. Sites will be provided a commercially labeled ramucirumab for investigational use.

2. Ramucirumab is supplied in single-use, 50-mL glass vials. Each vial contains 500 mg of ramucirumab at a concentration of 10 mg/mL in a sterile, preservative-free solution. Each vial is stoppered with a chlorobutyl elastomer stopper laminated with FluroTec® (West Pharmaceutical Services, Inc., Exton, PA), and secured with an aluminum 2-piece flip-top seal.

Ramucirumab formulated in an aqueous solution at a concentration of 10 mg/mL. The buffer contains 10mM histidine, 75mM sodium chloride, 133mM glycine, and 0.01% polysorbate 80.

Ramucirumab is a clear to slightly opalescent and colorless to slightly yellow liquid without visible particles. The pH is 6.0.

All excipients used for the manufacture of ramucirumab are of pharmacopeial grade. Ramucirumab molecular weight is 146.8 kDa.

See Section 3.6 for Drug Ordering and Accountability.

f. STORAGE, PREPARATION & STABILITY

1. Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light. DO NOT FREEZE OR SHAKE the vial.

   In case of temperature excursion outside of the storage range at the site, contact CTMM@lilly.com to obtain the Temperature Excursion Data Collection Form (TEDCF). Complete and submit the TEDCF to the location indicated on the form within one business day of resolution of the temperature excursion. Please use the following information when filling out the form:
   - Trial Alias: I4T-US-I015
   - Site Number: 101
   - Site monitor name(s) and e-mail: This should be a person at the site level to contact with outcome (i.e. research coordinator).

   Determine the cause of the excursion and implement preventive actions to prevent future occurrence. Study drug should be returned to acceptable storage conditions and segregated from active stock. Clearly mark the material as quarantined and do not dispense/use (note directly on package) until further instruction is provided by Eli Lilly and Company.

2. Preparation:
   - Inspect vial contents for particulate matter and discoloration prior to dilution. If particulate matter or discolorations are identified, discard the vial.
   - Withdraw the required volume of ramucirumab and further dilute with only 0.9% Sodium Chloride Injection in an intravenous infusion container to a final volume of 250 mL. DO NOT use dextrose containing solutions.
   - Gently invert the container to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.
   - Store diluted infusion for no more than 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature (below 25°C [77°F]).
   - Discard vial with any unused portion of ramucirumab, as the product contains no preservatives.

3. Compatibility information: DO NOT mix with dextrose containing solutions or infuse with electrolyte solutions or other medications.

3.5 Pembrolizumab (MK-3475) (NSC-776864) (IND 143217)
[Investigational Available Drug]

a. PHARMACOLOGY

Mechanism of Action: Pembrolizumab (MK-3475) is a humanized MAb of the IgG4/kappa isotype. The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells expressing PD-1 ligands to suppress immune control. Pembrolizumab (MK-3475) blocks the negative immune

regulatory signaling by binding to the PD-1 receptor, inhibiting the interaction between PD-1 and its ligands and thereby promoting the host immune system to recognize tumor cells as foreign bodies to be eliminated.

b. PHARMACOKINETICS

1. Absorption: N/A

2. Distribution: Limited distribution and protein binding (V_d= ~7.5 liters)

3. Metabolism: Pembrolizumab (MK-3475) follows general protein degradation pathways in the body. Cytochrome p450 enzymes are not involved in metabolism.

4. Elimination: Elimination half-life after IV administration was approximately 26 days. Steady state concentration levels were achieved within ~18 weeks of repeated dosing, with ~2.2-fold accumulation in exposure during administration Q3W relative to exposure observed following single dose administration. In the dose range studied for efficacy (2 to 10 mg/kg), pembrolizumab (MK-3475) exposure increases in a dose-proportional manner, with clearance being independent of time or pembrolizumab (MK-3475) concentration.

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. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for pembrolizumab (MK-3475).

Version 2.6, July 15, 2021[1]

Adverse Events with Possible Relationship to pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia[2] Lymph node pain[2]	Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura)[2]
CARDIAC DISORDERS		
		Myocarditis[2] Pericarditis[2]
ENDOCRINE DISORDERS		
	Adrenal insufficiency[2] Endocrine disorders - Other (thyroiditis)[2] Hyperthyroidism[2]	

Adverse Events with Possible Relationship to pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Hypophysitis[2] Hypopituitarism[2] Hypothyroidism[2]	
EYE DISORDERS		
		Uveitis[2] Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)
GASTROINTESTINAL DISORDERS		
	Abdominal pain Colitis[2] Diarrhea[2] Mucositis oral[2] Nausea Pancreatitis[2] Small intestinal mucositis[2]	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	Chills[2] Fever[2]	
HEPATOBILIARY DISORDERS		
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]	Hepatobiliary disorders - Other (sclerosing cholangitis)
IMMUNE SYSTEM DISORDERS		
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2] Immune system disorders - Other (sarcoidosis)[2]	Anaphylaxis[2] Cytokine release syndrome[2] Immune system disorders - Other (acute graft-versus-host-disease)[2,3] Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2] Serum sickness[2]
INFECTIONS AND INFESTATIONS		
	Infection[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Infusion related reaction
INVESTIGATIONS		
	Alanine aminotransferase increased[2] Alkaline phosphatase increased Aspartate aminotransferase increased[2]	GGT increased Serum amylase increased

Adverse Events with Possible Relationship to pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Blood bilirubin increased CPK increased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia Hyponatremia	Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2] Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia[2] Arthritis[2] Avascular necrosis[2] Back pain Joint effusion[2] Joint range of motion decreased Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2] Myalgia[2] Myositis[2]	
NERVOUS SYSTEM DISORDERS		
		Guillain-Barre syndrome[2] Nervous system disorders - Other (myasthenic syndrome)[2] Nervous system disorders - Other (neuromyopathy)[2] Nervous system disorders - Other (non-infectious encephalitis)[2] Nervous system disorders - Other (non-infectious meningitis)[2] Nervous system disorders - Other (non-infectious myelitis) Nervous system disorders - Other (polyneuropathy)[2] Paresthesia Peripheral motor neuropathy[2]
RENAL AND URINARY DISORDERS		
		Renal and urinary disorders - Other (autoimmune

Adverse Events with Possible Relationship to pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		nephritis)[2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough Pleuritic pain[2] Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Bullous dermatitis[2] Erythroderma Pruritus[2] Rash acneiform[2] Rash maculo-papular[2] Skin and subcutaneous tissue disorders - Other (dermatitis)[2] Skin hypopigmentation[2] Urticaria[2]	Erythema multiforme[2] Palmar-plantar erythrodysesthesia syndrome Stevens-Johnson syndrome[2] Toxic epidermal necrolysis
VASCULAR DISORDERS		
		Vasculitis[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-mediated adverse reactions have been reported in patients receiving pembrolizumab (MK-3475). Adverse events potentially related to pembrolizumab (MK-3475) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of pembrolizumab (MK-3475), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with pembrolizumab (MK-3475) who received hematopoeitic stem cell transplants.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on pembrolizumab (MK-3475) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that pembrolizumab (MK-3475) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia

EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: Pembrolizumab (MK-3475) 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: The central function of the PD-1/PD-L1 pathway is to maintain immune tolerance to the fetal allograft, and its important role in maintaining pregnancy has been recently emphasized in literature. The PD-L1 molecule expressed at the uteroplacental interface effectively protects the concepti from maternal T cell-mediated immunity. Blockade of PD-L1 signaling has been shown in murine models of allogeneic pregnancy to abrogate feto-maternal tolerance to the concepti and to result in an increase in fetal resorption. The evidence from these experimental results indicates that there is a theoretical risk associated with the administration of pembrolizumab (MK-3475) to women of child-bearing potential (WOCBP). It is therefore anticipated that the inhibition of PD-1 by treatment with anti-PD-1 monoclonal antibody (i.e.,

pembrolizumab) during pregnancy would have detrimental effects that might include increased rates of abortion and stillbirth.

It is not known whether pembrolizumab (MK-3475) is excreted in human milk. Because of the potential for drugs to be excreted in human milk, the risk to the nursing infant cannot be excluded and therefore pembrolizumab (MK-3475) should not be administered to nursing mothers.

Contraception should be used during treatment and for at least four months after the last dose of pembrolizumab (MK-3475).

3. Drug Interactions: No studies on pharmacodynamic drug interactions have been performed. Due to potential drug interactions, a complete patient medication list, including pembrolizumab (MK-3475), should be screened prior to initiation of and during treatment with pembrolizumab (MK-3475). See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

1. Pembrolizumab (MK-3475) will be supplied free of charge. It will be provided by Merck & Co., Inc. and distributed by Pharmaceutical Management Branch (PMB), CTEP/DCTD/NCI (PMB).

2. Pembrolizumab (MK-3475) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. Each vial contains 100 mg of pembrolizumab (MK-3475) in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab (MK-3475) and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

f. STORAGE, PREPARATION & STABILITY

1. Refer to the package label for expiration.

2. Pembrolizumab (MK-3475) should be stored under refrigeration at 2°C - 8°C (36°F – 46°F) and protected from light in the original box. Do not freeze or shake the vials.

Solution:

- Prepare the IV infusion using aseptic technique in a biological safety cabinet or hood.
- Pembrolizumab (MK-3475) should be prepared in 0.9% Sodium Chloride Injection, USP (normal saline) with a final concentration between 1mg/mL and 10mg/mL.
- Pembrolizumab (MK-3475) is compatible with the following bags: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, PE lined polyolefin.
- After adding the required amount of drug into the infusion bag, gently invert the bag 10-15 times to mix the solution.
- Pembrolizumab (MK-3475) should NOT be mixed with other reconstitution diluents. Pembrolizumab (MK-3475) is infused over 30 minutes and is to be administered through a sterile, low protein-binding 0.2 to 5 micron in-line filter. The following infusion set materials are compatible with pembrolizumab

(MK-3475): PVC plasticized with DEHP, PVC and TOTM, polyethylene lined PVC, PVC plasticized with DEHT or polyurethane sets. Maximum rate of infusion should not exceed 6.7ml/min using an infusion pump. Lines may be primed with normal saline.

- Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion. If refrigerated, allow the IV admixture to come to room temperature prior to use.
- Parenteral drug product should be visually inspected for particulate matter and discoloration prior to administration. Discard the drug product vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed.
- Discard any unused portion of pembrolizumab (MK-3475) vials immediately as the vials do not contain preservatives.
- Do not administer the product as an IV push or bolus.

3. If a storage temperature excursion is identified, promptly return pembrolizumab to between 2-8°C (36°F – 46°F) and quarantine the supplies. Contact Merck Sharp & Dohme Corp., by referencing the phone number listed on the commercial package insert, to obtain instructions and clinical complaint form.

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

5. Repackaging or other specific dispensing requirements: None

3.6 DRUG ORDERING & ACCOUNTABILITY FOR INVESTIGATIONAL AGENTS

For Commercial Agents
Commercial agents are labeled with an expiration date and that date should be followed.

a. Drug Ordering Investigational Agents provided by PMB
Confirmation of patient's enrollment is required for initial drug supply.

Drug ordering: NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number (**S1800A**) must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 and a CV. If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account <

https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

b. Drug Handling and Accountability

1. 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).

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

c. Drug Return and/or Disposition Instruction

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

2. Drug Expiration: PMB will send a stock recovery letter when the agent is no longer suitable for use

d. Contact Information and Useful Links

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

- 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

4.0 STAGING CRITERIA

Patients must have Stage IV or recurrent disease as outlined below (AJCC Cancer Staging Manual, 8th Edition, 2017):

Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

Primary Tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0 No evidence of primary tumor

Tis Carcinoma in situ
Squamous cell carcinoma in situ (SCIS)
Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤ 3 cm in greatest dimension

T1 Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)

T1mi Minimally invasive adenocarcinoma: adenocarcinoma (≤ 3 cm in greatest dimension) with a predominantly lepidic pattern and ≤ 5 mm invasion in greatest dimension

T1a Tumor ≤ 1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.

T1b Tumor > 1 cm but ≤ 2 cm in greatest dimension

T1c Tumor > 2 cm but ≤ 3 cm in greatest dimension

T2 Tumor > 3 cm but ≤ 5 cm or having any of the following features:

- Involves the main bronchus regardless of distance to the carina, but without involvement of the carina
- Invades visceral pleura (PL1 or PL2)
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung

T2 tumors with these features are classified as T2a if ≤ 4 cm or if the size cannot be determined and T2b if > 4 cm but ≤ 5 cm.

T2a Tumor > 3 cm but ≤ 4 cm in greatest dimension

T2b Tumor >4 cm but ≤ 5 cm in greatest dimension

T3 Tumor > 5 cm but ≤ 7 cm in greatest dimension or directly invading any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium, or separate tumor nodule(s) in the same lobe as the primary

T4 Tumor > 7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastases

N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

M1a Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or malignant pleural or pericardial effusion. nodules or malignant pleural (or pericardial) effusion. **

M1b Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)

M1c Multiple extrathoracic metastases in a single organ or in multiple organs

** Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Statistics and Data Management Center (SDMC) in Seattle at 206/652-2267 or LUNGMAPquestion@crab.org prior to randomization. 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, 21, 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have been assigned to **S1800A** by the SWOG Statistics and Data Management Center (SDMC). Patients who were screened under **S1400** (legacy screening/pre-screening study) must have had prior PD-L1 testing by the Dako 22C3 PharmDx IHC assay, and must have results available for stratification purposes.

b. Patients must not have EGFR sensitizing mutations, EGFR T790M mutation, ALK gene fusion, ROS 1 gene rearrangement, and BRAF V600E mutation unless they have progressed following all standard of care targeted therapy.

c. Patients must not have an active autoimmune disease that has required systemic treatment in past two years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

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

e. Patients must not have experienced the following:
- Any Grade 3 or worse immune-related adverse event (irAE). Exception: asymptomatic nonbullous/nonexfoliative rash.
- Any unresolved Grade 2 irAE.
- Any toxicity that led to permanent discontinuation of prior anti-PD-1/PD-L1 immunotherapy.

Exception to the above: Toxicities of any grade that requires replacement therapy and has stabilized on therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) are allowed.

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

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

h. Patients must not have history of (non-infectious) pneumonitis that required steroids or current pneumonitis/interstitial lung disease.

i. Patients must not have had a serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to sub-study randomization.

j. Patients must not have a history of gastrointestinal perforation or fistula within six months prior to sub-study randomization.

k. Patients must not have Grade 3-4 gastrointestinal bleeding (defined by NCI CTCAE v5) within three months prior to sub-study randomization.

l. Patients must not have any known allergy or reaction to any component of the investigational formulations.

If there is a known allergy or reaction to standard of care formulations, patients must be able to safely receive at least one of the standard of care options.

m. 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 six months prior to sub-study randomization, or serious uncontrolled cardiac arrhythmia (see **S1800A** Section 18.1).

Patients must not have experienced any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within six months prior to sub-study randomization.

n. Patients must not have documented evidence of acute hepatitis or have an active or uncontrolled infection.

o. Patients with known human immunodeficiency virus (HIV) infection are eligible, provided they are on effective anti-retroviral therapy and have undetectable viral load at their most recent viral load test and within 6 months prior to randomization.

p. Patients with evidence of chronic hepatitis B virus (HBV) infection are eligible provided viral load is undetectable on suppressive therapy, if indicated.

q. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

r. Patients must not have undergone major surgery within 28 days prior to sub-study randomization, or subcutaneous venous access device placement within 7 days prior to randomization. Any patient with postoperative bleeding complications or wound complications from a surgical procedure performed in the last two months should be excluded. The patient must not have elective or planned major surgery to be performed during the course of the clinical trial.

s. Patients must not have gross hemoptysis within two months of sub-study randomization (defined as bright red blood or ≥1/2 teaspoon) or with radiographic evidence of intratumor cavitation or has radiologically documented evidence of major blood vessel invasion or encasement by cancer.

t. 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.

u. Patients must not have been diagnosed with venous thrombosis less than 3 months prior to randomization. Patients with venous thrombosis diagnosed more than 3 months prior to randomization must be on stable doses of anticoagulants.

v. Patients must not have any of following:
- cirrhosis at a level of Child-Pugh B (or worse) (See Appendix 18.3);
- cirrhosis (any degree) and a history of hepatic encephalopathy; or
- clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.

5.2 Prior/Concurrent Therapy Criteria

a. Patients must have received at least one line of anti-PD-1 or anti-PD-L1 therapy for Stage III, IV or recurrent disease and at most one line of anti-PD-1 or anti-PD-L1 therapy for Stage IV or recurrent disease, given alone or in combination with platinum-based chemotherapy, an anti-CTLA4 therapy, or other immune-modulatory therapy. Patients must have experienced disease progression during or after this regimen. Disease progression during or after anti-PD-1 or anti-PD-L1 therapy must have occurred more than (>) 84 days following initiation (Cycle 1 Day 1) of anti-PD-1 or PD-L1 therapy (combination or monotherapy).

Patients who received consolidation anti-PD-1 or anti-PD-L1 therapy following concurrent chemoradiation for Stage III disease as their only line of anti-PD-1 or anti-PD-L1 therapy, are eligible if they experienced disease progression more than (>) 84 days but less than (<) 365 days from their first date of anti-PD-1 or anti-PD-L1 therapy.

Patients must have been exposed to platinum-based chemotherapy for Stage IV or recurrent disease and experienced disease progression during or after this regimen, with the following exception: patients that received adjuvant platinum-based chemotherapy post-surgical resection for Stage I-III disease meet this criterion if disease progression occurred within one year from the last dose that the patient received that therapy.

Prior tyrosine kinase inhibitor therapy for patients with targetable alterations is allowed if criteria 5.2a above is also met.

b. Patients must have progressed (in the opinion of the treating investigator) following the most recent line of therapy.

c. Patients must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 21 days prior to sub-study randomization. Patients must have recovered (≤ Grade 1) from any side effects of prior therapy, except for alopecia. Patients must not have received any radiation therapy within 14 days prior to sub-study randomization. (See Section 5.3 for criteria regarding therapy for CNS metastases).

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

e. Patients must not have received systemic treatment with corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within seven days prior to sub-study randomization. Inhaled or topical steroids, and adrenal replacement doses ≤ 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.

f. Patients must not have received a live attenuated vaccination within 28 days prior to sub-study randomization. (See Appendix 18.4)

g. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment while receiving

treatment on this study. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

h. Patients must not be receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents within 7 days prior to randomization. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.

i. Patient must not have received radiotherapy within 14 days before the first dose of study treatment or received lung radiation therapy of >30 Gy within 6 months before the first dose of study treatment.

Note: Participants must have recovered from all radiation-related toxicities to Grade 1 or less, not require corticosteroids, and not have had radiation pneumonitis.

5.3 Clinical/Laboratory Criteria

a. Patients must have measurable disease (see **S1800A** 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 **S1800A** Section 10.1c. Measurable disease must be assessed within 28 days prior to sub-study randomization. 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 randomization. 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 sub-study randomization. See **S1800A** Section 15.0 and **LUNGMAP** Section 15.6 for guidelines and submission instructions for required central radiology review. CT and MRI scans must be submitted for central review via TRIAD.

b. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to sub-study randomization. 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 sub-study randomization, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least seven days prior to sub-study randomization.

c. Patients must be able to safely receive at least one of the investigator's choice of standard of care regimens described in Section7.3a, per the current FDA-approved package insert(s).

d. 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 randomization.

e. 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 randomization (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).

f. Patients must have a serum creatinine ≤ the IULN or calculated creatinine clearance ≥ 50 mL/min using the following Cockroft-Gault Formula. This specimen

must have been drawn and processed within 28 days prior to sub-study randomization.

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

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.

Creatinine Calculator:
https://crawb.crab.org/TXWB/CreatinineClearanceCalculator.aspx

g. Patients' urinary protein must be ≤1+ on dipstick or routine urinalysis (UA). Random analysis of urine protein with a normal value is sufficient. If urine dipstick or routine analysis indicated proteinuria ≥2+, then a 24-hour urine is to be collected and demonstrate <1000 mg of protein in 24 hours to allow participation in the study.

h. Patients must not have a history of uncontrolled or poorly-controlled hypertension defined as SBP ≥ 150 mmHg or DBP ≥ 90 mmHg within 28 days prior to sub-study randomization. Patients are permitted to be receiving multiple anti-hypertensive medications (unless otherwise indicated in the study). All blood pressure measurements within the 14 days prior to registration must be SBP < 150 and DBP < 90. An exception can be made by a healthcare provider for a patient with a single blood pressure elevation who upon rechecking has a normal blood pressure.

i. For patients where an International Normalized Ratio (INR) is clinically indicated, INR must be ≤ 1.5 seconds above the institutional upper limit of normal (IULN) (unless receiving anticoagulation therapy) documented within 28 calendar days prior to sub-study randomization. For patients where a partial thromboplastin time (PTT) is clinically indicated, PTT must be ≤ 5 seconds above the institutional upper limit of normal (IULN) (unless receiving anticoagulation therapy) documented within 28 calendar days prior to sub-study randomization.

j. If receiving warfarin, the patient must have an INR ≤3.0. For warfarin, heparin and low molecular weight heparin (LMWH) there should be no active bleeding (that is, no bleeding within 14 days prior to first dose of protocol therapy) or pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices).

k. Patients must have Zubrod performance status 0-1 (see **S1800A** Section 10.4) documented within 28 days prior to sub-study randomization.

l. Pre-study history and physical exam must be obtained within 28 days prior to sub-study randomization.

m. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method during the study and 4 months after completion of study treatment. 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 during the study and 4 months after study completion.

5.4 Specimen Submission Criteria

a. Patients must agree to have blood specimens submitted for circulating tumor DNA (ctDNA) as outlined in Section 15.3.

b. Patients must also be offered participation in banking and in the correlative studies for collection and future use of specimens as described in **S1800A** Section 15.0.

5.5 Regulatory Criteria

a. As a part of the OPEN registration process (see **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.

b. 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).

c. 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

Randomization between treatment arms will be performed using a dynamic balancing algorithm.

Randomization will be stratified based on the following factors:

a. PD-L1 Status

1. negative (<1%) versus;

2. positive (>= 1%) or unknown PD-L1 status

Provided by PD-L1 testing performed at FMI as part of the **LUNGMAP** screening protocol unless patient was screened under the **S1400** (legacy screening/pre-screening study). The **S1400** patients must have had prior PD-L1 testing by the Dako 22C3 PharmDx IHC assay and must have results available for stratifying.

b. Histology

1. Patients with squamous cell lung cancer, including mixed histology with any squamous component.

2. Patients with non-squamous cell lung cancer (adenocarcinoma, large cell, NSCLC NOS).

c. If patient is randomized to standard of care arm, does the planned treatment include ramucirumab?
_ Yes
_ No

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Drs. Karen L. Reckamp and Konstantin H. Dragnev at S1800AMedicalQuery@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 Disease Assessment

See Section 9.0 for disease assessment time points. Disease assessment timing is to be based on calendar timing counted as weeks after registration, not based on cycles or drug administration.

Disease Assessment During Treatment

- For patients on Arm A: CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.3) must be repeated every 6 weeks (± 7 day window), for the first year regardless of treatment delays, then every 12 weeks until disease progression. The 6 weeks should start from Cycle 1 Day 1.

- For patients on Arm B: CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.3) must be repeated every 6 weeks (± 7 day window), for the first year regardless of treatment delays, then every 12 weeks until disease progression and discontinuation of protocol treatment. The 6 weeks should start from Cycle 1 Day 1.

Pre-study Brain CT/MRI is required 42 days prior to randomization per Section 5.3. If patient has brain metastases at baseline, scans must use the same modality as baseline and be repeated every 12 weeks (± 7 day window) while on treatment.

Disease Assessment During Off Protocol Treatment, Prior to Progression
After off protocol treatment prior to progression, disease assessments must continue every 12 weeks (± 7 day window) until progression.

If patient has brain metastases at baseline, continue brain CT or MRI scans (same modality as baseline) after off protocol treatment prior to progression, as clinically indicated. For alignment with the protocol and good clinical practice, recommended frequency of brain scans after off protocol treatment (and prior to progression) is at least every 12 weeks, unless more frequent scans are clinically appropriate.

7.2 Pre-Medication and Supportive Care

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

Pre-medication with a histamine H1 antagonist is recommended prior to infusion of ramucirumab. Recommended premedication agents include an intravenous histamine H1 antagonist such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at investigator discretion.

For patients who have experienced a Grade 1 or 2 infusion-related reaction, pre-medication antihistamine (e.g. diphenhydramine) in addition to dexamethasone and acetaminophen may be used prior to infusion on subsequent infusions. Dosing and administration route of pre-medications may be given per institutional policy.

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

7.3 Treatments

Patients will be randomized to one of the following treatment arms:

Arm A: Investigator's Choice of Standard of Care

Arm B: Ramucirumab plus Pembrolizumab (MK-3475)

a. **Arm A: Investigator's Choice of Standard of Care**

Treating Investigator and patient will choose the appropriate SoC drug (docetaxel, gemcitabine, pemetrexed, or ramucirumab plus docetaxel) based on patient's previous therapy and disease.

Note:
- Pemetrexed is only FDA-approved for non-squamous cell NSCLC.
- Patients who take docetaxel or ramucirumab plus docetaxel, must have adequate hepatic function per the current FDA-approved package insert.
- Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to Cycle 1 Day 1.

1. **Docetaxel**

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

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

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

2. **Gemcitabine hydrochloride**

Agent	Dose	Route	Day	Schedule*
Gemcitabine	1000 mg/m^2	IV 30 (± 5) minutes	Days 1, 8	Q 21 days

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

3. **Pemetrexed** *

Agent	Dose	Route	Day	Schedule*
Folic Acid	400-1000 mcg	Oral,	Daily; beginning 7 days before first dose of pemetrexed and continuing until 4 weeks after the last dose of pemetrexed	
Vitamin B_{12}	1 mg **	Intramuscular	Day -7	Q 63 days (every 3rd cycle)
Dexamethasone	4 mg BID**	Oral, beginning 24 hours prior to pemetrexed	Day 0-2	Q 21 days
Pemetrexed	500 mg/m^2	IV 10 minutes	Day 1	Q 21 days

NOTES:

* Pemetrexed is not FDA-approved for squamous cell NSCLC and should not be used to treat patients with squamous cell NSCLC.

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

** Dexamethasone and Vitamin B_{12} may be administered per local institutional guidelines. Recommended dose listed above.

4. **Ramucirumab plus Docetaxel**

Agent	Dose	Route	Day	Schedule [b]
Ramucirumab [a]	10 mg/kg	IV over 30-60 minutes [d]	Day 1	Q 21 days
Dexamethasone	8 mg BID [c]	Oral, beginning 24 hours prior to docetaxel	Day 0-2	Q 21 days
Docetaxel	75 mg/m^2 [e]	IV	Day 1	Q 21 days

NOTES:

[a] Pre-medication with a histamine H1 antagonist is recommended prior to infusion of ramucirumab. Recommended premedication agents include an intravenous histamine H1 antagonist such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at investigator discretion.

[b] A cycle of treatment is 21 days. Disease assessment must occur every 6 weeks. Treatment will continue until any criteria in Section 7.3 is met.

[c] Dexamethasone may be administered per local institutional guidelines. Recommended dose listed above.

[d] Ramucirumab will be administered over an approximately 60-minute intravenous (IV) infusion. If the first infusion is tolerated, all subsequent ramucirumab infusions may be administered over 30 minutes. Please refer to the package insert for the administration of ramucirumab

The actual doses of ramucirumab administered will be determined by measuring the patient's weight at the beginning of each cycle. If the patient's weight fluctuates by more than 10% from the weight used to calculate the dose at baseline, the dose must be recalculated using the most recent weight and this weight will become the baseline weight going forward. Recalculation of the ramucirumab dose for weight fluctuations of <10% is permitted but not required.

[e] Docetaxel may be administered per local institutional guidelines. Recommended dose listed above, but the use of a starting dose of 60 mg/m^2 is allowed at treating investigator's discretion. Ramucirumab is administered prior to docetaxel consistent with FDA-approved package labeling for ramucirumab. Per a study noted in the ramucirumab package insert "Due to an increased incidence of neutropenia and febrile neutropenia in patients enrolled in East Asian sites, Study 3 was amended and 24 patients (11 CYRAMZA plus docetaxel, 13 placebo plus docetaxel) at East Asian sites received a starting dose of docetaxel at 60 mg/m every 3 weeks." Sites should provide a justification in the patient's chart for using a starting dose of docetaxel at 60 mg/m^2.

b. **Arm B: Ramucirumab plus Pembrolizumab (MK-3475)**

Note that women of childbearing potential must have a negative serum pregnancy test within 7 days prior to Cycle 1 Day 1.

Agent	Dose	Route	Day	Schedule [b]
Ramucirumab [a]	10 mg/kg	IV over 30-60 minutes [c]	Day 1	Q 21 days
Pembrolizumab (MK-3475)	200 mg	IV over 30 minutes	Day 1	Q 21 days or up to 35 cycles without disease progression

NOTES:

[a] Pre-medication with a histamine H1 antagonist is recommended prior to infusion of ramucirumab. Recommended premedication agents include an intravenous histamine H1 antagonist such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at investigator discretion.

[b] A cycle of treatment is 21 days. Disease assessment must occur every 6 weeks. Treatment will continue until any criteria in Section 7.3 is met.

[c] Ramucirumab will be administered prior to pembrolizumab (MK-3475), over an approximately 60-minute intravenous (IV) infusion. If the first infusion is tolerated, all subsequent ramucirumab infusions may be administered over 30 minutes. Please refer to the package insert for the administration of ramucirumab.

The actual doses of ramucirumab administered will be determined by measuring the patient's weight at the beginning of each cycle. If the patient's weight fluctuates by more than 10% from the weight used to calculate the dose at baseline, the dose must be recalculated using the most recent weight and this weight will become the baseline weight going forward. Recalculation of the ramucirumab dose for weight fluctuations of < 10% is permitted but not required.

Pembrolizumab (MK-3475) 200 mg (fixed dose) will be administered over a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (that is, infusion time is between 25 and 40 minutes).

The first 2 cycles will require a 1-hr observation period i) between ramucirumab and pembrolizumab (MK-3475) administration, and ii) after pembrolizumab (MK-3475) infusion. For all cycles thereafter, no observation period will be required unless clinically indicated.

Patients will receive 35 cycles of pembrolizumab (MK-3475). Maintenance ramucirumab may continue for patients past 35 cycles until reaching a discontinuation criterion (Section 7.3), as long as the participant is receiving benefit.

7.4 Criteria for Removal from Protocol Treatment

a. Progression of disease as defined in Section 10.2 in **S1800A**. However, a patient on Arm B may continue protocol treatment as long as the patient is continuing to clinically benefit from treatment in the opinion of the treating investigator. Patients should still be removed from protocol treatment for criteria below.

* Upon progression, the Request for New Sub-Study Assignment Form may be submitted under the patient's screening (**LUNGMAP** or **S1400**) to receive a new sub-study assignment (see Section 14.0).

b. Symptomatic deterioration (as defined in Section 10.2 of **S1800A**).

c. Unacceptable toxicity.

d. Treatment delay for any reason > 84 days (or as noted in Section 8.0)

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

7.5 Discontinuation of Treatment

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

7.6 Follow-Up Period

All patients will be followed until death or 3 years after sub-study randomization, 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 MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 General Considerations

a. Patients on Arm B will receive pembrolizumab (MK-3475) for up to 35 cycles.

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

c. Dose reductions are allowed on ramucirumab only. Dose re-escalations are not allowed.

d. Dose interruptions and discontinuations are allowed to manage toxicity. If the toxicity is clearly related to only one of the drugs, the other agent may be continued. If the relationship cannot be established, there should be an option to hold both.

e. If one drug is discontinued due to toxicity, patient may remain on other study drugs as long as the remaining therapy is well tolerated and according to the treating physician the patient is still deriving clinical benefit.

f. The maximum dose delay for any reason is 84 days.

8.3 Dose Modifications for Chemotherapy

Treatment and dose modifications are at the discretion of the treating investigator.

NOTE: Pemetrexed is not FDA-approved for squamous cell NSCLC and should not be used to treat patients with squamous cell NSCLC.

8.4 Dose Modifications for Ramucirumab

Dose modifications should be made based on the observed toxicity, as summarized in the tables below.

Table 1: Dose Reductions for Ramucirumab

DRUG	DOSE LEVEL	DOSE
Ramucirumab	Full	10 mg/kg
	-1 Level	8 mg/kg
	-2 Level	6 mg/kg
	-3 Level	5 mg/kg
	-4 Level	Discontinue

Note: Once a dose reduction is applied, the reduced dose is maintained unless further dose reduction is needed.

Table 2: Dose Interruptions for Ramucirumab

Toxicity	Grade	Dose Interruptions	Toxicity Management
Infusion-Related Reactions	Any Grade		Manage per institutional standard at the discretion of treating 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.
	≥ Grade 3	Permanently discontinue ramucirumab.	Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

Table 3: Dose Modifications for Ramucirumab

Toxicity	Grade	Dose Modifications
Hypertension	Grade 1	No dose modification. Consider increased BP monitoring; start anti-hypertensive medication if appropriate.
	Grade 2 Asymptomatic	No dose modification. Begin anti-hypertensive therapy and continue ramucirumab.
	Grade 2 Symptomatic	Hold ramucirumab until symptoms resolve. Start or adjust anti-hypertensive medication.

Toxicity	Grade	Dose Modifications
	Grade 3	Hold ramucirumab until resolution of symptoms and returns to Grade 2.
	Grade 4	Permanently discontinue ramucirumab.
Hypothyroidism	Grade 2-4	No dose modification. Therapy with ramucirumab can be continued while treatment for the thyroid disorder is instituted.
Impaired Wound Healing	Prior to planned surgery	Withhold ramucirumab 28 days prior..
	After surgery	Do not administer ramucirumab for at least 14 days following major surgical procedure and until adequate wound healing. The safety of resumption after resolution of wound healing has not been established.
	Wound-healing complications developed during study treatment	Do not administer ramucirumab for at least 14 days following major surgical procedure and until adequate wound healing. The safety of resumption after resolution of wound healing has not been established.
Proteinuria	Grade 1	No dose modification.
	Grade 2 2+ proteinuria on urine dipstick	Check 24-hour urine protein levels. • If > 2 gram/24 hours, hold ramucirumab until resolution to < 2 gram/24 hours. Restart ramucirumab at the next lower dose. • If the protein level ≥2 g/24 hours reoccurs, interrupt ramucirumab and reduce the dose to the next lower level once the urine protein level returns to <2 g/24 hours.
	≥ Grade 3 ≥ 3.5 gram/24 hours	Permanently discontinue ramucirumab. If patient experiences nephrotic syndrome, permanently discontinue ramucirumab.
Non-life threatening and reversible	Grade 3	Hold ramucirumab until resolved to Grade 0-1.

Toxicity	Grade	Dose Modifications
		• If resolved to Grade 0-1, may reduce ramucirumab by one dose level. If NOT resolved to Grade 0-1 within 21 days, discontinue ramucirumab at treating investigator's discretion.
Other Adverse Events	Grade 4	Permanently discontinue ramucirumab immediately, with the exception of Grade 4 fever or Grade 4 laboratory abnormality, in which case: <u>First occurrence</u>: Delay ramucirumab until resolved to Grade 0-1. • If resolved to Grade 0-1, may resume ramucirumab original dose at the discretion of the treating investigator. • If NOT resolved to Grade 0-1 within 21 days, discontinue ramucirumab at treating investigator's discretion. <u>Second occurrence</u>: Delay ramucirumab until resolved to Grade 0-1. • If resolved to Grade 0-1, reduce ramucirumab by one dose level. If NOT resolved to Grade 0-1 within 21 days, discontinue ramucirumab at treating investigator's discretion.

Table 4: Dose Discontinuations for Ramucirumab

Toxicity	Grade	Dose Discontinuation
Arterial Thromboembolic Events,	Any Grade	Permanently discontinue ramucirumab.
Gastrointestinal Perforation	Any Grade	Permanently discontinue ramucirumab.
Gastrointestinal Hemorrhage/Bleeding	≥ Grade 3	Permanently discontinue ramucirumab.
Reversible posterior leukoencephalopathy syndrome	Any Grade	Permanently discontinue ramucirumab.
Congestive heart failure	≥ Grade 3	Permanently discontinue ramucirumab.

Liver injury/liver failure or Hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis	Any Grade	Permanently discontinue ramucirumab.
Fistula formation	Any Grade	Permanently discontinue ramucirumab.

8.5 Dose Modifications for Pembrolizumab (MK-3475)

Adverse events (both non-serious and serious) associated with pembrolizumab (MK-3475) exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in the following tables.

NOTE: Due to the possible effect of treatment with pembrolizumab (MK-3475)on the immunologic response to infectious disease vaccines, patients must not have had any infectious disease vaccination (e.g., standard influenza, H1N1 influenza, pneumococcal, meningococcal, tetanus toxoid) 1 week before or after any dose of pembrolizumab (MK-3475).

Table 1: Dose Interruptions for Pembrolizumab (MK-3475)

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

Toxicity	Grade (CTCAE V5.0)	Action with Pembrolizumab	irAE Management with corticosteroids and/or other therapies	Monitor and follow-up
Diarrhea/ Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT evaluation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Toxicity	Grade (CTCAE V5.0)	Action with Pembrolizumab	irAE Management with corticosteroids and/or other therapies	Monitor and follow-up
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.	• Monitor for signs and symptoms of thyroid disorders
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Toxicity	Grade (CTCAE V5.0)	Action with Pembrolizumab	irAE Management with corticosteroids and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
All Other Immune Related AEs	Persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids.	• Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a] AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

8.6 Dose Modification Contacts

For treatment or dose modification questions, please contact Drs. Karen L. Reckamp and Konstantin H. Dragnev at S1800AMedicalQuery@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/2017-10/Best%20Practices%20upddate.pdf.

8.7 Adverse Event Reporting

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

9.0 STUDY CALENDAR

9.1 Arm A: Investigator's Choice of Standard of Care

REQUIRED STUDIES	PRE-STUDY (w/in 28 days prior to randomization, unless otherwise noted)	Cycle Length = 21 days (+/- 3 days)					At Off Tx	Off Tx FU Prior to Prog	Off Tx FU After Prog [7]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles [5]			
PHYSICAL									
History & Physical Exam	X	X	X	X	X	X	X	X [6]	
Weight & Performance Status	X	X	X	X	X	X	X	X [6]	
Vital Signs (BP, HR, Temp)	X								
Toxicity Notation		X	X	X	X	X	X	X [9]	X [9]
Smoking Status Assessment	X						X		
LABORATORY									
	If labs obtained w/in 14 days prior to tx, tests need not be repeated on C1D1, unless otherwise noted.	Up to 48 hours prior to Day 1 tx							
CBC/Diff/Platelets/ Hgb	X	X [3]	X	X	X	X	X	X [9]	X [9]
Serum Bilirubin	X	X [3]	X	X	X	X	X	X [9]	X [9]
ALT or AST	X	X [3]	X	X	X	X	X	X [9]	X [9]
Serum Creatinine/Calc CrCl	X	X [3]	X	X	X	X	X	X [9]	X [9]
INR and PTT [17]	X (w/in 28 days prior to randomization)								
TSH w/ Reflex to Free T4	X [18]				X [18]	X [18] (every 3rd cycle)		X [9]	X [9]
Urine Protein Check	X		X [13]	X [13]	X [13]	X [13]		X [9]	X [9]

REQUIRED STUDIES	PRE-STUDY (w/in 28 days prior to randomization, unless otherwise noted)	Cycle Length = 21 days (+/- 3 days) Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles [5]	At Off Tx	Off Tx FU Prior to Prog	Off Tx FU After Prog [7]
HIV viral load test [19]	X (within 6 months)								
Serum Pregnancy Test		X [4] (w/in 7 days prior to C1D1)							
X-RAYS & SCANS									
CT or MRI for Disease Assessment	X			X [1]		X [1]		X [6]	
Brain CT/MRI [2]	X					X [2]		X [2]	
SPECIMEN SUBMISSION									
Whole Blood - ctDNA		X [14] (pre-tx)							X [14]
Buffy Coat /Plasma for Banking [8]	X [8] (pre-tx)		X [8]	X [8]	X [8]				X [8]
Arm A Treatment Choices (21 day cycle)									
Choice 1									
Dexamethasone [10]		X (Days 0-2)	X (Days 0-2)	X (Days 0-2)	X (Days 0-2)	X (Days 0-2)			
Docetaxel		X (Day 1)	X (Day 1)	X (Day 1)	X (Day 1)	X (Day 1)			
Choice 2									

REQUIRED STUDIES	PRE-STUDY (w/in 28 days prior to randomization, unless otherwise noted)	Cycle Length = 21 days (+/- 3 days)					At Off Tx	Off Tx FU Prior to Prog	Off Tx FU After Prog [7]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles [5]			
Gemcitabine [11]		X (Days 1 and 8)	X (Days 1 and 8)	X (Days 1 and 8)	X (Days 1 and 8)	X (Days 1 and 8)			
Choice 3 – Pemetrexed is not FDA-approved for squamous cell NSCLC and should not be used to treat patients with squamous cell NSCLC.									
Folic Acid [16]		X (7 days prior to tx)	X (7 days prior to tx)	X (7 days prior to tx)	X (7 days prior to tx)	X (7 days prior to tx)	X (until 4 wks after last dose)		
Vitamin B_{12} [12]		X (7 days prior to tx)			X (7 days prior to tx)	X (7 days prior to tx)			
Dexamethasone [10]		X (Days 0-2)	X (Days 0-2)	X (Days 0-2)	X (Days 0-2)	X (Days 0-2)			
Pemetrexed [15]		X (Day 1)	X (Day 1)	X (Day 1)	X (Day 1)	X (Day 1)			
Choice 4									
Ramucirumab		X (Day 1)	X (Day 1)	X (Day 1)	X (Day 1)	X (Day 1)			
Dexamethasone [10]		X (Days 0-2)	X (Days 0-2)	X (Days 0-2)	X (Days 0-2)	X (Days 0-2)			
Docetaxel		X (Day 1)	X (Day 1)	X (Day 1)	X (Day 1)	X (Day 1)			

NOTE: Forms are found on the CTSU website (www.ctsu.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/2019-07/BestPracticesupdate.pdf

Footnotes for Calendar Arm A: Investigator's Choice of Standard of Care

[1] CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.3 of **S1800A**) must be repeated every 6 weeks (± 7 day window), for the first year regardless of treatment delays, then every 12 weeks until disease progression and discontinuation of protocol treatment. The 6 weeks should start from Cycle 1 Day 1. See Sections 5.3 and 7.1 for additional details.

[2] Brain CT/MRI is required per Sections 5.3 and 7.1. If patient has brain metastases at baseline, scans must use the same modality as baseline and be repeated every 12 weeks (+/- 7 days) while on treatment. If patient has brain metastases at baseline, continue brain CT or MRI scans (same modality as baseline) after off protocol treatment prior to progression, as clinically indicated. For alignment with the protocol and good clinical practice, recommended frequency of brain scans after off protocol treatment (and prior to progression) is at least every 12 weeks, unless more frequent scans are clinically appropriate.

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

[4] Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to Cycle 1 Day 1.

[5] During continued treatment, items marked under physical and laboratory should be performed prior to every subsequent cycle unless otherwise noted. Disease assessments and image submission are to take place every 6 weeks (± 7 days) regardless of treatment delays. Treatment and evaluation will continue until any one of the criteria in Section 7.3 **S1800A** is met.

[6] After off protocol treatment prior to progression, patients should be followed by repeating indicated studies every 12 weeks or more often as clinically indicated until progression. Disease assessments should continue per Section 7.1.

[7] After off protocol 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 randomization.

[8] With patient's consent, additional research blood for banking will be collected at pre-study (prior to treatment initiation), on weeks 4, 7, and 10, and at first progression (defined in Section 10 of **S1800A**) after study treatment (see Section 15.0 of **S1800A**). First progression blood should be collected by the time of the next visit after documenting progression and prior to starting any non-protocol therapy.

[9] Assessments should continue if clinically indicated and until resolution of all acute adverse events.

[10] Dexamethasone should be given twice daily the day before, the day of, and the day after therapy, per institutional guidelines.

[11] Gemcitabine must be given on Days 1 and 8 of every cycle per Section 7.2

[12] Vitamin B12 should be given one week prior to pemetrexed every 3rd cycle.

[13] Urine protein should be performed throughout treatment as clinically indicated.

[14] ctDNA must be collected per Section 15.3. First progression blood should be collected by the time of the next visit after documenting progression and prior to starting any non-protocol therapy. Note: Kits must be ordered and will take up to 3 days to arrive.

[15] Pemetrexed is not FDA-approved for squamous cell NSCLC and should not be used to treat patients with squamous cell NSCLC.

[16] Folic Acid should be given daily beginning 7 days prior to first dose of pemetrexed until 4 weeks after last dose of pemetrexed.

[17] INR and PTT should be performed if clinically indicated, per Section 5.3i.

[18] **For all patients**: As clinically indicated, collect TSH pre-study and every 3rd cycle while on treatment to monitor for late endocrine toxicity from prior immune checkpoint inhibitor therapy. **For patients receiving ramucirumab**:, Collect TSH pre-study, if clinically indicated. While on treatment, monitor thyroid function every 3rd cycle. For all patients: If TSH is abnormal, reflex to Free T4 and other work up per investigator discretion. See Section 8.4 for ramucirumab dose modifications.

[19] See Section 5.1 for details.

9.2 Arm B: Ramucirumab plus Pembrolizumab (MK-3475)

REQUIRED STUDIES	PRE-STUDY (w/in 28 days prior to randomization, unless otherwise noted)	Cycle Length = 21 days (+/- 3 days)					At Off Tx	Off Tx FU Prior to Prog	Off Tx FU After Prog [7]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles [5]			
PHYSICAL									
History & Physical Exam	X	X	X	X	X	X	X	X [6]	
Weight & Performance Status	X	X	X	X	X	X	X	X [6]	
Vital Signs (BP, HR, Temp)	X	X	X	X	X	X			
Toxicity Notation		X	X	X	X	X	X	X [9]	X [9]
Smoking Status Assessment	X						X		
LABORATORY									
	If labs obtained w/in 14 days prior to tx, tests need not be repeated on C1D1.		Up to 48 hours prior to Day 1 tx						
CBC/Diff/Platelets/ Hgb	X	X [3]	X	X	X	X	X	X [9]	X [9]
Serum Bilirubin	X	X [3]	X	X	X	X	X	X [9]	X [9]
ALT or AST	X	X [3]	X	X	X	X	X	X [9]	X [9]
Serum Creatinine/Calc CrCl	X	X [3]	X	X	X	X	X	X [9]	X [9]
INR and PTT [12]	X (w/in 28 days prior to randomization)								
TSH w/ Reflex to Free T4	X [13]				X [13]	X [13] (every 3rd cycle)		X [9]	X [9]
Urine Protein Check	X		X [10]	X [10]	X [10]	X [10]		X [9]	X [9]

REQUIRED STUDIES	PRE-STUDY (w/in 28 days prior to randomization, unless otherwise noted)	Cycle Length = 21 days (+/- 3 days)					At Off Tx	Off Tx FU Prior to Prog	Off Tx FU After Prog [7]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles [5]			
HIV viral load test [14]	X (within 6 months)								
Serum Pregnancy Test		X [4] (w/in 7 days prior to C1D1)							
X-RAYS & SCANS									
CT or MRI for Disease Assessment	X			X [1]		X [1]		X [6]	
Brain CT/MRI [2]	X					X [2]		X [2]	
SPECIMEN SUBMISSION									
Whole Blood - ctDNA		X [11] (pre-tx)							X [11]
Buffy Coat /Plasma for Banking [8]	X [8] (pre-tx)		X [8]	X [8]	X [8]				X [8]
Arm B Treatment (21 day cycle)									
Ramucirumab		X	X	X	X	X			
Pembrolizumab (MK-3475)		X	X	X	X	X (up to 35 cycles)			

NOTE: Forms are found on the CTSU website (www.ctsu.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/2019-07/BestPracticesupdate.pdf

Footnotes for Calendar Arm B: Ramucirumab plus Pembrolizumab (MK-3475)

[1] CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.3 of **S1800A**) must be repeated every 6 weeks (± 7 day window), for the first year regardless of treatment delays, then every 12 weeks until disease progression and discontinuation of protocol treatment. The 6 weeks should start from Cycle 1 Day 1. See Sections 5.3 and 7.1 for additional details.

[2] Brain CT/MRI is required per Sections 5.3 and 7.1. If patient has brain metastases at baseline, scans must use the same modality as baseline and be repeated every 12 weeks (+/- 7 days) while on treatment. If patient has brain metastases at baseline, continue brain CT or MRI scans (same modality as baseline) after off protocol treatment prior to progression, as clinically indicated. For alignment with the protocol and good clinical practice, recommended frequency of brain scans after off protocol treatment (and prior to progression) is at least every 12 weeks, unless more frequent scans are clinically appropriate.

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

[4] Women of child bearing potential must have a negative serum pregnancy test within 7 days prior to Cycle 1 Day 1.

[5] During continued treatment, items marked under physical and laboratory should be performed prior to every subsequent cycle unless otherwise noted. Disease assessments and image submission are to take place every 6 weeks (± 7 days) regardless of treatment delays. Treatment and evaluation will continue until any one of the criteria in Section 7.3 **S1800A** is met.

[6] After off protocol treatment prior to progression, patients should be followed by repeating indicated studies every 12 weeks or more often as clinically indicated until progression. Disease assessments should continue per Section 7.1.

[7] After off protocol 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 randomization.

[8] With patient's consent, additional research blood for banking will be collected at pre-study (prior to treatment initiation), on weeks 4, 7, and 10, and at first progression (defined in Section 10 of **S1800A**) after study treatment (see Section 15.0 of **S1800A**). First progression blood should be collected by the time of the next visit after documenting progression and prior to starting any non-protocol therapy.

[9] Assessments should continue if clinically indicated and until resolution of all acute adverse events.

[10] Urine protein should be performed throughout treatment as clinically indicated.

[11] ctDNA must be collected per Section 15.3. First progression blood should be collected by the time of the next visit after documenting progression and prior to starting any non-protocol therapy. Note: Kits must be ordered and will take up to 3 days to arrive.

[12] INR and PTT should be performed if clinically indicated, per Section 5.3i.

[13] TSH and if abnormal, reflex to Free T4 and other work up per investigator, should be performed as clinically indicated at pre-study. While on treatment, monitor thyroid function every 3rd cycle. See Section 8.4 for ramucirumab dose modifications and Section 8.5 for pembrolizumab dose modifications.

[14] See Section 5.1 for details.

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.

2. 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.

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

4. 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 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.

10.7 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.

10.8 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.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design and Endpoint Justification

Overall survival has been chosen as the key primary endpoint because neither response nor PFS have been demonstrated to be a robust and reliable endpoint in the immunotherapy relapsed setting. The study design includes randomization against a standard-of-care (SoC) arm as there is limited historical data on response, PFS, and OS in this setting to be able to specify benchmarks. While responses are not necessarily expected, the design includes an evaluation of response rate as a key secondary objective. The standard of care is chemotherapy (monotherapy) for these patients. However, there is limited data on clinical outcomes for patients receiving chemotherapy after immunotherapy. To approximate the control arm event rates, we use published data on chemotherapy in the second-line setting.

11.2 Primary Objective

The primary objective is to evaluate if there is sufficient evidence to pursue an independent Phase III study by comparing overall survival (OS) between patients previously treated with platinum-based chemotherapy and immunotherapy for Stage IV or recurrent non-small cell lung cancer randomized to ramucirumab and pembrolizumab (MK-3475) versus standard of care (SoC).

11.3 Sample Size, Accrual Duration, and Estimated Analysis Times

The accrual goal is 65 eligible patients per arm. Assuming 10% of patients will be determined to be not eligible, the total accrual goal is 144 patients (72 patients per arm). The estimated accrual rate is 6-7 patients/month. The estimated duration of accrual is 21-24 months. It is assumed that the SoC arm will be a mixture of patients receiving docetaxel monotherapy or docetaxel combined with ramucirumab. The expected median OS for patients receiving docetaxel and ramucirumab is 10.5 months, based on the REVEL trial, and 8 months for single agent chemotherapy. We estimate that around 50% of patients will receive docetaxel/ramucirumab. Given this, we estimate that the median OS for all patients will be around 9 months on the control arm. Given these assumptions, the estimated timing of the final analysis is 30-32 months after activation (10-12 months after completion of accrual).

11.4 Design, Sample Size Justification

OS will be compared using the maximum of the standard and weighted log-rank test with weights equal to 1-S(t), where S(t) is the pooled survival estimate at time t (G(rho=0, gamma=1). See for example, Freidlin 1999 (Biometrics). This analysis will be done using the svylogrank function in the survey package in R (https://cran.r-project.org/web/packages/survey/survey.pdf). Testing will be done at the 1-sided 0.10 level.

Because the proportional hazards assumption may not hold, sample size calculations were not done using the standard approaches. Simulations were performed to evaluate the properties of the design. The final analysis would take place when 90 OS events are observed. The power to detect differences in OS, if the study reaches full accrual (N=130), using the combination test for various amounts of time delay in separation of curves is in Table 1.

Table 1. Power for Primary analysis of OS (90 events)

Hazard Ratio after Separation	Time Delay in Separation (months)			
	0	3	4	5
1.5	62%	53%	53%	47%
2.0	94%	90%	84%	80%
2.5	99%	97%	96%	91%
3.0	100%	100%	99%	97%

11.5 Interim Analysis Plan

The study will include two interim analyses evaluating early stopping for futility.

The first interim analysis evaluating early stopping for futility alone, will take place when at least 24 weeks have elapsed since the 18th eligible patient randomized to Arm B. The analysis will likely take place approximately 12-14 months after study activation (~7-8 months after the 18th eligible patient on Arm B has been enrolled to allow for required data to be submitted and reviewed). It is estimated that by this time a total of 40 eligible patients will have been randomized to ramucirumab and pembrolizumab, 30 eligible patients will be evaluable for disease control at 12 weeks, and a total of 80 eligible patients will have been enrolled onto the study. If the study reaches 80 total eligible patients prior to this time point, accrual to the study will be place on temporary hold until the decision of this analysis is determined.

The objective of the interim futility analysis is to evaluate the response rate among patients with at least 24 weeks of follow-up and the disease control rate at 12 weeks (after randomization) among patients randomized to ramucirumab and pembrolizumab (MK-3475) to determine if there is sufficient evidence to continue accrual to the study.

For the evaluation of response, a patient will be coded as a responder if they have a CR or PR, confirmed or unconfirmed, per the definition in Section 10. Patients not known to have a response will be coded as non-responder.

For the evaluation of disease control at 12 weeks, a patient will be coded as having disease control at 12 weeks if they have a CR, PR, or stable disease at 12 weeks (+/- 2 week window), per the definition in Section 10. Patients not known to have disease control at 12 weeks who have at least 12 weeks of follow-up, will be coded as not having disease control at 12 weeks.

The study will continue accrual (Section 11.3) if 1) 3 or more responses or, 2) DCR12 of 50% or greater and at least 1 response. If neither of these criteria are met, then the study will be closed to further accrual. The probability of continuing based on the response rates and DCR12 are presented in the following table.

Table 2. Probability of Continuing Past Interim Analysis

Probability of Response	Additional Probability of Disease Control at 12 weeks					
	+0.25	**+0.3**	**+0.35**	**+0.4**	**+0.45**	**+0.5**
0.025	0.9	1.3	3.6	8.1	11.8	20.2
0.05	6	6.9	9.9	16.3	23.4	36.7
0.1	27.1	28.5	31.4	41.6	50.9	64.2
0.15	52.9	54.9	59.3	64.7	72.2	79.8
0.2	73.4	74.3	76.6	82	87.7	92.5
0.25	87.8	88.5	89.4	92.7	94.1	95.7

For example, if the true response probability were 20% and the additional likelihood of DCR12 is 40%, or a 60% chance of DCR12, then the probability of continuing the study based on these criteria is 82%.

It is estimated that this interim analysis will take place approximately 12-14 months after study activation.

The second interim analysis evaluating futility will take place when at least 45 (50%) of the expected deaths have occurred, with the provision that this analysis will occur when at least two-thirds of these deaths were at least 3 months after randomization. This analysis will evaluate early stopping for futility testing the alternative hypothesis of a hazard ratio equal to 0.69 using a modified log-rank test for testing non-null hazard ratios at the 1-sided 0.075 level. The alternative was chosen given that we estimate the average hazard ratio to be 0.69 (46% improvement) at the interim analysis if there is a 3-month delay in treatment effect and the hazard ratio after 3 months is 0.5.

This approach results in a 7.5% chance of falsely concluding futility under the alternative and a 45% chance of not concluding futility under the null. It is estimated that the earliest this analysis would take place is around 19 months (under the null). The total estimated accrual duration is 21 months. Therefore, with the 3-month stipulation, we estimate this analysis will occur around the time of completion of accrual to the study (with approximately 55 events observed).

a. Analysis Plans

If the study continues to full accrual, the final analysis will take place upon the observation of 90 OS events, or a maximum of 15 months after completion of accrual. At this time, it is estimated that 110 PFS events will have been reported. OS will be evaluated at the one-sided 10% level, as the interim futility analysis does not affect the type I error for OS testing.

OS and PFS will be compared between the arms using the maximum of the standard log-rank test score statistic and a weighted log-rank test score statistic with weights equal to w(t) =1-S(t), the G(rho,gamma) weights with rho = 0 and gamma = 1 (Fleming and Harrington, 1996). The threshold for this score statistic was determined based on simulation under the null to achieve a type I error rate of 10%.

The primary analysis of OS is estimated to take place 10-12 months after completion of accrual (or at a maximum of 15 months after completion of accrual as noted above).

Survival distributions will be estimated using the method of Kaplan-Meier (OS, IA-PFS, DoR). Median and landmark time-point estimates will be based on the KM-estimates. The average hazard ratio will be estimated using a Cox Proportional hazards model. An assessment of the proportional hazards assumption will be performed, and an assessment of the time-dependent HR will be done.

Secondary objectives include a comparison of response rates (RR), toxicity, and IA-PFS between the arms. Binary proportions will be summarized with associated confidence intervals. IA-PFS will be summarized as above and using the same test statistic. RR and toxicities will be compared using a chi-squared test at the 1-sided 0.05 level. With 130 patients, this study has 92% power to detect a 20% improvement in RR between the arms (and 80% power to detect a 16% difference). An approximate 10% difference in proportions between the arms would be statistically significant at the 10% level. With 65 patients per arm, any toxicity with at least 5% prevalence is likely to be observed (96% chance). Binary proportions can be estimated to within 12% with 95% confidence.

If OS is not found to be significantly different between the two arms, but the RR is, then the investigational drug combination may be considered a candidate for definitive evaluation in a Phase III study if there is evidence to support a difference in other efficacy outcomes such as duration of response and/or IA-PFS. In this event, the study team and NCI will discuss the data in detail. If the decision is to pursue a follow-on Phase III within the Lung-MAP infrastructure, a follow-on Phase III study would be developed per SWOG/NCI procedures for new sub-studies.

Subgroup analyses will be performed comparing OS, PFS, response between the arms within the stratification factors (PD-L1 and histology) and by TMB status. It is estimated that 70% of patients will be PD-L1 positive and 25% of patients will have squamous histology. TMB will be evaluated both as a continuous factor at categorized as high and low/negative (>10 and <=10). There will be limited power to detect differences between the arms in the smaller of the subsets, but the analysis within the larger subgroups for these factors may have sufficient power to evaluate if there is a differential association within the entire study population versus the subgroup.

To address the analysis of ctDNA (objective 1.3c), a proposal to use these specimens will be submitted as an amendment to CTEP for approval prior to commencing NGS assays. This proposal will include a scientific justification, clear statement of objectives, and a statistical analysis plan and justification.

b. Summary of Planned Analyses

Table 3: Summary of Design and Planned Analyses

	Interim Analysis #1	**Interim Analysis # 2**	**Final Analysis (OS)**
Analysis Description	Futility evaluation	Futility evaluation	Primary objective
Analysis	Single arm evaluation	Compare OS	Compare OS
Analysis population	18 eligible patients on ramucirumab/pembrolizumab with at least 24 weeks of follow-up Estimated 30 evaluable for DCR12	Full population accrued, at observation of 45 OS events when at least 30 of these deaths were at least 3 months after randomization	All eligible patients accrued
Total Accrued	Up to 80 eligible patients (40/arm)	Up to 130 eligible	Up to 130 eligible patients (65/arm)
Decision Rule	Continue: 3+ responses or (DCR12 50% and Response 1+) Stop: 0 responses or (DCR12 < 50% and 1-2 Responses)	Test alternative, P<0.075	P< 0.10
Estimated Time of Analysis (months after study activation)	12-14 months	19 months	30-32 months (maximum 15 months after completion of accrual)

11.6 Accrual Justification

Accrual estimates are based on our observed experience with Lung-MAP. Eligibility to Lung-MAP has changed over the course of the study with a major modification from initially only allowing 2nd line squamous patients to allowing all previously-treated stage IV or recurrent patients. Given this, the accrual estimates included here are based on observed accrual to Lung-MAP between January 1, 2016 and December 31, 2017. While squamous histology only accounts for 25% of NSCLC, we conservatively estimated that the expansion of eligibility to all histologic types of NSCLC, will double our accrual numbers. Between January 1, 2016 and December 31, 2017, a total of 953 registered to be screened, 737 received a sub-study assignment, and 335 registered to a sub-study of **LUNGMAP**. However, in this time approximately 50% of patients not able to register to a sub-study was due to the lack of a study for non-match patients who had received immunotherapy previously, therefore we expect an additional 20-50% of sub-study registrations. Given these numbers, we estimate 400-500 patients registering to a sub-study.

We further estimate based on Lung-MAP experience, that approximately 60% of sub-study registrations will be to a non-match sub-study and 40% of the total registrations (2/3rds of non-match) will be previously-exposed to immunotherapy (IO). Given that this sub-study population is restricted to patients who received IO either concurrently or following platinum-based chemotherapy (estimated to be approximately 70% of patients) and must not have progressed within 12 weeks of IO (estimated to be approximately 60-65% of patients), the estimated proportion patients registering to **S1800A** of all sub-study registrations is 17%, or 68-85 patients per year (6-7/month).

11.7 Data and Safety Monitoring

The SWOG Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG, 3 SWOG 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. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

12.1 Radiology Review

Central collection is required but 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 **LUNGMAP** Section 18.2f.

a. To ensure the highest standards and consistency between different centers, all scans for disease assessment (baseline, interim and end of treatment scans) must be submitted to the National Cancer Institute's National Clinical Trials Network (NCTN) Imaging and RT Quality Assurance Service Core (IROC) in Ohio for centralized review (see **S1800A** Section 15.0).

b. Centralized review will be performed by 3 radiology experts. The scans will be submitted to IROC. IROC will transmit the scans to the reviewers who will transmit the results to the SWOG Statistics and Data Management Center.

c. Details of submission of scans to IROC for centralized review and on the central review process are listed in **S1800A** Section 15.0 and **LUNGMAP** Section 15.6.

13.0 REGISTRATION GUIDELINES

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

In order to open Lung-MAP studies at the site, a separate Study Specific Worksheet (SSW) is required to be submitted to the CIRB for the **LUNGMAP** screening protocol and each sub-study.

13.1 Registration Timing

Patients must plan to begin treatment within 10 calendar days after sub-study registration.

Note: Some of the standard of care treatments have premedications required prior to start of treatment. See Section 7.2.

13.2 Investigator/Site Registration

For investigator/site registration, please refer to Section 13.2 of the **LUNGMAP** screening protocol. In addition, a Delegation Task Log is required for this sub-study.

Delegation Tasks Log (DTL):
Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

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 page on the CTSU website (www.ctsu.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section below 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. Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the relevant LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must hold an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the Delegation of Tasks Log (DTL).

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Site staff 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. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

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

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (http://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.

d. The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.
To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

14.4 Data Submission Overview and Timepoints

a. WITHIN 15 DAYS OF **S1800A** RANDOMIZATION, SUBMIT:

S1800A Onstudy Form

If needed, also submit:
Radiation Therapy Form
Brain Metastases Form

S1800A 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*
If needed, RT summary and/or planning document*

If needed, radiology report from brain CT/MRI*

*(NOTE: Upload reports via the Source Documentation: Baseline form in Rave®)

For patients screened under legacy **S1400**: PD-L1 testing (Dako 22C3 PharmDX assay) report.
(NOTE: Upload report 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 **S1800A.**

c. WITHIN 15 DAYS AFTER EACH CYCLE (CYCLE = 21 DAYS) OF TREATMENT, SUBMIT:

S1800A Treatment Form

S1800A Adverse Event Form*

S1800A Laboratory Values Form

For Cycle 1 only: submit the **S1800A** Pre-Treatment Laboratory Values Form.

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

d. WITHIN 15 DAYS AFTER EVERY DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF PROTOCOL TREATMENT PRIOR TO DISEASE PROGRESSION [see **S1800A** 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 **S1800A** Section 15.5.

e. WITHIN 15 DAYS OF DISCONTINUATION OF TREATMENT SUBMIT:

Off Protocol Treatment Notice documenting reasons for off protocol treatment

Smoking Status Assessment Form

Forms specified in Section 14.4.c.

f. ONCE OFF PROTOCOL TREATMENT EVERY 6 MONTHS FOR THE FIRST 2 YEARS FROM **S1800A** RANDOMIZATION, THEN AT THE END OF YEAR 3 SUBMIT:

Advanced NSCLC Follow-Up Form

If needed, also submit:
Radiation Therapy Form
Brain Metastases Form

Late Adverse Events (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] adverse event that is possibly, probably, or definitely related to protocol treatment, or a Serious Adverse Event [SAE] of any grade/attribution, 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. See Section 14.4i.

g. WITHIN 15 DAYS OF PROGRESSION/RELAPSE, SUBMIT:

Site(s) of Progression or Relapse Form

Follow-Up Tumor Assessment Form (RECIST 1.1)

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

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in Section 15.5.

h. WITHIN 28 DAYS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information and **S1800A** 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. DATA SUBMISSION FOR PATIENTS WHO HAVE PROGRESSED AND WISH TO REGISTER TO A NEW SUB-STUDY:

WITHIN 15 DAYS OF PROGRESSION/RELAPSE:

Submit the Request for New Sub-Study Assignment Form under the patient's screening protocol (**LUNGMAP** or **S1400**) in Rave®. Continue follow-up on **S1800A** per Section 9.0. See Section 14 of the screening protocol for additional data submission requirements following request for new sub-study assignment.

j. WITHIIN 30 DAYS OF MAXIMUM FOLLOW-UP OF 3 YEARS:

S1800A End of Study Form

15.0 SPECIAL INSTRUCTIONS

15.1 SWOG Specimen Tracking System (STS)

See **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. Buffy Coat and Plasma:

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 buffy coat and plasma for **LUNGMAP** (see Section 15.0 of **LUNGMAP**) and the blood collection was within 42 days prior to the sub-study randomization, then no additional pre-study blood specimen is required.
- Weeks 4, 7, 10 - Patients that go off protocol treatment are not required to continue to submit specimens.
- First Progression after study treatment - First progression blood should be collected by the time of the next visit after documenting progression and prior to starting any non-protocol therapy.

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 must be shipped to the SWOG Biospecimen Bank on dry ice. Frozen specimens may be shipped in batches – refer to Section 15b.

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, every 3 months, with a maximum of 5 patients recommended, 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.)

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

15.3 LUNGMAP ctDNA Assay – Peripheral Whole Blood (**REQUIRED FOR PATIENTS prior to treatment initiation**)

Blood specimens will be collected in order to isolate and investigate circulating tumor DNA (ctDNA) and blood tumor mutational burden (bTMB) – a form of fragmented DNA released into patient peripheral circulation specifically from the tumors. Analysis of ctDNA can reveal the presence of tumor-specific mutations and other abnormalities that can serve as biomarkers. The information collected will be limited to tumor-specific abnormalities known or suspected to play roles in tumor evolution. Patient germ-line genetic information will not be collected.

a. Kit Ordering

Immediately after identifying a patient for trial and prior to treatment initiation, sites must contact Foundation Medicine Inc. – Blood Samples, Lab #232, to order kits as follows:

- Email request to FMI Client Services at lung.map@FoundationMedicine.com
- Site must identify itself as a participant in the **S1800A** SWOG Lung-MAP sub-study and request the “Lung-MAP ctDNA Clinical Trial Kit.”
- Reference the FMI Study ID: FoundationOneLiquidDx-AMC-PRO-20-1496
- Provide the following information:
    - Treating physician's name
    - Treating physician's email address
    - Contact name
    - Contact email address
    - Contact phone
    - Address to which kits should be sent
    - Number of kits needed (one per patient per timepoint)

Kits will arrive within 3 days after ordering (excluding weekends and holidays).

Kits will read “Foundation Medicine Clinical Trials Kit,” and include two Roche Cell-Free DNA blood collection tubes, collection instructions, FedEx return bags, and pre-printed FedEx airway bills. Blood collection tubes must be used before their expiration date.

b. Timepoints

Collect blood:

- After sub-study registration and prior to treatment initiation
  - Recommended to collect on Cycle 1 Day 1 (prior to treatment) during other labs to lessen patient visits

    Note: This is a separate requirement for a ctDNA whole blood specimen for all patients registered to **S1800A**, regardless of whether or not there was a ctDNA blood collection for **LUNGMAP**.

- At progression - First progression blood should be collected by the time of the next visit after documenting progression and prior to starting any non-protocol therapy

c. Specimen Collection and Shipment Instructions

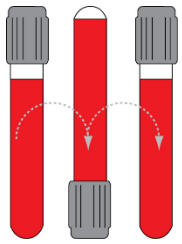
Specimen must be logged via the SWOG Specimen Tracking System.

Step 1: Check special tubes provided in kits to confirm liquid is clear and without cloudiness or crystals.

Step 2: Label tubes with date of collection, patient identifiers as requested on the included labels (patient date of birth can be added as an extra identifier), and sub-study number.

Step 3: Collect two tubes of whole blood (8.5 mL per tube)
- Prevent backflow: tubes contain chemical additives and it is important to avoid backflow into patient
- Collect specimen by venipuncture
- Fill tubes completely (8.5 mL per tube)

Step 4: Remove the tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results. One inversion is a complete turn of the wrist, 180° and back, per the figure below.



Step 5: Place specimen into the specimen collection kit.
- Confirm each tube is labeled with the supplied labels indicating the date of collection and two unique patient identifiers (label included in kit).

Step 6: Select “Ship this Shipment and Generate Packing List” in the SWOG Specimen Tracking System to generate the Packing List. A copy of the SWOG Specimen Tracking Packing List must be included in the shipment. Confirm that the tubes are labeled as specified on the Packing List.

Step 7: Preferably on the same day of collection, ship via FedEx overnight delivery at ambient temperature. Do not freeze or refrigerate blood samples. Keep at 43-99° F (6-37° C).

FMI accepts Saturday deliveries. If shipping on a Friday, please overnight shipment, and mark for Saturday delivery.

d. Specimen Usage

Cell-free, circulating DNA will be isolated from the plasma component of the whole blood. Using a hybrid-capture, next-generation sequencing technology (developed by Foundation Medicine), alterations in clinically significant cancer genes (oncogenes and tumor suppressor genes) will be identified and quantitated relative to wild-type sequences. Tumor-specific alterations will include point mutations, small insertions and deletions, chromosomal rearrangements and copy number/amplification events in (**LUNGMAP** ctDNA Assay) including an assessment of tumor mutation burden (TMB) will be conducted using ctDNA. A full proposal will be developed, reviewed, and approved by SWOG and CTEP once funding has been obtained.

The ctDNA results are for research purposes and will not be shared with the investigator or patient.

15.4 Specimen Flow Diagram

Please refer to Section 15 of **LUNGMAP** for the specimen flow diagram for the screening protocol.

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 for the first year, then every 12 weeks until progression and discontinuation of treatment.

All study participants must have a CT (or MR or PET/CT) exam prior to sub-study entry. Participants must then undergo additional imaging every 6 weeks for the first year, then every 12 weeks until progression of disease and discontinuation of treatment. 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 **LUNGMAP** Section 18.2f. 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 clinically 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 **LUNGMAP** Section 18.2f.

b. TRIAD Digital Image Submission

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. 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.

- A valid CTEP-IAM account (see **LUNGMAP** Section 13.2).
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on the NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

2. TRIAD Installations:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at: https://triadinstall.acr.org/triadclient/.

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

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice.

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312 and the CTEP Investigator's Handbook.

Publication and Industry Contact

The agents supplied by CTEP, DCTD, NCI used in this protocol are provided to the NCI under Collaborative Agreements (CRADA, CTA, CSA) between the Pharmaceutical Companies (hereinafter referred to as "Collaborators") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agents in this study:

1. Agents may not be used for any purpose outside the scope of this protocol, nor can Agents be transferred or licensed to any party not participating in the clinical study. Collaborators data for Agents are confidential and proprietary to Collaborators and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborators, the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to the Collaborators for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborators for advisory review and comment prior to submission for publication. Collaborators will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator's intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborators for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

   E-mail: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to the Collaborators. No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Trial Master File

This is an FDA registration study; therefore, all participating sites should be FDA "inspection ready". This entails maintaining a Trial Master File that includes essential documents that may be subject to FDA oversight. A list of essential documents is available on the SWOG website under QA/Audits, https://swog.org/Visitors/QA/Index.asp.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Serious Adverse Event Reporting Requirements

a. Definition and Purpose

   Definition: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (FDA, 21 CFR 312.32). See Table 16.1 for definition of a Serious Adverse Event (SAE) and reporting requirements.

   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.

b. Reporting method

This study requires that expedited adverse events be reported to SWOG Operations Office using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

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.

In the rare event when internet connectivity is disrupted, a 24-hour notification is made to SWOG by telephone at 210-614-8808 or by email at adr@swog.org. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

When the adverse event requires expedited reporting, submit the report via CTEP-AERS within the number of calendar days of learning of the event 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 Arm B of this study are ramucirumab and pembrolizumab (MK-3475). If there is any question about the reportability of an adverse event or if internet connectivity is disrupted, please telephone or email the SAE Program Manager at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 16.1 (or section 16.1f).

Table 16.1:

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Arm B: Ramucirumab plus Pembrolizumab (MK-3475)

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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events (if applicable) are found in 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 documentation supporting the CTEP-AERS report to the SWOG Operations Office by fax 210-614-0006. Specific instructions will be sent by email to the reporting site by the SAE Program Manager.

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

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

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 16.2.

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

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

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

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

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

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

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention,

radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

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

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

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

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

For more information see:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf
Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. Supporting documentation must also be submitted to SWOG Operations Office by fax to 210/614-0006

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

i. **Reporting Pregnancy, 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 210/614-0006. 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

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18.0 APPENDIX

18.1 New York Heart Association Classification

Class	Cardiac Symptoms	Need for Limitations	Physical Ability Additional Rest*	To Work**
I	None	None	None	Full Time
II	Only moderate	Slight or occasional	Usually only slight	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

18.2 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 timepoints 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 1 timepoint 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 to distribute specimens for testing, if applicable.

18.3 Child-Pugh Scoring

The score is used to assess the prognosis of chronic liver disease and employs five clinical measures of liver disease. Each measure is scored 1–3, with 3 indicating most severe derangement.

Measure	1 point	2 points	3 points
Total bilirubin, mmol/L (mg/dL)	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin, g/dL	>3.5	2.8–3.5	<2.8
Prothrombin time, prolongation in seconds (or INR)	<4.0 (<1.7)	4.0–6.0 (<1.7-2.2)	> 6.0 (>2.2)
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

	Class A	Class B	Class C
Total points	5-6	7-9	10-15

18.4 Live Vaccines Examples

Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

18.5 PD-L1 22C3 IHC Assay

The FMI Dako PD-L1 (22C3) IHC assay was done as part of the Lung-MAP Screening Study to randomize patients for **S1800A**. PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying NSCLC patients for treatment. The results are based on PD-L1 protein expression determined by Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. A specimen was considered to have PD-L1 expression if TPS ≥ 1% and high PD-L1 expression if TPS ≥ 50%. The clinical value for testing PD-L1 expression is well documented.(*1*)

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