SWOG CANCER RESEARCH NETWORK

Version Date: September 2, 2022

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office (E-mail protocols@swog.org)

RE: **S1619**, "A Feasibility Trial of Neoadjuvant Cisplatin-Pemetrexed with Atezolizumab in Combination and in Maintenance for Resectable Malignant Pleural Mesothelioma."
Primary Study Chair: Anne Tsao, M.D.

REVISION #6

Study Chair: Anne Tsao, M.D.
Phone number: 713/792-6363
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Status Change
(√) IRB Review only

Action Codes
(√) Expedited review allowed

Key Updates
(√) Editorial / Administrative changes to the Protocol
(√) Other: Planned Enrollment Table was updated

***Sites using the CIRB as their IRB of record*:** The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of distribution of this notice through the CTSU Bi-Monthly Broadcast email.

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

REVISION #6

This revision has been prepared in response to CTEP's request to remove the international accrual table in **S1619** to align with the NIH Human Subject System (HSS).

Protocol Changes

1. The version date has been updated.

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

3. **Section 2.0:** The international planned enrollment table has been removed to meet the HSS requirements.

Model Consent Form Changes

1. The version date has been updated.

The updated protocol and model informed consent form can be accessed from the CTSU website (www.ctsu.org). Please discard any previous versions of the documents and replace with the updated versions. Please contact lungquestion@crab.org or 206/652-2267 with any questions.

This study has been reviewed and approved by the NCI's Central Institutional Review Board (CIRB).

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

cc: PROTOCOL & INFORMATION OFFICE

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

SWOG

A FEASIBILITY TRIAL OF NEOADJUVANT CISPLATIN-PEMETREXED WITH ATEZOLIZUMAB IN COMBINATION AND IN MAINTENANCE FOR RESECTABLE MALIGNANT PLEURAL MESOTHELIOMA

NCT#03228537

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AGENTS:

IND-Exempt Agents:
Cisplatin (NSC 119875)
Pemetrexed (Alimta®) (NSC-698037)

NCI-Supplied Investigational Agent:
Atezolizumab (NSC-783608)
(DCTD-sponsored [redacted])

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NRG/NRG Oncology
SWOG/SWOG

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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 Submission sub-tab under the Regulatory tab. Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench via the SWOG website (www.swog.org).
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center by phone or email: 206/652-2267 lungquestion@crab.org **For treatment or toxicity related questions** contact the Study Chairs by phone or email: Anne Tsao, M.D., Phone: 713-792-6363 or E-mail: astsao@mdanderson.org or [redacted], M.D., Phone: [redacted] or Email: [redacted]		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

SCHEMA

Chemotherapy naive patients diagnosed with resectable malignant pleural mesothelioma

Step 1: Neoadjuvant

Treatment with cisplatin + pemetrexed + atezolizumab x 4 cycles

Stratification factor: EPP vs. P/D

Step 2: Surgery

Extrapleural pneumonectomy (EPP) and radiation therapy

OR

Pleurectomy/decortication (P/D)

Step 3: Maintenance

Maintenance atezolizumab for up to 1 year

1.0 OBJECTIVES

1.1 Primary Objective(s)

a. To evaluate if the regimen of neoadjuvant cisplatin-pemetrexed-atezolizumab, surgery +/- radiation, then maintenance atezolizumab is feasible and safe (as defined in Section 11.1) for patients with resectable malignant pleural mesothelioma.

1.2 Secondary Objective(s)

a. To evaluate progression free survival (both by RECIST 1.1 and also using a Modified RECIST for Pleural Tumors) in patients with resectable malignant pleural mesothelioma treated with a regimen of neoadjuvant cisplatin-pemetrexed-atezolizumab, surgery +/- radiation, followed by one year of maintenance atezolizumab.

b. To evaluate overall survival in patients with resectable malignant pleural mesothelioma treated with a regimen of neoadjuvant cisplatin-pemetrexed-atezolizumab, surgery +/- radiation, followed by one year of maintenance atezolizumab.

c. To evaluate response rate (confirmed and unconfirmed, complete and partial, both by RECIST 1.1 and also using a Modified RECIST for Pleural Tumors) in the subset of this patient population with measurable disease.

1.3 Translational Medicine Objective(s)

a. To evaluate the association between immunohistochemical (IHC) expression of PD-L1 in tumors and clinical outcomes in mesothelioma patients treated with trimodality/bimodality therapy including atezolizumab (anti-PD-L1).

b. To evaluate the association between expression of immune-related genes identified by Immune Nanostring (depending on RNA availability) and clinical outcomes in mesothelioma patients treated with trimodality/bimodality therapy including atezolizumab.

c. To evaluate the association between multiplex immunofluorescence (IF) of up to 10 immune markers in two panels and clinical outcomes in mesothelioma patients treated with trimodality/bimodality therapy including atezolizumab.

2.0 BACKGROUND

Malignant pleural mesothelioma (MPM) is a rare and aggressive tumor with a poor prognosis. *(1)* MPM is a challenging therapeutic and diagnostic cancer; consequently, there has been very little progress toward improved survival outcomes. In the United States, it is standard practice to administer 4 cycles of cisplatin-pemetrexed to multimodality therapy for resectable mesothelioma (NCCN guidelines). Ultimately, the decision to administer neoadjuvant or adjuvant systemic therapy should be made in a multidisciplinary setting. Neoadjuvant therapy has the inherent risk to adversely delay surgery or cause complications, with the extratrapleural pneumonectomy (EPP) completion rates ranging between 42-84%. *(2,3,4,5,6,7,8,9)* On the other hand, neoadjuvant therapy yields response rates between 29-44% and can give prognostic information with responders having better survival outcomes. *(10, 11, 12)* Adjuvant chemotherapy does not compromise surgical resection, but poor patient tolerance after surgery and radiation often preclude delivery of chemotherapy.

To date, there are no randomized trials comparing neoadjuvant or adjuvant therapy, and both approaches are accepted as standard practice. Although trimodality therapy is standard practice, both neoadjuvant and adjuvant studies still only yield median overall survival rates between 16.6 to 25.5 months. *(13,14,15,16,17,18,19,20)* There is a clear need for the addition of novel agents or immunotherapies to trimodality treatment to improve survival outcomes. These agents must improve response rates, have reasonably low toxicity profiles with no compromise of trimodality treatment, and must be able to be administered in a maintenance setting.

The standard choice of cisplatin-pemetrexed chemotherapy for neoadjuvant therapy is based on Phase III data in the unresectable setting which demonstrated an improvement in OS from 9.3 months to 12.1 months (HR 0.74, p=0.003) compared to cisplatin alone. *(21)* Since there are no actionable driver mutations, the use of targeted agents has been disappointing in MPM with the exception of bevacizumab, which recently demonstrated a two month median OS benefit in the unresectable frontline setting in the IIFCT-GFPC-0701 MAPS trial. *(22)* Unfortunately, cisplatin-pemetrexed-bevacizumab is not an acceptable neoadjuvant regimen due to the high risk of bleeding complications that would be associated with the subsequent resection. However, one promising avenue of discovery in MPM has been immunotherapy since MPM is considered to be an immunogenic tumor.

Programmed death 1 (PD-1) protein, a T-cell co-inhibitory receptor, and one of its ligands, PD-L1, are potential targets for immunotherapy. PD-1 receptor binds with PD-L1 and inhibits T-cell inhibition and downregulates T-cell responses. Inhibition of their interaction has been shown to lead to restoration of T-cell activity and a subsequent anti-tumor effect in several tumor types. Mansfield et al. reported a 40% positive PD-L1 IHC expression in pleural mesotheliomas (n=224) using a mouse monoclonal anti-human B7-H1 (clone 5H1-A3). *(23)* An IHC score of less than 5% expression was considered to be a negative result. Patients with positive PD-L1 IHC expression were associated with having more disease burden and being less likely to be a surgical candidate. Also, PD-L1 IHC expression was associated with a worse survival (6 months vs. 14 months, p<0.0001). *(24)*

There are several PD-1 and PD-L1 inhibitors under development including pembrolizumab (Merck), nivolumab (Bristol-Myers Squibb), BMS0936559 (Bristol-Myers Squibb), MEDI-4736 (Medimmune), avelumab (EMD Soreno, Merck) and atezolizumab (Genentech). Although limited and preliminary, there are a few reports of the use of these agents in mesothelioma, primarily as part of large solid tumor basket trials. At AACR 2015, KEYNOTE-028, a clinical trial administering pembrolizumab monotherapy (PD-1 inhibitor, 10 mg/kg every 2 weeks) to PD-L1 IHC positive solid tumor patients, reported results from 25 patients in the mesothelioma cohort. *(25)* Six patients had a response (24% ORR) and 12 patients had disease stabilization as the best response. This translated into a 76% disease control rate. This study is ongoing and accruing unresectable mesothelioma patients. *(26)* In a larger mesothelioma cohort study (n=53) from JAVELIN presented recently at ASCO 2016, avelumab (PD-L1 inhibitor) reported 5 partial responses (9% ORR) and 25 patients with stable disease (47% SD). *(27)* In the JAVELIN trial, patients with ≥ 5% PD-L1 IHC staining had a higher response rate compared to those with PD-L1 negative tumors (14.3% vs 8.1% ORR). *(28)*

There is a growing body of literature that supports the premise that mesothelioma is a highly immunogenic disease and there are multiple ongoing studies in the unresectable setting investigating anti-PD1/PD-L1 therapies. *(29)* One example of a biomarker-based study is the NivoMeso Trial in Amsterdam, which is a single arm Phase II study that administers nivolumab to recurrent metastatic mesothelioma patients and biopsies them at baseline and week 6 to assess the impact of nivolumab on T cells and PD-L1 tumor IHC expression.

Atezolizumab, a PD-L1 inhibitor, has been evaluated in preclinical models in combination with chemotherapy. Luoh et al. at AACR 2016 evaluated the effects of different classes of chemotherapeutic agents on the tumor immune microenvironment in syngeneic murine tumor models. *(30)* Most chemotherapies had a mild to moderate increase in CD8+ T cells in the tumor,

and some altered the activation states. Some of the chemotherapies altered the number of CD4+ cells, including regulatory T cells and affected the myeloid subpopulations. In addition to single agent studies, the combination of anti-PD-L1 therapy with chemotherapy led to pharmacodynamics marker changes. The results indicate that chemotherapy can stimulate the tumor immune microenvironment through multiple mechanisms and suggest that combined anti-PD-L1 inhibition with chemotherapy may be beneficial with an anti-tumor effect. Early ongoing clinical trials with cisplatin-pemetrexed-atezolizumab are being conducted presently. The large international ongoing clinical trials are in NSCLC. IMpower110, "A Study of Atezolizumab (MPDL3280A) Compared With a Platinum Agent (Cisplatin or Carboplatin) + (Pemetrexed or Gemcitabine) in Participants With Stage IV Non-Squamous or Squamous Non-Small Cell Lung Cancer (NSCLC)" is open for enrollment (NCT02409342) and IMpower 132, "A Study of Atezolizumab in Combination With Carboplatin or Cisplatin + Pemetrexed Compared With Carboplatin or Cisplatin + Pemetrexed in Participants Who Are Chemotherapy-Naive and Have Stage IV Non-Squamous Non-Small Cell Lung Cancer (NSCLC)" (NCT02657434).

Given the emerging literature on immunotherapies in MPM, we believe that the addition of atezolizumab to standard of care neoadjuvant chemotherapy prior to surgery with or without radiation will enhance T-cell activation against microscopic disease and will improve clinical outcomes for MPM. However, there is a knowledge gap on whether the immunotherapy agent, atezolizumab, will add toxicity to standard of care. It is also unclear how long to administer an immune checkpoint inhibitor but current trials in advanced cancers administer the agent for 1-2 years and adjuvant trials are administering immune checkpoint inhibitors for one year. Therefore, this trial will also evaluate the feasibility of one-year of maintenance immunotherapy.

If the regimen is shown to be feasible and safe a randomized Phase II trial comparing the atezolizumab containing regimen to the standard of care is planned. We have prespecified that this regimen will be considered feasible and safe to move forward to a Phase II setting if 18/24 (75%) of patients are able to receive at least one dose of adjuvant maintenance atezolizumab therapy and no Grade 4 or 5 autoimmune toxicity is seen.

Though mesothelioma is considered a highly immunogenic disease, little is known about mesothelioma PD-L1 IHC expression after treatment with immunotherapy. To further investigate and quantify changes in the tumor immune microenvironment in response to cisplatin-pemetrexed-atezolizumab treatment several correlative studies will be performed. We hypothesize that higher levels of PD-L1 IHC in tumor cells or immune infiltrate cells will be associated with improved clinical outcomes.

Inclusion of Women and Minorities

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	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	2	0	0	3
White	13	11	0	1	25
More Than One Race	0	0	0	0	0
Total	14	13	0	1	28

3.0 DRUG INFORMATION

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

For this study, cisplatin and pemetrexed are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, atezolizumab is investigational and is being provided under an IND held by the National Cancer Institute. The Investigator Brochure may be obtained by accessing PMB's Online Agent Ordering Processing (OAOP) application (http://ctep.cancer.gov/branches/pmb/agent_order_processing.htm). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via e-mail (IBCoordinator@mail.nih.gov).

3.1 Atezolizumab (NSC # 783608) [redacted]

a. PHARMACOLOGY

Mechanism of Action: Atezolizumab is a humanized immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary (CHO) cells. Atezolizumab targets programmed death-ligand 1 (PD-L1) on immune cells or tumor cells and prevents interaction with either programmed death-1 (PD-1) receptor or B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells. Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc-effector function. By eliminating Fc-effector function and antibody dependent cell-mediated cytotoxicity (ADCC), antibody-mediated clearance of activated effector T cells is also eliminated. Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients, and is being investigated as a potential therapy in a wide variety of malignancies.

b. PHARMACOKINETICS

On the basis of available preliminary PK data (0.03-20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1 mg/kg and 20 mg/kg dose groups, the mean apparent CL and the mean Vss had a range of 3.20 to 4.44 mL/day/kg and 48.1 to 65.7 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

Serum atezolizumab concentrations exhibited a biphasic disposition with an initial rapid distribution phase followed by a slow elimination phase. Atezolizumab exhibited nonlinear pharmacokinetics at doses <1 mg/kg (i.e., 0.03-0.3 mg/kg), likely due to target-mediated CL at lower concentrations. Atezolizumab exhibited linear pharmacokinetics at doses ≥ 1 mg/kg. At doses ≥ 1 mg/kg, the mean Cmax increased in a dose-proportional manner and was 26.0 mcg/mL for the 1-mg/kg dose group and 472 mcg/mL for the 20 mg/kg dose group. Similarly, at doses ≥ 1 mg/kg, the group mean AUC0-∞ had a range of 340-6050 Day x mcg/mL for 1 mg/kg and 20 mg/kg dose group and was approximately dose proportional, by similar CL across the dose range. The observed CL and Vss for atezolizumab at doses ≥ 1 mg/kg are consistent with these of a typical IgG1 antibody in humans.
Currently available PK and ATA data from Study PCD4989g suggest that the 15-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain trough concentration (Ctrough) ³ 6 mg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). From inspection of available observed Ctrough data, moving further to the 20-mg/kg atezolizumab q3w regimen does not appear to be warranted to maintain targeted Ctrough levels relative to the proposed 15-mg/kg atezolizumab q3w level.

Refer to the atezolizumab Investigator's Brochure for details regarding nonclinical and clinical pharmacology of atezolizumab.

c. ADVERSE EFFECTS

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Atezolizumab (MPDL3280A, NSC 783608)

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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). 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 3,097 patients.* Below is the CAEPR for Atezolizumab (MPDL3280A).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different

SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, March 11, 2021[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Heart failure[2]	
		Myocarditis[2]	
		Pericardial effusion[2]	
		Pericardial tamponade[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes)[2]	
	Hyperthyroidism[2]		
		Hypophysitis[2]	
	Hypothyroidism[2]		
EYE DISORDERS			
		Eye disorders - Other (ocular inflammatory toxicity)[2]	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
	Dysphagia		
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Fatigue			***Fatigue (Gr 2)***
	Fever[3]		
	Flu like symptoms[3]		
HEPATOBILIARY DISORDERS			
		Hepatic failure[2]	
		Hepatobiliary disorders - Other (hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
		Anaphylaxis[3]	
		Cytokine release syndrome[3]	
		Immune system disorders - Other (systemic immune activation)[2]	
INFECTIONS AND INFESTATIONS			
Infection[4]			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased[2]		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased[2]		
		Creatinine increased	
	GGT increased[2]		
	Lipase increased*		

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Platelet count decreased	
	Serum amylase increased*		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
		Hyperglycemia[2]	
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		
	Back pain		
		Generalized muscle weakness	
	Myalgia		
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Ataxia[2]	
		Encephalopathy[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (meningitis non-infective)[2]	
		Myasthenia gravis[2]	
		Paresthesia[2]	
		Peripheral motor neuropathy[2]	

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Renal and urinary disorders - Other (nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Hypoxia		
	Nasal congestion		***Nasal congestion (Gr 2)***
		Pleural effusion[2]	
		Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Bullous dermatitis[2]	
		Erythema multiforme[2]	
	Pruritus		
	Rash acneiform		
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])[2]	

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		
		Skin and subcutaneous tissue disorders - Other (exanthematous pustulosis)[2]	
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	

* Denotes adverse events that are <3%.

[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] Atezolizumab, being a member of a class of agents involved in the inhibition of "immune checkpoints," may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. Immune-mediated adverse reactions have been reported in patients receiving atezolizumab. Adverse events potentially related to atezolizumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of atezolizumab, administration of corticosteroids and supportive care.

[3] Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of atezolizumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of atezolizumab.

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

Adverse events reported on atezolizumab (MPDL3280A) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that atezolizumab (MPDL3280A) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia

CARDIAC DISORDERS - Cardiac arrest; Ventricular tachycardia
GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Portal vein thrombosis
INVESTIGATIONS - Lymphocyte count decreased; Neutrophil count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle cramp: Pain in extremity
NERVOUS SYSTEM DISORDERS - Headache
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Suicide attempt
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pulmonary hypertension; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin[2]; Hyperhidrosis
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: Atezolizumab (MPDL3280A) 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.

1. Pregnancy and Lactation: No developmental or reproductive toxicity studies have been conducted with atezolizumab as several nonclinical studies have already demonstrated that the PD-L1/PD-1 signaling pathway is essential in establishing maternal/fetal tolerance, which is necessary for embryo-fetal survival during gestation. Based on the critical role that PD-L1/PD1 pathway plays in the maintenance of maternal-fetal tolerance, atezolizumab should not be administered to pregnant women. The effects of atezolizumab on human reproduction or on the fetus or the developing infant are unknown but expected to have an adverse effect.

   It is not known whether atezolizumab is excreted in human milk. However, antibodies are known to cross the placenta and are excreted in breast milk during lactation. Atezolizumab should not be administered to nursing mothers.

   Male patients and female patients of childbearing potential should utilize contraception and take active measures to avoid pregnancy while undergoing atezolizumab treatment and for at least 5 months (150 days) after the last dose of atezolizumab.

2. Drug Interactions: Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

Atezolizumab is provided by Genentech/F. Hoffmann-La Roche LTD and distributed by the Pharmaceutical Management Branch, CTEP, NCI. The agent is supplied in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. Atezolizumab is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, at a pH of 5.8. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume.

f. STORAGE, PREPARATION & STABILITY

Atezolizumab must be refrigerated at 2°C-8°C (36°F- 46°F) upon receipt until use. No preservative is used in atezolizumab and therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Atezolizumab (1200 mg per vial) will be administered in 250 mL 0.9% NaCl IV infusion bags and infusion lines equipped with 0.2 micron in-line filters. The IV bag may be constructed of polyvinyl chloride (PVC) or polyolefin (PO); the IV infusion line may be constructed of polyvinyl chloride (PVC) or polyethylene (PE); and the 0.2 micron in-line filter may be constructed of polyehersulfone (PES). Atezolizumab must be prepared/diluted under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user.

The dose solution prepared for IV bag delivery may be stored at 2°C to 8°C (36°F to 46°F) and/or at room temperature for up to a total in-use storage time of 8 hours.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: Atezolizumab is an investigational agent supplied to Investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent 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 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/. 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 e-mail PMBAfterHours@mail.nih.gov any time.

2. Drug Handling and Accountability

   a. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, 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).
   Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

3. Drug Return and/or Disposition Instruction

   a. Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

   b. Drug expiration: If packaging has expiration date, indicate drug expiration date on the DARF under Manufacturer and Lot # and use the drug lots with shorter expiration date first.

4. Contact Information

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- RCR Help Desk: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB IB Coordinator: IBCoordinator@mail.nih.gov
- PMB e-mail: PMBAfterHours@mail.nih.gov

PMB phone and hours of service: 210/276-6675 Monday through Friday between 8:30 am and 4:30 pm (ET)

3.2 Cisplatin (CDDP, Platinol®, Platinol-AQ) (NSC-119875)

a. PHARMACOLOGY

Mechanism of Action:

Cisplatin (cis-diamminedichloroplatinum) is a heavy metal complex containing a central platinum atom surrounded by two chloride atoms and two ammonia molecules in the cis position. It is water soluble and acts as a bifunctional alkylating agent with cell cycle nonspecific characteristics. The intra-strand cross-links, in particular with guanine and cytosine, change DNA conformation and inhibit DNA synthesis leading to the cytotoxic and anti-tumor effects of cisplatin. Although cisplatin seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents and that cisplatin does not exhibit cross-resistance with other alkylating agents or nitrosoureas.

b. PHARMACOKINETICS

1. Absorption: Following rapid IV injection of cisplatin over up to one hour, peak plasma drug and platinum concentrations occur immediately. When cisplatin is administered by IV infusion over 6 or 24 hours, plasma concentrations of total platinum increase gradually during the infusion and peak immediately following the end of the infusion.

2. Distribution: Following intravenous dosing, cisplatin distributes rapidly into tissues, with highest concentrations in the liver, prostate and kidney. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding, which exceeds 90%. Cisplatin penetrates poorly into the CNS.

3. Metabolism: Cisplatin is non-enzymatically transformed to one or more metabolites that are extensively protein bound and have minimal cytotoxic activity. The non-protein bound (unchanged) fraction is cytotoxic.

4. Elimination: Urinary excretion is incomplete. Following bolus injection or infusion over a dose range of 40-140 mg/m^2 varying in length from 1-24 hours, from 10 to about 40% of the administered platinum is excreted in the urine in 24 hours. Renal clearance of free platinum exceeds the glomerular filtration rate, indicating that cisplatin or other platinum-containing molecules are actively secreted by the kidneys. Renal clearance of free platinum is nonlinear and variable, and is dependent on dose, urine flow rate, and individual variability in the extent of active secretion and possible tubular reabsorption.

c. ADVERSE EFFECTS

1. Possible Side Effects of cisplatin: Adverse effects reported in 10% or more of patients receiving cisplatin include peripheral neuropathy, nausea, vomiting, diarrhea, myelosuppression, liver enzymes elevation, nephrotoxicity (acute renal failure and chronic renal insufficiency), alopecia, tissue irritation, and ototoxicity.

Human toxicity includes anorexia, nausea, vomiting, renal toxicity (with an elevation of BUN, creatinine, serum uric acid and impairment of

endogenous creatinine clearance, as well as renal tubular damage), ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus), peripheral neuropathy and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Raynaud's phenomena and digital ischemia has been described. Anaphylactic-like reactions including facial edema, bronchoconstriction, tachycardia and hypotension may occur within minutes of administration. Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy. Alopecia, malaise and asthenia have been reported. Rare complications are alopecia, seizures, loss of taste and allergic reactions. Tetany may occur due to hypomagnesemia and/or hypocalcemia. Other electrolyte disturbances may occur. At high doses patients have experienced optic neuritis, papilledema, cerebral blindness, blurred vision, and altered color perception. Patients have also experienced cardiac abnormalities, elevated aspartate aminotransferase and rash. Subsequent courses should not be given until serum creatinine returns to normal if elevated. Audiometric analyses should be monitored and courses withheld until auditory acuity is within normal limits. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

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

2. Pregnancy and Lactation: Category D. Cisplatin can cause fetal harm when administered to a pregnant woman. In mice, cisplatin is teratogenic and embryotoxic. This drug has been found to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, patients receiving cisplatin should not breast feed.

3. Drug Interactions: During cisplatin therapy, plasma levels of anticonvulsant agents may become sub-therapeutic and should be monitored. For complete information refer to the current FDA-approved package insert.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

2. Refer to the current FDA-approved package insert for drug administration.

e. PREPARATION, STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

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

3.3 Pemetrexed for injection (Alimta®) (NSC-698037)

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/m2 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 (Cmax) 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.

4.0 STAGING CRITERIA

CRITERIA (AJCC 7TH EDITION, 2010)

4.1 Staging Criteria (AJCC Cancer Staging Manual, 7th edition)

Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Tumor limited to the ipsilateral parietal pleura with or without mediastinal pleura and with or without diaphragmatic pleural involvement

T1a No involvement of the visceral pleura

T1b Tumor also involving the visceral pleura

T2 Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:

Involvement of diaphragmatic muscle

Extension of tumor from visceral pleura into the underlying pulmonary parenchyma

T3 Locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:

Involvement of the endothoracic fascia

Extension into the mediastinal fat

Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall

Nontransmural involvement of the pericardium

T4 Locally advanced technically unresectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following:

Diffuse extension on multifocal masses of tumor in the chest wall, with or without associated rib destruction

Direct transdiaphragmatic extension of tumor to the peritoneum

Direct extension of tumor to the contralateral pleura

Direct extension of tumor to mediastinal organs

Direct extension of tumor into the spine

Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion or tumor involving the myocardium

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastases

N1 Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes

N2 Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary and peridiaphragmatic nodes

N3 Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis present

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

HISTOLOGICAL GRADE (G)

Grade is reported in registry systems by the grade value. A two-grade, three-grade, or four-grade system may be used. If a grading system is not specified, generally the following system is used:

GX Grade cannot be assessed

G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

G4 Undifferentiated

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 SWOG Statistics and Data Management Center in Seattle at 206/652-2267 or Lungquestion@crab.org prior to registration. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28 or 90 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 STEP 1: NEOADJUVANT

a. Disease Related Criteria

1. Patient must have Stage I-III malignant pleural mesothelioma that is deemed resectable and must be planning to undergo pleurectomy decortication (P/D) or extrapleural pneumonectomy (EPP).

2. Patient must have epithelioid or biphasic histology (sarcomatoid histology is excluded). Histologic diagnosis and typing of mesothelioma requires at least a core needle biopsy or surgical biopsy of the pleura via thoracoscopy and small thoracotomy. Cytology only will not be regarded as sufficient for the diagnosis.

3. Patient must have CT of the chest/abdomen with contrast or FDG-PET/CT scan performed within 28 days prior to Step 1 registration.

4. Patient must have non-measurable or measurable disease (see 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 Section 10.1c. Measurable disease must be assessed within 28 days prior to Step 1 registration. Non-measurable disease must be assessed within 42 days prior to Step 1 registration. All disease must be assessed and documented on the RECIST 1.1 and Modified RECIST Baseline Tumor Assessment Form.

5. Patient must have undergone extended surgical staging including mediastinoscopy or endobronchial ultrasound. At minimum, samples must be obtained from the mediastinal stations 4R, 7 (subcarinal), and 4L. This surgical staging must be performed within 42 days prior to Step 1 registration. Patient must be T1-3 and N0-N2 (single station).

6. Patient must undergo video-assisted thoracoscopic surgery and diagnostic laparoscopy within 28 days prior to Step 1 registration to rule out peritoneal disease spread.

7. Patient must have consultation with a surgeon within 21 days prior to Step 1 registration. The surgeon must confirm that the patient's disease is resectable by pleurectomy decortication (P/D) or extrapleural pneumonectomy (EPP) and that the patient is an appropriate candidate for the surgical procedures described in Section 7.3 and Appendix 18.3).

b. Prior/Concurrent Therapy Criteria

1. Patient must not have had prior immunotherapy or chemotherapy for malignant pleural mesothelioma.

c. Clinical/Laboratory Criteria

1. Patient must be ≥18 years of age.

2. Patient must have Zubrod performance status 0 or 1 documented within 28 days prior to Step 1 registration.

3. Patients requiring hearing aids or reporting hearing loss must have audiogram performed within 28 days prior to Step 1 registration.

4. Patient must have not had any major surgery or radiation within 28 days prior to Step 1 registration. Diagnostic thoracotomies and laparoscopies are not considered major surgeries.

5. Patient must not have any anticancer therapy or investigational agent within 28 days prior to Step 1 registration.

6. Patient must have adequate hematologic function defined as ANC ≥ 1,500/mcl, Hemoglobin ≥ 9 g/dl, and platelets ≥ 100,000/mcl documented within 28 days prior to Step 1 registration.

7. Patient must have adequate kidney function defined as creatinine ≤ 1.5 x ULN and creatinine clearance ≥ 45ml/min documented within 28 days prior to Step 1 registration.

8. Patient must have adequate liver function defined as total bilirubin ≤ 1.5 x upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN within 28 days prior to Step 1 registration.

9. 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 three years.

10. Patients must not be pregnant or nursing due to the potential teratogenic side effects of the protocol treatment. Women of reproductive potential and men must have agreed to use an effective contraceptive method for the duration of study treatment and for 5 months (150 days) after the last dose of atezolizumab. 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.

11. Patient must NOT have a history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.

12. Patient must NOT have a known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation.

13. Patient must not have severe infections within 28 days prior to Step 1 registration, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.

14. Patient must not have 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, etc.) is not considered a form of systemic treatment. Autoimmune diseases include, but are not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis. This protocol includes an immunotherapy agent which can precipitate known autoimmune diseases.

15. Patient must not have undergone prior allogeneic bone marrow transplantation or prior solid organ transplantation.

16. Patient must not have active tuberculosis.

17. Patient must not have history of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis. This protocol includes an immunotherapy agent which can precipitate known pneumonitis.

18. Patient must not have active (chronic or acute) hepatitis B virus (HBV) infection as evidenced by testing performed within 28 days prior to registration. Patients with past or resolved HBV infection are eligible.

    Active HBV is defined as having a positive hepatitis B surface antigen (HBsAg) test.

    Past or resolved HBV is defined as having a negative HBsAG test and a positive total hepatitis B core antibody (HBcAb) test.

    Patient must not have active hepatitis C virus (HCV) infection as evidenced by testing performed within 28 days prior to registration.

Active HCV is defined as having a positive HCV antibody test followed by a positive HCV RNA test.

19. Patient must NOT have a known positive test for HIV. Patients do not need to be screened for HIV. Patients with HIV are excluded due to a potential incompetent immune system and need for medications that could interfere with the treatment and immunotherapy.

20. Patient must not have significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to initiation of treatment, unstable arrhythmias, or unstable angina given the higher risks associated with surgical resection.

21. Patient must not receive live, attenuated influenza vaccine within 4 weeks prior to registration or at any time during the study and until 5 months after the last dose of atezolizumab.

d. Specimen Submission Criteria

1. Patient must be willing to have tissue specimens submitted for translational medicine studies as described in Section 15.1.

2. Patient must be offered the opportunity to participate in tissue and blood banking for future studies.

e. Regulatory Criteria

1. Patient ***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.

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

5.2 STEP 2: SURGERY

a. Disease Related Criteria

1. Patient must have a CT of chest/abdomen with contrast or FDG-PET/CT scan within 28 days prior to Step 2 registration. Patients must not have evidence of progression per RECIST 1.1 or Modified RECIST for Pleural Tumors.

2. Patients planning to receive EPP must also be evaluated for appropriateness of RT by a Radiation Oncologist within 14 days prior to Step 2 registration.

b. Clinical/Laboratory Criteria

1. Patient must have a Zubrod performance status of 0-1 documented within 28 days prior to Step 2 registration.

2. Patient must have postoperative predicted FEV1 > 35% and postoperative predicted DLCO > 35%. Pulmonary function tests to ascertain these values must be obtained within 28 days prior to Step 2 registration.

3. Patient must have received at least two cycles of triplet neoadjuvant therapy (all three drugs) during Step 1.

4. Patient must be registered to Step 2 no less than 21 days and no more than 90 days after the end of their final cycle of neoadjuvant therapy.

5.3 STEP 3: MAINTENANCE

a. Patient must have received either P/D or EPP and must have recovered from all effects of surgery with adequate wound healing. Patients who received radiation therapy (RT) must be registered to Step 3 within 90 days after discontinuing RT. Patients who did not receive RT must be registered to Step 3 within 90 days after surgery.

b. Patient must have a CT of chest/abdomen/pelvis with contrast or FDG-PET/CT scan within 28 days prior to Step 3 registration. Patient must not have evidence of progression per RECIST 1.1 or modified RECIST for pleural tumors.

c. Patient may have discontinued RT early due to toxicity or other reasons.

d. Patient must have a Zubrod performance status of 0-1 documented within 28 days prior to Step 3 registration.

e. Patient must have adequate hematologic function defined as ANC > 1,500/mcl, hemoglobin > 9 g/dl, and platelets > 100,000/mcl documented within 28 days prior to Step 3 registration.

f. Patient must have adequate kidney function defined as creatinine < 1.5 x ULN documented within 28 days prior to Step 3 registration.

g. Patient must have adequate liver function defined as total bilirubin ≤ 1.5 x upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN within 28 days prior to Step 3 registration.

6.0 STRATIFICATION FACTORS

Patients will be stratified prior to registration for Step 1 by the planned type of surgery: extrapleural pneumonectomy (EPP) versus pleurectomy/decortication (P/D). The decision regarding the type of surgery should be based on patient's physiologic status (ability to tolerate EPP), and on invasive pre-treatment staging.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Anne Tsao, M.D., Phone: 713-792-6363 or E-mail: astsao@mdanderson.org or [redacted] M.D., Phone: [redacted] or Email: [redacted] For surgical questions, please contact [redacted] M.D., Phone: [redacted], or Email: [redacted]

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 Treatment Overview

Protocol treatment consists of the following:

a. Neoadjuvant therapy (see Section 7.2)

b. Surgery – extrapleural pneumonectomy or pleurectomy/decortication (see Section 7.3)

c. Radiation Therapy – ONLY for patients who received extrapleural pneumonectomy (see Section 7.4)

d. Maintenance therapy (see Section 7.5)

7.2 Neoadjuvant therapy (Registration Step 1)

a. Supportive care

The following supportive care for pemetrexed is **required**.

Agent	Dose	Route	Schedule
Folic Acid	400 mcg	PO	Daily; beginning 7 days before first dose of pemetrexed and continuing until 3 weeks after the last dose of pemetrexed
Vitamin B12	1,000 mcg	IM	q 9 weeks; beginning 7 days before first dose of pemetrexed and continuing until 3 weeks after the last dose of pemetrexed [a]
[a] i.e., if a scheduled vitamin B12 dose falls within 3 weeks following pemetrexed, it should be given.			

In addition, the following supportive care for pemetrexed and cisplatin is **recommended**.

Agent	Dose	Route	Schedule
Dexamethasone	4 mg [a]	PO twice per day	q 12 hours on the day before Day 1 of each cycle unless clinically contraindicated
Dexamethasone	12 mg	IV	Day 1 of each cycle
Dexamethasone	8 mg	PO twice per day	q 12 hours for three days starting 12 hours after chemotherapy completion
Fosaprepitant [b]	150 mg	IV	Day 1 of each cycle
Ondansetron [b]	8 mg	IV	Day 1 of each cycle
Ondansetron [b]	8 mg	PO three times per day prn	q 8 hours as needed for nausea/vomiting
Prochlorperazine	10 mg	PO four times per day prn	Q 6 hours as needed for nausea/vomiting; use in addition to ondansetron if continued nausea
[a] Higher or additional doses are permitted for reasons other than routine rash prophylaxis (e.g., antiemetic prophylaxis) [b] Or acceptable alternative			

Premedication is not permitted for the first dose of atezolizumab. Premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) may be administered for subsequent infusions at the discretion of the treating physician.

b. Neoadjuvant therapy treatment details

Agent	Dose	Route	Day	Schedule
Atezolizumab	1200 mg	IV	D1 of 21 day cycle	X 4 cycles
Pemetrexed	500 mg/m^2	IV	D1 of 21 day cycle	X 4 cycles
Cisplatin	75 mg/m^2	IV	D1 of 21 day cycle	X 4 cycles

* Note: One cycle = 21 days

Deliver the initial dose of atezolizumab over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes.

After completion of atezolizumab, administer pemetrexed over 10 minutes.

Thirty minutes after completion of pemetrexed infusion, administer cisplatin over 2 hours (±15) minutes.

c. Infusion Related Reactions (atezolizumab)

Administration of atezolizumab must be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

The management of Infusion Related Reactions will be according to severity as follows:

- In the event that a patient experiences a Grade 1 Infusion Related Reaction during Cycle 1, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.

- In the event that a patient experiences a Grade 2 Infusion Related Reaction, or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the Infusion Related Reaction. For subsequent infusions, administer oral premedication with antihistamine and anti-pyretic and

monitor closely for Infusion Related Reactions.

- For Grade 3 or 4 Infusion Related Reactions, the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated (*e.g.*, oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). Atezolizumab should be permanently discontinued. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event; retreatment requires consultation with, and consent of, the trial Principal Investigator (PI).

For anaphylaxis precautions, use the following procedure:

Equipment Needed

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

Procedures

In the event of a suspected anaphylactic reaction during atezolizumab infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observation.

7.3 Surgery (Registration Step 2)

Prior to protocol surgery, patients must meet all of the eligibility criteria listed in Section 5.2 and be registered to Step 2 via CTSU OPEN.

Surgery must occur between 21 and 90 days following the end of patient's final cycle of neoadjuvant therapy.

All patients will undergo surgical resection with the intent to provide macroscopic disease eradication, unless: (1) there is objective evidence of progression of disease; or (2) deterioration of functional status occurs following induction therapy, which is felt to significantly increase operative mortality/morbidity.

Extrapleural pneumonectomy (EPP) and pleurectomy/decortication (PD) will be treated as equal surgical techniques in terms of their ability to achieve macroscopic cytoreduction and shall be performed in all cases.

Recognizing that there are individual variations required in surgical technique from patient to patient and surgeon to surgeon, Appendix 18.3 describes a standardized recommended approach to the operation and intraoperative decision-making regarding choosing one approach over the other.

Decision to proceed with surgical therapy for mesothelioma will be based on comprehensive physiologic work up, and invasive disease staging performed prior to initiation of therapy and patient enrollment on this clinical trial.

7.4 Radiation Therapy

Patients who have extrapleural pneumonectomy (EPP) must receive radiation therapy as described in this section. Patients who have pleurectomy/decortication (PD) **will not** receive radiation therapy.

See Section 12.2 for information regarding radiation therapy review requirements, TRIAD, and credentialing.

There is substantial literature supporting the safety of radiation therapy after EPP. While historically this treatment has been delivered using conventional techniques, over the past decade experience has been building in numerous centers with intensity modulated radiation therapy (IMRT). Indeed, IMRT is now considered the standard technique in this context.

a. Radiation Simulation

All patients will be treated with IMRT. Patients will undergo a 4D simulation to assess for treatment motion. Simulation will occur with a customized cradle, with the arms above the head if tolerated. Bolus can be placed over drainage and incision sites, though placement of bolus is optional.

b. Radiation Treatment Volumes

The treatment volume will consist of the ipsilateral hemithorax. Mediastinal lymph nodes will only be included if involved with disease. Target volumes will be contoured as follows:

- Gross tumor volume (GTV)=gross disease with respiratory motion (if applicable).
- Circumferential margin around GTV = GTVmargin
- internal target volume (ITV) = ipsilateral hemithorax (CTV) plus motion, with the external boundary of the chest wall/ribs. Longitudinally, this volume typically covers from the thoracic inlet/T1 to approximately L1/L2, or the chest wall as defined by the 12th (final) rib. The volume will exclude the external skin surface. The ITV should also encompass the GTVmargin.
- planning target volume (PTV)=ITV plus 5 mm for setup variation if daily kV orthogonal imaging is utilized and 3 mm if daily CT is utilized.

Therefore, the following steps should be used to contour patients for this protocol.

1. Identify gross disease with respiratory motion, if applicable, and contour as GTV.
2. Define a margin of 0-5 mm around the GTV, label GTVmargin.
3. Delineate CTV=the ipsilateral hemithoracic pleura to encompass the external margin of the first to twelfth ribs as noted in the figure below (blue region). The volume should be shaved off of the spinal canal when necessary. The heart and mediastinum are not included, other than the

region of the pleura/pericardium that is on the ipsilateral hemithorax of the heart (see images below).
When bolus is placed, the ITV can be expanded to the region of the bolus. When delineating the CTV, ensure that it also encompasses the GTV margin. Below the diaphragm, the volume will be a crescent-shaped contour which will be manually expanded to cover the pleura to the sternum, the diaphragm, and the diaphragmatic crura to midline anteriorly and the paravertebral space superiorly.

4. ITV=CTV plus target volume motion.
5. Expand the ITV by 0-5 mm for the PTV. While a PTV margin of 3-5 mm is standard, in regions such as the pericardium, to minimize the dose to the heart, the investigator may elect to reduce or eliminate the PTV margin.

Daily IGRT with kV imaging or cone-beam CT is recommended. As with the ITV, the PTV will exclude the external skin surface.

All volumes should be verified through each cycle of the respiratory phase. Note that it is important to not solely use the maximum projection image (MIP) for delineation, particularly in the region near the diaphragm where the MIP images can obscure target volumes.

Figure 1: Example of ITV volume (blue) in a patient after EPP.

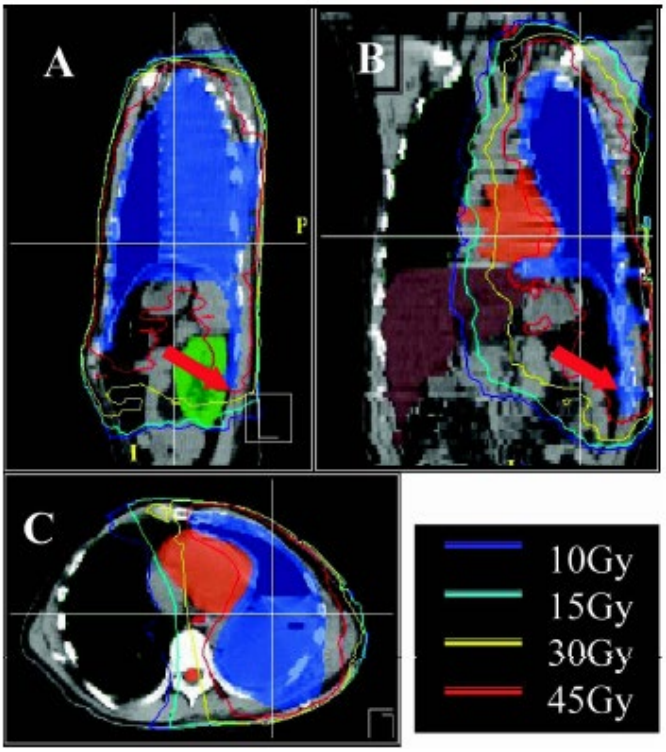
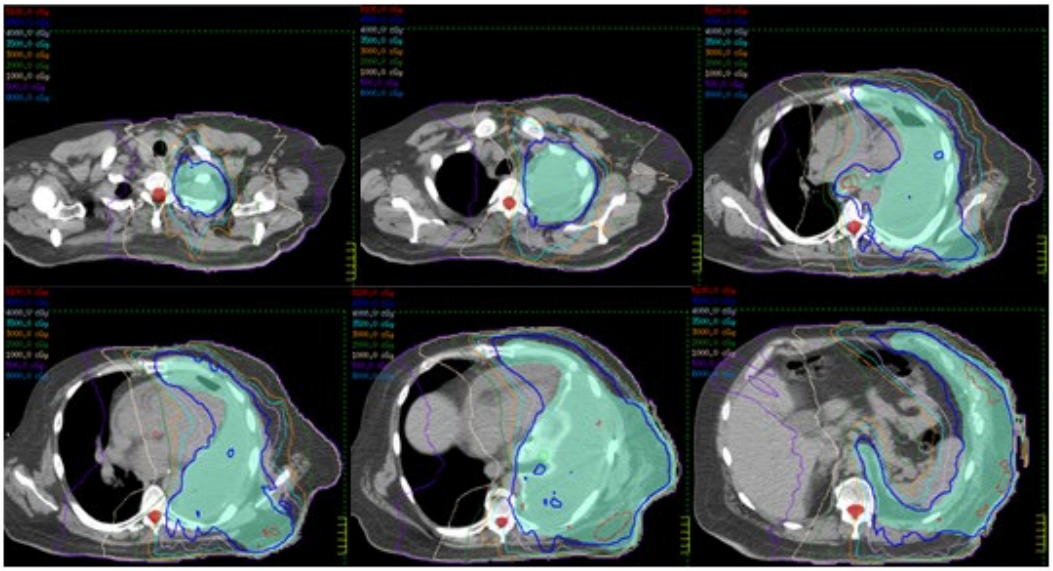


Figure 2: Cross-sectional examples of a patient with subcarinal involvement. The aqua volume depicts the PTV, which was expanded externally to the bolus.



c. Radiation Treatment Planning

Both static field IMRT and VMAT/arc therapy are acceptable techniques. For static field IMRT, 7-8 beams are typically used, equally distributed with a gantry angle separation of approximately 30 degrees. For VMAT/Arc therapy, 4 half arcs are commonly used, covering the ipsilateral side over approximately 200 degrees.

The required prescription dose to the PTV is 1.8 Gy x 28 = 50.4 Gy. However, dose de-escalation is allowed to 45 Gy to meet normal tissue constraints. In this case, RT would be given for 25 days. Note that while a simultaneous integrated boost (SIB) regimen has been explored in limited studies, for the purposes of this trial an SIB is not allowed. All patients should undergo daily orthogonal kV image guided radiation therapy (IGRT). Daily CT scanning is optional (cone beam CT) and if this IGRT technique is used, a PTV margin of 3 mm can be applied (vs. 5 mm for daily kV imaging).

The collapsed cone convolution algorithm for heterogeneity corrections will be used.

Target volume criteria and normal tissue dose constraints are below. All of these structures should be defined by the treating physician, to facilitate plan acceptability:

Target/Normal Structure	Standard Name	Criteria Value	Variation Acceptable	Deviation Unacceptable
Rx Dose		45-50.4 Gy in 1.8 Gy/fraction	None	<45 Gy in 1.8 Gy/fraction
GTV	GTV	D95 ≥95%	D95 90%≤D95<95%	D95<90%
ITV	ITV	D95 ≥95%	D95 85%≤D95<95%	D95<85%
PTV	PTV	D95 ≥95%	D95 85%≤D95<95%	D95<85%
Contralateral lung		V20≤8% Mean dose ≤8 Gy	None	Contralateral (e.g. total) lung V20>8% Contralateral lung mean dose >8 Gy
Esophagus	Esophagus	Mean dose ≤34 Gy	Mean dose >34 Gy	
Spinal cord (defined as spinal canal)	SpinalCord	Dmax≤50 Gy	None	Dmax>50 Gy
Heart	Heart	Right sided: V40≤25% Left sided: V40≤35%	Right sided meso: 25% < V40 ≤ 35% with mean dose ≤ 30 Gy Left sided meso: 35% < V40 ≤ 37% with mean dose ≤ 30 Gy	V_{30Gy} ≥ 50% D_{mean} ≥30 Gy
Left and Right Kidney	Kidneys	V18≤33%	V18>33%	V18>50%
Liver (not including the PTV)	Liver-PTV	Mean dose ≤30 Gy V30≤50%		Mean dose >30 Gy V30>50%
Stomach (not including PTV)	Stomach-PTV	Mean dose≤30 Gy Max dose≤50 Gy	Mean dose >30 Gy and ≤40 Gy	Mean dose >40 Gy Max dose >50 Gy
Bowel (upper abdomen, to include large and small bowel and inferiorly to 3 slices below the PTV)	Bowel	Dmax≤55 Gy D5cc≤50 Gy	D5cc>50 Gy and ≤55 Gy	D5cc >55 Gy

7.5 MAINTENANCE (Registration Step 3)

Prior to beginning maintenance therapy, patients must meet all of the eligibility criteria listed in Section 5.3 and be registered to Step 3 via CTSU OPEN.

Agent	Dose	Route	Day	Schedule
Atezolizumab	1200 mg	IV	D1 of 21 day cycle	X 1 year

* Note: One cycle = ***21*** days

For patients who had pleurectomy/decortication (PD), atezolizumab maintenance therapy will begin within 90 days after completion of surgery.

For patients who had extrapleural pneumonectomy (EPP) with or without radiation, atezolizumab maintenance therapy will begin within 90 days after completion of surgery or radiation therapy, whichever is last.

Maintenance atezolizumab is delivered as a flat dose 1200 mg IV over 60 minutes (+/- 15 minutes) every 3 weeks.

7.6 Full CDUS Reporting Requirement

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirements for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.4, the **S1619** Treatment Form, and the **S1619** Adverse Event Form). During neoadjuvant therapy and maintenance therapy, a cycle is defined as 21 days. Surgery +/- radiation therapy is considered one cycle.

7.7 Criteria for Removal from Protocol Treatment

a. Step 1: Neoadjuvant

1. Progression of disease by either RECIST 1.1 or by Modified RECIST for Pleural Tumors or symptomatic deterioration (as defined in Section 10.2).

2. Unacceptable toxicity.

3. Treatment delay for any reason > 2 weeks.

4. The patient may withdraw from the study at any time for any reason.

5. The patient receives less than two cycles of triplet neoadjuvant therapy (all three drugs).

6. Completion of neoadjuvant therapy.

b. Step 2: Surgery

7. Progression of disease by either RECIST 1.1 or by Modified RECIST for Pleural Tumors or symptomatic deterioration (as defined in Section 10.2).

8. Patient does not receive surgery for any reason (patient refusal, patient deemed inappropriate by attending surgeon, etc.).

9. Completion of surgery (+/- radiation).

c. Step 3: Maintenance

1. Progression of disease by either RECIST 1.1 or by Modified RECIST for Pleural Tumors or symptomatic deterioration (as defined in Section 10.2).

2. Unacceptable toxicity.

3. Treatment delay for any reason > 90 days.

4. The patient may withdraw from the study at any time for any reason.

5. Completion of maintenance therapy.

7.8 Discontinuation of Treatment

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

7.9 Follow-Up Period

All patients will be followed until death or 3 years after registration to Step 1, whichever occurs first.

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 Neoadjuvant Treatment (Atezolizumab, Pemetrexed, and Cisplatin)

a. General

For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes. When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.

If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment (i.e., atezolizumab, or cisplatin and/or pemetrexed if applicable) and the dose of that component is delayed or modified in accordance with the guidelines below, other components may be administered if there is no contraindication.

When treatment is temporarily interrupted because of toxicity caused by atezolizumab, cisplatin and/or pemetrexed (if applicable), the treatment cycles will

be restarted such that the atezolizumab (if applicable) infusions remain synchronized and aligned with the chemotherapy schedule.

If, in the opinion of the investigator, a toxicity is considered to be due solely to one chemotherapy drug, the dose of the other chemotherapy drug does not require modification.

The investigator may use discretion in modifying or accelerating the dose modification guidelines described below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care.

b. Atezolizumab

1. General guidelines

There will be no dose reduction for atezolizumab in this study.

Patients may temporarily suspend study treatment for up to 84 days (12 weeks) beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If atezolizumab is held because of AEs for > 84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in this protocol. If the AE resolves within 84 days and the patient is receiving corticosteroid therapy for the event, atezolizumab may be held for longer than 84 days (up to 4 weeks) in order to allow tapering of the steroid dose to ≤ 10 mg oral prednisone or equivalent.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the Study Chair in consultation with CTEP.

Atezolizumab must be **permanently discontinued** if the patient experiences any of the following events, regardless of benefit:

- Grade 4 pneumonitis
- AST or ALT >5×ULN or total bilirubin >3×ULN
- Grade 4 diarrhea or colitis
- Grade 4 hypophysitis
- Any grade myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis
- Grade 4 ocular inflammatory toxicity
- Grade 4 pancreatitis or any grade of recurrent pancreatitis
- Grade 4 rash
- Any grade myocarditis

Treatment may, under limited and compelling circumstances, be resumed in patients who have recovered from the following events, but only after consultation with the trial Study Chair:

- Grade 3 pneumonitis
- Grade 3 ocular inflammatory toxicity
- Grade 3 or 4 infusion-related reactions

Any toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most immune-related adverse events (irAEs) observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al., 2010). Discontinuation of atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. The investigator should consider the benefit-risk balance prior to further administration of atezolizumab.

For detailed information regarding management of adverse events associated with atezolizumab, please refer to the most current version of the Atezolizumab Investigator's Brochure and the FDA product label.

The primary approach to Grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab; for higher-grade irAEs, atezolizumab should be withheld and oral and/or parenteral steroids administered. Recurrent Grade 2 irAEs may also mandate withholding atezolizumab or the use of steroids. Assessment of the benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening irAEs.

Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to atezolizumab occurs at any time during the study, treatment with atezolizumab should be discontinued.

2. Systemic Immune Activation

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the Principal Investigator for additional recommendations.

3. Management of Specific Adverse Events (AEs)

Management of certain AEs of concern, including immune-related pneumonitis, hepatitis, colitis, endocrinopathies, pancreatitis, neuropathies, meningoencephalitis, and potential ocular toxicities are presented in the Atezolizumab Investigator's Brochure. See Section 7.2c for guidelines for the management of Infusion Related Reactions and Anaphylaxis.

Pleural and pericardial effusion

Patients experiencing dyspnea, chest pain, or unexplained tachycardia should be evaluated for the presence of a pericardial effusion. Patients with pre-existing pericardial effusion should be followed closely for pericardial fluid volume measurements and impact on cardiac function. When intervention is required for pericardial or pleural effusions, atezolizumab should be held, and appropriate workup includes cytology, lactate dehydrogenase (LDH), glucose, cholesterol, protein concentrations (with pleural effusions), and cell count.

Pulmonary events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in the table below.

Endocrine disorders

Patients experiencing one or more unexplained AEs possibly indicative of endocrine dysfunction (including fatigue, myalgias, impotence, mental status changes, and constipation) should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T3 and T4 levels should be obtained to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency. The table below describes dose management guidelines for hyperthyroidism, hypothyroidism, symptomatic adrenal insufficiency, and hyperglycemia.

Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from

potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines.

Neurologic disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies.

The table below presents management and dose modification guidelines for specific AEs. For recommendations to hold atezolizumab and begin corticosteroid treatment, use the following guidance for tapering the corticosteroid and resuming atezolizumab therapy after resolution of the event:

- Corticosteroids must be tapered over ≥1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- Atezolizumab may be held for a period of time beyond 12 weeks (up to four weeks) to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent.

AE Management and Dose Interruption Guidelines for Specific Toxicities

Toxicity	Severity/Duration	Management
Abdominal pain	Acute abdominal pain	Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests. See the guidelines for “Amylase and/or lipase increase” and “Immune-related

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/Duration**	**Management**
		pancreatitis" elsewhere in this table, as needed. Right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should be evaluated for potential hepatotoxicity (see the "Hepatotoxicity" guideline elsewhere in this table).
Adrenal insufficiency	Grade 2+ (symptomatic)	Hold atezolizumab. Refer patient to endocrinologist. Perform appropriate imaging. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to grade 1 or better and patient is stable on replacement therapy (if required) within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better or patient is not stable on replacement therapy within 12 weeks.
Amylase and/or lipase increased	Grade 1	Continue atezolizumab. Monitor amylase and lipase prior to dosing.
	Grade 2	Continue atezolizumab. Monitor amylase and lipase weekly.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/Duration**	**Management**
		For prolonged elevation (*e.g.*, >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
	Grade 3 or 4	Hold atezolizumab. Refer patient to gastrointestinal (GI) specialist. Monitor amylase and lipase every other day. If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, permanently discontinue atezolizumab.
Dermatologic toxicity/rash (*e.g.*, maculopapular or purpura)	Grade 1	Continue atezolizumab. Consider topical steroids and/or other symptomatic therapy (*e.g.*, antihistamines).
	Grade 2	Continue atezolizumab. Consider dermatologist referral. Administer topical corticosteroids. Consider higher potency topical corticosteroids if event does not improve.
	Grade 3	Hold atezolizumab. Refer patient to dermatologist. Administer oral prednisone 10 mg or equivalent. If the event does not improve within 48–72 hours, increase dose

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/Duration**	**Management**
		to1–2 mg/kg/day or equivalent. Restart atezolizumab if event resolves to grade 1 or better within 12 weeks. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks.
	Grade 4	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Otherwise, manage as above.
	Persistent and/or severe rash or pruritus, any grade	A dermatologist should evaluate the event. A biopsy should be performed unless contraindicated.
Diarrhea or colitis	Any grade	Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (*e.g.*, increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.
	Grade 1	Continue atezolizumab. Initiate symptomatic treatment. Endoscopy is recommended if symptoms persist for >7 days. Monitor closely.
	Grade 2	Hold atezolizumab. Initiate symptomatic treatment.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/Duration**	**Management**
		Patient referral to GI specialist is recommended. For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. Resumption of atezolizumab may be considered, after consultation with the trial PI, in patients who are deriving benefit and have fully recovered from the immune-related event.
	Grade 3	Hold atezolizumab. Refer patient to GI specialist for evaluation and confirmatory biopsy. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks. Resumption of atezolizumab may be considered, after consultation with the trial PI, in patients who are deriving benefit and have

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/Duration**	**Management**
		fully recovered from the immune-related event.
	Grade 4	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to GI specialist for evaluation and confirmation biopsy. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.
Hepatotoxicity	Right upper-quadrant abdominal pain and/or unexplained nausea or vomiting	Risk of immune-mediated hepatitis. LFTs should be performed immediately, and LFTs should be reviewed before administration of the next dose of study drug. For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should also include pancreatitis, as described below.
	Grade 1 hepatic event	Continue atezolizumab. Monitor LFTs until values resolve to within normal limits.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/Duration**	**Management**
	Grade 2 hepatic event, ≤5 days	Continue atezolizumab. Monitor LFTs more frequently until values resolve to baseline values.
	Grade 2 hepatic event, >5 days	Hold atezolizumab. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks.
	Grade 3 or 4 hepatic event	Permanently discontinue atezolizumab. Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.
Hyperglycemia	Grade 1 or 2	Continue atezolizumab. Initiate treatment with insulin if needed. Monitor for glucose control.
	Grade 3 or 4	Hold atezolizumab. Initiate treatment with insulin.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/Duration**	**Management**
		Monitor for glucose control. Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hyperthyroidism	Grade 1 (asymptomatic)	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** Continue atezolizumab. Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** Follow guidelines for symptomatic hyperthyroidism.
	Grade 2+ (symptomatic)	Hold atezolizumab. Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. Consider patient referral to endocrinologist. Resume atezolizumab when symptoms are controlled and thyroid function is improving. Permanently discontinue atezolizumab for life-threatening immune-related hyperthyroidism.
Hypothyroidism	Grade 1 (asymptomatic)	Continue atezolizumab. Start thyroid-replacement hormone. Monitor TSH weekly.
	Grades 2+ (symptomatic)	Hold atezolizumab. Start thyroid-replacement hormone. Consider referral to an endocrinologist. Monitor TSH weekly. Restart atezolizumab when symptoms are controlled and thyroid function is improving.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/Duration**	**Management**
Meningo-encepahlitis, immune-related (signs and symptoms in absence of an identified alternate etiology)	All grades	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to neurologist. Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
Myasthenia gravis and Guillain-Barré syndrome	All grades	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to neurologist. Initiate treatment as per institutional guidelines. Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.
Myocarditis	All grades	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit.
Neuropathy, immune-related (sensory and/or motor)	Grade 1	Continue atezolizumab. Evaluate for alternative etiologies.
	Grade 2	Hold atezolizumab. Evaluate for alternative etiologies. Initiate treatment as per institutional guidelines.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/Duration**	**Management**
		Resume atezolizumab if event resolves to grade 1 or better within 12 weeks. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks.
	Grade 3 or 4	Permanently discontinue atezolizumab. Initiate treatment as per institutional guidelines.
Ocular event (*e.g.*, uveitis, retinal events)	Grade 1	Continue atezolizumab. Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If symptoms persist, treat as a grade 2 event.
	Grade 2	Withhold atezolizumab. Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/Duration**	**Management**
	Grade 3 or 4	Permanently discontinue atezolizumab. Refer patient to ophthalmologist. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month. For grade 3 AEs, patient may only resume treatment after consultation with the trial PI; for grade 4, patient cannot resume treatment, regardless of benefit.
Pancreatitis, immune related	Grade 2 or 3	Hold atezolizumab. Refer patient to GI specialist. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. Patient may only resume treatment after consultation with the trial PI. For recurrent events, permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/Duration**	**Management**
	Grade 4	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to GI specialist. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.
Pulmonary toxicity	All pulmonary events	Evaluate thoroughly for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension.
	Grade 1	Continue atezolizumab and monitor closely. Re-evaluate on serial imaging. Consider patient referral to a pulmonary specialist. For recurrent pneumonitis, treat as a grade 3 or 4 event.
	Grade 2	Hold atezolizumab. Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage (BAL). Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/Duration**	**Management**
		If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, treat as a Grade 3 or 4 event.
	Grade 3 or 4	Permanently discontinue atezolizumab. Bronchoscopy or BAL is recommended. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month. For grade 3 AEs, patient may only resume treatment after consultation with the trial PI; for grade 4, patient cannot resume treatment, regardless of benefit.

c. Pemetrexed

The dose modification guidelines are applicable for pemetrexed used as a single agent or in combination with cisplatin or carboplatin.

Treatment with pemetrexed should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions or if treatment is delayed for more than 14 days due to toxicities (see table below).

1. Hematologic Toxicity

At the start of each cycle, the ANC must be ≥ 1500/mcl and the platelet count must be ≥ 100,000/mcL. Neoadjuvant treatment should be delayed for up to 14 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO)

and National Comprehensive Cancer Network (NCCN) guidelines. Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest (nadir) platelet and neutrophil values from the previous cycle (see table below).

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Table 1: Pemetrexed Dose Modification for Hematologic Toxicities

Toxicity [a]	Pemetrexed Dose
ANC < 500 cells/mcL and platelets ≥ 50,000/mcL	75% of previous dose
Platelets < 50,000/mcL, regardless of ANC	75% of previous dose
Platelets < 50,000/mcL with Grade ≥ 2 bleeding, regardless of ANC	50% of previous dose

[a]Nadir of prior cycle.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

If neoadjuvant chemotherapy must be withheld because of hematologic toxicity, full blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment then can be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the treating physician's institution's guidelines.

2. Non-Hematologic Toxicity

At the start of each cycle, the CRCL must be ≥ 45 mL/min. For enrollment and dosing decisions, CRCL will be estimated using the original, weight-based Cockcroft and Gault formula or measured using the appropriate radiolabeled method (51-CrEDTA or Tc99m-DTPA) to determine the GFR. The method of CRCL assessment used at baseline should be used throughout the study.

If a patient develops a non-hematologic toxicity (Table 2), pemetrexed should be withheld for up to 14 days until resolution to equal or less than the patient's baseline (or Grade ≤ 1 if patient did not have that toxicity at baseline). Treatment should be resumed according to the guidelines in Table 2.

Table 2: Pemetrexed Dose Modification for Non-Hematologic Toxicities

Toxicity	Pemetrexed Dose
Any diarrhea requiring hospitalization (irrespective of grade) or Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication	75% of previous dose
Neurotoxicity	
Grade 2	75% of previous dose
Grade 3 or 4	50% of previous dose or permanent discontinuation
Any other Grade 3 or 4 toxicities	75% of previous dose

For more details regarding pemetrexed dose modification, see the prescribing information for pemetrexed.

d. Cisplatin

Treatment with cisplatin should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions or if treatment is delayed for more than 14 days due to toxicities.

1. Hematologic Toxicity

At the start of each cycle, the ANC must be ≥ 1500/mcL and the platelet count must be ≥ 100,000/mcL. Neoadjuvant chemo treatment should be delayed for up to 14 days to allow sufficient time for recovery. Growth factors may be used in accordance with ASCO and NCCN guidelines. Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table 3).

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

If chemotherapy must be withheld because of hematologic toxicity, full blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment then can be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the treating physician's institution's guidelines.

Table 3: Cisplatin Dose Modification for Hematologic Toxicities

Toxicity [a]	Cisplatin Dose
ANC < 500 cells/mcL and platelets ≥ 50,000/mcL	75% of previous dose
Platelets < 50,000/mcL, regardless of ANC	75% of previous dose
Platelets < 50,000/mcL with Grade ≥ 2 bleeding, regardless of ANC	50% of previous dose
ANC < 1000/mcL plus fever of ≥ 38.5°C	75% of previous dose

[a] Nadir of prior cycle.

2. Non-Hematologic Toxicity

If a patient develops a non-hematologic toxicity (see Table 4) cisplatin should be withheld for up to 14 days until resolution to equal or less than the patient's baseline (or Grade ≤ 1 if patient did not have that toxicity at baseline). Treatment should be resumed according to the guidelines in Table 4.

Diarrhea should be controlled with adequate anti-diarrhea medication. Nausea and/or vomiting should be controlled with adequate anti-emetics.

Table 4: Cisplatin Dose Modification for Non-Hematologic Toxicities (Excluding Neurotoxicity)

Toxicity	Cisplatin Dose
Any diarrhea requiring hospitalization (irrespective of grade) or Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication	75% of previous dose
Grade 3 or 4 nausea/vomiting [a]	75% of previous dose
Any other Grade 3 or 4 toxicity	75% of previous dose

[a] Despite the use of anti-emetics.

3. Nephrotoxicity

CRCL must be 45 mL/min prior to the start of any cycle. If there is a decrease in CRCL between cycles, but the CRCL is still above 45 mL/min at time of next cycle, the treating physician should use his or her clinical judgment regarding continuing cisplatin, dose reduction, or delaying the cycle. If a patient's CRCL value has not returned to 45 mL/min within 21 days following last cisplatin administration, the patient must be discontinued from cisplatin.

4. Neurotoxicity

In the event of neurotoxicity, the recommended dose adjustment for cisplatin is documented in Table 5. For a Grade 3 or 4 neurotoxicity, cisplatin should be resumed at 50% of the previous dose upon improvement or discontinued immediately (based on investigator's clinical judgment).

Table 5: Cisplatin Dose Modification for Associated Neurotoxicity

Toxicity	Cisplatin Dose
Grade 0–1 neurotoxicity	100% of previous dose
Grade 2 neurotoxicity	75% of previous dose
Grade 3 or 4 neurotoxicity	50% of previous dose or permanent discontinuation

5. Ototoxicity

Audiogram should be obtained any time the patient experiences subjectively worsening hearing loss. If hearing impairment is ≥ CTCAE Grade 3, permanently discontinue cisplatin.

6. Non-Hematologic Toxicity

For a non-hematologic toxicity (see Table 4), treatment should be delayed for up to 14 days until resolution to less than or equal to the patient's baseline value (or Grade ≤ 1 if patient did not have that toxicity at baseline). Dose reductions at the start of the subsequent cycle will be made on the basis of non-hematologic toxicities from the dose administered in the preceding cycle. Table 4 provides the relevant dose adjustments for non-hematologic toxicities.

7. Potential Overlapping Toxicities

To date, the risk of overlapping toxicities between atezolizumab, cisplatin, and pemetrexed is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin, and gastrointestinal toxicity) may not be unambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with these chemotherapeutic agents (e.g., hepatotoxicity) could be exacerbated by the immunostimulatory activity of atezolizumab.

Toxicities should initially be managed according to the recommendations in Section 8.2b with dose holds and modifications (if applicable) applied to the component of the study drug judged to be the primary cause. For severe (Grade 3) or persistent Grade 1 or 2 diarrhea, an endoscopic evaluation should be considered. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology for adverse events listed above.

If, in the opinion of the investigator, atezolizumab is a potential inciting factor, the dose of atezolizumab may be withheld for a maximum of 7 days beyond when the next dose should have been given (see Section 8.2 b). Prompt symptomatic management is appropriate for mild immune-related adverse events. In severe cases, immune-mediated toxicities may be acutely managed with systemic corticosteroids or TNF-α inhibitors. These cases should be discussed with the Study Chair.

8.3 Maintenance (Atezolizumab)

There will be no dose reductions for atezolizumab in this study. In the maintenance setting, patients may temporarily suspend study treatment for up to 90 days beyond the last dose if they experience an adverse event that requires a dose to be withheld. If atezolizumab is withheld because of adverse events for more than 90 days beyond the last dose, then the patient will be discontinued from atezolizumab treatment and will be followed up for safety and efficacy.

If, in the judgment of the treating investigator, the patient is likely to derive clinical benefit from maintenance atezolizumab after a hold beyond 90 days, study drug may be restarted with the approval of the Study Chair.

If a patient must be tapered off steroids used to treat adverse events, maintenance atezolizumab may be withheld for additional time beyond 90 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Study Chair.

Dose interruptions for reason(s) other than adverse events, such as surgical procedures, may be allowed with Study Chair approval. The acceptable length of interruption will depend on agreement between the investigator and the Study Chair.

For additional information, see Section 8.2b.

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact Anne Tsao, M.D., Phone: 713-792-6363 or E-mail: astsao@mdanderson.org or [redacted], M.D., Phone: [redacted] or Email: [redacted]

8.5 Adverse Event Reporting

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

9.0 STUDY CALENDAR

9.1 Neoadjuvant (Registration Step 1)

	PRE-REG [A]	AFTER REG, PRIOR TO CYCLE 1	Cycle 1	Cycle 2	Cycle 3	*Cycle 4*	*At Step 1 Off Tx*	For patients not continuing on to registration Step 2	
			(Each cycle = 21 days)					Follow-Up Prior to Progression[J]	Follow-Up After Progression[K]
			Day 1	Day 1	Day 1	Day 1			
PHYSICAL									
History & Physical Exam	X		X	X	X	X	X	X	
Weight & Zubrod Performance Status	X		X	X	X	X	X	X	
Height	X								
Disease Assessment[B]	X				X		X	X	
Toxicity Notation	X		X	X	X	X	X	X[L]	X[L]
Baseline Abnormalities	X								
Vital signs[C]	X		X	X	X	X	X		
LABORATORY									
CBC/Diff/Platelets/Hgb	X		X[H]	X	X	X	X		
Creatinine and creatinine clearance	X		X[H]	X	X	X			
Total bilirubin, AST, and ALT	X		X[H]	X	X	X			
Hepatitis serology[D]	X								
TSH w/ Reflex Free T4			X[P]	X[P]		X[P]			

Calendar 9.1 continued on next page. Click here for footnotes.

	PRE-REG[A]	AFTER REG, PRIOR TO CYCLE 1	Cycle 1	Cycle 2	Cycle 3	Cycle 4	*At Step 1 Off Tx*	For patients not continuing on to registration Step 2	
			(Each cycle = 21 days)					Follow-Up Prior to Progression[J]	Follow-Up After Progression[K]
			Day 1	Day 1	Day 1	Day 1			
SCANS									
Audiogram[F]	X								
CT chest/abdomen with contrast, FDG-PET/CT Scan[B], or MRI for Disease Assessment	X[N]				X		X	X	
STAGING									
Mediastinoscopy or endobronchial ultrasound (EBUS)	X[G]								
Diagnostic laparoscopy	X								
Video-assisted thoracoscopic surgery	X								
SPECIMEN SUBMISSION									
Tumor Tissue for translational research		X							
Plasma and buffy coat for banking (if patient consents)		X					X		X[M]
TREATMENT									
Folic Acid		X	See Section 7.2a for schedule						
Vitamin B12		X							
Atezolizumab			X	X	X	X			
Pemetrexed			X	X	X	X			
Cisplatin			X	X	X	X			

Click here for footnotes.

Calendar 9.1 Footnotes:

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

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

A To be performed within 28 days prior to registration, except as otherwise indicated.

B Scanning method must meet diagnostic quality criteria in protocol Section 10.1.c. Disease assessments must be repeated every 6 weeks (+- 7 day window until registration to Step 2.

C Vital signs include the following: blood pressure, heart rate, oxygen saturation, respiratory rate.

D Hepatitis serology includes the following: HBsAg, HBcAb, and anti-HCV.

F Audiogram to be performed at baseline if patient requires hearing aids or reports hearing loss. Audiogram to be repeated while on cisplatin as clinically indicated (see Section 8.2.d.5).

G Mediastinoscopy / endobronchial ultrasound (EBUS)must be performed within 42 days prior to registration to Step 1.

H Does not need to be completed if pre-registration labs were performed within 14 days prior to Cycle 1 Day 1.

J After off treatment prior to progression, patients should be followed by repeating indicated tests every three months for the first year, then every six months for the second year, then at the end of year three from the date of Step 1 registration.

K After off treatment after progression, follow-up will occur every six months for two years, then at the end of year three from the date of Step 1 registration.

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

M Plasma and buffy coat submission optional at time of progression.

N For patients receiving adjuvant radiation therapy on Step 2, this baseline scan is part of the RT planning materials that must be submitted to IROC as detailed in Section 12.2.

P TSH with reflex free T4 to be performed prior to treatment on Cycle 1, at the end of Cycle 2, and at the end of Cycle 4.

9.2 Surgery +/- Radiation (Registration Step 2)

	PRE-REG (to STEP 2)	P/D or EPP	Adjuvant radiation treatment [D]	Post-Surgery/Radiation (At Step 2 Off Tx)[E]	For patients not continuing on to registration Step 3	
					Follow-up Prior to Progression / Relapse[F]	Follow-up After Progression / Relapse[G]
PHYSICAL						
History & Physical Exam	X		X	X	X	
Weight & Zubrod Performance Status	X (within 28 days prior to reg)		X	X	X	
Disease Assessment[A]	X (within 28 days prior to reg)				X	
Toxicity Notation	X			X	X[H]	X[H]
Vital signs[B]			X	X		
Consultation with surgeon	X					
Consultation with radiation oncologist [C]	X (within 14 days prior to reg)					
LABORATORY STUDIES						
CBC/Diff/ Platelets/Hgb	X			X		
CARDIOPULMONARY CLEARANCE TESTING						
Pulmonary function testing	X (within 28 days prior to reg)					

Calendar 9.2 continued on next page. Click here for footnotes.

	PRE-REG (to STEP 2)	P/D or EPP	Adjuvant radiation treatment [D]	Post-Surgery/Radiation (At Step 2 Off Tx)[E]	For patients not continuing on to registration Step 3	
					Follow-up Prior to Progression / Relapse[F]	Follow-up After Progression / Relapse[G]
SPECIMEN SUBMISSION						
Tumor Tissue for translational research		X				
Plasma and buffy coat for banking (if patient consents)						X[J]
SCANS						
CT chest/abdomen with contrast, FDG-PET/CT Scan[A], or MRI for Disease Assessment	X (within 28 days prior to reg)			X	X	

Calendar 9.2 Footnotes:

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.
NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

A Scanning method must meet diagnostic quality criteria in protocol Section 10.1.c.

B Vital signs includes the following: blood pressure, heart rate, oxygen saturation, respiratory rate.

C For patients planning to receive EPP. **Submit materials via TRIAD to IROC as detailed in Section 12.2.**

D For patients receiving EPP. Should be started no later than 45 days following surgery. See Section 7.4. **Submit materials via TRIAD to IROC as detailed in Section 12.2.**

E To be completed within 28 days following surgery (if no radiation) or radiation.

F After off treatment prior to progression/relapse, patients should be followed by repeating indicated tests every three months for the first year, then every six months for the second year, then at the end of year three from the date of Step 1 registration.

G After off treatment after progression/relapse, follow-up will occur every six months for two years, then at the end of year three from the date of Step 1 registration.

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

J Plasma and buffy coat submission optional at time of progression.

9.3 Maintenance (Registration Step 3)

	PRE-REGISTRATION (to STEP 3) [A]	Maintenance (every 21 days for up to 1 year)	Every 2 cycles for Up to 1 Year	At Step 3 Off Tx	Follow-up Prior to Progression / Relapse[E]	Follow-up After Progression / Relapse[F]
PHYSICAL						
History & Physical Exam	X		X	X	X	
Weight & Zubrod Performance Status	X		X	X	X	
Disease Assessment [B]	X		X	X	X	
Toxicity Notation	X	X		X	X[G]	X[G]
Vital signs [C]	X		X	X		
LABORATORY STUDIES						
CBC/ Diff/ Platelets/Hgb	X	X		X		
Creatinine and creatinine clearance	X	X		X		
Total bilirubin, AST, and ALT	X	X				
TSH w/ Reflex Free T4		X[P]				
SCANS						
CT chest/abdomen with contrast, FDG-PET/CT Scan [B], or MRI for Disease Assessment	X		X	X	X	
TREATMENT						
Atezolizumab		X [D]				
SPECIMEN SUBMISSION						
Plasma and buffy coat for banking (if patient consents)						X[H]

Click here for footnotes.

Calendar 9.3 Footnotes:

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.
NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

A To be completed within 28 days of step 3 registration.
B Scanning method must meet diagnostic quality criteria in protocol Section 10.1c. Disease assessments must be repeated every 6 weeks (+- 7 day window) while on treatment.
C Vital signs include the following: blood pressure, heart rate, oxygen saturation, respiratory rate.
D Must start within 90 days following completion of definitive surgery (P/D or EPP) or radiation.
E After off treatment prior to progression/relapse, patients should be followed by repeating indicated tests every three months for the first year, then every six months for the second year, then at the end of year three from the date of step 1 registration.
F After off treatment after progression/relapse, follow-up will occur every six months for two years, then at the end of year three from the date of step 1 registration.
G Assessments should continue until resolution of all acute adverse events.
H Plasma and buffy coat submission optional at time of progression.
P TSH with reflex free T4 to be performed prior to treatment on Cycle 1, at the end of Cycle 2, then after every two cycles while on maintenance.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

In this study, disease is to be assessed using both RECIST 1.1 and the Modified RECIST for Pleural Tumors. This means that pleural tumors must be assessed using BOTH methods. RECIST 1.1 criteria are outlined in Sections 10.1-10.2. In addition, modified RECIST measurements as determined by six pleural thickness measurements perpendicular to the chest wall are to be obtained and incorporated into determination of objective status as outlined in Section 10.5. For a practical guide to modified RECIST and RECIST measurements, please see Tsao et al. *(31)*

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. 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 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. Body scans should by performed with breath-hold scanning techniques, if possible.
2. 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 conventional CT.
3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.
4. 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.
5. 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 0.0cm 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, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. 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 Section 10.2f).

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.
2. 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.

e. **Relapse/Progression, Following Surgery**: 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.

f. **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.

g. **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.

h. 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.

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 Modified RECIST

Modified RECIST for Pleural Tumors: Response is to be assessed both via RECIST and also modified RECIST for pleural tumors. *(32)*

For RECIST 1.1, the definitions outlined in Section 10.1 must be followed. The longest diameter of the pleural lesion, as defined in Section 10.1a.1, must be recorded in the target lesion section of the RECIST and Modified RECIST Baseline Tumor Assessment Form (Form #35990) and the Follow Up Tumor Assessment Form-RECIST and Modified RECIST (Form #23757). If a longest diameter that fulfills the criteria outlined in Section

10.1a.1 cannot be obtained, then it should be recorded in the non-target lesion section of the respective forms.

In addition, for modified RECIST, measurements based on the sum of 6 CT cuts in the pleura perpendicular to the chest wall are to be obtained via the description below and applied (along with unidimensional measurements from other non-pleural lesions) to standard RECIST criteria (sum of 6 = one univariate diameter). The six pleural thickness measurements are to be documented on the Mesothelioma Baseline Tumor Assessment Form and the Mesothelioma Follow-Up Tumor Assessment Form.

Tumor thickness perpendicular to the chest wall or mediastinum should be measured in two positions at three separate levels on transverse cuts of the CT scan. The sum of the six measurements defines a pleural unidimensional measure. Transverse cuts at least 1 cm apart and related to anatomical landmarks in the thorax should be chosen to allow for reproducible assessment at later time points. If measurable tumor is present, transverse cuts in the upper thorax, above the level of the division of the main bronchi are preferred. At reassessment, pleural thickness should be measured at the same position at the same level and by the same observer. This is not necessarily the greatest tumor thickness at that level. Nodal, subcutaneous and other measurable lesions should be measured unidimensionally as per the RECIST criteria. Unidimensional measurements are added to obtain the total tumor measurement.

10.6 Progression-free survival by RECIST 1.1

From date of registration to Step 1 to date of first documentation of progression by RECIST 1.1 (defined in Section 10.2d), symptomatic deterioration (as defined in Section 10.2f), or death due to any cause. Patients last known to be alive and progression free are censored at date of last disease assessment.

10.7 Progression-free survival by Modified RECIST 1.1

From date of registration to Step 1 to date of first documentation of progression by modified RECIST 1.1 (defined in Section 10.5), symptomatic deterioration (as defined in Section 10.2f), or death due to any cause. Patients last known to be alive and progression free are censored at date of last disease assessment.

10.8 Relapse-Free Survival

From date of Step 2 registration to date of first documentation of relapse/progression (as defined in Section 10.2e), symptomatic deterioration (as defined in Section 10.2f), or death due to any cause. Patients last known to be alive and free of disease are censored at date of last disease assessment.

10.9 Time to Death

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

11.0 STATISTICAL CONSIDERATIONS

11.1 This study will evaluate the safety/tolerability and feasibility of neoadjuvant cisplatin-pemetrexed-atezolizumab, followed by surgery +/- radiation, followed by adjuvant maintenance atezolizumab

The accrual goal to this study is 24 eligible and evaluable patients, with a goal of 12 patients undergoing EPP and 12 P/D. A patient will be deemed evaluable if they receive

at least two cycles of the triplet neoadjuvant therapy (all three drugs). Patients who are not evaluable will be replaced. Both cohorts will be open in parallel. The regimen will be pursued in a future study if it satisfies **both** the safety and feasibility criteria.

The regimen will be considered safe and tolerable if no patients experience a Grade 4-5 immune-related adverse event. The following table describes the probability of observing Grade 4-5 non-hematologic toxicity or Grade 4-5 immune-related event if the true prevalence is 1%, 5%, or 10%.

Table 1: Probability of observing Grade 4-5 immune-related event

True Prevalence	1%	5%	10%
Probability at least one patient observed with an event:	21%	71%	92%

The regimen will be considered feasible if 18/24 (75%) patients receive at least one dose of maintenance therapy. Given data from other studies, the anticipated rate of patients receiving maintenance therapy is 70-80%. We would consider the observation of at least 18/24 to be evidence that maintenance therapy is feasible in this setting. With at least 18 patients receiving maintenance therapy following neoadjuvant cisplatin-pemetrexed-atezolizumab, estimates of the safety/tolerability of maintenance therapy have precision of 23.5% (95% CI width) and any toxicity with at least 10% prevalence has at least an 85% chance of being observed.

Analyses will separately evaluate patients who receive P/D and those who receive an EPP for their surgical procedure.

Survival outcomes (PFS, OS, mR-PFS) will be evaluated using the method of Kaplan-Meier. Confidence intervals around the median will be calculated using the Brookmeyer-Crowley method, confidence intervals around landmark time points will use the Greenwood formula for standard errors. With 24 evaluable patients, proportions (toxicity, response rate, landmark survival percentage) can be estimated within 20% with 95% confidence.

It is anticipated that a total of 28 patients will need to be registered in order to accrue 24 eligible and evaluable patients.

There is no formal Data and Safety Monitoring Committee for this study. Accrual reports are generated weekly and study-specific accrual monitoring is done by the Study Chair, Study Statistician and the Disease Committee Chair. Reports summarizing adverse events, serious adverse events (SAEs) and treatment administration are provided monthly to the Study Chair and Study Statistician for monitoring. In addition, all SAEs, which by definition require expeditious reporting, are reviewed and processed by the Adverse Event Coordinator at the SWOG Operations Office and a physician reviewer based on data provided via the NCI CTEP-AERS system. Cumulative study-specific SAE reports are provided to the Study Chair and Study Statistician upon occurrence of an event. Formal reports summarizing the study are prepared for all SWOG members every 6 months.

12.0 DISCIPLINE REVIEW

12.1 Surgery Review

Operative reports and a pathology report are to be submitted within 14 days after protocol surgery. The primary operative report and the SWOG Surgical Form will be reviewed by the Surgical Study Chair.

12.2 Radiation Therapy Review

a. Submission of Digital Radiation Therapy Data

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. This study uses TRIAD for RT data submission. Use of TRIAD requires several preliminary steps (see Section 12.2b). Additional information is available at:
http://triadhelp.acr.org/ClinicalTrials/NCISponsoredTrials.aspx

Use of SFTP will also be accepted as an alternate method of data submission on this study. See the instructions for submission of data via SFTP on the IROC Rhode Island website under Digital Data.

Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data.

One week prior to the start of radiotherapy, the following data must be submitted for pre-treatment review for all cases:

1. Treatment Planning System Output
   - RT treatment plans including CT from baseline in Step 1, structures, dose and plan files. These items are included in the digital plan.
   - Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. For all RT plans, a DVH shall be submitted for a category of tissue called “unspecified tissue.” This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.
   - Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
2. Supportive Data
   - Copies and reports of all imaging studies used to define the target volume.
   - Prescription sheet for entire treatment.
3. Forms
   - RT-1 Dosimetry Summary Form
   - Motion Management Reporting Form

Within 21 days after the completion of radiotherapy (Step 2), the following data must be submitted for all patients:

- The RT-2 Radiotherapy Total Dose Record Form
- A copy of the patient's radiotherapy record including the prescription, and the daily and cumulative doses to all required areas.
- Documentation listed above showing any modifications from the original submission.

Supportive data and forms may be included with the transmission of the digital RT data or submitted separately via e-mail to DataSubmission@qarc.org.

Questions regarding the dose calculations or documentation should be directed to:
Protocol Dosimetrist
IROC Rhode Island QA Center
Phone: (401) 753-7600

Email: physics@qarc.org

b. Digital RT Data Submission Using TRIAD

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

TRIAD Access Requirements:

Site staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account.

To submit digital RT data and images (DICOM and DICOM RT), the site user must be on the site's roster and be assigned the 'TRIAD site user' role. Users should contact the site's roster Administrator to request assignment of the TRIAD site user role.

TRIAD Installations:

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

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

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

c. Credentialing

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**	
	Treatment Modality	
	Photon	Key Information
Facility Questionnaire	x	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link.
Phantom Irradiation	x	An IMRT phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org).
IGRT	x	Only institutions interested **in using reduced margins** will be required to complete this credentialing step. Instructions for IGRT credentialing may be found on the

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**	
	Treatment Modality	
	Photon	Key Information
		IROC Houston website (http://irochouston.mdanderson.org).
Credentialing Status Inquiry Form	x	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org).
Credentialing Notification Issued to:		
Institution		Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and SWOG Headquarters that all desired credentialing requirements have been met.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

a. Step 1: Neoadjuvant

Patients must be registered prior to initiation of neoadjuvant therapy (no more than seven calendar days prior to planned start of treatment).

b. Step 2: Surgery

Patients must be registered prior to receiving surgery (no more than seven calendar days prior to surgery date).

c. Step 3: Maintenance

Patients must be registered prior to initiation of maintenance therapy (no more than seven calendar days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored clinical trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to

OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

b. CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

1. **IRB Approval:**

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572

- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

2. **Downloading Site Registration Documents:**

Site registration forms may be downloaded from the **S1619** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select trial protocol **S1619**
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

3. **Requirements for S1619 Site Registration:**

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- CTSU RT Facilities Inventory Form
  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Image and Radiation Oncology Core (IROC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

4. **Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

5. **Checking Your Site's Registration Status:**

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by

the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 888/823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

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

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see 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. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login

(https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

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

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

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

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. STEP 1: NEOADJUVANT

1. WITHIN 7 DAYS OF REGISTRATION TO STEP 1: NEOADJUVANT, SUBMIT:

S1619 Onstudy Form

Baseline Abnormalities Form

Mesothelioma Baseline Tumor Assessment Form

Pathology Report*

All reports from surgical staging*

Radiology reports from all scans performed to assess disease at baseline*

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

2. SUBMIT SPECIMENS:

Specimens as outlined in Section 15.0.

3. WITHIN 7 DAYS AFTER EACH CYCLE (1 CYCLE = 21 DAYS) OF NEOADJUVANT THERAPY, SUBMIT:

S1619 Neoadjuvant Treatment Form

S1619 Adverse Event Form

4. WITHIN 7 DAYS AFTER EACH DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION), SUBMIT:

   Mesothelioma Follow Up Tumor Assessment Form

   Radiology reports from all scans performed to assess disease at follow up*

   *NOTE: Upload these reports via the Source Documentation: Follow Up form in Rave®

5. WITHIN 21 DAYS OF DISCONTINUATION OF NEOADJUVANT THERAPY SUBMIT:

   Off Treatment Notice

   S1619 Neoadjuvant Treatment Form

   S1619 Adverse Event Form

6. WITHIN 14 DAYS OF PROGRESSION ON NEOADJUVANT THERAPY, SUBMIT:

   Mesothelioma Follow Up Tumor Assessment Form

   Lung Carcinoma First Site(s) of Progression or Relapse Form

   Radiology reports from all scans performed to document progression*

   If the patient was off treatment, also submit **S1619** Follow Up Form

   *NOTE: Upload these reports via the Source Documentation: Follow Up form in Rave®

b. STEP 2: SURGERY

   1. WITHIN 7 DAYS OF REGISTRATION TO STEP 2: SURGERY, SUBMIT:

      S1619 Surgery Eligibility Form, confirming patient's eligibility for surgery

      Mesothelioma Follow Up Tumor Assessment Form

      Radiology reports from all scans performed to assess disease at follow up*

      All reports from pulmonary function tests*

      *NOTE: Upload these reports via the Source Documentation: Follow Up form in Rave®

   2. SUBMIT RADIATION THERAPY REVIEW MATERIALS:

      Submit radiation therapy materials via TRIAD as described in Section 12.2

3. WITHIN 30 DAYS OF COMPLETION OF SURGERY, SUBMIT:

S1619 Adverse Event Form**

Lung Carcinoma Surgeon's Post-Operative Assessment Form

Operative Report from Surgery*

Pathology Report from Surgery*

*NOTE: Upload these reports via the Source Documentation: Follow Up form in Rave®

**Only for patients who received P/D.

4. WITHIN 30 DAYS OF COMPLETION OF RADIATION THERAPY, IF APPLICABLE, SUBMIT:

Lung Carcinoma Radiation Therapy Form

S1619 Adverse Event Form**

Radiation Summary Note*

*NOTE: Upload these reports via the Source Documentation: Follow Up form in Rave®

**Only for patients who received EPP + RT

c. STEP 3: MAINTENANCE

1. WITHIN 7 DAYS OF REGISTRATION TO STEP 3: MAINTENANCE, SUBMIT:

S1619 Maintenance Therapy Eligibility Form

S1619 Disease Assessment Form

Radiology reports from all scans performed to assess disease at follow up*

*NOTE: Upload these reports via the Source Documentation: Follow Up form in Rave®

2. WITHIN 7 DAYS AFTER EACH CYCLE OF MAINTENANCE THERAPY (1 CYCLE = 21 DAYS) UP TO 1 YEAR, SUBMIT:

S1619 Maintenance Treatment Form

S1619 Adverse Event Form

3. WITHIN 7 DAYS AFTER EACH DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION/RELAPSE), SUBMIT:

S1619 Disease Assessment Form

Radiology reports from all scans performed to assess disease at follow up*

*NOTE: Upload these reports via the Source Documentation: Follow Up form in Rave®

4. WITHIN 21 DAYS OF DISCONTINUATION OF MAINTENANCE THERAPY, SUBMIT:

Off Treatment Notice

S1619 Maintenance Treatment Form

S1619 Adverse Event Form

5. WITHIN 14 DAYS OF PROGRESSION/RELAPSE ON MAINTENANCE THERAPY, SUBMIT:

S1619 Disease Assessment Form

Lung Carcinoma First Site(s) of Progression or Relapse Form

Radiology reports from all scans performed to document progression/relapse*

*NOTE: Upload these reports via the Source Documentation: Follow Up form in Rave®

d. APPLY TO ALL REGISTRATION STEPS

1. ONCE OFF STUDY, EVERY 3 MONTHS FOR FIRST YEAR, THEN EVERY 6 MONTHS FOR THE SECOND YEAR, THEN AT THE END OF YEAR 3, SUBMIT:

Lung Carcinoma Follow Up Form

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

2. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH, SUBMIT:

Notice of Death.

If the patient was still on protocol treatment, also submit the forms listed in Section 14.4a.5 (if on neoadjuvant therapy) or Section 14.4c.5 (if on maintenance therapy).

If the patient was off treatment, also submit the Lung Carcinoma Follow-Up Form.

15.0 SPECIAL INSTRUCTIONS

15.1 Specimens for Translational Medicine and Banking

a. Tumor Tissue (MANDATORY for patient)

Tissue must be collected at two time points: (1) pre-registration; and (2) protocol surgery.

Within 14 days after registration and again within 14 days after surgery, submit a paraffin-embedded tissue block containing 10% normal buffered formalin fixed tumor. Please note that only 10% normal buffered formalin fixation is acceptable for tissue submission. Cytology (e.g. fine-needle aspirations, pleural effusion specimens) can be accepted only if they are paraffin embedded as cell blocks, positive for malignant cells, and provide sufficient number of required blocks or slides. Submission of blocks is strongly encouraged. However, if blocks are unavailable, submit ALL of the following:

- Two H&E slides
- 14-20 FFPE slides (5-7 microns) per timepoint

Refer to the general labeling, packaging, and shipping instructions at https://www.swog.org/member-resources/biospecimen-resources and ship to Lab #201 (SWOG Biospecimen Bank - Solid Tissue, Myeloma, and Lymphoma Division - see the Specimen Tracking System).

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

These specimens will be used for the translational medicine studies described in Section 18.2. Any tissue remaining after testing will be banked and, with additional patient consent, may be used for future unspecified research.

b. Plasma and Buffy Coat (OPTIONAL for patient)

With patient consent, blood must be collected at three time points: (1) before beginning neoadjuvant treatment; (2) after completing neoadjuvant treatment; and (3) at progression.

Follow the procedures below for processing plasma and buffy coat. DO NOT use the processing instructions from the SWOG website.

At each time point, draw approximately 10 mL blood in 1-2 lavender (EDTA) tubes. Place blood on wet ice immediately after collection and process as soon as possible (preferably within 2 hours). Centrifuge vacutainer tubes at approximately 800 x g for 10 minutes (preferably in a refrigerated centrifuge, if available). Immediately after centrifugation, carefully transfer plasma to a new 15 mL conical tube using a pipette and being careful not to aspirate the interface between the plasma and the platelets (buffy coat layer). Set aside original purple top tubes for later processing. Then centrifuge plasma a second time at 1200 x g for 10 minutes. After the second centrifugation, aliquot plasma in 500 mcl aliquots into 6-10 labeled 1.8-2.0 ml cryovials, being careful not to disturb the pellet in the bottom of the tube. The buffy coat, a whitish layer of cells between the plasma and red blood cell layers, should be collected from the original purple top tube(s) and transferred into 2 labeled 1.8-2.0 ml cryovials (contamination with RBC not a concern). Freeze cryovials immediately and store at or below -70° until shipped to the SWOG Biospecimen Bank on dry ice.

Refer to the general labeling, packaging, and shipping instructions at http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp and ship to Lab #201 (SWOG Biospecimen Bank - Solid Tissue, Myeloma, and Lymphoma Division - see the Specimen Tracking System).

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

Plasma and buffy coat will be banked and used for future unspecified research.

15.2 SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org). Non-SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

Lab #201: SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201
Phone: 614/722-2865
Contact: SWOG Repository Coordinator
Email: bcpbal@nationwidechildrens.org

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. 46, No. 17, January 27, 1981, part 50) 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 (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) 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.

Publication and Industry Contact

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") 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 Agent in this study:

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) 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 Collaborator(s), 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 Collaborator(s) 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 Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) 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)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) 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 Collaborator(s). 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 protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31.

   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 Adverse Event Reporting Requirements

a. Purpose

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

b. Reporting Method

This study requires that expedited adverse events be reported 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. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1).

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

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301/897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

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

d. Other recipients of adverse event reports

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

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

e. **Expedited reporting for investigational agents**

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

Table 16.1:
Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] atezolizumab, cisplatin, and pemetrexed

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

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

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

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or [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 3, 4, and Grade 5 AEs

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

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 and Early Phase 2 Studies Utilizing an Agent under a CTEP-IND:**

1. **Group-specific instructions**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the SWOG Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical sourced documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Statistics and Data Management Center, copies of Off Treatment Notice and/or Notice of Death.

2. **Adverse Events of Special Interest in Atezolizumab Studies**

The following AEs are considered of special interest in patients receiving atezolizumab and must be reported expeditiously through CTEP-AERS, irrespective of regulatory seriousness criteria:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, hyperthyroidism, hypophysitis, and adrenal insufficiency
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, systemic immune activation, or infusion-related reactions
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis

g. Reporting Secondary Malignancies, 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.

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

- Leukemia secondary to oncology chemotherapy (e.g., Acute

Myelocytic Leukemia [AML])

- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

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

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

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

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

   A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

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

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

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

h. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

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

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

2. **Pregnancy loss Pregnancy loss defined in CTCAE as "Death in utero." should be reported expeditiously, as Grade 4 "Pregnancy**

loss" under the Pregnancy, puerperium and perinatal conditions SOC.

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

   A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

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

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

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

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18.0 APPENDIX

18.1 New York Heart Association Functional Classifications

18.2 Translational Medicine Studies and Instructions for SWOG Biospecimen Bank

18.3 Surgical Guidelines

18.4 Autoimmune Serious Adverse Events and URLs

18.1 New York Heart Association Functional Classifications

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 Translational Medicine Studies and Instructions for SWOG Biospecimen Bank

Malignant pleural mesothelioma (MPM) is an orphan disease that is difficult to treat. *(1)* In early stage disease, patients can be resectable. However, it is clear that multi-modality therapy is essential to increase survival outcomes. *(2,3,4)* Mesothelioma is considered an immunogenic disease and it is surmised that the addition of a PD-L1 inhibitor to cisplatin-pemetrexed in the neoadjuvant setting would be clinically beneficial for our patients. However, little is known about the immunologic phenotype in mesothelioma and additional translational research is needed.

Inhibition of programmed death 1 (PD-1) protein, a T-cell co-inhibitory receptor, and its ligand PD-L1 has been shown to restore T-cell activity and lead to a subsequent anti-tumor effect in several tumor types. *(5,6,7,8)* In non-small cell lung cancer, response rates ranging between 10% to 26% have been reported using these PD-L1 inhibitors as monotherapy in Phase I and II trials. *(9,10,11)* In general, although nivolumab was FDA approved without a prerequisite biomarker, it is widely surmised that patients with PD-L1 immunohistochemical (IHC) expression are more likely to have improved response rates and survival. Preliminary data suggest that response to atezolizumab across multiple indications is associated with PD-L1 expression in the tumor microenvironment by IHC as well as with markers of Th1 cells in tumor tissue by gene expression. *(12,13)* There is little data on the IHC expression patterns in mesothelioma. As discussed in the protocol, it is known that mesothelioma tumors have PD-L1 IHC expression in cell membranes, but less data is known about the microenvironment.

Mansfield et al. reported a 40% PD-L1 IHC expression in pleural mesotheliomas (n=224) using a mouse monoclonal anti-human B7-H1 (clone 5H1-A3). *(14,15)* A score of <5% IHC expression was considered negative. PD-L1 IHC expression was associated with more disease burden and less offers of surgery to the patient. Also, PD-L1 IHC expression was associated with a worse survival 6 months vs 14 months, p<0.0001). *(16)* However, little is known about the mesothelioma PD-L1 IHC expression after treatment with immunotherapy.

Experimental approach, validated assays employed and expertise of PIs:

PD-L1
We will evaluate all of the enrolled patients at 2 time points for PD-L1 IHC expression – at the time of VATS and at the time of definitive resection (EPP/PD). We hypothesize that patients with higher levels of PD-L1 IHC will have improved survival outcomes with the addition of atezolizumab to their trimodality or bimodality therapy.

To investigate PD-L1 expression, Dr. [redacted]'s lab will utilize the Dako 22C3 PD-L1 pharmDx assay. The Hirsch Biomarker Analysis Laboratory is CLIA certified. PD-L1 IHC will be evaluated in tumor cell cytoplasm and/or membrane staining of infiltrating lymphocytes. Standard IHC parameters will be used. Tumor specimens will be batch stained.

The Dako 22C3 PD-L1 pharmDx assay is a qualitative immunohistochemical assay using mouse monoclonal anti-PD-L1 clone 22C3 intended for use in the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) using the EnVision FLEX visualization system on the Link 48 autostainer. SK00621-5 50 tests PD-L1 protein expression is determined using the Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity (≥ 1%). Patients will be considered high PD-L1 IHC expressers if the TPS is ≥ 50%. These will be the cutoffs used for the initial translational

correlate endpoint, given that most trials in mesothelioma have been utilizing this antibody and these cutoffs.

The FDA approved PD-L1 Dako 22C3 pharmDx kit will be used for staining all specimens. Use of this kit requires operation with the manufacturer's automated protocol and does not allow any changes to be made by the user. This ensures accurate and reproducible PD-L1 staining as identified in the manufacturer's FDA approval. PD-L1 expression in mesothelioma has been reported in several studies and therefore, preliminary staining is not required. *(17,18,19)* Each staining run will include an in-run control slide provided by Dako containing the FFPE cell lines MCF-7 (PD-L1 negative) and NCD-H226 (PD-L1 positive). In addition, the Hirsch Lab has added a pre-qualified section of tonsil shown to express PD-L1. This custom control slide is reviewed by both the histotechnologist and pathologist within the Hirsch lab and scored by both the primary and QC pathologist. Data from multiple staining runs are compared to ensure staining consistency.

Immune Nanostring panels

Further tissue will be collected to analyze RNA expression of immune related genes. Only limited data on the expression of immune genes have been generated in mesothelioma to date, however thorough investigations are ongoing in NSCLC. The Nanostring immune panel has been utilized in solid tumor samples obtained from patients enrolled into clinical trials delivering atezolizumab. *(20,21,22,23)* For NSCLC, data generated with this assay have been presented at multiple conferences since 2013 and have led to the identification of a 8-gene T effector immune signature that is potentially predictive for response to atezolizumab in NSCLC; however detailed validation and confirmation of this hypothesis are currently ongoing in NSCLC. *(24)* The Nanostring immune panel will assess the RNA expression of immune-related genes.

Extensive RNA expression profiling of immune-related genes will be assessed by Genentech's Immune Nanostring panel. The Nanostring panel is optimized to assess expression of ~800 genes, including PD-L1 and markers of Th1, Th2, myeloid, DC and NK cells, in RNA isolated from FFPE tumor specimens. This approach has been validated on solid tumors obtained from clinical trials delivering Atezolizumab. The GNE nanostring panel includes 784 targets related to multiple aspects of immunologic function and cancer biology. In terms of immunologic function, the panel includes markers that can identify T-cell subsets such as Th1, Th2, and Tregs; myeloid subsets such as MDSC, monocytes/macrophages, B-cells, and NK cells. The panel also includes markers associated with activated signal transduction in solid tumors such as those in the MAPK and PI3K pathways, DNA damage response, and EMT.

Multiplex Immunofluorescence (IF) Analysis

Dr. [redacted] laboratory will conduct multiplex immunofluorescence analysis of up to 10 immune markers, 2 panels, at MD Anderson Cancer Center. Currently, there are 2 Vectra panels optimized: Panel#1, CD3, CD4, CD8, CD68, PD-L1, pan-cytokeratin and DAPI; Panel #2, PD-1, CD45RO, FOXP3, Granzyme B, CD57, pan-cytokeratin and DAPI. For the multiplex IF analysis, we will use the Opal chemistry and multispectral microscopy Vectra system (Perkin-Elmer) which includes the Nuance software; analysis will be performed using the InForm software. The appropriate cellular localization of the markers and the type of cells that express the markers will be taken into account when scoring them, e.g. PD-L1 is scored only on cells with membranous staining. For quantification of immune markers (immune cells infiltrates, immune checkpoints and other proteins) whole tissue sections or five randomly selected one-mm square areas within the tumor region will be selected for analysis. The expression of markers in malignant cells will be evaluated using image analysis to determine the percentage of positive cells (0 to 100) and intensity

(0 to 3+), with a total score ranging from 0 to 300 (H-score system). The intensity is classified as 0 (absent), 1 (weak apparently only on 100x magnification), 2 (moderate apparent on 50x magnification), and 3 (strong apparent on 16x magnification). This scoring system provides criteria that can be reproduced more consistently by pathologists. The expression of protein markers and inflammatory cells will be examined using an infiltrate density score established by the number of cells expressing a determined marker by tissue area. The data and digital images will be available for sharing.

Biomarker Evaluation

Blood samples will be obtained for future biomarker evaluation (including but not limited to biomarkers that are related to mesothelioma or tumor immune biology) from all eligible patients pre and post-neoadjuvant therapy and at time of progression. Samples will be processed to obtain plasma and buffy coat for the determination of changes in blood-based biomarkers (e.g., ctDNA). Whole blood samples may be processed to obtain their derivatives (e.g., RNA and DNA) and evaluated for immune-related, tumor type related, and other exploratory biomarkers (e.g., alterations in gene expression or single nucleotide polymorphisms).

Translational Medicine Analyses

The SWOG Biospecimen Bank will bank the tumor tissue from baseline and also the resected specimen. Peripheral blood will also be collected at these two time points and possibly at time of progression and banked with the SWOG Biospecimen Bank for future analysis. When the study is completed, tumor tissue will be distributed to Dr. [redacted]'s laboratory [redacted] for PD-L1 IHC, Dako 22C3, and Genentech for the Nanostring gene expression analysis, and Dr. [redacted] laboratory (Houston, Texas) for immunofluorescence analysis.

It is assumed that 20 of the 24 patients will have sufficient tissue for these analyses.

Statistical analyses will be conducted to evaluate the association between clinical outcomes (progression free survival, modified RECIST progression free survival, overall survival, response rate) and PD-L1 expression levels, RNA expression levels, and Multiplex Immunofluorescence measurements. The focus will be on genes with a known role in the PD-1/PD-L1 pathway, the T effector signature as determined in NSCLC patients, as well as additional genes identifying T cell subsets such Th1, Th2, Tregs, myeloid subsets such as MDSC, monocytes / macrophages, B-cells, and NK cells.

Data analysis performed by:

SWOG Statistics and Data Management Center

Testing Performed by:

PD-L1 IHC on baseline and resected mesothelioma specimens
Dr. [redacted]
Univ of Colorado Cancer Center
PO Box 6511, MS 8117
Aurora, CO 80045
Phone: [redacted]
Email: [redacted]

Immune nanostring panel on baseline and resected tumor specimens
Covance Genomics Laboratory
9911 Willows Rd NE, suite 175
Redmond, WA 98052

Phone: 425-979-5000

Tumor Immunofluorescence Analysis on baseline and resected tumor specimens
Dr. [redacted]
MD Anderson Cancer Center
2130 W Holcombe Blvd
Unit 2951, LSP9.4029
Houston, TX 77030
Phone: [redacted]
Email: [redacted]

Instructions for SWOG Biospecimen Bank

Tumor tissue blocks from baseline (archived specimens allowed) and resection will be obtained. At baseline, it is anticipated that 1-2 tissue blocks will be available. At time of resection, we anticipate 3-4 tissue blocks will be created.

a. 2-3 Tumor slides (5-7 microns) will be obtained from the tumor tissue blocks and stained for PD-L1 immunohistochemistry by Dr. [redacted] labs.

b. Dr. [redacted] will require 8 slides each from baseline and also the resected specimen to support the analysis as follows:

   i. H&E: 1 slide
   ii. Immunofluorescent analysis: 7 slides (5-7 microns) sections

c. Genentech will require 11 sections each from baseline and also the resected specimen, to support the analysis as follows:
   i. H&E: 1 slide
   ii. Gene expression (Nanostring) 10 sections (5-7 microns). Genentech is looking to extract at least 500 ng of RNA (as assessed by Ribogreen)

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18.3 Surgical Guidelines

Perioperative and post-operative pain control will be at the discretion of surgeons and anesthesia teams. Both epidural analgesia or rib infiltration with long acting local anesthetic, such as liposomal bupivacaine will be acceptable.

After induction of general anesthesia patient will be intubated with a double lumen endotracheal tube. Intraoperative monitoring includes use of a central venous pressure line, arterial line and a pulse oximeter. The patient is then placed in the lateral decubitus position and operative side is prepped and draped in the usual sterile manner. The patient's hemithorax is approached via an extended posterolateral thoracotomy incision through the 6th or 7th interspace, and the anterior part is taken down towards the costal margin to facilitate exposure to the hemidiaphragm. The 7th rib maybe removed to facilitate extrapleural dissection and later diaphragm reconstruction. An additional parallel incision at the 9th or 10th intercostal space posteriorly may be used, but is not recommended and generally not required for diaphragmatic resection. The parietal pleural tumor is mobilized away from the chest wall in the extrapleural plane, carrying the dissection to the apex of the hemithorax superiorly down to the diaphragm inferiorly, to the sternum anteriorly and to the spine posteriorly. Previous thoracoscopy and thoracotomy sites used previously for biopsy purposes may be excised but this is not necessary because of the postoperative radiation administered in this study. The chest retractor is inserted and dissection is continued circumferentially in the extrapleural plane, mobilizing the parietal and mediastinal pleural tumor back to the hilum in all directions. Once this has been accomplished, attention is turned to the diaphragmatic resection. The diaphragmatic tumor is mobilized along with the partial or full thickness of the diaphragm. Care is taken not to violate the underlying peritoneum. While not possible in all cases, preservation of the peritoneum is preferred, and therefore any tears in the peritoneum should be closed. Dissection of the diaphragmatic tumor and diaphragm is carried from the lateral toward the medial aspect back to the pericardium, and then up on the pericardium to the level of the inferior pulmonary vein. For right-sided resections, care should be taken to identify the small branches of the front vessels which drain from the diaphragm into the inferior vena cava and to ligate and divide those branches.

Following complete mobilization of the tumor and lung in the extrapleural plane, resection of the diaphragm and portion of the pericardium, nodal sampling/dissection should be performed from the following nodal stations: on the right side: level 4R,7, 8R, 9R, 10R, internal mammary, and any visible intercostal lymph nodes if possible. On the left side: level 5, 6, 7, 8L, 9L, 10L, plus internal mammary lymph nodes, and any visible intercostal lymph nodes if possible. Frozen section should be sent from each nodal station for intra-operative staging purposes.

If all lymph nodes come back negative (N0 status), and patient's physiologic status would tolerate pneumonectomy, it is acceptable to proceed with EPP. However, if any of the nodes come back positive, it is advisable to proceed with PD rather than EPP. However, this decision will be left up to the treating surgeon.

Examination of the N1 lymph nodes (stations 10-14) within the resected specimen should be requested from the pathologist. To proceed with EPP, once the mainstem bronchus has been mobilized, it should be ligated with a stapling device and divided. Phrenic nerve is usually divided during the mobilization of diaphragm resection. The vagus nerve should be preserved. The hilar vessels can then be ligated and divided, again with vascular stapling devices. Resection of the pericardium is not required if the pleural tumor can be mobilized away from the pericardium completely. Pericardial resection for complete resection of all gross tumor should be performed as required. Pericardial resection is most safely accomplished at the time of division of the hilar vessels. Tacking sutures should be placed

on the anterior border of pericardial resection to prevent retraction of the pericardium toward the contralateral hemithorax as the pericardial resection is performed. The pericardial defect can be reconstructed with either an absorbable (Dexon) or non-absorbable (preferably Gortex) patch. Non-absorbable material is required for diagrammatic and pericardial replacement left sided resections. Either absorbable or non-absorbable material can be used for the right sided diaphragmatic reconstruction. The selection of the reconstructive material will be at surgeon's discretion. The prosthetic diaphragmatic patch is secured in place to the rim of remaining diaphragm along the pericardium medially. Care should be taken to secure this appropriately to and around the esophagus to prevent postoperative intrathoracic herniation of abdominal contents at that level. Posteriorly the prosthetic patch is secured to the endothoracic fascia. Laterally, it is secured with sutures placed around the ribs. The prosthetic patch should be placed as low as possible to mimic the normal position of the diaphragm. Therefore, the lateral sutures should be placed around the 8th, 9th and 10th ribs. This is particularly important to reduce the radiation exposure of the liver on the right and the stomach on the left during postoperative adjuvant radiotherapy. Hemostasis in the operated hemithorax is facilitated by use of cautery, argon beam coagulator, aquamentys device, or topical hemostatic agents.

If PD is chosen as an operative approach, the steps of the procedure are identical to EPP, with the exception of leaving the lung in situ. After the tumor, lung, and diaphragm are completely mobilized, the visceral pleura is stripped from the lung parenchyma. Hemostasis is again achieved with available devices, and small bronchial injuries are over sewn or stapled to decrease the postoperative air leak. Reconstruction of the diaphragm and pericardium are performed on the same manner as for EPP. Chest cavity is then inspected to ensure there is no evidence of any visible tumor. **Surgeon should document in the operative note, his or her impression of the completeness of surgical resection (R1 versus R2).**

It is preferable to completely remove all visible tumor. Any intra-operative thermal ablation techniques, photodynamic therapy, intra-operative heated chemotherapy are not permitted.

At the end of the procedure a chest tube is inserted which is then placed to balanced drainage (such as a pneumonectomy Pleur-Evac). Reinforcement of the bronchial stump with a pericardial fat pad may be used but is not required. Use of an intercostal muscle flap for this purpose is not recommended. The thoracotomy incision is closed in the usual manner, but care should be taken to achieve a completely watertight seal during the closure. It is particularly important to achieve good approximation and watertight closure of the intercostal muscles to prevent pleural fluid from leaking out of the hemithorax in the immediate postoperative period. The chest tube is usually left in place for up to 72 hours following EPP and as needed following PD, until the pleural fluid draining through the chest tube has become serous or serosanguinous, rather than bloody, and the air leak has resolved.

Perioperative antibiotic coverage should be provided according to institutional guidelines. This may include the entire length of time that the chest tube is in place. Perioperative anti-arrhythmia prophylaxis may be considered according to institutional guidelines.

In the instance where exploration reveals disease that cannot be completely resected, the operation should be aborted, and the reasons for abandoning the surgery documented (example: chest wall invasion, invasion of the esophagus, spine, heart or great vessels). Other common reasons for un-resectability include diffuse invasion of tumor through the endothoracic fascia, extrathoracic subcutaneous disease in discontinuous sites, direct extension of tumor though the diaphragm or metastatic disease involving the peritoneum which is not suspected preoperatively by imaging studies. Postoperative pathway and care will be at the discretion of individual surgeons.

18.4 Autoimmune Serious Adverse Events and URLs

The NCI CTCAE defines autoimmune at this URL:

https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=CTCAE&ns=ctcae&code=E11258

The NCI CTCAE defines immune system disorders at this URL:

https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=CTCAE&ns=ctcae&code=E13871