NRG ONCOLOGY

NRG-LU006

(ClinicalTrials.gov NCT #04158141)

PHASE III RANDOMIZED TRIAL OF PLEURECTOMY/DECORTICATION PLUS SYSTEMIC THERAPY WITH OR WITHOUT ADJUVANT HEMITHORACIC INTENSITY-MODULATED PLEURAL RADIATION THERAPY (IMPRINT) FOR MALIGNANT PLEURAL MESOTHELIOMA (MPM)

Amendment 2: April 13, 2022

NRG ONCOLOGY

NRG-LU006
(ClinicalTrials.gov NCT #04158141)

PHASE III RANDOMIZED TRIAL OF PLEURECTOMY/DECORTICATION PLUS SYSTEMIC THERAPY WITH OR WITHOUT ADJUVANT HEMITHORACIC INTENSITY-MODULATED PLEURAL RADIATION THERAPY (*IMPRINT*) FOR MALIGNANT PLEURAL MESOTHELIOMA (MPM)

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and SWOG.

Coordinating Center:
NRG Oncology
Four Penn Center; 1600 JFK Blvd; Suite 1020; Philadelphia, PA 19103

Study Team (15-MAR-2022)

Principal Investigator/Radiation Oncology Andreas Rimner, MD Memorial Sloan Kettering Cancer Center Department of Radiation Oncology 1275 York Ave. New York, NY 10065 212-639-6025/Fax: 929-321-7153 Rimnera@MSKCC.ORG	Radiation Oncology Co-Chair Charles B. Simone, II, MD Department of Radiation Oncology New York Proton Center 225 East 126th Street New York, NY 10035 646-968-9012 csimone@nyproton.com
Surgical Oncology Co-Chair Valerie W. Rusch, MD Memorial Sloan Kettering Cancer Center Department of Surgery 1275 York Ave New York, NY, 10065 212-639-5873/Fax: 646-422-2086 ruschv@MSKCC.ORG	Medical Oncology Co-Chair Marjorie G. Zauderer, MD Memorial Sloan Kettering Cancer Center Department of Medicine 1275 York Avenue New York, NY 10065 646-888-4656 zauderem@MSKCC.org
Radiology Co-Chair Ritu R. Gill, MD Beth Israel Deaconess Medical Center Department of Radiology 330 Brookline Avenue Boston, MA 02215-5400 rgill@bidmc.harvard.edu	Medical Physics Co-Chair Ellen Yorke, PhD Memorial Sloan Kettering Cancer Center Department of Medical Physics 1275 York Ave New York, NY, 10065 212-639-8637 yorkee@mskcc.org

Study Team continued

Proton Physics Co-Chair Xiaoying Liang, PhD, DABR Mayo Clinic 4500 San Pablo Rd. S. Jacksonville, FL 32224 904-957-0456 Liang.xiaoying@mayo.edu	QOL Co-Chair Khinh Ranh Voong, MD MPH Sidney Kimmel Cancer Center Johns Hopkins Bayview 300 Mason Lord Dr. Baltimore MD, 21224 410-367-3205/Fax: 410-550-6598 kvoong1@jhmi.edu
Translational Science Co-Chair Tobias Peikert, MD Mayo Clinic Cancer Center Division of Pulmonary and Critical Care Medicine, 200 First Street Rochester, MN 55901 507-284-4162 Peikert.Tobias@mayo.edu	Pathology Co-Chair Ming S. Tsao, MD University Health Network, Princess Margaret Cancer Center 101 College St., 11th floor Toronto, ON M5G 1L7, Canada 416-634-8721 Ming.Tsao@uhn.ca
Lead Statistician Chen Hu, PhD NRG Oncology Statistical and Data Mgmt Ctr & John Hopkins Univ School of Medicine 50 South 16th Street, Ste. 2800 Philadelphia, PA 19102 215-940-4842/Fax: 215-928-0153 HuC@NRGOncology.org	

NRG ONCOLOGY
NRG-LU006

STUDY CHAMPIONS (15-MAR-2022)	
ECOG-ACRIN Champion John Varlotto, MD Department of Radiation Oncology Edwards Cancer Center – Marshall University 1400 Hal Greer Blvd. Huntington, WV 25701 304 399 6501/Fax: 304 399 6528 varlotto@marshall.edu	Alliance Champion Jeremy Brownstein, MD Department of Radiation Oncology Ohio State University 460 W. 10th Ave., Ste. A206 Columbus, OH 43210 614-293-8415/Fax: 614-293-4044 Jeremy.Brownstein@osumc.edu
SWOG Champion Robert Samstein, MD, PhD Department of Icahn School of Medicine Mount Sinai 1470 Madison Avenue, PO Box 208032 New York, NY 10029 212-241-4173 robert.samstein@mountsinai.org	

NRG Oncology Contact Information (15-MAR-2022)	
Data Management For questions concerning eligibility or data submission	Matthew Novak and Tammy Bausinger NRG Oncology 50 South 16th Street, Ste. 2800 Philadelphia, PA 19102 215-574-3211 (Novak) / 215-574-3223 (Bausinger) NovakM@NRGOncology.org BausingerT@NRGOncology.org
RTQA For questions concerning RT data submission	Jennifer Presley, B.S., R.T.(R)(M)(T) IROC Philadelphia – RT QA Center ACR Center for Research and Innovation 50 South 16th Street, Ste. 2800 Philadelphia, PA 19102 215-574-3153 jpresley@acr.org
RT Credentialing	http://irochouston.mdanderson.org OR IROC-Credentialing@mdanderson.org
RT data submission to TRIAD	Triad-Support@acr.org
Protocol Development: For questions concerning protocol and informed consent versions & amendments	Fran Bradley NRG Oncology 50 South 16th Street, Ste. 2800 Philadelphia, PA 19102 215-940-8893/Fax: 215-928-0153

	BradleyF@NRGOncology.org
Lung Committee Chair	Jeffrey D. Bradley, MD Department of Radiation Oncology Emory University School of Medicine Winship Cancer Institute Atlanta, Georgia 30322 404-778-3630 jeffrey.d.bradley@emory.edu

Protocol Agent

Agent	**Supply**	**NSC #**	**IND #**	**IND Sponsor**
Cisplatin	Commercial	119875	Exempt	N/A
Carboplatin	Commercial	241240	Exempt	N/A
Pemetrexed	Commercial	698037	Exempt	N/A

Participating Sites (15-MAR-2022)
☒ U.S.
☒ Canada
☒ Approved International Member Sites

Document History

	Version Date
Amendment 2	**April 13, 2022**
Amendment 1	March 15, 2022
Initial	January 2, 2020

<table>
<tr><td colspan="3">CONTACT INFORMATION (15-MAR-2022)</td></tr>
<tr><td>For regulatory requirements:</td><td>For patient enrollments:</td><td>For data submission:</td></tr>
<tr><td>Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select Regulatory > Regulatory Submission.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org, to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.</td><td>Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

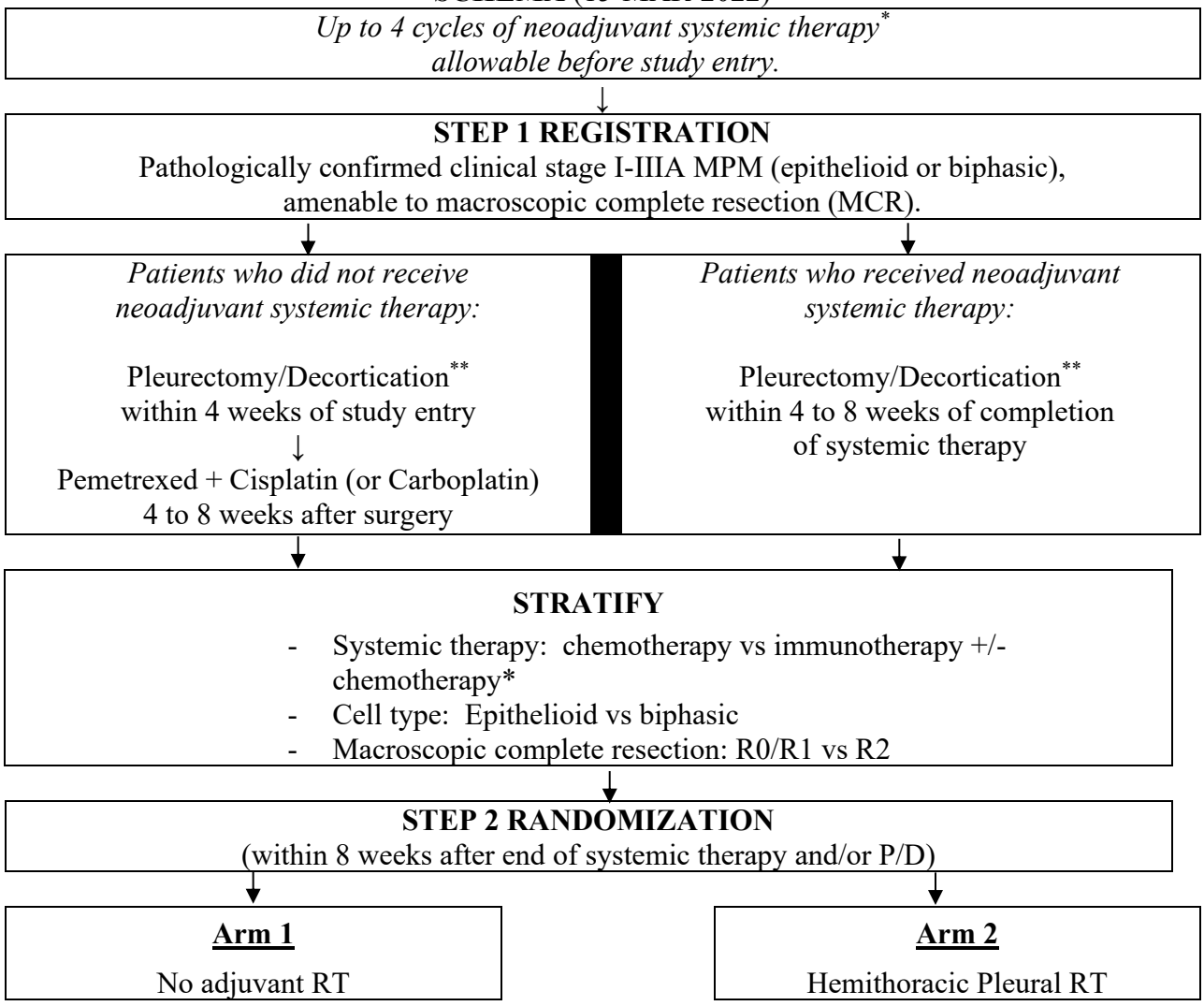
Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log in with CTEP-IAM username and password.</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e. patient eligibility or treatment-related)</u> Contact the Study PI of the Lead Protocol Organization.</td></tr>
<tr><td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> 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.</td></tr>
</table>

TABLE OF CONTENTS

NRG ONCOLOGY
NRG-LU006

PHASE III RANDOMIZED TRIAL OF PLEURECTOMY/DECORTICATION PLUS SYSTEMIC THERAPY WITH OR WITHOUT ADJUVANT HEMITHORACIC INTENSITY-MODULATED PLEURAL RADIATION THERAPY (*IMPRINT*) FOR MALIGNANT PLEURAL MESOTHELIOMA (MPM)

SCHEMA (15-MAR-2022)



* Acceptable neoadjuvant systemic therapy options before study entry: 1) cisplatin/carboplatin + pemetrexed; 2) cisplatin/carboplatin + pemetrexed + anti-PD-1/L1 agents; or 3) ipilimumab/nivolumab

** Pleurectomy/Decortication (P/D) to be performed with the goal of a macroscopic complete resection (MCR).

Randomization will be 1:1 to both arms. **NOTE:** Patients who cannot be randomized will be considered as having completed participation in NRG-LU006, and no additional data will be collected.

Required Sample Size: 150 patients

1. OBJECTIVES

1.1 Primary Objective (15-MAR-2022)

To detect an improvement in overall survival with the addition of adjuvant hemithoracic IMPRINT to surgery and systemic therapy compared to surgery and systemic therapy alone.

1.2 Secondary Objectives (15-MAR-2022)

- To determine local failure-free survival, distant-metastases-free survival, and progression-free survival with the addition of adjuvant hemithoracic IMPRINT to surgery and systemic therapy compared to surgery and systemic therapy alone.
- To evaluate the treatment-related toxicities in both arms per CTCAE v5.0.
- To detect a clinically meaningful 10-point change in global health status mean scores at 9 months after randomization with the addition of adjuvant IMPRINT as compared to surgery and systemic therapy alone.

1.3 Exploratory Objectives (15-MAR-2022)

- To evaluate the degree of under-staging, concordant and upstaging between centrally-reviewed clinical staging (based on PET, CT and/or MRI) and pathologic staging.
- To identify immunologic and pathologic biomarkers as predictors of response and potential targets for future combination trials.
- To determine the magnitude of radiation dose escalation to gross residual disease based on combined modality imaging and associated local control rates with dose-painting IMRT.
- To determine the rate of R0/R1 and R2 resections, and type of procedures (extended Pleurectomy/Decortication (P/D), P/D and partial pleurectomy).
- To evaluate the trajectory of EORTC QLQ-Q30 and LC13 symptoms in patients treated with IMPRINT by comparing the proportion of patients who respond with "quite a bit" or "very much" LC13 symptoms at 9-12 months post-randomization compared to at 3 months post-randomization.
- To evaluate changes in health-related quality of life, functional domains, and symptoms over time with the addition of adjuvant IMPRINT as compared to surgery and systemic therapy alone.
- To evaluate the prognostic values of center patient volume (≤10 versus >10 P/D/year) and systemic therapy type (Chemotherapy versus Immunotherapy).
- To optimize quality assurance methodologies and processes for radiotherapy and imaging with machine learning strategies.

2. BACKGROUND

2.1 Pleurectomy/Decortication and Adjuvant Conventional Hemithoracic Radiation Therapy

This study builds on the promising initial experience with this novel pleural IMRT technique that was developed at MSKCC (Rosenzweig et al., 2012 and Rimner et al., 2016) as well as the preliminary results of the ongoing expanded multicenter phase II study of chemotherapy +/- pleurectomy/ decortication (P/D) followed by IMRT (NCT00715611). Since one of the greatest issues with malignant pleural mesothelioma is

poor local disease control, much effort has focused on harnessing radiation to improve this. Historically, extrapleural pneumonectomy (EPP) has been the standard surgical procedure for MPM. However, locoregional recurrences still occur in up to 80% despite this aggressive resection. A phase II study performed at MSKCC demonstrated that the addition of 54 Gy of conventional hemithoracic RT could decrease that risk to 13% (Rusch et al., 2001). This study was followed by a multicenter phase II study that tested the combination of neoadjuvant cisplatin/pemetrexed followed by EPP and adjuvant hemithoracic radiation therapy (Krug et al., 2009). This approach led to a median survival of 16.6 months and a 2-year survival of 34%. However, EPP is associated with significant morbidity and mortality risks.

P/D is an alternative lung-sparing surgical approach that involves a complete pleural resection but leaves the ipsilateral lung intact. A multi-institutional retrospective study initiated at MSKCC found on multivariable analysis that the adjusted hazard rate for death from EPP was 1.4 when compared to P/D (Flores et al., 2008). While not powered for an overall survival endpoint, the adjusted hazard rate in a recent randomized trial of EPP versus no resection was found to be 2.75 (Treasure et al., 2011). While these studies indicate a potential survival advantage or at least no disadvantage of less extensive surgery, P/D potentially results in a less complete resection. Local failure of MPM in the chest is the major cause of morbidity and mortality in patients treated with lung-sparing treatment approaches. The extent of macroscopic resection appears to be of prognostic importance. Therefore, combination with additional local treatment modalities such as radiation therapy may significantly decrease the risk for locoregional recurrences. This paradigm was previously tested by adding adjuvant conventional radiation therapy to P/D. The results were disappointing, with a median overall survival of 13.5 months and one-year actuarial local control of 42%. In addition, this treatment was associated with a significant risk for radiation pneumonitis, including two patients with grade 5 toxicity (Gupta et al., 2005). Therefore, conventional radiation therapy cannot be delivered to patients with two intact lungs after P/D without an excessive risk of radiation pneumonitis.

2.2 **Systemic Therapy** (15-MAR-2022)

Conventional systemic therapy

Until recently, the standard of care for systemic therapy for patients with resectable MPM was platinum-pemetrexed for up to 4 cycles of therapy (Vogelzang 2003).

Immunotherapy

Single-agent immunotherapy

There is now evidence for activity of immunotherapy in MPM. The first data on the safety and activity of pembrolizumab in MPM were demonstrated in KEYNOTE-028 which showed 20% grade 3 toxicities and a durable median response duration of 12 months (Alley 2017). The majority of patients (72%) had stabilization of their disease, including 20% with a partial response. The Japanese phase 2 MERIT study demonstrated an objective response rate of 29% with a median response duration of 11.1 months and a 68% disease control rate. (Okada 2019) The MAPS2 trial found a 12-week disease control in 44% of patients with nivolumab alone. (Scherpereel 2019) In the JAVELIN

trial single-agent avelumab achieved an objective response rate of only 9%, but with a median duration of response of 15.2 months and disease control rate of 58%, indicating the ability of even single-agent immunotherapy to achieve durable responses in a subset of patients. (Hassan 2019)

Dual checkpoint inhibition (ipilimumab/nivolumab)
In the second open-label non-comparative randomized of the MAPS2 trial the combination of ipilimumab plus nivolumab showed promising results of 12-week disease control in 50% of patients (Scherpereel 2019), This was followed by the CheckMate 743 trial that compared first-line ipilimumab/nivolumab with standard platinum/pemetrexed chemotherapy in newly diagnosed mesothelioma patients (Baas 2021), This trial showed an OS benefit with a median OS of 18.1 months with ipilimumab-nivolumab versus 14.1 months with chemotherapy (HR 0.74, p=0.002). Patients with biphasic or sarcomatoid histology benefitted the most with this particular dual checkpoint immunotherapy combination, while epithelioid patients derived a smaller benefit.

Combination systemic therapy plus immunotherapy
The field of systemic therapy for MPM is currently very dynamic with several ongoing trials that may further establish the role of immunotherapy in multiple settings. Many ongoing efforts explore the combination of chemotherapy and immunotherapy, with some studies already completed. The DREAM (durvalumab in combination with first-line chemotherapy in mesothelioma) trial already demonstrated the safety of combination chemo-immunotherapy with a median progression-free survival of 6.2 months. Of the 54 patients followed for 6 months 46% achieved a partial response (Nowak 2020). PrE0505 enrolled 55 patients with combination of durvalumab and chemotherapy and demonstrated a median overall survival of 20.4 months. Fifty-six percent achieved partial response and 40% achieved stable disease (Forde 2020). The promising results of the DREAM3R and PrE0505 trials led to the design of the DREAM3R trial (NCT04334759) which will study the addition of durvalumab to cisplatin/pemetrexed.

Additional studies on the role of chemo-immunotherapy include a Canadian Cancer Trials Group study (NCT02784171) that evaluates the addition of pembrolizumab to platinum/pemetrexed chemotherapy. The BEATMeso trial (NCT03762018) investigates the addition of atezolizumab to platinum/pemetrexed/bevacizumab. These studies are likely going to further change the landscape of systemic treatment options for patients with MPM in the near future.

As several neoadjuvant chemotherapy/immunotherapy combinations are commonly being delivered in the community, these will be permissible prior to study entry. On study only adjuvant platinum/pemetrexed will be delivered in patients who have not received neoadjuvant therapy.

2.3 Hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) (15-MAR-2022)
Consequently, a novel, highly conformal IMRT technique has been developed to treat the ipsilateral pleura with maximal sparing of the ipsilateral and contralateral lungs (Figure

1) (Rimner et al., 2012). Initially it was shown that this treatment technique was associated with a 20% risk of ≥ grade 3 radiation pneumonitis, which appears acceptable in this high-risk patient population and is comparable to pneumonitis risks for locally-advanced non-small cell lung cancer (Rosenzweig et al., 2012). In resectable MPM patients (n=20), the 2-year overall survival rate of 53% was very promising, with a median survival of 26 months.

A phase II trial at MSKCC and MDACC showed that out of 27 patients only 6 developed grade 2 and only 2 developed grade 3 radiation pneumonitis with no grade 4 or 5 radiation-related toxicities observed (Rimner, Zauderer et al., 2016). The median progression-free and overall survival was 12.4 and 23.7 months, respectively. Thus, hemithoracic IMPRINT was deemed feasible and safe for selected centers with significant expertise. Currently this approach is being tested in a multicenter phase II study to examine the safety and exportability of this approach in a total of 5 centers (NCT00715611).

Figure 1
Example of an adjuvant IMRT plan after P/D to a total dose of 48.6 Gy (Rimner et al., 2012).

This randomized phase III study, NRG-LU006, builds on this experience to date, with the goal to establish the IMPRINT technique as an essential component of a lung-sparing trimodality treatment approach. Therefore testing the impact of adjuvant IMPRINT in a randomized fashion is required to lead to a change in the standard of care for operable patients of P/D and systemic therapy alone.

2.4 Rationale for a randomized phase III study on IMPRINT (15-MAR-2022)

This trial is important because there is currently neither a uniform radiation field design/dose/technique to treat patients with MPM nor an established role of adjuvant hemithoracic IMPRINT. Most will agree that there is a role for maximal surgical debulking of MPM, and studies have suggested that a macroscopic complete resection is associated with prolonged outcomes in patients with MPM. The role of chemotherapy with cisplatin and pemetrexed is clearly established as the standard systemic therapy.

With the increasing use of lung-sparing P/D there is a need for improved locoregional control, as patients remain at high risk for local failure after lung-sparing P/D, despite frequently being the optimal surgical approach. The orthotopic presence of the ipsilateral lung represents a formidable challenge to the ability to deliver adjuvant radiation therapy without exceeding normal tissue dose constraints, especially the dose to the lungs. A new IMRT technique has been established that targets the entire hemithoracic pleura at risk for recurrence while avoiding the underlying ipsilateral lung tissue.

A review of the current literature of the outcomes of P/D reveals that there is significant heterogeneity in the reported outcomes between studies. The endpoints are calculated from various time points, i.e. surgery, randomization, or diagnosis; patients of a variety of stages and histologic subtypes are included; adjuvant and neoadjuvant therapies are usually not specified or not accounted for, follow up is variable in terms of intervals between follow up visits and length of follow up. Overall survival has been reported to range from 7.1 months to 23 months, with the average across studies being about 12 to 15 months. Outcomes of pleural IMRT have primarily been published by Memorial Sloan Kettering Cancer Center (MSKCC) and a cancer center in Aviano, Italy. To date, the reported OS from surgery or the start of RT have been very encouraging, ranging from 18 to 33 months. It is therefore suggested that pleural IMRT may be associated with an overall survival benefit, possibly related to the ability to deliver a higher radiation dose than with conventional techniques and increased dose homogeneity with a lesser risk for areas of underdosing.

Should this phase III trial result in an overall survival benefit associated with the use of IMPRINT, it would establish the multimodality approach of P/D, systemic therapy and adjuvant hemithoracic pleural IMRT as a new standard treatment paradigm for MPM.

The phase II study utilized an induction chemotherapy approach in order to maximize resectability as well as patient selection for surgery and radiation therapy (Rimner, Zauderer et al., 2016). However, the response rate to induction chemotherapy was less than anticipated with 29% (n=13) partial responses among 27 evaluable patients. There were 15 patients (33.3%) who even progressed during induction chemotherapy, thus potentially having missed an opportunity for optimal tumor debulking and resection. While induction chemotherapy will be permitted, this study will preferentially use surgical resection as the initial treatment step followed by adjuvant chemotherapy and randomization to hemithoracic IMPRINT versus no IMPRINT. The prospective phase II study on the safety of adjuvant IMPRINT in combination with neoadjuvant chemotherapy +/- P/D showed a low rate of ≥ grade 3 radiation pneumonitis, with only two out of 27 evaluable patients having experienced grade 3 pneumonitis. Six patients developed grade 2 pneumonitis. All eight patients with radiation pneumonitis had resolution of their symptoms after standard management with systemic steroids. No grade 4 or 5 toxicities of any kind were observed. A failure pattern analysis of an expanded series of patients treated with this IMPRINT approach at MSKCC revealed that the majority of failures occur at sites of previous gross disease, with local failure being the first site of failure in 30% of patients (Rimner et al., 2014). This indicates that (1) completeness of surgical resection is critical, and (2) a higher radiation dose to sites of gross residual disease may

be necessary to achieve higher local control rates in the pleural space. Therefore, this study allows a simultaneous integrated boost (SIB) using "dose-painting" IMRT to areas of gross residual disease without exceeding normal tissue constraints.

3. PATIENT ELIGIBILITY AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

Inclusion of Women and Minorities
NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

3.1 Eligibility Criteria (15-MAR-2022)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to STEP 1 REGISTRATION – ALL PATIENTS

3.1.1 Pathologically (histologically or cytologically) confirmed diagnosis of epithelioid or biphasic MPM;

3.1.2 Imaging proof of clinical stage (AJCC 8th edition) I-IIIA MPM by PET/CT at diagnosis;
- Diagnostic volumetric CT scan of the chest is preferred; however, the CT portion of the PET/CT may be used if CT imaging is of diagnostic quality.

3.1.3 MPM is amenable to resection by P/D as determined by a thoracic surgeon;

3.1.4 History/physical examination within 42 days prior to Step 1 Registration;

3.1.5 Age ≥ 18;

3.1.6 ECOG Performance Status 0-1 within 42 days prior to Step 1 Registration;

3.1.7 Required Initial Laboratory Values prior to study entry (must be at least 14 days after last infusion of pre-study entry neoadjuvant therapy, if given):
- Absolute neutrophil count ≥1500 cells/$mm^{3;}$
- Platelets ≥100,000 cells/$mm^{3;}$
- Hemoglobin ≥ 8.0 g/dL;
- Serum total bilirubin ≤ 1.5 X ULN;
- AST (SGOT) and ALT (SGPT) ≤ 3.0 X ULN;
- Creatinine clearance ≥45 mL/min by the Cockcroft-Gault (C-G) equation:

CrCl (mL/min) =	[140 – age (years)] x weight (kg) / 72 x serum creatinine (mg / dL)	{x 0.85 for female patients}

3.1.8 Negative urine or serum pregnancy test within 14 days of Step 1 Registration for women of childbearing potential;

3.1.9 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial. Note: HIV testing is not required for eligibility for this protocol.

3.1.10 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry;

Prior to STEP 1 REGISTRATION – PATIENTS WHO RECEIVED SYSTEMIC THERAPY BEFORE STUDY ENTRY

3.1.10 The following systemic therapy and immunotherapy combinations are permissible: 1) cisplatin/carboplatin + pemetrexed; 2) cisplatin/carboplatin + pemetrexed + anti-PD-1/L1 agents; and 3) ipilimumab/nivolumab.

3.1.11 Patients must have received at least 2 cycles of neoadjuvant systemic therapy (as defined in section 5).

Prior to STEP 2 RANDOMIZATION – ALL PATIENTS

3.1.12 No evidence of progression as defined by PET/CT within 30 days prior to Step 2 randomization. Cases of possible progression or equivocal results must be discussed with Dr. Rimner prior to randomization.

3.1.13 Patients must have received at least 2 cycles of systemic therapy and undergone a pleurectomy/decortication with the goal of macroscopic complete resection;

3.1.14 ECOG Performance Status 0-1 within 30 days prior to Step 2 Randomization;

3.1.15 History/physical examination within 30 days prior to Step 2 Randomization;

3.2 Ineligibility Criteria (15-MAR-2022)

Patients with any of the following conditions are NOT eligible for this study.

Prior to STEP 1 REGISTRATION – ALL PATIENTS

3.2.1 Pregnancy or women who are breastfeeding and unwilling to discontinue.

3.2.2 Participants of childbearing potential (participants who may become pregnant or who may impregnate a partner) unwilling to use highly effective contraceptives during and for six months after end of treatment because the treatment in this study may be significantly teratogenic.

3.2.3 Diagnosis of sarcomatoid mesothelioma.

3.2.4 Severe, active co-morbidity defined as follows:

- NYHA Class III or IV heart failure
- COPD requiring chronic oral steroid therapy of > 10 mg prednisone daily or equivalent at the time of registration. Inhaled corticosteroids are allowed;
- Unstable angina requiring hospitalization and/or transmural myocardial infarction within the last 3 months;
- Interstitial lung disease;

- Hemodialysis or peritoneal dialysis;
- Concurrent active malignancy (with the exception of current or prior non-melanomatous skin cancer or low-grade malignancies followed observantly for which treatment has not or does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen)
    - If evidence of disease < 3 years, institution must consult with the Principal Investigator, Andreas Rimner, MD.
- Hepatic impairment defined by ChildPugh Class (ChildPugh Class B & C);
    - For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy within 30 days prior to registration, if indicated. Note: HBV viral testing is not required for eligibility for this protocol.
    - Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load within 30 days prior to registration.
- Active lung infection requiring IV antibiotics;
- Patients on immunosuppressive therapy, for example with a history of organ or bone marrow transplant or other hematologic disorders that are expected to compromise life expectancy or tolerance of treatment;

3.2.5 Prior nephrectomy on the contralateral side of MPM;

3.2.6 Ipsilateral thoracic electronic implant, e.g. pacemaker, defibrillator, unless switched to the contralateral side prior to initiation of RT;

3.2.7 Prior thoracic radiation therapy (patients with prior thoracic RT cannot be planned to 50-60 Gy without exceeding normal tissue constraints);

3.2.8 Use of bevacizumab or other antiangiogenic therapy to treat current mesothelioma (due to potential for increased complications from local therapy).

3.2.9 For patients who received neoadjuvant systemic therapy prior to study entry, surgery planned to occur greater than 8 weeks following neoadjuvant systemic therapy.

Prior to STEP 2 RANDOMIZATION – ALL PATIENTS

3.2.10 Supplemental oxygen use;

3.2.11 Third space fluid that cannot be controlled by drainage or insufficient lung expansion after P/D (this prevents targeting the pleura without exceeding normal tissue constraints);

3.2.12 Prior intrapleural therapy (i.e. intrapleural chemotherapy, photodynamic therapy); pleurodesis is permitted;

3.2.13 Bulky residual disease in the major fissure preventing pleural IMRT;

3.2.14 Patients who have undergone extrapleural pneumonectomy;

3.2.15 Patients with active infection that requires systemic I.V. antibiotics, antiviral, or antifungal treatments.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP (13-APR-2022)

PRE-TREATMENT ASSESSMENTS

Assessments	Prior to Step 1 Registration
Pathologic confirmation of epithelioid or biphasic MPM	X
History, physical examination (including weight), performance status, vital signs including O_2 saturation, temperature, heart rate, blood pressure, and respiratory rate	≤42 days
Surgical confirmation that MPM is amenable to resection by P/D	X
PET/CT for staging	At diagnosis
Diagnostic volumetric CT scan of the chest*	At diagnosis
Functional MRI of the thorax or MRI of the chest (optional)	≤42 days
Urine or serum pregnancy test (women of childbearing potential)	≤14 days
CMP (Complete Metabolic Panel) and CBC with differential†	Prior to study entry (must be at least 14 days after pre-study entry neoadjuvant therapy if given, and within 42 days prior to Registration for patients who did not receive pre-study neoadjuvant therapy)

* Diagnostic CT scan of the chest 1-3 mm slice thickness (intravenous contrast is preferred, CT volumetry, modified RECIST criteria). This can be obtained as part of PET/CT if CT imaging is of diagnostic quality.

† CMP to include creatinine, total bilirubin, AST and ALT, electrolytes (potassium, sodium, and chloride). CBC with differential to include absolute neutrophil count, lymphocyte count, platelet count, and hemoglobin.

ASSESSMENTS FOR PATIENTS RECEIVING SURGERY FOLLOWED BY CHEMOTHERAPY (SYSTEMIC THERAPY NOT RECEIVED BEFORE STUDY ENTRY)

Assessments	After Enrollment, Prior to Surgery	After Surgery Prior to First Chemo. Cycle	During Chemo. (prior to every cycle)
History, physical examination (including weight), performance status, vital signs including O_2 saturation, temperature, heart rate, blood pressure, and respiratory rate		X	X
Toxicity Assessment Grade per NCI CTCAE, v 5.0		X	X
Quantitative V/Q scan as indicated*	Within 30 days (may be prior to enrollment but must be within 30 days prior to surgery)		
Pulmonary Function Tests (FEV1 and DLCO)	Within 30 days (may be prior to enrollment but must be within 30 days prior to surgery)		
CMP (Complete Metabolic Panel) and CBC with differential†	As clinically indicated	Within 14 days prior to first cycle of chemotherapy	X
Urine or serum pregnancy test (women of child-bearing potential)		Within 14 days prior to first cycle of chemotherapy	
EORTC QLQ-C30 and QLQ-LC13	X	Within 30 days prior to first cycle of chemotherapy	
Biospecimen Collection: tissue and blood for future exploratory analysis – see Section 10 for details	X		

* Preop quantitative V/Q scan strongly recommended for patients with ≤60% predicted post-op

FEV1 and/or DLCO.

† CMP to include creatinine, total bilirubin, AST and ALT, electrolytes (potassium, sodium, and chloride). CBC with differential to include absolute neutrophil count, WBC, lymphocyte count, platelet count, and hemoglobin. Collection timeframes prior to treatment per institutional standards.

ASSESSMENTS FOR PATIENTS RECEIVING SURGERY ONLY (SYSTEMIC THERAPY RECEIVED BEFORE STUDY ENTRY)

Assessments	**After Enrollment, Prior to Surgery**	**After Surgery (4 wks after surgery +\- 2 wks)**
History, physical examination (including weight), performance status, vital signs including O_2 saturation, temperature, heart rate, blood pressure, and respiratory rate	X	X
Toxicity Assessment Grade per NCI CTCAE, v 5.0		X
Quantitative V/Q scan as indicated**	Within 30 days (may be prior to enrollment but must be within 30 days prior to surgery)	
PET/CT	Within 30 days (may be prior to enrollment but must be within 30 days prior to surgery)	
Pulmonary Function Tests (FEV1 and DLCO)	Within 30 days (may be prior to enrollment but must be within 30 days prior to surgery)	
CMP (Complete Metabolic Panel) and CBC with differential *	X	
EORTC QLQ-C30 and QLQ-LC13	X	
Biospecimen Collection: tissue and blood for future exploratory analysis – see Section 10 for details	X	

* CMP to include creatinine, total bilirubin, AST and ALT, electrolytes (potassium, sodium, and chloride). CBC with differential to include absolute neutrophil count, WBC, lymphocyte count, platelet count, and hemoglobin.

** Preop quantitative V/Q scan strongly recommended for patients with ≤60% predicted post-op FEV1 and/or DLCO.

ASSESSMENTS PRIOR TO RANDOMIZATION AND DURING RT

(Patients who cannot be randomized will not be followed, and any assessment post-randomization will not apply)

	BOTH ARMS	**ARM 2 ONLY**	
Assessments	**Step 2 Randomization**	**After Step 2 Randomization, Prior to RT**	**During RT**
History, physical examination (including weight), performance status, vital signs including O_2 saturation, temperature, heart rate, blood pressure, and respiratory rate	Within 30 days prior to randomization		Weekly
EORTC QLQ-C30 and QLQ-LC13	Within 30 days prior to randomization		
Toxicity Assessment Grade per NCI CTCAE, v 5.0			Weekly
PET/CT	Within 30 days prior to randomization		
Diagnostic volumetric CT scan of the chest*		Within 30 days after randomization	
Pulmonary Function Tests (FEV1 and DLCO)	Within 30 days after randomization		
CMP (Complete Metabolic Panel) and CBC with differential †		Within 14 days after randomization	If clinically indicated
Renal scan in patients with impaired renal function (GFR<60)		Within 30 days after randomization	
Urine or serum pregnancy test (women of childbearing potential)		Within 14 days after randomization	
Biospecimen Collection: blood for future exploratory analysis – see Section 10 for details	Within 14 days after randomization (prior to RT in Arm 2)		

* Diagnostic Chest CT with 1-3 mm slice thickness (1mm preferred; with intravenous contrast preferred), CT volumetry, modified RECIST criteria. This can be obtained as part of PET/CT if CT imaging is of diagnostic quality.

† CMP to include creatinine, total bilirubin, AST and ALT, electrolytes (potassium, sodium, and chloride). CBC with differential to include absolute neutrophil count, WBC, lymphocyte count, platelet count, and hemoglobin.

ASSESSMENTS IN FOLLOW UP
(Patients who cannot be randomized will not be followed, and any assessment post-randomization will not apply)

Assessments	Arm 1 and 2: From Randomization: q3 mos. (+/- 2 weeks) x 2 yrs., then q6 mos. (+/- 4 weeks) x 3 yrs.	As clinically indicated
History, physical examination (including weight), performance status, vital signs including O_2 saturation, temperature, heart rate, blood pressure, and respiratory rate	X	
Diagnostic volumetric CT scan of chest*	X as noted below: From Randomization: q 3 mos. +/- 2 weeks x 2 yrs., then 6 mos. (if clinically indicated) then annually to yr. 5 and as clinically indicated	
CMP (Complete Metabolic Panel)**	For Arm 2 patients – recommended (not mandatory) at 3 and 6 months ONLY All other time points as clinically indicated	X (for Arm 1 patients)
PET/CT		X (if suspicious findings on CT chest)
Toxicity Assessment Graded per NCI CTCAE, v 5.0†	X	
EORTC QLQ-C30 and QLQ-LC13	At 3, 9, 15, and 21 months from Randomization (+/- 2 weeks)	
Biopsy of recurrent disease		X (if suspicious findings on CT and/or PET)
Biospecimen Collection: blood for future exploratory analysis – see Section 10 for details	3 months only	

* Diagnostic Chest CT with 1-3 mm slice thickness (1mm preferred; with intravenous contrast preferred), CT volumetry, modified RECIST criteria.

** CMP to include creatinine, total bilirubin, AST and ALT, electrolytes (potassium, sodium, and chloride).

† Report AEs reasonably related (possibly, probably, definitely) to protocol treatment and persistent AEs

Definition of Disease Assessments

CT scan with contrast will be used for response assessment. In cases where PET-CT scans are being acquired, response assessment will be done in accordance with the EORTC criteria. Additionally, exploratory data from MRI scans and volumetric calculations from CT scans will be collected for exploratory analysis per section 13.3. DICOM data from imaging studies will be collected per section 13.3.

Response and progression will be evaluated in this study by using the modified Response Evaluation Criteria in Solid Tumors (Byrne et al., 2004). Changes in the largest diameter (LD) (unidimensional measurement) of the tumor lesions perpendicular to the chest wall or mediastinal structures at two levels and three sites are used in the mRECIST criteria. The measurement of lymph nodes is in accordance with RECIST criteria.

The following terms and definitions may guide investigators but official mRECIST criteria should be employed for all study evaluations.

Complete Response (CR)
Disappearance of the target lesion; this determination will be made based on CT image evaluation.

Partial Response (PR)
At least a 30% decrease in the LD of the target lesion, taking as reference the baseline LD; this determination will be made based on CT image evaluation.

Stable Disease (SD)
Neither sufficient shrinkage to qualify for CR/PR above nor sufficient increase to qualify for LE below, taking as reference the smallest LD since the treatment started

Local Enlargement (LE)
At least a 20% increase in the LD of target lesions, taking as reference the smallest LD recorded since the treatment started; this determination will be made based on CT image evaluation

Local Failure (LF)
Refers to progression of pleural tumor thickness or appearance of a site of pleural thickness greater than 5 mm in the site of treated tumor.

For outcome analysis: modified RECIST criteria (mRECIST) will be used to assess progression free survival and Overall survival.

Evaluation of Non-Target Lesions
Marginal Failure (MF)
Refers to the appearance of a new measurable site of pleural tumor greater than 5mm within the treated site or enlarging tumor dimensions corresponding to a 20% increase in the longest diameter compared to initial appearance on imaging evaluation.

Regional Failure (RF)
Refers to the appearance of measurable tumor or lymph nodes along the natural lymphatic drainage typical for the location of the treated primary disease only with dimension of at least 1.0 cm on imaging studies (preferably CT scans) within the hilum, and the mediastinum. Equivocally appearing enlarged lymph nodes should be positive on PET imaging or biopsied to confirm involvement with carcinoma.

Metastatic Dissemination (MD)
Refers to the appearance of cancer deposits characteristic of metastatic dissemination from Mesothelioma. Appropriate evaluations for making this determination include physical examination and imaging studies. PET scan OR biopsy to confirm MD is encouraged but not required.

5. TREATMENT PLAN/REGIMEN DESCRIPTION (15-MAR-2022)

Participants will undergo surgical resection with P/D as the initial treatment step, within 4 weeks after study entry. Participants who did not receive neoadjuvant systemic therapy prior to study entry will receive an adjuvant chemotherapy regimen of pemetrexed and cisplatin (or carboplatin), 4 to 8 weeks after surgery.

Patients who received neoadjuvant systemic therapy prior to study enrollment will undergo surgical resection with P/D within 4 to 8 weeks of completion of neoadjuvant systemic treatment. Note: neoadjuvant systemic therapy is defined as 2 to 4 cycles of one of the following regimens: 1) Platinum/pemetrexed; 2) platinum/pemetrexed + anti-PD-1/L1 agent; or 3) ipilimumab/nivolumab. No additional systemic therapy will be given on the study for these patients.

Randomization occurs after the second treatment modality (chemotherapy or P/D). Participants randomized to Arm 1 will receive no further treatment, and participants randomized to Arm 2 will receive photon radiation using Intensity-Modulated Radiation Therapy (IMRT) or Pencil Beam Scanning (PBS) Proton Therapy to the hemithoracic pleura.

5.1 Surgery (15-MAR-2022)

For patients who received neoadjuvant systemic therapy as the initial treatment, surgery (P/D) must take place within 4 to 8 weeks from the end of neoadjuvant systemic therapy. For patients who undergo adjuvant chemotherapy, it must begin within 8 weeks after surgery.

5.1.1 Technique, timing, other

Complete surgical resection of all gross tumor (i.e. " macroscopic complete resection", also termed "MCR") via a lung-sparing procedure is required.

Prior to surgery, FEV1 and DLCO values must be:

- Post-operative predicted FEV1>40%;
- Post-operative predicted DLCO >40% (corrected for Hgb).

The approach to achieving MCR is dictated by the extent of disease at exploration and may include partial pleurectomy, pleurectomy/decortication (P/D) or extended pleurectomy/ decortication (EPD) as described in guidelines developed by the IASLC (Rice et al., 2011). The

procedure performed should be accompanied by lymph node sampling or dissection of all peribronchial / hilar / mediastinal lymph node stations according to the AJCC / UICC lymph node map described in the 7th and 8th editions of the international staging systems for malignant pleural mesothelioma. Intraoperative adjunctive therapies such as heated intrapleural chemotherapy or photodynamic therapy are NOT allowed in this study.

Procedure	Description	Trial eligibility
Extra Pleural Pneumonectomy (EPP)	en bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium, and diaphragm. In cases where the pericardium and/or diaphragm are not involved by tumor, these structures may be left intact.	Not eligible
Extended Pleurectomy/Decortication (extended P/D)	parietal and visceral pleurectomy to remove all gross tumor with resection of the diaphragm and/or pericardium.	Eligible
Pleurectomy Decortication (P/D)	parietal and visceral pleurectomy to remove all gross tumor without diaphragm or pericardial resection.	Eligible
Partial Pleurectomy/Decortication (partial (P/D)	partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but leaving gross tumor behind.	Eligible (Only minimal residual gross disease)

5.2 Chemotherapy/ /Other Agent-Based Therapy (15-MAR-2022)

For patients who underwent P/D as the initial treatment, adjuvant chemotherapy protocol treatment must begin within 4 to 8 weeks after surgery. The combination of pemetrexed and cisplatin (or carboplatin) will be given every 3 weeks for 4 cycles.

5.2.1 Pemetrexed based chemotherapy with cisplatin (or carboplatin)

Recommended administration guidelines or per institutional standard

500 mg/m^2 administered by IV over 10 minutes on Day 1 of a 21-day cycle with cisplatin or carboplatin. Doses can be rounded per institution policy.

When given in combination with platinum-based therapy, administer the pemetrexed prior to the platinum. Cisplatin is preferred over carboplatin. However, pre-existing renal impairment, hearing deficit and/or neuropathy may be acceptable reasons to use carboplatin instead of cisplatin.

Recommended pre-medications or per institutional standard

NOTE: Pemetrexed administration requires vitamin supplementation initiated one week prior to first dose of pemetrexed

- Vitamin Supplements to be started 7 days prior to initial pemetrexed dose:
    a. Vitamin B12: Patients should receive one intramuscular (IM) injection of 1000 mcg vitamin B12 seven days prior to the first pemetrexed dose then

every 3 cycles thereafter. Subsequent vitamin B12 injections may be administered on the same day as pemetrexed.

b. Folic acid: Folic acid 400-1000 mcg PO once daily started seven days prior to pemetrexed dose, continued during treatment, and for 21 days after last pemetrexed dose.

- Premedications
  a. Pemetrexed has low emetic risk but use of dexamethasone is required to prevent cutaneous reactions, doses may vary per institutional standard, the following are two options:
     i. Dexamethaxone 4 mg PO twice daily for 3 days, starting the day before pemetrexed administration.
     ii. Dexamethasone 8-12 mg PO/IV once prior to pemetrexed infusion.
  b. Other premedications can be used per institutional standard.

5.2.2 Cisplatin

Recommended administration guidelines or per institutional standard
75 mg/m^2 IV once every 3 weeks (on Day 1 of a 21-day cycle with pemetrexed), as a 60-minute infusion. Prepare and administer per institution policy. Doses can be rounded per institution policy.

Recommended pre-medications or per institutional standard

- Cisplatin anti-emetic administration guidelines: 5-HT$_3$ antagonists (e.g. ondansetron 8 mg IV/PO +. Dexamethasone 10-20 mg IV 30 minutes prior to chemotherapy). (Note: can give pre-medications by oral route 60 minutes prior to infusion). Continue ondansetron 8 mg PO twice a day for three days then as needed. Rescue antiemetic such prochlorperazine 10 mg PO up to four times a day should be provided. Use of other anti-nausea meds such as fosaprepitant/aprepitant, metoclopramide, or olanzapine is left to the discretion of the investigator.
- Cisplatin pre-hydration guidelines: Pre-hydration with 0.45 % sodium chloride 1000 mL with 16 mEq magnesium sulfate infused over 2 hours prior to cisplatin.
- Cisplatin post-hydration guidelines: Following the end of the cisplatin administration, an additional give 0.9% sodium chloride 1000 mL with 20 mEq potassium chloride and 16 mEq magnesium sulfate infused over 2 hours. Patients should be encouraged to self-hydrate throughout the week with frequent fluid intake with non-caffeinated beverages. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with NS.

5.2.3 Carboplatin

Recommended administration guidelines or per institutional standard
See Appendix A for the carboplatin dosing worksheet
AUC=5 once every 3 weeks (on Day 1 of a 21-day cycle after pemetrexed infusion is completed), over 60 minutes. Prepare and administer per institution policy. Doses can be rounded per institution policy. Carboplatin dose will be calculated using the Calvert formula: Carboplatin dose (mg) = target AUC x (GFR + 25).

For the purposes of this protocol, the glomerular filtration rate is considered equivalent to the creatinine clearance calculated by Cockcroft-Gault and is capped at 125 mL/min. Actual body weight should be used unless patient is greater BMI > 25, then use an adjusted body weight. Lower limit of serum creatinine should be the lower limit of assay – i.e. usually = 0.7 mg/dL:

Clcr (mL/min) =	[140 – age (years)] x weight (kg) / 72 x serum creatinine (mg / dL)	{x 0.85 for female patients}

Recommended pre-medications or per institutional standard

- Antiemetic regimen including a $5HT_3$-antagonist and steroid as described above in 5.2.2.

5.3 Radiation Therapy – Arm 2 only (15-MAR-2022)

Radiation therapy protocol treatment must begin within 4 to 8 weeks from the end of Step 1 treatment. Radiation therapy will be administered 5 days/week over approximately 6 weeks at 45 to 50.4 Gy (RBE), with RBE = 1.1 for protons and RBE = 1.0 for photons, in 25-28 fractions. Note that Gy for photons and Gy (RBE) for protons are used interchangeably in this protocol as applicable for each modality. An optional concomitant boost to 60 Gy (maximum dose per fraction of 2.4 Gy) for gross residual disease may be incorporated if normal tissue constraints can be met.

A Contouring Atlas has been developed by Memorial Sloan Kettering Cancer Center that offers general guidance for delineation of targets for epithelioid or biphasic malignant pleural mesothelioma in the context of intensity-modulated pleural radiation therapy. The Atlas is posted on the NRG-LU006 page of the CTSU website and is to be used as a reference for treatment planning. All pre-treatment radiation therapy quality assurance reviews will be assessed based on conformity to Atlas structures.

Pre-treatment review is required for all patients randomized to Arm 2 prior to delivery of radiation treatment. The patient cannot start treatment until they have received approval from the Imaging and Radiation Oncology Core (IROC)-Philadelphia. Due to the complexity of the RT planning, the Pre-Treatment review process is accomplished in two steps. Step 1 is a preliminary contour review where all required structures are submitted and evaluated for protocol compliance. Once the contour review is approved, Step 2 is a pre-treatment review of the full planning dataset to confirm contours and evaluate the plan for dose compliance is done. Each of these steps requires 3 business days from the receipt of complete data via TRIAD. If revisions are required, the process begins again.

5.3.1 Treatment Technology

Intensity Modulated Radiation Therapy (IMRT) will be used for all photon therapy; permitted delivery platforms include conventional linear accelerators (both fixed gantry IMRT and Volumetric Arc Therapy techniques at discretion of prescribing physician), MR-linacs and TomoTherapy units. A photon beam energy of 6-10 MV will be used. In these platforms, multi-leaf collimation (MLC) will be used to spare normal tissues outside of the target volume.

Pencil beam scanning (PBS), commonly referred to as intensity-modulated-proton-therapy

(IMPT), will be used for all proton beam therapy; permitted optimization techniques include single-field-uniform-dose (SFUD) or single-field optimization (SFO); or multi-field optimization (MFO).

Daily image guided radiation therapy (IGRT) using orthogonal X-rays, MV CT or MR guidance and weekly volumetric imaging, including kV cone-beam CT, helical MV CT (e.g. TomoTherapy), or CT-in-room must be used for all patients, regardless of radiation treatment techniques.

5.3.2 Immobilization and Simulation

Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices. Alpha cradles, Vac-Lok, or similar devices are used for shoulder immobilization. Immobilization of proton therapy patients should be performed such that beam range variations due to daily differences of patient settling into the immobilization devices are minimized. Arms should be abducted bilaterally with hands above the head and setup must be reproducible daily.

Simulation Imaging

Simulation CTs should be CT slices of no more than 3 mm slice thickness starting from the level of the cricoid cartilage and extending inferiorly to the iliac crest. Administration of intravenous (I.V.) contrast during simulation CT is preferred. A 4D scan capturing all phases of the respiratory motion should be obtained. Images to be used for proton therapy treatment planning should be acquired prior to IV contrast injection. If available, an FDG-PET study in the treatment position should be performed. Otherwise a diagnostic PET scan prior to RT start should be used for fusion and treatment planning. This PET scan (and associated DICOM registration file if applicable) will be submitted with digital RT treatment planning data as part of the pre-treatment review.

Motion Management Technique

A motion assessment (4D scan) or management technique must be used and documented. The use of four-dimensional radiation treatment planning is preferred to account for respiratory motion in the treatment planning process. Other methods permitted are treatment in breath hold (using Active Breathing Coordinator (ABC), Real-Time Position Management (RPM), surface imaging or otherwise supervised breath hold) and abdominal compression. The motion management scans should include the entire thorax, extending from above the lung apex to the bottom of the lungs with at least 2 cm margin, typically around L2 inferiorly.

For PBS treatment delivery, in addition to those methods listed above, use of layer- or volume-repainting techniques is strongly encouraged. Other methods to reduce interplay effect of PBS delivery include limiting max spot MU and increasing spot size by use of range shifters.

5.3.3 Imaging for Structure Definition and Image Registration

A volumetric treatment planning CT study and a recent, registered FDG-PET scan will be required to define gross tumor volume (GTV), internal target volume (ITV) (if 4D scan is used), clinical target volume (CTV), and planning target volume (PTV) (see definitions in Section 5.3.4

below). Contiguous CT slices, having no more than 3 mm thickness are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the iliac crest. The GTV, CTV, and PTV and critical structures will be outlined on all appropriate CT slices. In the case where the PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan. Otherwise, a diagnostic PET/CT used for staging could be used for target delineation with image co-registration with the planning CT.

5.3.4 Definition of Target Volumes and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

If residual disease is identified, it will be delineated as GTV. On slices containing GTV, the outer and inner CTV (CTV_Outer and CTV_Inner) must include a 3mm margin surrounding the GTV. On slices containing normal lung, the CTV_Outer and CTV_Inner must be delineated at the lung/chest wall interface. Below the level of the diaphragm, the CTV_Outer is typically only a single crescent-shaped contour which is named CTV_Outer and needs to be manually expanded to cover the pleura towards the sternum, the diaphragm and diaphragmatic crura to midline anteriorly and the paravertebral space posteriorly.

An internal target volume (ITV_Inner and ITV_Outer) will be delineated as an expansion of the CTV_Inner and CTV_Outer to account for respiratory and cardiac motion seen on the 4D-CT study. If breath-hold or compression are used for motion management, if the institution's experience indicates there is minimal residual motion in their application, there may be no ITV (ITV and CTV will be identical). The instructions below refer to the ITV approach. These volumes will then be expanded and combined to form an equivalent PTV as follows.

On slices where the ITV is the region between outer and inner contours, PTV_Outer is defined as the ITV_Outer plus 1 cm externally into the chest wall. Where necessary, the PTV_Outer will be further adjusted to cover the entire thickness of the chest wall, including the ribs and intercostal muscles. It will be expanded to the lateral edge of the sternum or midline anteriorly, to include the costovertebral joint and the lateral edge of the vertebral body, the costodiaphragmatic and costomediastinal recess and the crus of the diaphragm. Below the level of the diaphragm use only PTV_Outer as this will be a crescent shaped structure and there is no lung internally to avoid. Typically, the volumes extend inferiorly to about the bottom of the L2 vertebral body.

This volume will exclude the external skin surface and stay 5mm off of the spinal cord medially bounded by the vertebral body edge. The PTV_Outer may be shaved off the spinal canal where necessary.

PTV_Inner is the ITV_Inner with 6mm expansion into the lung parenchyma for photons or a comparable margin to account for range uncertainties and uncertainties in the stopping power for

protons. The PTV for planning purposes is the volume between PTV_Outer and PTV_Inner, represented by the Boolean structure PTV_Outer minus PTV_Inner. A detailed target volume contouring description is provided in Table 5.3.4 below.

Table 5.3.4

Target Structure Definitions

Gross Tumor Volume (**GTV**)

- Gross tumor based on CT and PET scan

Clinical Target Volume (**CTV**)

- **CTV_Inner**: lung/chest wall interface on slices *without* GTV; 3mm internal margin surrounding the GTV on slices *with* GTV
- **CTV_Outer:** lung/chest wall interface on slices *without* GTV; 3mm external margin surrounding the GTV on slices *with* GTV

Internal Target Volume (**ITV**)

- **ITV_Inner**: internal expansion (i.e. shrinkage) of the CTV_Inner to account for respiratory and cardiac motion seen on 4DCT scan
- **ITV_Outer**: external expansion of the CTV_Outer to account for respiratory and cardiac motion seen on 4DCT scan

Planning Target Volume (**PTV**)*

- **PTV_Inner**: 6mm internal expansion of the ITV_Inner
- **PTV_Outer**: 10mm external expansion of the ITV_Outer; where necessary, the PTV_Outer will be further adjusted to cover the entire thickness of the chest wall, including the ribs and intercostal muscles; it will be expanded to the lateral edge of the sternum or midline anteriorly, the costovertebral joint and the lateral edge of the vertebral body, the costodiaphragmatic and costomediastinal recess and the crus of the diaphragm

If desired, gross residual disease may be treated with a Simultaneous Integrated Boost to 60 Gy while respecting normal tissue constraints. The involved structures shall be named GTV_6000, ITV_6000 (if ITV approach is used), CTV_6000 (3mm margin), and PTV_6000 (5mm margin).

For target structures, users will consult the Contour Atlas that is posted on the NRG-LU006 page of the CTSU website.

5.3.5 Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard

DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard Name	**Description**	**Validation** *Required/Required when applicable*
GTV	Target Structure Delineation descriptions found above in Table 5.2.4	Required when Applicable
CTV_Inner		Required
CTV_Outer		Required
ITV_Inner		Required when Applicable (*with use of 4DCT ITV approach*)
ITV_Outer		Required (*with use of 4DCT ITV approach*)
PTV_Inner		Required
PTV_Outer		Required
PTV_Out-PTV_In	PTV_Outer minus PTV_Inner	Required
PTV	Volume between PTV_Outer and PTV_Inner	Required
Bolus_x.x cm	Scar bolus 0.5cm to 1.0 cm maximum, if used; x.x = thickness of bolus	Required when Applicable
GTV_6000	Tumor Volumes for ***optional*** Simultaneous Integrated Boost (SIB) if used for planning additional dose to gross residual disease	Required when Applicable (*SIB*)
CTV_6000		Required when Applicable (*SIB*)
ITV_6000		Required when Applicable (*SIB with ITV approach*)
PTV_6000		Required when Applicable (*SIB*)
SpinalCord	Spinal Cord (spinal canal from most superior slice to 3 slices inferior of PTV)	Required
Lungs	Combined Right and Left Lungs	Required
Lungs-GTV	Combined lungs minus GTV	Required when applicable
Lung_R	Right Lung	Required

Lung_R-GTV	Right lung minus GTV	Required when applicable
Lung_L	Left Lung	Required
Lung_L-GTV	Left lung minus GTV	Required when applicable
Esophagus	Esophagus (entire esophagus from cricoid cartilage to stomach)	Required
Heart	Heart (pericardial sac; superior border at level of the right pulmonary artery crossing to the right side of the mediastinum)	Required
BrachialPlexus_L	Left Brachial Plexus	Required
BrachialPlexus_R	Right Brachial Plexus	Required
BrachialPlexus	Combined Brachial Plexus	Required
Liver	Liver	Required
Liver-GTV	Liver minus GTV	Required when applicable
Spc_Bowel	Space occupied by large bowel and small bowel	Required
Kidney_L	Left Kidney	Required
Kidney_R	Right Kidney	Required
Kidneys	Combined Kidneys	Required
Stomach-PTV	Stomach minus PTV	Required
E-PTV	All tissue within the external contour minus PTV	Required

5.3.6 Dose Prescription

The prescribed dose per fraction is 1.8 Gy and the total prescribed dose is 50.4 Gy. An optional concomitant boost to 60 Gy for gross residual disease may be incorporated if normal tissue constraints can be met with a maximum dose per fraction of 2.4 Gy. See table below for examples of optional boost fractionation.

Total Fractions	Dose Per Fraction	Total Prescribed Dose	Optional Boost	Total Boost Dose
25	1.8 Gy	45.0*	2.40 Gy	60 Gy
26	1.8 Gy	46.8	2.30 Gy	60 Gy
27	1.8 Gy	48.6	2.22 Gy	60 Gy
28	1.8 Gy	50.4	2.14 Gy	60 Gy

**The total prescribed dose may be reduced to a minimum of 45 Gy (in 1.8 Gy increments) if required to satisfy the normal tissue constraints, while aiming for the highest dose within dosimetric constraints.*

The total prescribed dose may be reduced to a minimum of 45 Gy (in 1.8 Gy increments) if required to satisfy the normal tissue constraints, while aiming for the highest dose within dosimetric constraints. An optional bolus of clinically appropriate thickness (0.5 cm to 1.0 cm maximum) may be applied to the scar. If bolus is utilized, a contour to represent the bolus site will be included in the treatment plan and submitted. This structure will be labeled as indicated in Section 5.3.5 above.

5.3.7 Planning Constraints

Planning constraints are tabulated below. All doses are in Gy. Note that the heart constraints are different for a left-versus right-sided target.

Structure Name	Dosimetric Parameter	Per Protocol	Variation Acceptable	Deviation Unacceptable
GTV	D95%[%]	>=95	>=90	< 90
PTV	D95%[%]	>=94	>=90	< 90
	V95%[%]	>=94	>=90	< 90
	D5%[%]	<=115	<=120	>120
	D0.03cc[%]	<= 130	<=150	>150
GTV_6000 *	D95%[Gy]	>= Rx Dose and <=60 Gy	N/A	< Rx Dose
Lungs-GTV *(if no GTV, use Lungs)*	V20Gy[%]	<=37	<=40	>40
	Mean[Gy]	<=20.5	N/A	>20.5
Lung_R Lung_L (Ipsi-lateral)	V40Gy[%]	<=67	<=90	>90
Lung_R Lung_L (Contralateral)	V5Gy [%]	<=50	<=80	>80
	Mean [Gy]	<=8	<=10	>10
	V20Gy[%]	<=5	<=7	>7
Esophagus	Mean[Gy]	<=34	<=38	>38
	V60Gy [%]	<=17	<=18	>18
SpinalCord	D0.03cc[Gy]	<=50	N/A	>50
Kidney_R	V18Gy[%]	<=33	<=50	>50

Kidney_L				
Kidneys	V18Gy[%]	<=33	<=50	>50
Stomach-PTV	Mean[Gy]	<=30	<=32	>32
Spc_Bowel	D0.03cc[Gy]	<=55	<=56	>56
	D5cc[Gy]	<=45	<=50	>50
BrachialPlexus_R **BrachialPlexus_L**	D0.03cc[Gy]	<=65	N/A	>65
Liver-GTV *(if no GTV, use Liver)*	Mean[Gy]	<=30	<=31	>31
	V30Gy [%]	<=45	<=50	>50
Heart (right meso)	V40Gy[%]	<=25	<=35	> 35
	Mean [Gy]	<=30	N/A	>30
Heart (left meso)	V40Gy[%]	<=35	<=37	>37
	V30Gy[%]	<=50	N/A	>50
	Mean [Gy]	<=30	N/A	>30
E-PTV	D0.03cc[%]	<=110	<=115	>115

Hotspots exceeding 110% of prescription (Variation Acceptable 115%) should be inside the PTV;

*Boost to GTV is optional. If no boost is intended, use the constraints for GTV. If optional concomitant boost to 60 Gy is intended, use structure GTV_6000 and follow the constraints in Table 5.3.7.

Dose Calculations

Acceptable choices of algorithm are listed at http://irochouston.mdanderson.org. Any algorithm used for this study must be credentialed by IROC Houston.

Photon dose calculations

For Convolution/Superposition type algorithms, dose should be reported as computed inherently by the given algorithm. For Monte Carlo or Grid Based Boltzmann Solver algorithms, conversion of Dm (dose-to-medium) to Dw (dose-to-water) should be avoided. Dm, computed inherently by these algorithms, should be reported.

Proton dose calculations

Monte Carlo dose calculation algorithm is required for final dose calculations in this protocol.

Primary dataset for dose calculation

The primary dataset for dose calculation must be a free-breathing CT that was acquired along with 4DCT, an average intensity pixel CT (AveIP) generated from the 4DCT or the breath-hold/gated CT, or the CT acquired with compression. Maximum Intensity Pixel (MIP) generated images from 4DCTs may not be used as the primary dose calculation dataset. In the case in which contrast is present during the treatment planning CT, the density of the contrast should be overridden to a representative background electron density.

Dose matrix resolution
Dose grid size should be ≤ 3 mm in all directions.

5.3.8 Daily Treatment Localization/IGRT

Image-guided radiation therapy (IGRT) is radiation therapy using imaging to facilitate accuracy and precision throughout its entire process from target and normal tissue delineation, to radiation delivery, to adaptation of therapy to anatomic and biological changes over time in individual patients. In this section we use the terminology IGRT to focus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment.

Daily image guidance that allows for 3D shifts is a requirement for this trial. Acceptable image guidance consists of daily orthogonal radiographs (2D imaging) matched on the spine for setup verification (or their equivalent per department guidelines) supplemented by weekly volumetric imaging at the treatment machine, which may include kV cone-beam CT, MV CT, CT-on- rails. More frequent volumetric imaging can be done per departmental guidelines when applicable.

<u>Guidelines for LINAC-based treatment planning (when applicable)</u>
The isocenter is approximately at the center of the treatment field. It is set by centering it on a field that ranges from the top of T1 to the bottom of L2, the contralateral edge of the vertebral body to lateral flash on the chest wall. Treatment is delivered with 6 to 10 MV photon beams, either static-gantry intensity modulated with the dynamic multi leaf collimator (DMLC or sliding window) technique or arc therapy (VMAT). Suggested beam angles for static-gantry IMRT are 6 to 9 beam directions, approximately equispaced over a range of 190 to 200 degrees and chosen to avoid the contralateral lung as much as possible. Suggested beam angles for arc therapy are 4-6 partial arcs going from 181 degrees to 20 degrees (right side) or 179 degrees to 340 degrees (left side) and determined by the shape of the lungs (the "lung limit"). Arc 1 should start from anterior oblique.

<u>Guidelines for proton therapy treatment planning:</u>
Proton therapy treatment plans should likewise use 2 – 4 treatment fields when field size limit allows. Treatment fields should not traverse the base frame of patient head immobilization device, unless a proton therapy-compatible head immobilization device, such as a base-of-skull frame, is used. Fields should not traverse through treatment table corners. Beam-specific PTVs may be implemented for single-field-optimization (SFO) or single-field-uniform-dose (SFUD) plans or for multi-field optimization (MFO) with appropriate distal and proximal margins to ensure robustness of the treatment plans. Alternatively, IMPT plans may be created using robust optimization on dose coverage objectives using robust optimization criteria that include range uncertainties >=5% and setup errors >=5 mm on CTV. Robust optimization using the same robustness criteria should be applied to high risk critical organs, such as the spinal cord, if such

OARs are expected to receive near their maximum tolerance doses. Care must be taken to assure that appropriate dose fall-off gradients are introduced in the field or target sub-volume junction regions to assure junction line dose homogeneity in the presence of setup errors. If necessary, the maximum extent of diaphragm movement may be contoured and overridden with tissue HU value as appropriate, with distal and proximal margins of fields traversing through the diaphragms selected to assure adequate target coverage on reconstructed CT sets with and without diaphragm HU overrides. When such tissue overrides are used, OAR doses should be reported from a verification plan on the AveIP CT set with no overrides. Alternatively, 4D robust optimization that accounts for additional image sets, like the maximum inhale and exhale phases, may be used. Air cavities within the ipsilateral lung should be reviewed for need to override during planning likewise, in a manner similar to that of diaphragm movements. Beam angles tangential to periodically moving chestwall should be avoided due to potential range perturbations caused by chestwall movements. Range shifters should be considered as needed. Motion mitigation techniques for proton therapy treatment planning and delivery should be evaluated and selected based on organ motion magnitude and follow recommendations of the PTCOG Thoracic Work Group Consensus Guidelines document (Chang *et al.*, IJROBP 2017).

For proton therapy treatments, pleural effusion filling variations and other anatomical changes that might occur through the course of patient treatment should be evaluated weekly, using either in-room volumetric imaging techniques (CBCT, CT-on-rail) that prompts for repeat CT imaging, or repeat imaging on the simulation CT. Dose distributions should be re-calculated on the repeat CT scans to assure adequate target coverage and normal organ protection, and treatment plans should be modified when necessary.

The robustness of PBS treatment plans, optimized either using or not using robust optimization algorithms, should be evaluated. Due to the large volume and geometric complexity of the target, as well as the higher likelihood of patient anatomy changes through the case of treatment, the following evaluation scenarios should be used:

Scenario	% Range Error	Setup Error (mm)		
		X	Y	Z
1	5.0 %	0	0	0
2	5.0 %	0	0	0
3	0	5.0	0	0
4	0	-5.0	0	0
5	0	0	5.0	0
6	0	0	-5.0	0
7	0	0	0	5.0
8	0	0	0	-5.0

For plan robustness evaluation, at least 6 of 8 scenarios should achieve CTV coverage >=95% and all scenarios should achieve CTV coverage >=90%. One to 2 scenarios <90% CTV coverage is an acceptable variation. More than 2 scenarios with <90% CTV coverage is an unacceptable deviation.

5.3.9 RT Case Review

Pre-treatment reviews are required for all cases. Due to the complexity of the RT planning, the

Pre-Treatment review process is accomplished in two steps. Step 1 is a preliminary contour review where all required structures are submitted and evaluated for protocol compliance. Once the contour review is approved, Step 2 is a pre-treatment review of the full planning dataset to confirm contours and evaluate the plan for dose compliance. Each of these steps requires 3 business days from the receipt of complete data via TRIAD. If revisions are required, the process begins again. See Section 12 for specifics on submission process and requirements. RT may not begin until full plan approval is received.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

5.4.2 Prohibited or Restricted Medications

Cisplatin

Use caution with other renally excreted drugs or other nephrotoxic and ototoxic drugs.

Carboplatin

Use caution with concomitant administration with, IV contrast dye, iohexol, aminoglycosides or other nephrotoxic medications.

Pemetrexed

Ibuprofen may reduce pemetrexed clearance. Ibuprofen therapy should be held 2 days prior to pemetrexed administration, during therapy, and for 2 days after last pemetrexed dose in patients with a CrCl between 45-79 mL/minute. If ibuprofen must be continued during pemetrexed therapy, monitor for myelosuppression, renal, and gastrointestinal toxicity. Other NSAIDs (e.g. naproxen, diclofenac, ketorolac) should also be used with caution.

Avoid concomitant use with BCG, cladribine, deferiprone, dipyrone, natalizumab, pimecrolimus, topical tacrolimus, and live vaccines.

5.4.3 Participation in Other Trials

Concurrent participation in other therapeutic trials is not permissible. However, trials that do not add experimental agents are allowed (e.g. imaging trials, quality of life, etc). Patients developing recurrence after treatment on NRG-LU006 may participate in other trials.

5.4.4 Herbal and Nutritional Supplements

The concomitant use of herbal therapies is not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However the use of general nutritional foundation supplements will be allowed including: calcium with vitamin D and/or minerals, Omega 3's (fish oil), Vitamin B6, Vitamin B12, a basic multivitamin , L-glutamine, or probiotics oral supplements will be permitted at long as at or below the FDA approved recommended dose allowance (RDA) by a healthcare provider. Herbal-based multivitamins are not allowed. Any additional supplements will need prior review and approval by the Medical Oncology Co-Chair Marjorie G. Zauderer, MD.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 7
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT (15-MAR-2022)

Please note that institutions are permitted to follow their local institutional standards for dose modifications as standard of care, and in accordance with package insert guidelines for these agents.

When chemotherapy related toxicity is observed, dose delays and/or reductions in drug administration are allowed per package insert and institutional standards as described below.

6.1 Pemetrexed

Parameters to use:

- ANC ≥1,500/mm^3 and platelets ≥100,000/mm^3
- CrCl ≥45 mL/minute by the Cockcroft-Gault equation
- Recovery of non-hematologic toxicity to ≤ grade 2

Dose Modifications

Renal dose adjustment is not necessary for CrCl ≥45 mL/minute. Use is not recommended with CrCl <45 mL/minute.

There are no recommended dose adjustments for hepatic impairment.

Potential Adverse Drug Reactions (and management) or refer to Institutional Standard

Hematologic Toxicity

	Pemetrexed Dose Modification/Management
ANC <1500/mm^3	Hold until ANC ≥1,500/mm^3 Resume pemetrexed at same dose
ANC <500/mm^3 and platelets ≥50,000/mm^3	Hold therapy until ANC ≥1,500/mm^3 and platelets ≥100,000/mm^3 Administer 375 mg/m^2
Platelets <100,000/mm^3 without bleeding	Hold therapy until platelets ≥100,000/mm^3 Resume pemetrexed at same dose
Platelets <50,000/mm^3 without bleeding	Hold therapy until platelets ≥100,000/mm^3 Administer 375 mg/m^2

Platelets <50,000/mm^3 with bleeding	Hold therapy until platelets ≥100,000/mm^3 Administer 250 mg/m^2
Recurrent Grade 3 or 4 Myelosuppression after two dose reductions	Discontinue pemetrexed

Non-Hematologic Toxicity

	Pemetrexed Dose Modification/Management
Diarrhea (any grade) requiring hospitalization, grade 3 or 4 diarrhea	Hold until toxicity recovers to grade ≤ 2 Administer 375 mg/m^2
Grade 3 or 4 Mucositis	Hold until toxicity recovers to grade ≤ 2 Administer 250 mg/m^2
Grade 3 or 4 Neurotoxicity	Discontinue pemetrexed
Skin toxicity	Pre-treatment administration of dexamethasone is required to reduce incidence of serious and occasionally fatal dermatologic toxicities. Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Permanently discontinue pemetrexed if severe/life-threatening bullous, blistering, or exfoliating dermatologic toxicity occurs.
Pulmonary toxicity	Withhold pemetrexed and evaluate patient in setting of acute onset new or progressive pulmonary symptoms (e.g. dyspnea, cough, or fever). If interstitial pneumonitis is confirmed, permanently discontinue pemetrexed.
All other Grade 3 or 4 non-hematologic toxicities	Hold until toxicity recovers to grade ≤ 2 Administer 375 mg/m^2
Recurrent Grade 3 or 4 non-hematologic toxicities after two dose reductions	Discontinue pemetrexed

Management of hypersensitivity reactions or refer to institutional standard

Hypersensitivity reactions include anaphylactic-like reactions. Tachycardia, bronchoconstriction, hypotension, facial edema and erythema may occur and should be should be treated with antihistamine, corticosteroids, and epinephrine as per institutional hypersensitivity management protocol. These reactions typically occur in patients with prior exposure to the drug. For future doses, pretreat with the same medications.

6.2 Cisplatin (15-MAR-2022)

Parameters to use:

- Absence of pre-existing grade 2 neuropathy or hearing loss
- Creatinine clearance > 50 mL/min
- ANC $\geq$ 1500 mm^3
- Hg $\geq$ 8 g/dL
- Platelets $\geq$ 100 K/mm^3

Dose modifications (based on organ function; toxicity)

Dosage with renal impairment: In general, patients should not be retreated with cisplatin until serum creatinine is below 1.5 mg/dL. According to the FDA and manufacturer, cisplatin is contraindicated in patients with preexisting renal impairment.

Creatinine clearance	% previous dose	Dose to administer
46-60	75%	56 mg/m^2
30-45	50%	38 mg/m^2
<30	Do not give	Do not give

Dosage with hepatic impairment: There are no dosage adjustments provided in the manufacturer's labeling. Dosage adjustment is likely not necessary as cisplatin is believed to undergo spontaneous degradation in the bloodstream and is not hepatically metabolized. Cisplatin is predominantly eliminated by the kidneys.

Dosage with toxicity:

- Grade 2 neurotoxicity/ototoxicity — Reduce to 56 mg/m^2
- Grade 3 or 4 neurotoxicity/ototoxicity — Discontinue
- Other grade 3 non-hematologic/organ toxicity — Reduce to 56 mg/m^2
- Other grade 4 non-hematologic/organ toxicity — Discontinue
- Hemolysis, optic neuritis, arterial thromboembolism, severe hypersensitivity reactions, grade 3 or 4 increased LFTs — Discontinue
- Grade 4 platelets, grade 4 ANC >/= 5 days, thrombocytopenic bleeding or febrile neutropenia — Reduce to 56 mg/m^2

Potential Adverse Drug Reactions: Adverse effects include myelosuppression, nausea/vomiting, peripheral neuropathy, nephrotoxicity, ototoxicity, alopecia, and hypersensitivity. **For management please refer to institutional standard.**

Hypersensitivity reactions include anaphylactic-like reactions: Tachycardia, bronchoconstriction, hypotension, facial edema and erythema may occur and should be should be treated with antihistamine, corticosteroids, and epinephrine as per institutional hypersensitivity management protocol. These reactions typically occur in patients with prior exposure to cisplatin. For future doses, pretreat with the same medications.

6.3 Carboplatin (15-MAR-2022)

Parameters to use

- Creatinine Clearance
- PLT ≥ 100 K/mm^3

Dose modifications (based on organ function; toxicity)

- Renal impairment
    - Dose determination with Calvert formula uses GFR or estimated CrCl and inherently adjusts for renal dysfunction (see Appendix A)
- Hepatic impairment: There are no dosage adjustments provided in the manufacturer's labeling
- Adjustment for toxicity
    - Platelets < 50,000 cells/mm^3 or ANC < 500 cells/mm^3: dose reduced to AUC=4

Potential Adverse Drug Reactions Recommended Management or refer to Institutional Standard

- Myelosuppression
    - Monitor blood counts closely
    - Reduce dosage and/or delay cycles until WBC and platelet counts have recovered
    - Anemia may require blood transfusion
- Nausea and vomiting
    - Pretreatment with antiemetics is recommended
- Ototoxicity
    - Clinically significant hearing loss reported in pediatric patients
    - Long-term audiology monitoring is recommended if patient experiences changes in hearing during chemotherapy
- Nephrotoxicity
    - Use caution with concomitant administration with aminoglycosides or other nephrotoxic medications
- Vision loss
    - Discontinue carboplatin; usually reversible within weeks of discontinuation
- Electrolyte wasting
    - Monitor closely and replace as indicated by IV or PO supplementation

Management of hypersensitivity reactions or refer to institutional standard
Hypersensitivity reactions include anaphylactic-like reactions. Tachycardia, broncho-constriction, hypotension, facial edema and erythema may occur and should be treated with antihistamines, corticosteroids, and epinephrine as per institutional hypersensitivity management protocol. These reactions typically occur in patients with prior exposure to platinum therapy. For future doses, consider desensitization protocol or alternative medication.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Commercial Agents: The commercial agents in NRG-LU006 are pemetrexed, cisplatin and carboplatin.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.2.3 Adverse Events for Pemetrexed

Refer to the package insert for detailed pharmacologic and safety information

7.2.4 Adverse Events for Cisplatin

Refer to the package insert for detailed pharmacologic and safety information

7.2.5 Adverse Events for Carboplatin

Refer to the package insert for detailed pharmacologic and safety information

7.3 Expedited Reporting of Adverse Events (15-MAR-2022)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made NRG Oncology by phone at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

While CTEP-AERS may be used for this study, please note that reports submitted to this database will neither be reviewed nor submitted to the FDA by NCI, as this study is not being conducted under a CTEP-held IND.

7.3.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERS-24 Hour Notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS-24-hour notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. Deidentified supporting source documentation should be uploaded to the Source Document Portal via the CTEP-AERS integration.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.3.2 Expedited Reporting Requirements for Adverse Events

Step 1: Surgery and Adjuvant Chemotherapy

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

NOTE: Investigators **MUST** immediately report to the sponsor **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.

Attribution	Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected
Unrelated Unlikely			10 day	10 day
Possible Probable Definite	24-h/5 day		24-h/5 day	24-h/5 day

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:

- Unexpected Grade 4 and all Grade 5 AEs

Arm 2: Any Phase Study Utilizing Radiation Therapy (including chemoRT studies)[1]

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

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

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

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

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

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 protocol treatment and are related to treatment, i.e. have an attribution of possible, probable, or definite to protocol treatment, require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 3 adverse events

7.3.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.3.4 Secondary Malignancy

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 during or subsequent to treatment with an agent be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must 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 AE reporting unless otherwise specified.

7.4 Routine Reporting Requirements for Adverse Events

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

7.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 6 months after the end of study treatment must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (15-MAR-2022)

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored 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 at (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the, Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;

- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
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 Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN must be rostered at the enrolling site with a participating organization.

Additional information is located 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.

8.1 Cancer Trials Support Unit Registration Procedures (13-APR-2022)
This study is supported by the NCI CTSU.

IRB Approval
For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP)

Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status;
- Active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements for Protocol NRG-LU006 Site Registration

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- Surgeon credentialing (see Section 8.1. 3);

- IRB/REB approved consent (International and/or Canadian sites only: English and native language versions*);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

*Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational letterhead/stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in protocol Section 8.2 to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will automatically send the approval to the Regulatory Support System (RSS) to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification. IROC will continue to copy the provider and/or enrolling site on modality approvals.

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

8.1.1 Additional Requirements for sites in Canada

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines [per section 6.2.5 of ICH E6(R2)]. This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result essential documents must be retained for 25 years following the completion of the trial at the participating site (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by the sponsor, NRG Oncology, that documents no longer need to be retained [per C.05.012 (4) of the FDR]. In addition, upon request by the auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access [per section 4.9.7 of ICH]. Prior to clinical trial commencement, sites in Canada must also complete and submit the following documents to NRG Regulatory (regulatory-phl@NRGOncology.org):

- Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form,
- Research Ethics Board Attestation Form.
- Protocol Signature Page
- Delegation of Task Log (DTL)
- List of Laboratories
- SIV/Training Confirmation of Completion Form – Research Associate (please refer to the activation memo for details)
- SIV/Training Confirmation of Completion Form – Qualified Investigator (please refer to the activation memo for details)
- IRB/REB approved consent (English and native language versions; submitted to NRG Regulatory for review prior to IRB/REB submission).

The following items are collected by NRG Oncology Regulatory on a yearly or biyearly basis:

- IRB/REB Membership Roster
- Laboratory Certificates and Normal Values
- CVs for Qualified Investigator and Sub-Investigators noted on the DTL log

8.1.2 Additional Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS

- IRB/REB approved consent (English and native language versions*)
  ***Note**: International Institutions must submit their consent form in English to NRG Regulatory (regulatory-phl@NRGOncology.org) for review prior to IRB submission (initial and amendments). Certification/verification of IRB/REB consent translation is also required (described below).

8.1.3 Surgeon Credentialing

Participating surgeons must complete and sign a credentialing form prior to their institutions entering any patients onto this study. This form can be accessed on the protocol-specific page of the CTSU website. The study Research Associate will email the completed form to Surgical Oncology Co-Chair Dr. Valerie Rusch

(ruschv@MSKCC.ORG) for review and approval. Dr. Rusch will email approval to NRG Data Management and the Research Associate, then the Research Associate submits the form to the Regulatory Submission Portal on the CTSU website. Institutions should allow adequate processing time (7-10 days) before registering the first patient.

8.1.4 Site P/D Volume

Sites must complete a Site P/D Volume Form indicating the number of pleurectomy/decortication procedures performed at the site per year. The form can be found on the protocol-specific page of the CTSU website, and should be submitted to the Regulatory Submission Portal using the instructions below (see **Submitting Regulatory Documents**).

8.1.5 Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG Oncology* and protocol number [NRG-LU006];
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to CTSU.)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log in to the CTSU members' website, to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Checking Your Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
  - Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status given only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

8.2 RT-Specific Pre-Registration Requirements (15-MAR-2022)

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, IROC Houston will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. The credentialing notification document (sent as an email) must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated.

Proton centers wishing to participate in this study must comply with the NCI proton guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, which are available on the IROC Houston (http://irochouston.mdanderson.org) and IROC (https://www.irocqa.org) websites. These requirements include, but are not limited to, completion of a proton facility questionnaire, a successful IROC site visit, which identifies the proton technique(s) which can be used, annual monitoring of the proton beam calibration, e.g. IROC Houston's monitoring program, and successful digital data submission to TRIAD. Once these requirements are successfully met, the proton center is approved to use proton therapy in NCI sponsored clinical trials. Each trial may require additional proton therapy credentialing steps prior to being allowed to enter a patient treated with protons onto a specific study. IROC Houston will coordinate the completion of the proton therapy use approval process in conjunction with the appropriate other IROC QA Centers for any additional protocol specific credentialing requirements. See the table below for the credentialing requirements of this study.

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**		
	Treatment Modality		
	Proton	Photon	Key Information

Credentialing Status Inquiry Form	**X**	**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**).
Facility Questionnaire	**X**	**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**	**X**	An IMRT or proton lung 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**).
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 NRG Headquarters that all desired credentialing requirements have been met.

8.2.1 Digital Radiation Therapy Data Submission Using Transfer of Images and Data

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

TRIAD Access Requirements:

- A valid Cancer Therapy Evaluation Program (CTEP-) Identity and Access Management (IAM) (CTEP-IAM) account.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

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

which the provider is linked in OPEN.

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

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

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

8.3 Patient Enrollment (15-MAR-2022)

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.3.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/ randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments: Must be on a LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- Surgeon credentialing for appropriate site staff prior to enrollment;
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

9.0 DRUG INFORMATION

9.1 Commercial Agent: Pemetrexed (15-MAR-2022)
US sites must refer to the package insert and sites in Canada must refer to the product monograph for detailed pharmacologic and safety information.

9.1.1 Adverse Events
Please refer to the package insert.

9.1.2 Availability/Supply
Please see Section 5.2.1 for administration details. Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage. Sites in Canada must refer to the product monograph for this information.

9.2 Commercial Agent: Cisplatin (15-MAR-2022)
US sites must refer to the package insert and sites in Canada must refer to the product monograph for detailed pharmacologic and safety information.

9.2.1 Adverse Events
Please refer to the package insert.

9.2.2 Availability/Supply
Please see Section 5.2.2 for administration details. Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage. Sites in Canada must refer to the product monograph for this information.

9.3 Commercial Agent: Carboplatin (15-MAR-2022)
US sites must refer to the package insert and sites in Canada must refer to the product monograph for detailed pharmacologic and safety information.

9.3.1 Adverse Events
Please refer to the package insert.

9.3.2 Availability/Supply
Please see Section 5.2.3 for administration details. Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage. Sites in Canada must refer to the product monograph for this information.

10. PATHOLOGY/BIOSPECIMEN

10.1 Optional Specimen Submissions (15-MAR-2022)

Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

See detailed specimen collection/processing/shipping instructions on the protocol-specific page of the CTSU website.

This study will include collection of biospecimens for future analyses. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines or via the Navigator portal after the trial has been reported. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

Specimen Collection for Banking for Future Research

- Required Forms: ST form, pathology reports. All forms must be completely filled out with an NRG Label including the Study #, Case #, NRG Institution name and # or Institution NCI ID, and patient initials. The pathology accession number and date of procedure must remain visible on the pathology report but all other PHI information must be redacted/removed.
- Kits are available for Frozen biospecimens from the NRG Oncology Biospecimen Bank at San Francisco (NRGBB-SF). Sites should include the following information in their email: Ship to Fed Ex address with room number, confirm site has IRB approval for study, how many patients site enrolled in past month.
  Detailed Processing and shipping instructions are provided on the protocol-specific page of the CTSU website.
- Shipping days for Frozen Specimens: Monday-Wednesday (U.S. sites); Monday-Tuesday (Canada and Non-North American). International sites must contact the NRGBB-SF before shipping. Check NRG Broadcasts for bank holiday closures. We are unable to accept shipments on Saturdays or holidays. Check Fed Ex site for storm delays and do not ship during severe weather.
- Shipping costs: A single use prepaid Fed Ex label is provided for each case in LU006 kits provided to the site (U.S. sites only) for batch shipping frozen biospecimens to the NRGBB-SF. Ship all Biospecimens to:

  NRG Oncology Biospecimen Bank – San Francisco
  2340 Sutter Street- Room S341
  UCSF
  San Francisco, CA 94115
  415-476-7864/Fax 415-476-5271
  Email: NRGBB@ucsf.edu

For questions about banking biospecimens contact:
NRG Oncology Biospecimen Bank – San Francisco
NRGBB@ucsf.edu
415-476-7864/Fax 415-476-5271

Specimen Type	**Collection Time Points**	**Collection Information and Requirements/ Instructions for Site**	**Shipping**
H&E slide(s) of Primary tumor	Pre-treatment (including neoadjuvant therapy): obtained as part of routine diagnostic procedures	H&E stained slide, ST form and pathology report. H&E slide can be a duplicate cut slide, does not have to be the diagnostic slide.	Ship ambient to NRGBB-SF
FFPE Block	Pre-treatment (including neoadjuvant therapy): obtained as part of routine diagnostic procedures	Site should make every effort to submit the block that corresponds to the H&E for this study. If Site is unable to submit a Block then the following alternative is acceptable: A) Two 2mm (or 3mm) punches (tumor size dependent) embedded in paraffin with a corresponding H&E. (Punch kits available from NRGBB-SF upon request.). If sites are unable to embed the punches they may send the punches to the biobank to be embedded.	Ship to NRGBB-SF (use cold packs during warm weather)
Plasma- EDTA tube	Pre-treatment after enrollment and prior to surgery For all randomized patients: after randomization (prior to RT for Arm 2 patients) and at 3 month follow up visit only	Process and aliquot a minimum of 0.5 ml into each of five 1 ml cryovials. Freeze and store at -80°C and ship frozen on dry ice. Forms: ST form	Ship on Dry Ice by Priority Overnight Courier to NRGBB-SF

Serum- Red top tube	Pre-treatment after enrollment and prior to surgery For all randomized patients: after randomization (prior to RT for Arm 2 patients) and at 3 month follow up visit only	Process and aliquot a minimum of 0.5 ml into each of five 1ml cryovials. Freeze and store at -80°C and ship frozen on dry ice. Forms: ST form	Ship on Dry Ice by Priority Overnight Courier to NRGBB-SF
Whole Blood-EDTA tube	Pre-treatment after enrollment and prior to surgery For all randomized patients: after randomization (prior to RT for Arm 2 patients) and at 3 month follow up visit only	Sites collect and mix blood and aliquot a minimum of 1.5 mls blood into three 2ml cryovials. Freeze and Store at -80C and ship frozen on dry ice. Forms: ST forms	Ship on Dry Ice by Priority Overnight Courier to NRGBB-SF

11. SPECIAL STUDIES (NON-TISSUE)

11.1 Quality of Life (15-MAR-2022)

11.1.1 Background/Rationale for Studying Patient Report Outcome Measures (PROMs) in NRG-LU006

NRG-LU006 is the first randomized phase III study that evaluates the benefit of lung-sparing trimodality therapy in patients with malignant pleural mesothelioma. Given the rarity of MPM and the recently demonstrated feasibility of hemithoracic pleural IMRT (Rimner 2016), there exists no data describing the impact of hemithoracic pleural RT on well-being and symptoms from a patient's perspective.

Patient reported outcome measures (PROMs) report health status and symptoms directly from the patient without the influence of clinicians. PROMs complement physician-reported treatment effects. Furthermore, patient-reported symptoms are more closely associated with cancer patients' overall function and well-being when compared to physician-reported treatment toxicity (Basch 2009). PROMs in NRG-LU006 provide a unique and exciting opportunity to understand the impact of pleural IMRT on patients' quality of life, function, and symptoms. Importantly, these patient reports of pleural IMRT's impact would serve as the benchmark for understanding the effect of lung-sparing trimodality therapy in the treatment of this rare disease entity.

Only two PROMs have been validated in malignant pleural mesothelioma (Nowak 2004, Hollen 2006). The European Organization for Research and Treatment of Cancer quality of life core questionnaire (EORTC QLQ-C30), supplemented with the lung cancer

specific module (QLQ-LC13), has been extensively used in malignant pleural mesothelioma trials. EORTC QLQ-C30 and QLQ-LC13 were originally developed and validated for lung cancer patients, and subsequently validated for malignant mesothelioma patients (Nowak 2004). The EORTC QLQ-C30 covers global quality of life (QOL), 5 functional domains (physical, role, cognitive, emotional, social), 3 symptom domains (fatigue, pain, nausea/vomiting) and specific symptoms (dyspnea, appetite loss, insomnia, diarrhea, constipation, financial impact). A higher score for functional domain indicates better health status, whereas a lower score for symptoms domains and single-items indicates fewer symptoms. The EORTC QLQ-LC13 is a supplementary module that includes additional evaluation of cancer-specific symptoms and treatment-related side effects, including use of pain medication. Specific symptoms evaluated include: cough, hemoptysis, dyspnea, pain, sore mouth, dysphagia, peripheral neuropathy, and alopecia. A lower QLQ-LC13 score indicates fewer symptoms. We will collect this information alongside QLQ-C30, to better understand baseline-specific symptoms and treatment-related side effects throughout management of this rare disease entity.

EORTC QLQ functional domain and symptom scales capture changes in a patient's well-being and predicted for survival in malignant pleural mesothelioma patients who received chemotherapy. In cohort study of 53 MPM patients with measurable disease who received platinum doublet chemotherapy, baseline global health was reported at 50% of a normal healthy reference population and questionnaire compliance was 82% approximately 6 months after start of chemotherapy. On average during treatment, there was an absolute numeric decline in patient-reported global health status by 5 points and a statistically significant decline from baseline in multiple functional domains (physical: -3, social: -9, and cognitive: -11 points, respectively; all $p<0.05$) (Nowak 2004). Functional domains (physical, role, cognitive, emotional) and specific symptoms (QLQ-C30 fatigue, pain, and dyspnea), but not global quality of life, predicted for overall-survival after chemotherapy. Patient-reported dyspnea correlated with forced vital capacity, a measure of pulmonary function.

EORTC quality of life questionnaires show improved global quality of life in patients with MPM after P/D and chemotherapy. In a retrospective study of 36 patients with MPM who underwent extended P/D, of which 78% underwent adjuvant platinum/pemetrexed chemotherapy and no adjuvant radiation was given, global quality of life increased 5 to 25 points on average 7-8 months after P/D (Burkholder 2015). In a similar cohort of n=28 patients who underwent P/D, EORTC QLQ-C30 showed improved fatigue in all patients at 9 months post P/D. In the subset of these patients initially presenting with symptoms (ECOG 1) at baseline, patients had improvement in QOL and dyspnea after P/D (Mollberg 2012). This analysis excluded 25% (n=6 of 28 patients) who had significant disease progression at 5-6 (n=1) and 8-9 months (n=5), in whom follow-up was not continued.

A description of the effect of IMPRINT on well-being from the patient's perspective is critical to informing patients and oncologists about the impact of adjuvant lung-sparing radiation. There is no current understanding of the additional impact of IMPRINT on

quality of life, functional status, and symptoms after the addition of IMPRINT compared to P/D and systemic therapy alone.

Quality of life between EPP and P/D have been directly compared. In a retrospective study of 77 patients with stage I and II MPM who received P/D or EPP associated with multimodality treatment, only patients who received P/D returned to their baseline QOL at 12 months (Rena 2012). QOL has been evaluated after receipt of the different types of pleurectomy and decortication (extended P/D, P/D, and partial P/D). A prospective observational series of 28 patients with MPM treated with extended P/D (Burkholder 2015) and a randomized trial of partial P/D versus talc pleurodesis (Rintoul 2014) have both demonstrated a higher QOL score reported at 6-12 months after P/D compared to baseline. However, a direct QOL comparison between the different types of P/D has not been performed. Thus, it is not known if there exists a QOL difference between the different types of P/D. We do not expect QOL to be different between the different types of P/D in NRG-LU006, but we will be able to account for types of P/D in the NRG-LU006 QOL analysis.

11.1.2 Administration of NRG-LU006 EORTC QLQ

Time Points

See Section 4 Assessment Tables for details. EORTC QLQ performed at randomization will serve as the baseline assessment for the secondary endpoint QOL analysis.

EORTC QLQ performed at randomization will serve as the baseline assessment for the exploratory QOL analysis. EORTC QLQ assessments during follow up may be evaluated in relation to EORTC QLQ assessments at randomization and assessments collected prior to receipt of surgery and receipt of systemic therapy to improve the understanding of quality of life, function, and symptoms throughout management of this rare disease entity.

Recall Period

The recall period is stipulated by the EORTC quality of life questionnaires. Most items use a “past week” recall period.

Instructions

Questionnaires may be completed on paper at the appropriate patient visit. Questionnaires are to be administered at follow-up visits, so that when a follow-up visit is delayed, completion of the EORTC QLQ-C30 and LC-13 assessments may also be delayed. These assessments should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. Once the questionnaires are completed by the patient, the staff member should review it to ensure that no items were unintentionally left blank. When absolutely necessary, it may also be administered by mail or phone. The completed form will then be data entered into Medidata Rave.

If a patient declines to complete a scheduled QLQ-C30 and LC-13 form or if the questionnaires are not completed for any other reason (and cannot be completed by phone or mail), the QOL coversheet must be completed in Medidata Rave.

11.1.3 **Quality of Life Patient Population**
All patients enrolled in NRG-LU006 who understand English, Spanish or French will be required to participate in the QOL study.

11.2 Quality of Life Primary and Exploratory Endpoints (15-MAR-2022)

For the primary QOL endpoint: We hypothesize that addition of IMPRINT will improve disease control that will translate into an improvement in the overall health status at the 9 month time point after randomization.

EORTC QLQ performed at randomization will serve as the baseline for QOL analysis, since the primary endpoint as the purpose of this study is to evaluate the effect of the addition of IMPRINT to surgery and systemic therapy. EORTC QLQ assessments will also be collected prior to receipt of surgery and receipt of systemic therapy to improve the understanding of quality of life, function, and symptoms throughout management of this rare disease entity.

For the exploratory QOL analyses: We hypothesize that for patients receiving IMPRINT, there will be a lower proportion of patients responding with "quite a bit" or "very much" EORTC QLQ-C30 and LC13 treatment-related specific symptoms at 9-12 months post-randomization when compared to 3 month post-randomization.

We will also descriptively explore the effect of IMPRINT on overall health-related quality of life, functional domains (physical, role, cognitive, emotional) and symptoms over time from the patient's perspective.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews (15-MAR-2022)
The Principal Investigator, Dr. Rimner, or study Co-Chair Dr. Simone, will perform a Pre-Treatment Radiation Therapy quality assurance review of all treatment plans for those patients randomized to Arm 2. This will be conducted in two parts. Step 1 is the contour review and Step 2 is the full plan review to confirm contours and evaluate the dose compliance of protocol dose constraints. Three (3) business days are to be allotted for each step of the pre-treatment review once all required data are received for each in completion as indicated in Section 5.3.

12.2 Medical Oncology Modality Quality Assurance Reviews (15-MAR-2022)
The Medical Oncology Co-Chair, Dr. Zauderer, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive systemic therapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **1) Per Protocol, 2) Acceptable Variation, 3) Unacceptable Deviation, and 4) Not Evaluable**. Systemic therapy delivered prior to study entry will not be included in this review.

Dr. Zauderer will perform a Quality Assurance Review after NRG Headquarters has received complete data for the first 20 cases enrolled. Dr. Zauderer will perform the next review after NRG Headquarters has received complete data for the next 100 cases enrolled. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as NRG Headquarters has received complete data for all cases enrolled, whichever occurs first.

12.3 Surgical Quality Assurance Reviews

The Surgical Oncology Co-Chair, Dr. Rusch, will perform a Quality Assurance Review for verification of protocol compliance, on a continuous basis. For this review, sites must submit an operative report, pathology report and discharge summary for each patient. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as NRG Headquarters has received complete data for all cases enrolled, whichever occurs first.

12.4 Imaging Retrospective Central Review

Upon completion of this study and at the time of final analysis, the Radiology Co-Chair, Dr. Ritu Gill, will perform a retrospective central review of the NRG-LU006 Diagnostic Imaging Data via MIM software (or similar IROC-DI platform) on the NRG Oncology CITRIX-XEN environment.

13. DATA AND RECORDS

13.1 Data Management/Collection (13-APR-2022)

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

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

Rave role requirements:

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

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

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data*

Management > *Rave Home* and click to accept the invitation in the *Tasks* pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the eLearnings link in the *Tasks* pane located in the upper right-corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

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

13.2 Summary of Data Submission (15-MAR-2022)

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 the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Sections 7.3 and 7.4 for information about expedited and routine reporting.

Summary of All Data Submission: Refer to the CTSU website.

See Section 8.2.1 for TRIAD account access and installation instructions.

See RT data submission table for TRIAD below.

DICOM files to export from Treatment Planning System to TRIAD	**Step 1: Preliminary Contour Review** • DICOM Planning CT • DICOM Baseline PET or PET/CT (used for tumor volume delineation) • DICOM RT Structure **Step 2: Full Plan Review** *(after approval for Step 1 is given)* • DICOM Planning CT • DICOM RT Structure • DICOM RT Dose • DICOM RT Plan	**Must submit and receive approval of full plan review prior to start of RT** **TRIAD Time Point:** ***RT Digital Plan***

All required structures must be labeled per the tables in Sections 5.3.4 and 5.3.5
Upon submission of the RT digital data via TRIAD, complete an online **Digital Data Submission Information Form (DDSI)**: https://www.irocqa.org/Resources/TRIAD
NOTE: ALL SIMULATION AND PORTAL IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

See Diagnostic Imaging submission table for TRIAD below.

DICOM files to export to TRIAD	**Baseline**	TRIAD Time Point:
	• PET/CT • CT Chest	• See Section 4 Pre-Treatment Assessments table
	• MRI Scans if Available	
	During Treatment	
	• CT Chest • Quantitative V/Q scan	• See Section 4 Assessments If Surgery Is First table and also Prior to Randomization and During RT table
	• PET/CT	• See Section 4 Assessments If Systemic therapy Is First table and also Prior to Randomization and During RT table
	• CT Chest • Renal scan	• See Section 4 Assessments Prior to Randomization and During RT table
	F/U Scans	
	• CT Chest • PET/CT	See Assessments in Follow Up table
All required structures must measure and be labeled per the tables in Section 5.3.		

13.3 Data Quality Portal (15-MAR-2022)

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

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

The DQP is accessible by site staff that are rostered to a site and have access to

the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

13.4 Global Reporting/Monitoring (15-MAR-2022)

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design (15-MAR-2022)

The study is an open-label, randomized, phase III trial to evaluate the addition of adjuvant hemithoracic IMPRINT to surgery and systemic therapy compared to surgery and systemic therapy alone for malignant pleural mesothelioma patients. Patients will be enrolled prior to any modality treatment (step 1) and randomized 1:1 between IMPRINT and observation after systemic therapy or pleurectomy/decortication (P/D). Patients who cannot be randomized will not be followed post-randomization, and will not be included in any endpoint analyses.

14.2 Study Endpoints

14.2.1 Primary Endpoint

The primary endpoint is overall survival (OS), which is defined as the time between the date of randomization and the date of death due to any cause.

14.2.2 Secondary Endpoints

- Local-failure-free survival, defined as the time from randomization to local disease progression (per Section 4) or death due to any cause, whichever occurs first.
- Distant-metastases-free survival, defined as the time from randomization to distant metastases (per Section 4) or death due to any cause, whichever occurs first.
- Progression-free survival, defined as the time from randomization to any documented progression or death due to any cause, whichever occurs first.
- Treatment-related toxicity
- Quality of life as measured by EORTC quality of life questionnaires

14.3 Primary Objectives Study Design (15-MAR-2022)

14.3.1 Primary Hypothesis and Endpoints

The primary objective of this randomized phase III trial is to determine whether the addition of adjuvant hemithoracic IMPRINT to surgery and systemic therapy (Arm 2) will improve OS as compared to surgery and systemic therapy alone (Arm 1) for malignant pleural mesothelioma patients. Based on Shaikh et al. (J Thorac Oncol. 2017), the median OS in Arm 1 is assumed to be 12 months, and a hazard ratio of 0.6

(approximately equivalent to improving the median OS from 12 months to 20 months [H1]).

14.3.2 How Primary Endpoints Will Be Analyzed

The primary analysis for OS will be performed on an intent-to-treat (ITT) basis, such that all randomized cases will be included in the treatment arm to which they were randomized regardless of what treatment the patients actually received. This is the primary dataset for analyses of demography, baseline characteristics, and efficacy outcome research.

OS is defined as the time from randomization to death due to any cause. Patients without documented death at the time of analysis will be censored at the date of last known contact. The primary analysis of OS will occur when at least 105 deaths are available, and the study will be considered as "positive" if the log-rank test statistics Z-value > 1.721 (1-sided $p<0.043$), which is the threshold adjusted for type 1 error using group sequential methods.

We will compare the distributions of OS between treatment arms using a one-sided stratified log-rank test (using stratification factors as strata). The rates at various timepoints (e.g., every 6 months after randomization) and medians of OS for each arm will be estimated using the Kaplan-Meier method. The associated 90% confidence interval (CI) will be calculated using Greenwood's formula and based on a log-log transformation applied on the survival function. Hazard ratios will be estimated using a stratified Cox regression model. Results from an unstratified analysis will also be provided. If any stratum has less than 5 events, the stratification factor which contains the level with the smallest number of patients will be removed from the stratified analyses.

14.3.3 Sample Size and Power Calculations:

We hypothesize a hazard ratio (HR) of 0.6 (Arm 1 is the reference level), which is equivalent to an improvement in median OS from 12 months to 20 months [H1]. With 132 randomized patients and at least 105 deaths, the study provides at least 80% power to detect a HR of 0.6 at a 1-sided significance level of 0.05. Due to the rarity of the disease, we make a practical compromise for feasibility by setting the type 1 error at 1-sided level of 0.05, instead of the conventional level of 0.025. Guarding against a lack-of-data rate of up to 5.5%, a total of 140 patients will be randomized at step 2. Assuming about 6% of all patients may be unable to be randomized after receiving systemic therapy/PD, we project to accrue 150 patients at step 1 registration.

14.4 Study Monitoring of Primary Objectives

Two interim analyses for both efficacy and futility of OS are planned. The results of the analyses will be reported to the NRG Oncology DMC for its review and recommendations. The efficacy early stopping boundary is based on the Lan-DeMets implementation of O'Brien-Fleming boundary, and the futility early stopping boundary is based on Freidlin et al., 2010. These analyses will occur when approximately 53 deaths (50% information) and 79 deaths (75% information) have been reported, with the

corresponding early-stopping boundary for efficacy set at 2.524 and 2.013, and the early-stopping boundary for futility set at 0.037 and 0.251 (all boundaries in Z-value scale), respectively. If there are any deviations from the assumptions, group sequential methods will be used to properly adjust for the stopping boundary based on cumulative information.

Interim Analysis for the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. An interim study summary report will be prepared at each meeting accordingly until the initial study results have been released. In general, the interim reports will contain information about patient accrual rate, a projected completion date for the accrual phase, distributions of pretreatment characteristics and important prognostic baseline variables, and the frequencies and severity of treatment-related adverse events. The interim reports will not contain the results from the treatment comparisons with respect to the primary or any secondary endpoints, with the exception of reporting of adverse events. The DMC also will review the study on an "as needed" basis.

14.5 Accrual/Study Duration Considerations

During the first 6 months following activation, little accrual is anticipated while the trial is being approved by institutional review boards (IRBs). We assume a uniform monthly accrual rate of 3.4 patients (3 patients to be randomized) following the 6 month ramp-up period. Based on the design parameters in Section 14.3.3, study accrual is projected to last 50 months (4.2 years). The final analysis is anticipated to occur approximately 68 months (5.7 years) after study initiation.

The above projected study durations are based on the hypothesized design parameters. If the actual study parameters deviate from the hypothesized ones, the actual study duration may be different from the projection. In this case the protocol will be amended accordingly to reflect the revised duration.

14.6 Secondary or Exploratory Endpoints (including correlative science aims) (15-MAR-2022)

14.6.1 Secondary Endpoints:

- Local-failure-free survival, defined as the time from randomization to local disease progression (per Section 4) or death due to any cause, whichever occurs first.
- Distant-metastasis-free survival, defined as the time from randomization to distant metastases (per Section 4) or death due to any cause, whichever occurs first.
- Progression-free survival, defined as the time from randomization to any documented progression or death due to any cause, whichever occurs first.
- Treatment-related toxicity
- The change quality of life at 9 months from randomization, as measured by EORTC quality of life questionnaires

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Local-Failure-Free Survival, Distant-Metastases-Free Survival, and Progression-Free Survival

Local-failure-free survival (LFFS) is defined as the time from randomization to local disease progression or death due to any cause, whichever occurs first. Distant-metastases-free survival (DMFS) is defined as the time from randomization to distant metastases or death due to any cause, whichever occurs first. Progression-free survival (PFS) is defined as the time between the date of randomization and the first date of documented progression or death due to any cause, whichever occurs first. For these endpoints, disease progression will be determined per Section 4. Subjects who do not progress or die will be censored on the date of their last evaluable tumor assessment as determined with radiographic evidence. Subjects who do not have any on-study tumor assessments and do not die will be censored on the second day of their date of randomization. As the disease management will change once local failure or distant metastasis occurs, for the purpose of evaluating the role of adjuvant IMPRINT, we use the following analysis plans: for LFFS, patients are censored when a distant metastasis as the sole progression occurs as the first progression event; for DMFS, patients are censored when a local failure as the sole progression occurs as the first progression event. For these endpoints, intent-to-treat (ITT) population will be used. We will compare the distributions of LFFS, DMFS and PFS between treatment arms using a one-sided stratified log-rank test (using stratification factors as strata). The rates at various timepoints (e.g., every 6 months after randomization) and medians of LFFS, DMFS and PFS for each arm will be estimated using the Kaplan-Meier method (1958). The associated 95% confidence interval (CI) will be calculated using Greenwood's formula and based on a log-log transformation applied on the survival function. Hazard ratios for LFFS, DMFS and PFS will be estimated using a stratified Cox regression model. Results from an unstratified analysis will also be provided. If any stratum has less than 5 events, the stratification factor which contains the level with the smallest number of patients will be removed from the stratified analyses.

Treatment-Related Toxicity

Adverse events (AEs) will be graded with CTCAE version 5.0. For the purpose of evaluating the role of adjuvant IMPRINT, the As-Treated (AT) patient population will be used for the analysis of safety data in this study. The AT population consists of all randomized subjects based on the treatment they actually received after randomization. Treatment-related adverse events observed after randomization will be summarized as assessed by the investigator. The worst overall grade per patient will be tabulated for both arms. Other toxicities of interest will also be assessed as necessary. All adverse events, adverse events leading to withdrawal, interruption or modification of protocol treatment, Grade ≥ 3 adverse events, and serious adverse events will be summarized. Deaths and cause of death will be summarized. The rate of treatment-related adverse events will be reported with the frequency and severity (e.g., type, grade, and attribution) by arm.

Quality of Life (QOL)/Patient-reported Outcome (PRO)

EORTC quality of life scores are transformed to a 0-100 point scale and interpreted using a minimally important difference approach. Differences in means scores is commonly

presented, which allows comparison between cohorts or from baseline within the same cohort of patients (Nowak 2004). A clinically meaningful or modest effect is defined as a difference of 10 to 20 points in a HRQOL parameter (Osoba et al., 1998). A large effect is defined as changes of ≥20 points.

For the purpose of evaluating the role of adjuvant IMPRINT, the QOL analyses for any changes between two timepoints will be performed based on all randomized patients with assessments at both timepoints, compared between the treatment arms to which they were randomized regardless of what treatment the patients actually received. The primary QOL endpoint is whether a patient experiences a clinically meaningful improvement (CMI) in EORTC-QLQ global health status score (≥10 points), from randomization to 9 months after randomization. The rates of patients experiencing a CMI changes will be compared between Arm 1 and Arm 2 using Cochran-Mantel-Haenszel test, with the exception that if at least one cell has counts less than 5, a Fisher's exact test will be used. The associated 90% confidence interval will be calculated for each arm using Clopper-Pearson method. Results from an as-treated analysis will also be provided.

As a sensitivity analysis, a mixed effects model will be used to assess changes of EORTC-QLQ global health status score across time using all available data while adjusting for stratification variables and other baseline characteristics. Mixed models are a general class of models for analyzing repeated measures data, which allow modeling of the covariance among the repeated measures as well as random effects such as patient-specific intercepts and slopes and can incorporate fixed and time-varying covariates. Fixed effects will consist of stratification factors and potentially other baseline covariates of interest. Since missing data is expected, patients with missing data will be compared to patients with complete data at each follow-up time with respect to baseline characteristics. If any of these characteristics are found to be significantly different, then they will be incorporated into the mixed effects model. Prior to performing analyses, an evaluation of the amount, reasons and patterns of missing data will be performed, using the well-known categories of missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (Fairclough 2010, Verbeke 2000). If missing data are MCAR or MAR, then a mixed model using maximum likelihood is sufficient because all available data can be used. A joint model that allows a shared parameter between the repeated measurements and time to death or drop out can be used if considered MNAR due to the high number of patient deaths or dropouts (Rizopoulos 2012). Other options for MNAR data are pattern mixture and selection models (Fairclough 2010, Little 1995). Sensitivity analyses will be performed to compare the results of different analytic strategies (Fairclough 1998).

14.6.3 Interim Analysis for Pneumonitis in Patients Receiving Immunotherapy

In addition to monitoring severe adverse events and unexpected adverse events closely and having them reviewed at the semi-annual DMC meetings, as described in section 14.4, treatment-related grade 3 or higher pneumonitis in patients who have received immunotherapy and then receive radiation therapy will be closely monitored by the study team. For the first 24 eligible patients randomized to Arm 2 who received immunotherapy, the frequency of treatment-related grade 3 or higher pneumonitis will be

continuously monitored.

Special safety interim analyses of grade 3 or higher treatment-related pneumonitis that does not improve to grade 0-2 within 4 weeks of onset will be conducted when 6, 9, 12, 15, 18, 21 and 24 patients become analyzable (e.g., patients who have been treated with immunotherapy at any time, have received at least 1 fraction of RT, and have been observed for at least 4 months after RT completion). Based on the following Bayesian toxicity monitoring rule, if the rate is considered as concerning, the study team and group leaders will discuss with CTEP about the most appropriate actions to mitigate the potential risks, including a possible major modification to study design or accrual suspension. Based on rates of grade 3 or higher treatment-related pneumonitis from IMPRINT trial and existing immunotherapy trials, we assume a priori that Arm 2 has an average grade 3 or higher pneumonitis rate of approximately 8% and that there is an approximately 14% chance that the risk will be 18% or higher (e.g., 10% or more increase), which corresponds to a Beta (0.08, 0.92) prior distribution. We then consider the rate of toxicity to be concerning if the posterior probability of the grade 3 or higher pneumonitis rate ≥18% is more than 70%. Table 14.1 summarizes the Bayesian monitoring rule when the 6^{th}, 9^{th}, 12^{th}, 15^{th}, 18^{th}, 21^{st} and 24^{th} patients become analyzable.

Table 14.1 Bayesian Toxicity Monitoring Rule

Total # of analyzable patients	6	9	12	15	18	21	24
# patients with grade 3 or higher pneumonitis	2	3	4	4	5	6	6

Table 14.2 summarizes the operating characteristics based on 5,000 simulations with 12 patients in terms of how frequent Arm 2 may be considered "alarming" for accrual suspension.

Table 14.2 Operating characteristics of the monitoring rule

Underlying risk	0.1	0.15	0.2	0.25	0.3
% of time stopping considered	14.7%	33.6%	54.8%	73.3%	86.9%

14.6.4 Power Calculations for Quality of Life (QOL) Research:

The primary QOL hypothesis is that the proportion of patients in Arm 2 who experience clinically meaningful improvement (CMI) in QOL at 9 months after randomization (p2) is larger than that in the control arm (p1), e.g., p2>p1. This hypothesis will be tested at a 1-sided type 1 error of 5%, using Fisher's exact test to compare the proportions of patients experiencing CMI between the two arms.

By definition, only participants who are alive at 9 months after randomization could potentially be analyzable for QOL analysis. Based on the primary hypothesis of OS, the survival rate at 9 months is approximately 59% under H_0, and 73% under H_1. We define patients as analyzable if they are randomized and have assessments at both timepoints (at randomization and 9 months post-randomization). While great efforts will be made to minimize patients' attrition such that the number of analyzable cases can be maximized, it is well acknowledged that uncertainty still exists in the total number of analyzable

cases. Furthermore, to our best knowledge, there are no existing data available in this population that can be used for the control group, nor a widely accepted difference in patients experiencing CMI. Therefore, we argue the sample size of the QOL component should not be determined by detecting a fixed difference between patients' proportions of experiencing CMI. Instead, we demonstrate that, under reasonable assumptions, it is reasonable and justifiable to offer QOL to all patients to detect non-trivial differences in proportions of patients experiencing CMI. The following table assumes 85% of randomized patients who remain alive at 9 months after randomization are analyzable (e.g., an attrition rate of 15%). When the attrition rate is lower, e.g., smaller than 15%, greater power is expected to detect same differences in CMI proportions.

Table 14.3: Power of Comparing Primary QOL Endpoint at 9 months post-randomization

% Experienced CMI in Arm 2 (p_2)	% Experienced CMI in Arm 1 (p_1)	Power
30%	10%	62%
40%	10%	90%
40%	20%	52%
50%	20%	84%

14.7 Exploratory Hypothesis and Endpoints (15-MAR-2022)

14.7.1 Exploratory endpoints

- The degree of under-staging, concordant and upstaging between centrally-reviewed clinical staging (based on PET, CT and/or MRI) and pathologic staging
- Immunologic and pathologic biomarkers as predictors of response
- Association between radiation dose to gross residual disease and local control
- Rate of R0/R1 and R2 resections, by type of procedures (extended Pleurectomy/Decortication (P/D), P/D and partial pleurectomy)
- EORTC QLQ-Q30 and LC13 symptoms in patients treated with IMPRINT who respond with "quite a bit" or "very much" LC13 symptoms at 9-12 months post-randomization and at 3 months post-randomization
- Changes in health-related quality of life, functional domains, and symptoms over time with the addition of adjuvant hemithoracic IMPRINT as compared to surgery and systemic therapy alone.
- Prognostic values of center patient volume (≤10 versus >10 P/D/year) and systemic therapy type (chemotherapy vs immunotherapy).
- Optimization of quality assurance methodologies and processes for radiotherapy and imaging with machine learning strategies

14.7.2 Analysis plans for exploratory endpoints

For each subject, the centrally-reviewed clinical staging (based on PET, CT and/or MRI) will be compared with pathologic staging to determine whether it is under-staging (clinical staging is more extensive than pathologic staging), concordant (clinical staging is same as pathologic staging), or upstaging (clinical staging is less extensive than pathologic staging). The proportion of under-staging, concordant and upstaging, along

with the associated 95% confidence intervals, will be reported.

For each immunologic and pathologic biomarker of interest, response status between patients with and without respective biomarker will be summarized and compared. Chi-square test will be used for univariate comparisons between biomarker positive and negative cases. Assessment of potential prognostic factors will be evaluated in multivariable analyses using logistic regression. A stepwise model selection approach will be used to identify all significant risk factors. Each step of model building will contain the main effect for each biomarker as well as treatment arm. Factors which are significant at a 5% level will be kept in the final model. The potential interactions between the main effect and all significant risk factors, as well as treatment arm, will be tested.

Gross residual disease and local failure will be analyzed as competing risk data (death without gross residual disease or death without local failure as the respective competing event). Association between radiation dose to gross residual disease and local failure will be evaluated similarly in multivariable analyses using Fine-Gray regression model.

Proportions of R0/R1 and R2 resections, by type of procedures (extended Pleurectomy/Decortication (P/D), P/D and partial pleurectomy), along with 95% confidence intervals, will be reported.

A mixed effects model will be used to assess changes in health-related quality of life, functional domains, and symptoms over time using all available data while adjusting for stratification variables and other baseline characteristics, as elaborated in Section 14.6.2.

Prognostic values of center patient volume (≤10 versus >10 P/D/year) and systemic therapy type (Chemotherapy versus Immunotherapy), with respect to OS and PFS, will be determined using Cox regression model.

<u>Radiotherapy and imaging with machine learning strategies</u>
MPM treatment planning is difficult and complex due to the presence of large target volumes (PTVs), the possibility of concurrent integrated boost, and attempts to spare many organs at risk (OARs) (eg, spinal cord, lung, esophagus, heart, brachial plexus, liver, bowel, kidneys, stomach and other organs at risk). Both the delineation of target and organ-at-risk structures and the planning of radiation are complicated. IMRT/IMPT optimization is iterative in nature in order to fulfill the treatment planning process's objectives. The time required to construct a decent plan and the plan's quality are both dependent on the planner's experience; thus, variance in the quality of plans and the time required for planning is always recognized (efficiency).

The Center for Innovation in Radiation Therapy (CIRO) and the Imaging and Radiation Oncology Core's (IROC) radiation therapy quality assurance center (RTQA) will use machine learning technologies to assess the quality of radiotherapy plans and to enhance them. Machine learning and artificial intelligence models will be trained using multi-institutional data to help ensure the consistency and quality of MPM radiation.

14.8 Gender/Ethnicity/Race Distribution (15-MAR-2022)

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	2	0	0	2
Asian	0	7	0	0	7
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	10	0	0	12
White	24	86	1	3	114
More Than One Race	0	0	0	0	0
Total	26	105	1	3	135

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	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	0	1	0	0	1
White	3	10	0	1	14
More Than One Race	0	0	0	0	0
Total	3	11	0	1	15

REFERENCES (15-MAR-2022)

Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. Lancet Oncol. 2017 May 18(5):623-630.

Basch E, Jia X, Heller G, et al. J Natl Cancer Inst. 2009 Dec 2; 101(23):1624-32: PMID: 19920223.

Baas P, Scherpereel A, Nowak A, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2021 Jan 30;397(10272):375-386.

Burkholder D, Hadi D, Kunnavakkham R, et al. Ann Thorac Surg, 2015 May;99(5):1775-80; PMID: 25827675.

Byrne MJ and Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol, 2004 Feb; 15(2):257-60.

Chang JY, Xiaodong Z, Knopf A, et al. Consensus Guidelines for Implementing Pencil-Beam Scanning Proton Therapy for Thoracic Malignancies on Behalf of the PTCOG Thoracic and Lymphoma Subcommittee. IJROBP 2017 Sept 1; 99(1) 41-50.

ClinicalTrials.gov Identifier: NCT02784171 - Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma

ClinicalTrials.gov Identifier: NCT02899195 - Phase II MEDI4736 in Combination With Chemotherapy for First-Line Treatment of Unresectable Mesothelioma (PrE0505).

ClinicalTrials.gov Identifier: NCT03762018 - BEAT-meso: Bevacizumab and Atezolizumab in Malignant Pleural Mesothelioma (BEAT-meso)

ClinicalTrials.gov Identifier: NCT04334759 - DuRvalumab With chEmotherapy as First Line treAtment in Advanced Pleural Mesothelioma (DREAM3R)

ClinicalTrials.gov Identifier: NCT00715611 - Pleurectomy/Decortication (Neo) Adjuvant Chemotherapy and Intensity Modulated Radiation Therapy to the Pleura in Patients With Locally Advanced Malignant Pleural Mesothelioma.

Cockcroft, DW and Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41.

Fairclough D. Design and analysis of quality of life studies in clinical trials (2nd ed.). Boca Raton, FL: Chapman & Hall/CRC; 2010.

Fairclough DL, Peterson HF, Cella D, Bonomi P. Comparison of several model-based methods

for analysing incomplete quality of life data in cancer clinical trials. *Stat Med*. Mar 15-Apr 15 1998;17(5-7):781-796.

Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/ decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. J Thorac Cardiovasc Surg 2008; 135:620-626.

Forde, PM, Anagnostou V, Sun Z, et al. Durvalumab with platinum-pemetrexed for unresectable pleural mesothelioma: survival, genomic and immunologic analyses from the phase 2 PrE0505 trial. Nat Med 27, 1910–1920 (2021).

Freidlin B, Korn EL, Gray R. A general inefficacy interim monitoring rule for randomized clinical trials. Clin Trials 2010; Jun;7(3):197-208.

Gupta V, Mychalczak B, Krug L, et al. Hemithoracic radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma. Int J Radiation Oncol Biol Phys 2005; 63(4):1045-1052.

Hassan R, Thomas A, Nemunaitis JJ, et al. Efficacy and Safety of Avelumab Treatment in Patients With Advanced Unresectable Mesothelioma - Phase 1b Results From the JAVELIN Solid Tumor Trial. JAMA Oncol. 2019;5(3):351-357.

Hollen PJ, Gralla RJ, Liepa AM, et al. Support Care Cancer. 2006 Jan;14(1):11-21; PMID: 15999264.

Krug LM, Pass HI, Rusch VW, et al. J Clin Oncol 2009; 27(18): 3007-3013; PMCID: PMC3646305.

Lan KK and DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983; 70: 659-663.

Little RA. Modeling the Drop-out Mechanism in Repeated-Measures Studies. *J Am Stat Assoc*. 1995;90(431):1112-1121

Mollberg NM, Vigneswaran Y, Kindler HL, et al. Ann Thorac Surg. 2012 Oct;94(4):1086-92. PMID: 22921241.

Nowak AK, Lesterhuis WJ, Kok PS, et al. Durvalumab with first-line chemotherapy in previously untreated malignant pleural mesothelioma (DREAM): a multicentre, single-arm, phase 2 trial with a safety run-in. Lancet Oncol. 2020 Sep;21(9):1213-1223.

Okada M, Kijima T, Aoe K, et al. Clinical Efficacy and Safety of Nivolumab: Results of a Multicenter, Open-label, Single-arm, Japanese Phase II study in Malignant Pleural Mesothhelioma (MERIT). Clin Cancer Res. 2019 Sep 15;25(18):5485-5492.

Osoba D, Rodrigues G, Myles J, et al. J Clin Oncol. 1998 Jan;16(1):139-44; PMID: 9440735.

Rimner A and Rosenzweig K. Novel radiation therapy approaches in malignant pleural mesothelioma. Ann Cardiothorac Surg 2012; 1(4):457-461; PMCID: PMC3741784.

Rena O, Casadio C. Extrapleural pneumonectomy for early stage malignant pleural mesothelioma: a harmful procedure. Lung Cancer. 2012 Jul;77(1):151-5; PMID: 22244608.
Rice D, Rusch V, Pass H, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the international association for the study of lung cancer international staging committee and the international mesothelioma interest group. J Thorac Oncol, 2011; Aug;6(8):1304-12.

Rice D, Rusch V, Pass H, et al. Recommendations for Uniform Definitions of Surgical Techniques for Malignant Pleural Mesothelioma: A Consensus Report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group. Journal of Thoracic Oncology. Vol 6(8);Aug 2011:1304-1312.

Rimner A, Zauderer MG, Gomez DR, et al. J Clin Oncol 2016; 34(23):2761-2768; PMCID: PMC5019761.

Rimner A, Spratt DE, Zauderer MG, et al. Int J Radiation Oncol Biol Phys 2014; 90(2):394-401; PMCID: PMC5560169.

Rintoul RC, Ritchie AJ, Edwards JG, et al. Lancet. 2014 Sep 20;384(9948):1118-27; PMID: 24942631.

Rizopoulos D. Joint models for longitudinal and time-to-event data with applications in R. Boca Raton, FL: Chapman & Hall/CRC; 2012
Rosenzweig KE, Zauderer MG, Laser B, et al. Int J Radiation Oncol Biol Phys 2012; 83(4):1278-1283; PMCID: PMC4359620.

Rusch VW, Rosenzweig K, Venkatraman E, et al. A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2001; 122:788-795.

Shaikh F, Zauderer MG, von Reibnitz D, et al. Improved Outcomes with Modern Lung-Sparing Trimodality Therapy in Patients with Malignant Pleural Mesothelioma. J Thorac Oncol. 2017 Jun;12(6):993-1000.

Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. Lancet Oncol. 2019 Feb;20(2):239-253.

Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol. 2016 Aug;11(8)1204-1223.

Treasure T, Lang-Lazdunski L, Waller D, et al. Lancet Oncol 2011; 12:763-772; PMCID: PMC3148430.

Verbeke G, Molenberghs G. Linear Mixed Models for Longitudinal Data. New York, NY: Springer-Verlag; 2000.

Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. JCO 2003 Jul 15;21(14):2636-44.

Zauderer MG and Krug LM. .Ann Cardiothorac Surg 2012; 1(4):487-490; PMCID: PMC3741800**.**

APPENDIX A (15-MAR-2022)
CARBOPLATIN DOSE CALCULATION INSTRUCTIONS

1) The Cockcroft-Gault formula will be used in NRG Oncology trials.

Dosing of Carboplatin:

1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using creatinine clearance (mL/min) from the Cockcroft-Gault formula.

2) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using **a minimum value of 0.7 mg/dL.**

3) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin will not need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

4) Carboplatin doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have systemic therapy doses recalculated for < 10% weight changes.

5) At the time of dose modification, if the patient's age had changed (the patient has had a birthday), the site can use the current age.

CALVERT FORMULA:
Carboplatin dose (mg) = target AUC x (GFR [or estimated CrCl] + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.
Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

The maximum allowed doses of carboplatin are:
AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (mL/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (years)] x actual body Weight* (kg)}}{\textbf{72 x serum creatinine (mg/dl)}} \quad \textbf{\{x 0.85 } \textit{\textbf{if female}}\textbf{\}}$$

Notes:

1) Weight in kilograms (kg):
   a. Body Mass Index (BMI) should be calculated for each patient.

   b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.

   c.***Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**

   d. Adjusted weight calculation:
   Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) (+ 45.5 females) or (+ 50 for men)
   Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

   At the time of a dose modification for toxicity:
   If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.