NRG ONCOLOGY

NRG-LU002

(ClinicalTrials.gov NCT #03137771)

MAINTENANCE SYSTEMIC THERAPY VERSUS LOCAL CONSOLIDATIVE THERAPY (LCT) PLUS MAINTENANCE SYSTEMIC THERAPY FOR LIMITED METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC): A RANDOMIZED PHASE II/III TRIAL

Amendment 11: October 18, 2023

NRG ONCOLOGY
NRG-LU002
(ClinicalTrials.gov NCT #03137771) (18-MAY-2018)

MAINTENANCE SYSTEMIC THERAPY VERSUS LOCAL CONSOLIDATIVE THERAPY (LCT) PLUS MAINTENANCE SYSTEMIC THERAPY FOR LIMITED METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC): A RANDOMIZED PHASE II/III TRIAL (18-MAY-2018)

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 (22-FEB-2023)

Principal Investigator/Radiation Oncology
Puneeth Iyengar, MD, PhD
UT Southwestern Medical Center
5323 Harry Hines Blvd
Dallas, TX, 75235
214-645-7603/Fax: 214-645-8526
puneeth.iyengar@utsouthwestern.edu

Co-Investigator/Radiation Oncology (SWOG)
Daniel Gomez, MD
Memorial Sloan Kettering Cancer Center
1275 York Ave.
New York, NY 10021
212-639-2485
gomezd@mskcc.org

Radiation Oncology Co-Chair
Robert Timmerman, MD
UT Southwestern Medical Center
5801 Forest Park Road
Dallas, TX 75390-9183
214-645-7651/Fax: 214-645-7624
Robert.Timmerman@UTSouthwestern.edu

Study Team (Continued)

Radiation Oncology Co-Chair
Charles Simone, MD
New York Photon Center
225 East 126 Street
New York, MD 10035 US
646-968-9012
csimone@nyproton.com

Radiation Oncology Co-Chair
Clifford Robinson, MD
Washington University School of Medicine
4921 Parkview Place, Floor LL
Campus Box 8224
St. Louis, MO 63110
crobinson@radonc.wustl.edu

Medical Oncology Co-Chair
David Gerber, MD
UT Southwestern Medical Center
5323 Harry Hines Blvd., Mail Code 8852
Dallas, TX 75390-8852
214-648-4180/Fax: 214-648-1955
david.gerber@utsouthwestern.edu

Medical Oncology Co-Chair
Saiama N. Waqar, MBBS, MSCI
Washington University School of Medicine
660 S Euclid Ave, Campus Box 8056
Saint Louis, MO 63110
314-747-8475/Fax: 314-362-7086
saiamawaqar@wustl.edu

Surgical Co-Chair
Jessica S. Donington, MD MSCR
The University of Chicago Medicine
5841 South Maryland Avenue
Mc5040
Chicago, IL 60637 US
773-702-0819
jdonington@uchicago.edu

Surgical Co-Chair
Stephen G. Swisher, MD
M D Anderson Cancer Center
1400 Pressler, Unit 1447
Houston, Texas 77030-4009
713-792-8659/Fax: 713-563-1918
sswisher@mdanderson.org

Medical Physics Co-Chair
Michael Weldon, MSc, DABR
Department of Radiation Oncology
The Ohio State University
460 W. 10th Ave. Room A201
Columbus, OH 43210
614-293-2077/Fax: 614-685-5219
michael.weldon@osumc.edu

Medical Physics Co-Chair
Jackie Wu, PhD
Duke University Radiation Oncology
201 Trent Dr., Box 3295
Durham, NC 27710
919-681-1841/Fax: 919-681-7183
jackie.wu@duke.edu

MAINTENANCE SYSTEMIC THERAPY VERSUS LOCAL CONSOLIDATIVE THERAPY (LCT) PLUS MAINTENANCE SYSTEMIC THERAPY FOR LIMITED METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC): A RANDOMIZED PHASE II/III TRIAL

Study Team (Continued)

Quality of Life Co-Chair
Ben Movsas, MD
Henry Ford Health System
2799 West Grand Blvd
Detroit MI 48202
313-916-5188/Fax 313-916-3264
bmovsas1@hfhs.org

Pathology Co-Chair
Jeffry P. Simko, MD, PhD
University of California, San Francisco
Dept. of Pathology
Box 4066, 1825 4th St., Room M2360
San Francisco, CA 94143
415-353-7581/Fax: 415-353-1612
jeff.simko@ucsf.edu

Translational Co-Chair
Maximilian Diehn, MD, PhD
Stanford University
Lorry Lokey Stem Cell Research Bldg
Rm G2120A, 265 Campus Dr.
Stanford, CA 94305-5458
650-721-1550/Fax: 650-725-8231
diehn@stanford.edu

Translational Co-Chair
Adam P. Dicker, MD, PhD
Jefferson University
Bodine Center, Ste. G-301
111 South 11th St.
Philadelphia, PA 19107
215-955-6702/Fax: 215-955-0412
Adam.Dicker@jefferson.edu

NCORP Community Chair
Bryan Faller, MD
Heartland NCORP
Missouri Baptist Medical Center
3015 N. Ballas Rd.
Saint Louis, MO 63105
314-996-5514
Bryan.faller@bjc.org

Senior Statistician
Chen Hu, PhD
NRG Oncology Statistical and Data Management Center & John Hopkins University School of Medicine
50 South 16th Street, Suite 2800
Philadelphia, PA 19102
215-940-4842/Fax: 215-928-0153
HuC@NRGOncology.org

The following NCTN Group Study Champions have been added to this trial:

The Alliance for Clinical Trials Oncology	Pranshu Mohindra, MD University of Maryland School of Medicine, Baltimore 22 S. Green St., Rm GGJ35 Baltimore, MD 21201 410-328-6080/Fax: 410-328-5279 PMohindra@som.umaryland.edu
SWOG	Daniel Gomez, MD Division of Radiation Oncology Memorial Sloan Kettering Cancer Center 1275 York Avenue New York, NY 10021 212-639-2485 gomezd@mskcc.org
	Sukhmani Kaur Padda, MD Cedars Sinai Medical Center Department of Hematology/Oncology 8700 Beverly Blvd., SCCT 1S31 Los Angeles, CA 90036 310-423-0377 sukhmani.padda@cshs.org
ECOG-ACRIN	Devika Das, MD 700 South 19th Street Research Services 151 Birmingham, AL 35233 205-933-8101 Devika.Das@va.gov

NRG Oncology Contact Information(18-OCT-2023)

Data Manager: For questions concerning eligibility or data submission	Leila Williams NRG Oncology 50 South 16th Street, Suite 2800 Philadelphia, PA 19102 215-717-3211 Williamsl@NRGOncology.org

	Tammy Bausinger NRG Oncology 50 South 16th Street, Suite 2800 Philadelphia, PA 19102 215-574-3223 BausingerT@NRGOncology.org
RTQA Dosimetrist: For questions concerning RT data submission	Jennifer Presley, B.S., R.T., (R)(M)(T), ARRT IROC Philadelphia – RT QA Center ACR Center for Innovation and Research 50 South 16th Street, Suite 2800 Philadelphia, PA 19102 215-574-3153 jpresley@acr.org
RTQA: For questions concerning data submission to TRIAD	Triad-Support@acr.org
Protocol Development: For questions concerning protocol and informed consent versions & amendments	Jennifer Petrask NRG Oncology 50 South 16th Street, Suite 2800 Philadelphia, PA 19102 215-717-3909 PetraskJ@ NRGOncology.org
Lung Cancer Committee Chair:	Jeffrey D. Bradley, MD University of Pennsylvania/Abramson Cancer Center Philadelphia, PA 19104 215-662-4853 Jeffrey.bradley@pennmedicine.upenn.edu

Protocol Agent (30-MAR-2021)

Agent	**Supply**	**NSC #**	**IND #**
Pemetrexed	Commercial	698037	Exempt
Gemcitabine	Commercial	613327	Exempt
Pembrolizumab	Commercial	776864	Exempt
Atezolizumab	Commercial	783608	Exempt
Nivolumab	Commercial	748726	Exempt
Ipilimumab	Commercial	732442	Exempt

Participating Sites:
☒ U.S.
☒ Canada
☒ Approved International Member Sites

Document History

	Version Date	**Broadcast Date**
Amendment 11	**October 18, 2023**	**N/A**
Amendment 10	August 18, 2023	N/A
Amendment 9	February 22, 2023	N/A
Amendment 8	October 25, 2021	N/A
Amendment 7	July 19, 2021	N/A
Amendment 6	May 26, 2021	N/A
Amendment 5	March 30, 2021	N/A
Amendment 4	March 02, 2020	N/A
Amendment 3	November 22, 2019	N/A
Amendment 2	June 22, 2018	N/A
Amendment 1	May 18, 2018	N/A
Activation	March 17, 2017	April 7, 2017

<table>
<tr><th colspan="3">CONTACT INFORMATION (18-AUG-2023)</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For data submission:</th></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 the 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), or CTSURegHelp@coccg.org 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). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e. patient eligibility or treatment-related)</u> Contact the study data manager listed on the NRG Oncology contact information table on the protocol cover page.</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>

For imaging data submission questions:
IROCimagearchive@acr.org; please include trial number in the email subject line.

For TRIAD access and installation support:
TRIAD-Support@acr.org
Triadhelp.acr.org

TRIAD Software Installation:
https://triadinstall.acr.org/triadclient/

TABLE OF CONTENTS

NRG-LU002

SCHEMA (30-MAR-2021)

Patients with metastatic NSCLC having completed at least 4 cycles or courses* of first-line/induction systemic therapy Restaging studies reveal no evidence of progression and limited metastatic disease (0-3 discrete extracranial sites), all of which must be amenable to SBRT/ radiation +/- Surgery A minimum of one disease site (metastasis or primary) needs to be present after first-line/induction systemic therapy and treatable with local consolidative therapy	**S T R A T I F Y**	**Histology:** Squamous vs. Non-squamous **Systemic Therapy:** Immunotherapy-containing Induction Regimens vs. Cytotoxic Chemotherapy-Only Induction Regimens**	**R A N D O M I Z E**	**Arm 1**: Maintenance systemic therapy alone** **Arm 2:** SBRT/radiation or SBRT/ radiation and Surgery to all sites of metastases (0-3 discrete sites) and/or irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance systemic therapy. All Arm 2 patients, even if treated with Surgery, must have one site of disease (metastasis or primary) treated with radiation*** If a metastatic site is best treated with hypofractionated radiation, this will be permitted if SBRT or surgery not indicated *** **As noted in Section 5**

* Patients must be registered after 4 courses of first-line/induction systemic therapy but before the administration of course 6.

** Acceptable systemic therapy for NRG-LU002 is listed in Sections 5 and 9.

*** Randomization will be 2:1 between Arm 2 and 1.

Systemic Therapy (see Section 5 for a list of treatment options):
(Arm 1): Maintenance systemic therapy should begin/continue within 2 weeks of randomization.
(Arm 2): Radiation should begin within 2 weeks of randomization and maintenance systemic therapy should begin/continue within 2 weeks of the completion of radiation. Maintenance systemic therapy must begin/continue within 3 weeks after completion of surgery if last local therapy modality.

Radiotherapy and Surgery for Local Therapy:
Investigators are *strongly* encouraged to directly contact the study PI and/or radiation oncology/surgery co-chairs about any questions concerning eligibility or concerns regarding

radiation delivery (i.e., SBRT in the setting of concurrent SBRT/hypofractionated RT to the primary, SBRT in the setting of prior RT to the primary, SBRT to multiple sites, etc.) or surgical approaches (i.e., resection after thoracic radiation, extent of resections, resection techniques for metastatic sites, timing of resections and delivery of SBRT).

1.0 OBJECTIVES

1.1 Primary Objectives (18-MAY-2018)

1.1.1 Phase II:
To evaluate the impact of adding LCT (local consolidative therapy) to maintenance systemic therapy versus maintenance systemic therapy alone on progression-free survival for patients with metastatic NSCLC with no evidence of progression and limited metastatic sites after first-line systemic therapy

1.1.2 Phase III:
To evaluate the impact of adding LCT to maintenance systemic therapy versus maintenance systemic therapy alone on overall survival for patients with metastatic NSCLC with no evidence of progression and limited metastatic sites after first-line systemic therapy

1.2 Secondary Objectives (18-MAY-2018)

1.2.1 To evaluate the impact of adding LCT to maintenance systemic therapy versus maintenance systemic therapy alone on in-field local failure;

1.2.2 To evaluate the impact of adding LCT to maintenance systemic therapy versus maintenance systemic therapy alone on the time to development of new lesions;

1.2.3 To evaluate the impact of adding LCT to maintenance systemic therapy versus maintenance systemic therapy alone on toxicity;

1.2.4 To evaluate the impact of adding LCT to maintenance systemic therapy versus maintenance systemic therapy alone on duration of maintenance systemic therapy usage.

1.2.5 To evaluate the effect of adding LCT to systemic therapy in limited stage IV NSCLC on Quality of Life (QOL)

1.2.6 To collect biospecimens and evaluate the correlation between clinical outcomes and circulating tumor DNA (ctDNA)

2.0 BACKGROUND

2.1 Rationale for Selected Approach and Trial Design (30-MAR-2021)

Approximately 50-60% of all non-small cell lung cancer (NSCLC) patients present with stage IV disease (National Cancer Institute SEER Cancer Statistics Review 2019). Likewise, a significant proportion of stage I-III NSCLC patients eventually develops metastases after their initial definitive therapy. Traditionally, systemic therapy has been the treatment of choice for these patients. First-line cytotoxic chemotherapy provides a partial response or stable disease in more than two-thirds of patients with metastatic NSCLC (Brodowicz 2006, Ramalingam 2008). Maintenance systemic therapy also improves outcomes in patients with metastatic non-small cell lung cancer. Subsets of maintenance systemic therapy patients have significant OS outcomes tied to progression-free survival (PFS) improvements, suggesting that better local control may help improve PFS and subsequently OS. In reviewing a consecutive series of stage IV NSCLC patients treated with systemic therapy alone, the majority failed at original sites of gross disease (Rusthoven 2009).

The landscape of systemic therapy options for patients whose tumors do not harbor a targetable molecular alteration (eg, EGFR, ALK) has evolved from platinum based chemotherapy to immunotherapy plus or minus platinum-based chemotherapy for immunotherapy-eligible patients. Chemotherapy with a platinum doublet continues to be the standard of care for individuals who are not candidates for immunotherapy in the first line setting. As of October 2020, National Comprehensive Cancer Network (NCCN)-recommended regimens include the following:

If tumor PD-L1 expression ≥50%:

- Atezolizumab (anti-PDL1) monotherapy

If tumor PD-L1 expression ≥1%:

- Pembrolizumab (anti-PD1) monotherapy
- Nivolumab (anti-PD1) plus ipilimumab (anti-CTLA4)

For any PD-L1 expression:

- Pembrolizumab plus (carboplatin or cisplatin)-pemetrexed (non-squamous)
- Pembrolizumab plus carboplatin-(paclitaxel or albumin-bound paclitaxel) (squamous)
- Atezolizumab (anti-PDL1) plus carboplatin-paclitaxel + bevacizumab (non-squamous)
- Atezolizumab plus carboplatin and albumin-bound paclitaxel (non-squamous)
- Nivolumab + ipilimumab plus pemetrexed + (carboplatin or cisplatin) (chemotherapy for first two cycles only) (non-squamous)
- Nivolumab + ipilimumab plus paclitaxel + carboplatin (chemotherapy for first two cycles only) (squamous)

Approvals for these regimens reflect their improved efficacy and acceptable toxicity profiles compared to chemotherapy-alone regimens and are summarized in the table below:

REGIMEN	STUDY	RESPONSE RATE	MEDIAN PFS (MONTHS)	MEDIAN OS (MONTHS)	REFERENCE
Atezolizumab	IMpower110	38.3%	8.1	15.7	Herbst RS etal. NEJM 2020
Atezolizumab plus carboplatin or cisplatin and pemetrexed	IMpower 132	38-72% (based on PD-L1 expression)	7.6	18.1	Papadimitrakopoulou VA et al. WCLC Meeting 2018
Atezolizumab plus carboplatin and albumin-bound paclitaxel	IMpower130	49.2%	7.2	18.6	West H et al. Lancet Oncol 2019
Atezolizumab plus carboplatin,	IMpower150	63.5%	8.3	19.2	Socinski MA et al. NEJM 2018

paclitaxel and bevacizumab					
Pembrolizumab (PD-L1>50%)	KEYNOTE-024	44.8%	10.3	NR	Reck M et al. NEJM 2016
Pembrolizumab (PD-L1>1%)	KEYNOTE-042	27-39% (based on TPS score)	5.4-7.1 (based on TPS score)	17.7	Mok TS et al. Lancet 2019
Pembrolizumab plus carboplatin or cisplatin and pemetrexed	KEYNOTE-189	47.6%	8.8	NR	Gandhi, L et al. NEJM 2018
Pembrolizumab plus carboplatin and paclitaxel or albumin-bound paclitaxel	KEYNOTE-407	57.9%	6.4	15.9	Paz-Ares L et al. NEJM 2018
Nivolumab plus ipilimumab	CheckMate 227	35.9%	-	17.1	Hellman M et al. NEJM 2019
Nivolumab + ipilimumab plus + (platinum doublet (chemotherapy for first two cycles only)	CheckMate 9LA	38%	6.7	15.6	Reck M. et al. JCO 2020

*NR: not reached

For patients with contraindications to immune checkpoint inhibitors, there remain numerous platinum-doublet regimens, some including the antiangiogenic agent bevacizumab (NCCN Guidelines). NCCN recommended first-line platinum-based options include:

- Carboplatin and albumin-bound paclitaxel
- Carboplatin or cisplatin and gemcitabine
- Carboplatin or cisplatin and paclitaxel
- Cisplatin or carboplatin and etoposide
- Carboplatin or cisplatin and pemetrexed (non-squamous)
- Carboplatin or cisplatin, pemetrexed and bevacizumab (non-squamous)
- Carboplatin, paclitaxel and bevacizumab (non-squamous)

In patients with no evidence of disease progression following 4-6 cycles of platinum-based chemotherapy plus or minus immunotherapy and/or bevacizumab, maintenance therapy may be continued in patients with preserved performance status, who are tolerating treatment well. Continuation of systemic therapy that was included in the first-line regimen is referred to as continuation maintenance therapy, while switching to a maintenance drug which was not part of the original systemic therapy regimen is known switch maintenance.

Depending on the induction regimen, continuation maintenance therapy may include:

- Continuation of atezolizumab monotherapy
- Continuation of pembrolizumab monotherapy
- Continuation of nivolumab plus ipilimumab
- Pemetrexed plus pembrolizumab OR pembrolizumab monotherapy OR pemetrexed monotherapy after platinum-pemetrexed + pembrolizumab
- Pembrolizumab monotherapy after carboplatin-(paclitaxel or albumin-bound paclitaxel) + pembrolizumab
- Atezolizumab monotherapy after carboplatin-(paclitaxel or albumin-bound paclitaxel) + atezolizumab
- Atezolizumab plus bevacizumab OR atezolizumab monotherapy OR bevacizumab monotherapy after carboplatin-paclitaxel + atezolizumab + bevacizumab
- Pemetrexed and bevacizumab maintenance therapy after platinum, pemetrexed and bevacizumab
- Bevacizumab maintenance therapy after platinum-paclitaxel and bevacizumab

NOTE: Although approved for advanced non-squamous NSCLC, bevacizumab-containing regimens are not permitted in NRG-LU002 due to the potential for increased complications from local therapy.

Role of local therapy in advanced NSCLC

A large number of patients with stage IV NSCLC found at initial diagnosis or those who develop metastases after curative intent treatment for earlier-stage disease are clinically found to have metastases in limited distinct anatomic locations, within the same or different organ sites (lung, liver, adrenal, bone, etc.). Mehta et al reported that 74% of patients presenting with newly diagnosed stage IV NSCLC had metastases in one to two organs, and 50% had three or fewer metastatic sites in addition to the primary lung cancer (Mehta 2004). In a consecutive series of patients with metastatic NSCLC, more than 50% had disease patterns amenable to stereotactic body radiation therapy (SBRT) in an oligometastatic distribution (Rusthoven 2009). Ultimately, based on these and other reports, approximately 50% of all stage IV patients would potentially be eligible for studies evaluating therapies in a limited metastatic NSCLC disease population.

Historically, subsets of patients with limited metastatic sarcoma and colorectal primaries have had extended PFS and OS after aggressive, local therapy to these metastatic deposits (Hellman 1995, Weichselbaum 2011, Fong 1999, Pastorino 1997, Strong 2007). Knowing that more than half of all stage IV NSCLC patients have lesions potentially amenable to local non-invasive treatments in the form of SBRT provides a clear rationale for determining if local therapies add value to systemic therapy in patients with limited metastatic NSCLC in enhancing control and survival endpoints (Rusthoven 2009).

The oldest series supporting use of local consolidative therapy (LCT) for stage IV NSCLC involved use of lung resection and brain radiation for patients with isolated brain metastasis with evidence for prolongation of survival and improved survival compared to chemotherapy alone. (Patchell 1990, Burt 1992) Resection by lobectomy remains a

standard treatment option for patients with isolated brain metastasis, with improved survival for node negative patients and those undergoing complete resection (Kozower 2013). The majority of series using surgery in oligometastatic disease are single institution retrospective series and are dominated by metastasis to the brain and adrenal glands.

Previously, non-randomized, prospective and retrospective data suggested a potential survival benefit from radiation for limited metastatic NSCLC. In a single arm prospective trial, either radiation or surgery was used in consolidation of NSCLC patients with synchronous NSCLC metastases in an oligometastatic distribution, demonstrating significant survival outcomes when compared to historical findings for similar patients treated with only systemic therapy (De Ruysscher 2012). Radiotherapy alone in consolidation following first-line chemotherapy in stage IV NSCLC to 5 or fewer locations of limited metastatic disease plus the primary tumor demonstrated a positive outcome even in patients who progressed through first-line therapy, with an OS of 22.7 months and PFS of 7.6 months (Salama 2012). A parallel experience of oligometastatic NSCLC patients treated with definitive doses of local irradiation to all disease sites suggested an OS of 22 months (Xanthopoulos 2015). Other groups have observed similar survival findings retrospectively with radiation given in a consolidative fashion for oligometastatic disease (highlighted in subsequent sections).

Prospective, multi-institutional single-arm, phase II data from UT Southwestern and the University of Colorado in patients with progressive disease who received second-line erlotinib plus SBRT to 6 or fewer locations of limited disease (metastatic sites plus primary) showed a PFS of nearly 15 months and OS of nearly 20.4 months. EGFR mutation testing on tissue available from half of the patients enrolled (24 total patients in the phase II study) found all to be EGFR wild type, suggesting that most of the survival benefit came from the radiation (Iyengar 2014). A phase II, single-arm study published in the *Annals of Oncology* from Europe reported that treatment of limited metastatic NSCLC up front in the first-line setting with hypofractionated radiation established an OS of 23 months (Collen 2014). A meta-analysis of oligometastatic NSCLC, mostly 1-3 lesions treated with surgery or radiation, described OS in the range of 26 months (Ashworth 2014). More recently, a phase II randomized study was completed which demonstrated that local consolidation with radiation or surgery of limited metastatic NSCLC stable after induction systemic therapy provided a tripling of PFS and an improvement in OS when compared to systemic therapy alone (Gomez 2019). A second study, SABR-COMET, had a small subset of patients with oligometastatic NSCLC randomized to standard of care versus consolidative radiation plus standard of care and also showed an OS benefit (Palma 2019). Finally, another phase II randomized study evaluating local therapy in the form of radiation alone plus maintenance chemotherapy vs maintenance chemotherapy alone demonstrated a nearly three-fold improvement in the primary endpoint of PFS in limited metastatic NSCLC patients who had stable disease/response after induction chemotherapy (Iyengar 2017).

Combining LCT with maintenance systemic therapy in stage IV/metastatic NSCLC patients with limited metastatic disease patterns who have partial responses or stable

disease after first-line therapy may provide a new paradigm for improving OS and PFS. We predict that the LCT will aid the maintenance systemic therapy in eliminating disease in sites most at risk for developing progression/recurrence, the very initial locations that characterized the patient's metastatic designation. LCT may also permit patients to remain on systemic therapy regimens that offer partial, but significant tumor kill capacity. Furthermore, it is most likely that patients will demonstrate stable disease or decreased disease burden after first-line systemic therapy rather than during or from maintenance systemic therapy. Hence, with the current study, we are aiming to consolidate treatment with surgery or SBRT after induction systemic therapy, when we believe that response can be optimized.

Importantly, we are including surgery as a local therapy option in the study for multiple reasons. Surgery has been a mainstay of treatment for oligometastatic disease in sarcoma and colorectal cancer, offering a survival benefit. Secondly, in Gomez et al, approximately 20% of patients received surgery as part of their consolidative treatment, with no delay in resumption of systemic therapy and no detriment to the PFS benefits (Gomez 2016). Furthermore, nearly all patients who had surgery also had a metastatic site treated with radiation. Finally, it is apparent that some oligometastatic patients could safely and effectively receive surgery for their disease and be the treatment modality of choice in a thoracic multidisciplinary setting. As such, we have permitted surgery to represent a local therapy option in our randomized study for metastatic disease.

Patients receiving any standard of care/FDA approved first line therapy will be eligible with the following maintenance therapies permitted – pemetrexed, gemcitabine, pembrolizumab, pembrolizumab-pemetrexed, atezolizumab, and nivolumab and ipilimumab combinations.

We offer the current study with OS as the primary end point. Specifically, we will be evaluating in a randomized fashion how the addition of LCT to maintenance systemic therapy may improve OS in a population of limited metastatic NSCLC patients. In a review of completed maintenance cytotoxic chemotherapy and induction/maintenance immunotherapy trials for stage IV NSCLC, and taking into account the potential that limited metastatic/oligometastatic patients may have more favorable survival, we anticipate median OS in the maintenance systemic therapy alone arm to be approximately 13 months (measured from initiation of maintenance therapy) for patients receiving cytotoxic therapies and several months longer for patients receiving immunotherapy-containing combinations. Along with all of the large, randomized maintenance studies detailed previously, disease burden was evaluated in 759 stage IV NSCLC patients having received cytotoxic therapies with a correlation to survival (Gerber 2013). It was concluded that the patients with the least burden of disease, measured by lowest quartile baseline sum longest diameter, a potential surrogate for patients with oligometastatic or limited metastatic disease, had the greatest survival – in the range of 12-14 months (measured from time of diagnosis) – after receiving systemic therapy alone. Including patients receiving immunotherapy, median OS for all those eligible for treatment may be expected in the range of approximately 17-20 months.

We anticipate LCT to lead to a significantly longer median OS in this patient population, an estimate based on 1) findings from two small, but randomized phase II trials showing approximate tripling of PFS with the addition of local therapy (Gomez 2016, Iyengar 2017) and more recently an update suggesting OS benefit for patients with and without targetable mutations (Gomez 2019) and OS findings from SABR-COMET demonstrating that the subset of NSCLC patients receiving local therapy do better (Palma 2019), and 2) findings from retrospective and single-arm prospective evaluations in which oligometastatic NSCLC patients were treated with local modalities of treatment in addition to systemic therapy. When SBRT was administered prospectively in a second-line setting for a patient population with poorer prognoses than those with response after first-line treatment, the median OS for patients progressing through first-line therapy was 20.4 months (Iyengar 2014). Another prospective study utilized SBRT-like hypofractionation to all oligometastatic disease sites and found a median OS of 23 months (Collen 2014). A meta-analysis that evaluated a large population of limited metastatic NSCLC patients treated with surgery or SBRT suggested a median OS of 26 months (Ashworth 2014). Retrospective evaluations were also considered, evaluated, and incorporated, including the University of Chicago experience that suggested a 22-month OS in patients with limited metastatic NSCLC (1-5 metastases) treated with radiation to disseminated disease deposits (Salama 2012).

2.2 Significance of the Study (30-MAR-2021)

Lung cancer is a leading cause of cancer-related mortality. Nearly 230,000 new cases of lung cancer were diagnosed in 2019 in the United States with approximately 160,000 deaths (National Cancer Institute SEER Cancer Statistics Review 2019). While advances in local and systemic therapy have been achieved in recent years, there remains a great need for improvement in clinical management that improves median survivals, objective responses, and duration of responses. Approximately half of patients present with advanced-stage NSCLC and are treated with chemotherapy/systemic therapy alone (Brodowicz 2006). With only cytotoxic chemotherapy as platinum doublet, disease remains poorly controlled and fatal, with estimates of median survival of 11 months in the first line setting (Ramalingam 2008). Immunotherapy offers improved median survival in subsets of patients, but there is significant room to improve the percentage of patients with durable responsiveness. From a recently concluded immunotherapy study, at 6 months, an estimated rate of OS was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (HR=0.60, p=0.005) (Reck 2016).

The principle of oligometastases was popularized in 1995 by Hellman and Weichselbaum who hypothesized that metastatic disease occurs in a step-wise manner, initially with limited metastases followed by progression to widespread disease. Early on, metastases were thought to be limited in number and location based on interaction of tumor cells with target organs in a “seed and soil” pattern (Hellman 1995, Weichselbaum 2011). With improvements in imaging, including PET/CT and MRI, identification of isolated metastatic deposits has now been accomplished with higher sensitivity and specificity than ever before. A significantly greater proportion of patients may now be identified early in the metastatic spectrum and offered potentially curative local treatment, creating a new paradigm in the management of limited volume metastatic NSCLC. The traditional

grouping of all patients with metastatic disease into a single clinical characterization may also be less relevant with potential implications in changing of tumor staging based on survival outcomes. With additional data that metastases do not always progress in multiple sites and that stage IV patients primarily progress after induction chemotherapy in original sites of gross disease if at all, a role for local therapy becomes ever more relevant.

Support for the benefit provided by local treatment of oligometastatic or limited metastatic disease was first derived from surgical metastasectomy experiences. Patients traditionally treated with surgery of hepatic, pulmonary, or adrenal metastases had improved rates of survival with resection, especially in the setting of colorectal cancers and sarcoma (Fong 1999, Pastorino 1997, Strong 2007). Resection by lobectomy has been the standard of care for the treatment of individuals diagnosed with isolated brain metastasis and no evidence for N2 disease (Kozower 2013, NCCN 2019). Furthermore, advancements in systemic therapy began to help convert a greater proportion of patients with widely metastatic disease to a limited volume metastatic state.

Meta-analyses, retrospective studies, and single-arm prospective trials using radiation therapy in a consolidative fashion all have suggested enhanced survival in limited metastatic NSCLC patients compared to historical findings for all comers of stage IV NSCLC disease (Salama 2012, Xanthopoulos 2015, Iyengar 2014, Collen 2014, Ashworth 2014, De Ruysscher 2012). With current first-line platinum doublet chemotherapy in NSCLC, up to 70%-80% of patients achieve either a partial response or stable disease (Brodowicz 2006, Ramalingam 2008, Gerber 2013). In those patients who do show progression of disease, up to 65% progress only at sites present at the start of first-line chemotherapy (Rusthoven 2009). This group represents a large cohort of NSCLC patients who may be candidates for early local treatment of limited metastatic disease, sites at greatest risk for progression and consequently contributing most to reduced survival.

More recently, a phase II randomized study was completed which demonstrated that local consolidation with radiation or surgery of limited metastatic NSCLC stable after induction systemic therapy provided a tripling of PFS when compared to systemic therapy alone (Gomez 2016). Recent updates of this trial also now suggest an OS benefit to local consolidative therapy (Gomez 2019). This study permitted inclusion of patients with tumors carrying targetable mutations and allowed patients to have surgery or chemoradiation as local therapy and either receive maintenance chemotherapy or observation. A second phase II randomized study in a limited metastatic NSCLC patient population (without tumors with targetable mutations) that responded to first line therapy included two cohorts of patients – those getting maintenance chemotherapy and those getting SBRT plus maintenance chemotherapy. The patients receiving radiation also had a near tripling of PFS (Iyengar 2017). Finally, though with very limited oligometastatic NSCLC patients with metachronous disease only, SABR-COMET showed a significant improvement in OS (Palma 2020).

Maintenance therapy with cytotoxic and targeted agents has now shown small but statistically significant benefits in both PFS and OS (Gerber 2013) for NSCLC. Most would argue, however, that a median 2-month OS benefit could and should be improved if there were means. By intervening with non-invasive focal stereotactic radiation therapy or surgery prior to maintenance systemic therapy, there is the potential for greater benefits in PFS and OS. In parallel, immunotherapy has established a new paradigm for treating metastatic NSCLC patients, but to improve upon these regimens with respect to durability and the number of patients with any benefit may require addition of local therapy.

Additionally, it is critical that we establish a true OS and PFS for limited metastatic patient populations treated with systemic therapy with or without consolidative local therapy. From retrospective data, meta-analyses, and prospective (randomized and non-randomized) evaluations of all patients receiving local interventions, there is a signal to suggest a significant OS in limited metastatic NSCLC patients. Yet, we cannot be certain that the OS is not related to the limited metastatic disease state rather than to the therapeutic intervention. It is another hopeful sign that OS rates are high, suggesting a lack of survival limiting toxicity from local therapies in these evaluations. None of the studies offered as evidence for a potential benefit from local therapy were randomized, however. For these reasons, it is incumbent on us not only to use this trial to potentially show a survival benefit with local therapy use in metastatic NSCLC, but also to demonstrate a true, unbiased OS and PFS for patients treated with systemic therapy alone who have limited metastatic disease.

Ultimately, more frequent use of SBRT for limited metastatic/oligometastatic NSCLC is being employed off protocol and without randomized data in clinics globally with retrospective studies, single-arm studies, and meta-analyses as justification. Data from an international survey with more than 1000 respondents from 43 countries showed that: 1) 83% began SBRT use after 2005 for metastases; 2) 61% were using SBRT to treat ≤ 3 sites of limited metastatic/ oligometastatic disease for improving durable disease control and for research purposes; and 3) lung, liver, and spine represented the most common sites of SBRT treatment, sites highly representative of NSCLC disease spread (Lewis 2015). The main reason cited for the 39% who did not use SBRT for oligometastatic disease was lack of randomized data. Furthermore, 63% of those using SBRT for metastatic disease stated that they would increase use of the modality for this specific indication, and 59% of those not using SBRT for metastatic disease stated they anticipated initiating programs (Lewis 2015). As suggested by the survey, in 3 years, nearly 88% of radiation oncologists will be using SBRT for oligometastatic disease in a consolidative manner or for salvage of oligoprogression. Accordingly, we need to establish with a phase III randomized study whether this treatment approach is justified, necessary, beneficial, and safe. With increasing use of SBRT for these scenarios, a greater urgency for completing our randomized trial exists.

2.3 Rationale for Use of Maintenance Systemic Therapy for Metastatic Non-Small Cell Lung Cancer (30-MAR-2021)

The introduction of maintenance chemotherapy has led to statistically significant, albeit modest, gains in PFS and OS following standard first-line platinum doublet

chemotherapy (Brodowicz 2006, Gerber 2013). These findings have certainly improved with the use of immunotherapy and immunotherapy-cytotoxic chemotherapy combinations, though a significant number of NSCLC patients still do not benefit from these regimens and for those that do outcomes may not be durable.

A contemporary meta-analysis has proven the benefit of switch maintenance over continuation maintenance in both OS and PFS in the stage IV NSCLC population (Behera 2012). Unfortunately, these drugs alone provide modest gains and have a proclivity for recurrences in previously identified sites.

2.4 Rationale for Use of Stereotactic Body Radiation Therapy (SBRT) for Limited Metastatic Non-Small Cell Lung Cancer (30-MAR-2021)

Stereotactic body radiation therapy (SBRT) is an emerging treatment paradigm defined in the American Society of Therapeutic Radiology and Oncology guidelines as a "treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body" (Potters 2010). SBRT allows for the delivery of ablative or significant non-ablative treatment doses using highly conformal radiotherapy to an increasing number of sites/locations in the body. By providing treatment in a short course of therapy, patients are not subjected to prolonged treatment times that may compromise quality of life. Treatment is delivered non-invasively and with an increasing body of data supporting its tolerability with limited toxicity.

Until two small phase II randomized trials by Gomez et al 2016 and Iyengar et al 2017, there were no completed, prospective randomized studies that examine the role of locally aggressive therapy in the form of radiation/SBRT (or surgery) for limited metastatic stage IV NSCLC. The NCCTG initiated a randomized phase III trial in patients with stage IV NSCLC, treating 1 to 3 locations of metastatic disease following 4-6 cycles of systemic therapy. SBRT was not used. When randomized to radiation, patients were treated with traditional fractionation to 60 Gy in 30 fractions or 45 Gy in 15 fractions (Schild 2008). A second study from the University of Chicago randomized patients with oligometastatic NSCLC to SBRT during the third and fourth cycle of docetaxel first-line chemotherapy (Vokes NCT00887315). Neither study was completed for several potential reasons – including a lack of desire of patients to receive 6 weeks of radiation treatment after 6 cycles of chemotherapy for the former study, low reimbursement below institutional costs to enroll and provide data for the latter study, and loosely written SBRT sections that failed to pass peer review due to lack of dose-volume guidelines for various organs, also for the latter study. For our current trial, the length of radiation treatment after first-line systemic therapy would be limited by design with use of SBRT for metastatic disease deposits and potentially a hypofractionated course for the primary disease or metastases that cannot be treated with SBRT as needed.

A randomized phase II trial comparing radiation or surgery plus maintenance chemotherapy versus maintenance chemotherapy for oligometastatic NSCLC was recently closed early from predetermined stopping rules after the local therapy (radiation or surgery) plus systemic therapy arm had significantly better PFS (Gomez 2016,

NCT01725165). The study demonstrated that local consolidation with radiation or surgery of limited metastatic NSCLC stable after induction systemic therapy provided a tripling of PFS when compared to systemic therapy alone (Gomez 2016). This study permitted inclusion of patients with tumors carrying targetable mutations and allowed patients to have surgery or chemoradiation as local therapy and either receive maintenance chemotherapy or observation. A recent update suggested an OS improvement with local therapy (Gomez 2019). Another randomized phase II trial only permitting SBRT in consolidation for limited metastatic NSCLC with up to 6 sites including the primary tumor (Iyengar 2014, NCT02045446) also showed a near tripling in PFS with local therapy, the primary endpoint. Finally, a study in Europe and Canada has used SBRT to consolidate metachronous oligometastatic disease from multiple different primaries (Palma 2016, NCT01446744) now reports an OS benefit with local therapy for all histologies (Palma 2019).

A Dutch study by De Ruysscher and colleagues (2012) showed that aggressive local treatment with radiation or surgery for synchronous oligometastatic NSCLC led to promising survival outcomes in a single arm phase II study. We subsequently evaluated other studies to gain a sense of OS benefits with local therapies in these limited metastatic NSCLC patient populations. Data from a prospective, phase II single-arm study, opened at University of Texas Southwestern Medical Center at Dallas and the University of Colorado Medical Center, demonstrated impressive outcomes in both PFS and OS in patients with stage IV NSCLC treated with SBRT plus erlotinib compared to previously established findings. The patient population chosen in this study was unique, with treatment delivered to patients who progressed through first-line platinum doublet chemotherapy but demonstrated limited metastases (up to 6 locations including primary disease). Historically, the outcomes in this population of NSCLC patients progressing through first-line therapy are quite poor. In this multi-institutional study, however, PFS was nearly 15 months with median OS of 20.4 months (measured from the time of disease progression (Iyengar 2014). Furthermore, among 13 patients tested for EGFR mutations, none were positive. It is known that the benefits of erlotinib are most pronounced in patients who possess the EGFR mutation, which lends support to the credence that in the study by Iyengar et al, local radiotherapy with SBRT may have contributed substantially to the prolonged PFS and OS observed (Iyengar 2014). Furthermore, a phase II, single-arm study published in the *Annals of Oncology* from Europe reported that limited metastatic NSCLC treated up front in the first-line setting with hypofractionated radiation established an OS of 23 months (Collen 2014). Finally, a meta-analysis of oligometastatic NSCLC, mostly 1-3 lesions treated with surgery or radiation, described OS in the range of 26 months (Ashworth 2014).

Non-randomized prospective and retrospective data from the University of Chicago is available for patients with oligometastatic NSCLC treated with hypofractionated radiation to 1 to 5 locations of metastatic or primary disease following systemic therapy. Patients were treated to all known locations of active disease at a minimum of 2 weeks following first-line systemic therapy. The most commonly used fractionation schedule was 50 Gy in 10 fractions. A total of 62 lesions were treated in 25 patients with a median of 2 lesions treated per patient. The median lesion size was 2.65 cm. Treatment was well

tolerated with only 2 patients suffering grade 3 toxicity. With a median follow-up of 14 months, the median PFS was 7.6 months and median OS was 22.7 months. Progressive disease was identified in 52% of patients following initial first-line chemotherapy. Analysis of PFS and OS in patients with progressive versus stable/regressive disease following first-line chemotherapy showed the former population to possess significantly worse PFS and OS relative to the latter. Despite the significant number of patients with progressive disease, the results of this study show a PFS that is higher than those historically achieved by maintenance chemotherapy alone with a parallel significant OS (Hasselle 2012). Having potentially learned from previous experiences, the University of Chicago only initiated radiation after first-line therapy was completed but still used 10 fraction hypofractionated regimens.

Further support for selection of stage IV NSCLC patients with stable or partial response to first-line chemotherapy for aggressive local radiation therapy with SBRT is available from the University of Rochester. Patients with up to 5 locations of limited metastatic disease of any histology were treated to all areas of disease with SBRT. There were 121 patients enrolled prospectively with 74% treated to 50 Gy in 5 fractions. Patients who achieved a response or stable disease to initial systemic therapy prior to SBRT showed significantly higher rates of OS and freedom from distant metastases compared to those with progressive disease following initial systemic therapy (Milano 2012).

Another evaluation of patients treated at the University of Rochester compared outcomes of patients with stage III NSCLC treated with curative intent radiotherapy against patients with limited volume stage IV NSCLC who received SBRT. Oligometastases as an inclusion criteria was expanded in this review to include patients treated with 8 or fewer sites of disease. Patients with stage III NSCLC were treated to an average dose of 60 Gy via a 3-D conformal technique with or without chemotherapy. Patients with limited volume metastases were treated with SBRT to a dose of 50-60 Gy in 5-10 fractions. Patients with limited volume stage IV NSCLC treated with SBRT had higher rates of 5-year survival relative to patients with stage III NSCLC treated definitively, 14% versus 7%, respectively. Though the 5-year survival data for Stage III patients was lower than expected in this study, the survival of patients with limited volume stage IV NSCLC is comparable to historical data of patients with stage III NSCLC treated definitively (Cheruvu 2011).

The most commonly treated anatomic sites of extracranial metastatic disease with SBRT are locations within the lung and liver. A multi-institutional phase I/II trial from the University of Colorado enrolled patients with 1-3 pulmonary metastases from a solid tumor, cumulative tumor diameter < 7 cm, and adequate pulmonary function (FEV1 > 1.0 L, DLCO > 40%). The planning target volume (PTV) was constructed from the gross tumor volume (GTV) by expanding 5 mm radially/10 mm craniocaudally and 7 mm radially/15 mm craniocaudally, when using active breathing control and abdominal compression, respectively. In the initial phase, the SBRT dose was escalated from 48 Gy to 60 Gy in 3 fractions. The percent of normal lung receiving more than 15 Gy (V15) was restricted to less than 35%. Dose-limiting toxicities (DLT) included acute grade 3 lung or esophageal toxicities or any acute grade 4 toxicity. Thirty-eight patients were enrolled

on the study, 9 patients in the phase I portion and 29 on phase II, receiving 60 Gy in 3 fractions, for a total of 63 lesions treated. With a median follow-up of 15.4 months, the actuarial in-field local control at 2 years was 96% with a median overall survival of 19 months. Treatment was well tolerated with only 7.9% of the population suffering grade 3 toxicity with no grade 4 or 5 toxicity (Rusthoven 2009).

A second multi-institutional phase I/II trial from the University of Colorado enrolled patients with 1-3 liver metastases from any solid tumor, cumulative maximum tumor diameter < 6 cm, adequate liver and kidney function, and no chemotherapy 14 days before or after SBRT. In the phase I portion, the SBRT dose was escalated from 36 Gy to 60 Gy in 3 fractions. Thirteen patients were treated with a dose of less than 60 Gy and 36 patients treated at 60 Gy, with 63 total hepatic lesions irradiated. Volume delineation was similar to that in the lung oligometastases trial, with the PTV defined as GTV expanded by 5 mm radially/10 mm craniocaudally and 7 mm radially/15 mm craniocaudally, with active breathing control and abdominal compression, respectively. At least 700 cc of normal liver had to receive a total dose <15 Gy and the sum of the left and right kidney volume receiving 15 Gy had to be less than 35%. With a median follow-up of 16 months, the 2-year actuarial in-field local control was 92% with a median OS of 20.5 months. Treatment was well tolerated with 1 patient suffering grade 3 soft-tissue toxicity, no grade 4 or 5 toxicity, and no instances of radiation induced liver dysfunction (RILD) (Rusthoven 2009).

Finally, a prospective dose escalation study at the University of Chicago enrolled patients with 1 to 5 metastases of any histology to receive SBRT to any location amenable to treatment. The starting dose was 24 Gy in 3 fractions. Treatment dose was escalated at 2 Gy per fraction intervals with a ceiling of 60 Gy in 3 fractions. A total of 61 patients were evaluated with 113 treated lesions. The final dose cohort with sufficient follow-up and enrollment was 42 Gy. With a median follow-up of 20.9 months, the median PFS was 5.1 months. Patients with 1 to 3 metastases were found to have significantly longer PFS than patients with 4 to 5 metastases. It is significant to note that in this study, 55% of patients had a limited pattern of disease progression to 3 or fewer locations after initial therapy, areas that were amenable to further SBRT (Salama 2012).

With the inclusion of immunotherapy as an induction and continuation/ “maintenance” regimen for this study, there may be some question regarding patient tolerance with the further addition of local therapy, especially radiation/SBRT. Multiple studies have now been completed in the phase I setting evaluating both concurrent and sequential use of immunotherapy with SBRT and other forms of radiation in the concurrent or sequential setting. Welsh and colleagues report no increased toxicity when combining SBRT with various types of immunomodulators (Welsh 2017). Other groups have demonstrated similar findings.

Based on available retrospective studies, meta-analyses, single-arm, and multiple recently completed phase 2 randomized, prospective trials, we believe a strong case can be made that: 1) Failures in metastatic NSCLC occur most frequently in sites of original gross disease, 2) Local therapy in the form of surgery and/or radiation can drastically reduce

the local failures, 3) SBRT or surgery can be used safely to treat these limited metastatic disease foci with efficacy and timelines, 4) Maintenance systemic therapy alone offers improving survival benefits though ultimately durability of benefit could be improved, 5) There is significant OS findings with use of LCT but in smaller studies, and 6) There is a need to determine what the true OS and PFS is for limited metastatic NSCLC patient populations independent of local therapy in a large randomized phase 3 trial. Taken together, these observations provide a strong rationale for the design and conduct of this study.

This study uses 1, 3, or 5 fraction SBRT regimens that have biologically equivalent doses (BED) based on the Universal Survival Model (Park 2008). These SBRT doses also have similar BEDs to the hypofractionated 45Gy in 15fx regimen allowed in the treatment of primary/hilar/mediastinal disease or metastatic disease that cannot receive SBRT, permitting a more apropos comparison of local control between irradiated disease sites. The different fractionation schemes were created to give physicians flexibility in delivering the SBRT however they choose and within their comfort level. The doses offered represent our efforts to reduce any likelihood of radiation induced toxicity that would limit patients from receiving the appropriate subsequent maintenance chemotherapy. RTOG 0236 demonstrated a 17% grade 3 or higher toxicity with use of 20Gy x 3fx (without heterogeneity corrections). Our consolidative radiation in this trial is aimed to aid systemic therapy in controlling gross deposits of metastatic disease without the associated toxicity from ablative SBRT. Hence, we are using lower ablative doses, which, in multiple multi-institutional trials, demonstrate a long term local control rate in the range of 96%, even without systemic therapy or treatments not felt to be beneficial (Iyengar 2014).

2.5 Rationale for Surgery for Limited Metastatic Non-Small Cell Lung Cancer (30-MAY-2021)

Historically, surgery for patients with stage IV cancer was limited to palliation, but in the 1980s series began to appear that reported prolonged survival following complete resection of primary tumors and oligometastatic disease (Magilligan 1976). It is now recognized that there is a subset of patients where an isolated metastasis represents the entire disease burden and removal can confer significant survival prolongation.

The use of surgery for metastases from numerous primary locations, including the lung, has increased significantly over the past decade. Metastasectomy for primary non-small cell lung cancer (NSCLC) being second in incidence only to colon cancers (Bartlett 2015). An analysis from the National Inpatient Sample (NIS) uncovered a 5.8% average annual percent increase resections of NSCLC metastases between 2000 and 2011 (Bartlett 2015). This increase is attributed to several factors, including more efficacious and better tolerated chemotherapies and the introduction of targeted agents, which have slowed the progression of metastatic spread and altered patterns of resistance. Simultaneously, there have been significant improvements in surgical techniques, with increased use of minimally invasive approaches, making resection better tolerated and negating long interruption from systemic treatments.

The majority of patients considered for resection of metastatic NSCLC fall into three categories, those with isolated metastasis to the brain, adrenal glands, or contralateral lung. Occasional patients with isolated metastasis to other sites are considered, but evidence for prolonged survival following local therapy is sparse. Patients who present de novo with a single metastasis after full staging should be evaluated for curative resection of both sites.

Some of the oldest series on surgical treatment of stage IV NSCLC relate to treatment of isolated brain metastasis (Wronski 1995, Nakagawa 1994) Up to one quarter of all patients with stage IV NSCLC harbor brain metastasis. Adenocarcinomas are associated with higher rates of brain metastasis, but in 10% of patients with metastatic adenocarcinoma the brain is the only site of involvement (Kozower 2013) Aggressive curative intent treatment of the primary and metastatic site is encouraged in those with good performance status and in whom both sites are amenable to complete resection or ablation (Kozower 2013). Curative intent local treatments can only be considered after a thorough search for disease at other sites. Mediastinal lymph node involvement portends poor prognosis (Granone 2001, Bonnette 2001, Girard 2006, Furak 2005, Modi 2009). Multiple brain metastases are not an absolute contraindication to this aggressive treatment approach, but most recommend three or fewer lesions (Kozower 2013). Treatment of the brain lesion can be by resection or radiosurgery ablation. Five year survival following definitive treatment of isolated brain metastasis and primary NSCLC is 15%, and not significantly impacted by synchronous or metachronous presentation. Prognosis is improved in patients who are younger, female, have lower t-stage, and good performance status (Granone 2001, Bonnette 2001, Girard 2006).

In well-selected patients with isolated adrenal metastasis from NSCLC, survival following complete resection of primary and metastasis is 25% (Raz 2011, Lucchi 2005, Strong 2007, Mercier 2005, Porte 2001). Similar to those with isolated brain metastasis, mediastinal lymph node involvement portend worse prognosis (Porte 2001). Histology and laterality appear to have no impact on survival and adjuvant chemotherapy is recommended. Operative mortality is extremely low in reported series and the majority of patients die of disease progression.

The appearance of bilateral NSCLC lesions with the same histology is a staging challenge. In the absence of other disease it is difficult to distinguish bilateral primary tumors from stage IVa disease. Analysis of mutational status and genetic clonality difference are being investigated, but not clinically reliable at this time. The clinical judgement of an experienced multi-modality team is essential (Kozower 2013) and the criteria described by Martini and Melamed in 1975 remains relevant (Martini 1975). As with isolated brain and adrenal metastasis, an exhaustive search for additional metastatic disease and invasive mediastinal staging are recommended prior to considering curative resection to both lesions. Parenchymal sparing resections are typically recommended when possible in this setting.

2.6 Translational Research

A major goal of translational research in NSCLC is the identification of non-invasive biomarkers for response assessment, outcome prediction, and/or early detection. One potential non-invasive biomarker that has recently gained increasing attention is circulating tumor DNA (ctDNA) (Diaz 2011). Tumors continually shed DNA into the circulation, where it can be isolated as a component of cell-free DNA (cfDNA). Within plasma, ctDNA is present in a background of wild type DNA, and except in very advanced cases usually makes up significantly less than 1-5% of cfDNA. Detection of ctDNA can be accomplished by a variety of methods, although next generation sequencing (NGS)-based approaches have become increasingly feasible and attractive given their ability to detect multiple mutations at one time (Chaudhuri 2015). One NGS-based method called CAPP-Seq was designed specifically for NSCLC and can detect the presence of ctDNA with high sensitivity specificity (Newman 2014, Newman 2016). See Section 10.2 for more details.

3. PATIENT SELECTION, 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 (via the contact list on the protocol title page). For radiation therapy-related eligibility questions, please contact RTQA (via the contact list on the protocol title page).

3.1 Patient Selection Guidelines (18-MAY-2018)

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of contraception during treatment on this study and for up to 180 days after completion of all treatment to prevent pregnancy or fathering a child.

3.2 Eligibility Criteria (30-MAR-2021)

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

3.2.1 Pathologically proven diagnosis of NSCLC, with metastases (stage IV disease) present prior to registration. This includes patients newly diagnosed with metastatic disease or those initially diagnosed and treated for stage I-III NSCLC who ultimately develop limited metastases. Limited metastases is defined as 3 or fewer sites of metastatic disease;

- Some examples of what constitutes sites can be found in Section 5.4.

3.2.2 Appropriate stage for study entry based on the following diagnostic workup:

- History/physical examination by a radiation oncologist (and a surgeon if surgery is planned) within 30 days prior to registration;
- Imaging proof of limited metastatic disease and response to therapy/stable disease, by at least diagnostic quality CT chest through the adrenals or PET/CT, within 30 days prior to registration;

3.2.3 Age ≥ 18 years;

3.2.4 Zubrod Performance Status 0, 1, or 2 within 30 days prior to registration;

3.2.5 Adequate organ and hematologic/bone marrow function within 14 days prior to registration, defined as follows:

- Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 × upper limit of normal (ULN) or ≤ 5 × ULN with metastatic liver disease
- Total bilirubin ≤ 1.5 × ULN
- Absolute neutrophil count (ANC) ≥ 500 cells/mm^3
- Platelets ≥ 50,000 cells/mm^3
- Renal:
    - Creatinine ≤ 1.5 x ULN; or
    - Creatinine Clearance > 45 mL/min if creatinine > 1.5 x ULN (calculated CrCl based on Cockcroft-Gault equation)

3.2.6 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.2.7 For patients who will undergo resection of disease (if randomized to Arm 2 and dispositioned to receive surgery), adequate pre-surgical work-up for anticipated surgery, as defined by institutional guidelines.

3.2.8 Negative serum pregnancy test within one week prior to registration for females of childbearing potential;

3.2.9 Patients must have received first-line/induction systemic therapy comprising of immunotherapy and/or platinum-based chemotherapy (at least 4 cycles or courses but less than 6, i.e. 4-5 cycles/courses), and achieved stable disease or a partial response. Though the intention is for every course/cycle to be identical in an induction regimen, Some but not all of the 4-5 cycles may omit an immunotherapy or platinum compound if the treating physician determines it is in the patient's best interest secondary to toxicity or other institutional parameter.

- For patients treated with nivolumab, ipilimumab and 2 cycles of chemotherapy, the 4-5 cycles requirement will be met by 4-5 total doses of nivolumab.
- For patients treated with nivolumab and ipilimumab, this requirement will be met by 2 doses of ipilimumab and 4-5 doses of nivolumab.

3.2.10 After induction systemic therapy, patients must have a minimum of one site of disease, primary or metastasis, present for potential consolidation with local therapy. All sites of disease present after induction systemic therapy, primary and metastases (up to 3) are able to be consolidated with local therapy;

- Some examples of what constitutes specific radiation treatment sites defining distinct metastatic disease sites can be found in Section 5.4

3.2.11 Prior systemic therapy as part of concurrent treatment approach for previously diagnosed stage I-III NSCLC, adjuvant or neo-adjuvant therapy for stage I-III NSCLC, as adjuvant therapy for previously resected or irradiated NSCLC, or for other previous cancers is permitted;

3.2.12 For de novo stage IV NSCLC patients (patients with metastatic disease at first presentation), primary disease must be treatable with local therapy in the form of SBRT or hypofractionated radiation. If the primary disease is found in the peripheral or central lung parenchyma without nodal disease, for instance, SBRT may be employed at the discretion of the treating institution. If primary disease is more advanced with involvement of the mediastinum (T4 tumor, N1-N3 disease, etc.), these volumes should be technically treatable with hypofractionated radiation; surgery should only be used for metastatic tumors that can be completely resected by lobectomy, segmentectomy, or wide wedge resection.

3.2.13 If primary disease in the thoracic cavity was previously treated with local therapy in the form of surgery or radiation, any new local/regional disease recurrence should be technically treatable with SBRT or hypofractionated radiation after induction systemic therapy.

3.2.14 The patient or a legally authorized representative must provide study-specific informed consent prior to registration.

3.2.15 Radiotherapy for patients with brain metastases prior to registration is acceptable.

3.2.16 Patients with brain metastases are eligible if these lesions have been previously treated or resolved and the patients have no clinical or radiographic evidence of progression prior to registration.

3.2.17 Subjects may receive palliative radiotherapy for symptomatic metastases or primary disease prior to registration provided that there is at least one other non-irradiated lesion amenable to LCT at the time of registration.

3.3 Ineligibility Criteria (30-MAR-2021)

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

3.3.1 Clinical or radiologic evidence of new, untreated, and/or progressive brain metastases prior to registration after induction systemic therapy.

3.3.2 Cutaneous metastasis of NSCLC.

3.3.3 Metastatic disease invading the esophagus, stomach, intestines, or mesenteric lymph nodes if not a candidate for surgery for these lesions.

3.3.4 Prior invasive malignancy (except non-melanomatous skin cancer, low or intermediate risk prostate cancer, or in situ carcinoma of breast, oral cavity, skin, or cervix) unless disease free for a minimum of one year.

3.3.5 Metastases located within 3 cm of previously irradiated (< 3Gy per fraction) structures if not a candidate for surgery for these lesions and if:

- Spinal cord previously irradiated to > 40 Gy
- Brachial plexus previously irradiated to > 50 Gy
- Small intestine, large intestine, or stomach previously irradiated to > 45 Gy
- Brainstem previously irradiated to > 50 Gy
- Lung previously irradiated with prior V20Gy > 35%

3.3.6 Patients with NSCLC who have driver mutations for which targeted therapies (non-cytotoxic, non-immunotherapy based systemic therapy including but not limited to tyrosine-kinase inhibitors) are available. Such designations would include but not be limited to treatments targeting EGFR mutant or ALK positive NSCLC.

3.3.7 If a patient has progressed in previous areas of primary disease that received definitive doses of radiation, these patients would require re-irradiation in previous high dose anatomic areas and are not eligible for this study.

3.3.8 Patients with malignant pleural effusions that do not resolve after first-line systemic therapy. Patients with pleural effusions that have become too small for thoracentesis at the time of registration would be permitted on study, indicating a significant response to first-line systemic therapy.

3.3.9 Patients with more than 3 discrete locations of extra-cranial metastatic disease after first-line systemic therapy requiring more than 3 radiation/surgery plans to cover these distinct metastatic disease entities.

3.3.10 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration.

3.3.11 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception during treatment and for 180 days after the completion of all treatment. This exclusion is necessary because the treatment involved in this study may be significantly teratogenic. Women who are breastfeeding (and unwilling to discontinue) are also excluded.

3.3.12 Participation in any investigational drug study for the treatment of cancer within 4 weeks prior to registration.

3.3.13 For patients who received immunotherapy during induction, patients on chronic steroids or who have active autoimmune disease for which they received systemic treatment in the previous 2 years with corticosteroids, disease modifying agents, or immunosuppressive drugs are not eligible. Replacement therapy (thyroxine, insulin or physiological corticosteroid replacement for adrenal or pituitary insufficiency) is allowed. Patients with active interstitial lung disease or who have a history of pneumonitis for which they had received glucocorticoids are not eligible.

3.3.14 Use of bevacizumab or other antiangiogenic therapy in first-line or planned maintenance therapy (due to potential for increased complications from local therapy);

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP (30-MAR-2021)

PRE-TREATMENT ASSESSMENTS

Assessments	Prior to Registration (calendar days)	Prior to Treatment (calendar days)	Arm 2 Patients if Surgery is Selected as LCT
Pathologic proof of NSCLC	X		
Evaluation by a radiation oncologist	30 days		
Evaluation by a thoracic surgeon			Within 30 days prior to registration
Performance status	30 days		
Diagnostic CT chest through the adrenals or PET/CT	30 days		
Complete Metabolic Panel (CMP)*	14 days		
CBC/differential (with ANC)	14 days		
TSH[t] (only required for patients receiving immunotherapy)		As clinically indicated	
Serum pregnancy test (if applicable)	7 days		
PROs: EQ-5D-5L, FACT-L, C-TUQ		X (after consent, prior to initiation of systemic therapy/RT)	
FFPE tissue, whole blood, serum and plasma collection for banking for consenting patients		X	

* CMP to include: Sodium, Potassium, CO2, Chloride, BUN, Creatinine, ALT, AST, Total Bilirubin, Blood Glucose, and Calcium to be reported on study specific CRFs.

[t] With reflex to T4; then T3 only if clinically indicated afterwards

ASSESSMENTS DURING TREATMENT

Assessments	Weekly During Radiation	During Maintenance Systemic Therapy	Arm 2 Patients if Surgery is Selected as LCT
History and Physical Exam	X	Prior to every cycle of systemic therapy (as appropriate for standard of care for specific maintenance regimen)	
Post-surgical consult			2-4 weeks after surgery
CT chest through the adrenals		After every 9 weeks of maintenance systemic therapy	
CT abdomen/pelvis		After every 9 weeks of maintenance systemic therapy (**only required if** metastatic lesions in these anatomic areas were known at registration)	
Toxicity Assessment Graded per NCI CTCAE, v5.0	X	Prior to every administration of maintenance systemic therapy	
CBC/differential (with ANC)		As clinically indicated / per institutional guidelines	
TSH[t] (only required for patients receiving immunotherapy)		As clinically indicated	
Complete Metabolic Panel*		As clinically indicated/per institutional guidelines	
PRO: FACT-L**		1, 3, 6, 9 and 12 months after patient registration	
PRO: EQ-5D-5L, C-TUQ**		3, 6 and 12 months after patient registration	
Serum and plasma collection for banking for consenting patients		Once approximately 3 months after the initiation of maintenance systemic therapy	

* Sodium, Potassium, CO2, Chloride, BUN, Creatinine, ALT, AST, Total Bilirubin, Blood Glucose, Calcium

[t] With reflex to T4; then T3 only if clinically indicated afterwards

** PROs should continue on this schedule even if the patient progresses or stops treatment early and enters follow-up.

ASSESSMENTS IN FOLLOW UP

Assessments	From End of Last Dose of Maintenance Systemic Therapy (+/- 30 days);
Vital Status	q3 mos. x 2 yrs, then q6 mos. x 3 yrs, then annually
CT chest through the adrenals	q3 mos. x 2 yrs, then q6 mos. x 3 yrs, then annually
CT abdomen/pelvis	q3 mos. x 2 yrs, then q6 mos. x 3 yrs, then annually only required if metastatic disease was identified in abdomen or/and pelvis at registration
History and Physical Examination	q3 mos. x 2 yrs, then q6 mos. x 3 yrs, then annually
Toxicity Assessment Graded per NCI CTCAE, v5.0	q3 mos. x 2 yrs, then q6 mos. x 3 yrs, then annually
CBC/differential (with ANC)	Per institutional guidelines or as clinically indicated
Complete Metabolic Panel*	Per institutional guidelines or as clinically indicated
Serum and plasma collection for banking for consenting patients	At the time of first progression (local or distant)

* Sodium, Potassium, CO2, Chloride, BUN, Creatinine, ALT, AST, Total Bilirubin, Blood Glucose, Calcium

Definition of Disease Assessments

Evaluation of Target Lesions
Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eisenhauer 2009]. Changes in the largest diameter (LD) (unidimensional measurement) of the tumor lesions and the shortest diameter (SD) in the case of malignant lymph nodes are used in the RECIST criteria. For those patients receiving immunotherapy, irRC guidelines for treatment response should be employed (Nishino 2013, Garon 2014)

The following terms and definitions may guide investigators but official RECIST 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 lesion, 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 the primary treated tumor and corresponds to meeting both of the following two criteria: 1) Increase in tumor dimension of 20% as defined above for local enlargement (LE); 2) The appearance of a measurable tumor at a resection suture line; 3) The measurable tumor with criteria meeting LE should be avid on Positron Emission Tomography (PET) imaging with uptake of a similar intensity as the pretreatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma.

For outcome analysis, Marginal Failures (MF; see below) will also be counted as LF; however, they should be distinguished specifically as MF, not LF, on all report forms. The EORTC criteria for post-treatment PET evaluation will be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathological for cancer recurrence vs. inflammation.

Local Control (LC)
The absence of Local Failure.

Evaluation of Non-Target Lesions

Marginal Failure (MF)
Refers to the appearance of a measurable tumor appearing since treatment within 1.0 cm of the treated PTV or the resection suture line and meeting the following two criteria: 1) Enlarging tumor dimensions corresponding to a 20% increase in the longest diameter compared to initial appearance on imaging evaluation. Ideally, this determination will be made based on CT image evaluation; 2) The measurable tumor within 1.0 cm of the treated PTV or resection suture line should be avid on Positron Emission Tomography (PET) imaging with uptake of a similar intensity as the pre-treatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma.

Regional Failure (RF)
Refers to the appearance of measurable tumor within 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 lung, bronchial hilum, or 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 non-small cell lung cancer. 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

5.1 Systemic Therapy (19-JUL-2021)

There will be a 2:1 randomization between Arms 2 and 1 on study. By a 2:1 ratio, more patients will be randomized to the arm of treatment receiving local therapy in the form of radiation or radiation and surgery. NOTE: All patients in the trial will receive maintenance therapy.

Systemic therapy protocol treatment must begin either:

- within 2 weeks of registration on the maintenance systemic therapy (Arm 1)
- within 2 weeks of the completion of all local therapy if no surgery included or within 3 weeks after all LCT if surgery is included (Arm 2)

Systemic therapy - approved regimens and associated references:
Patients may receive only one of the following regimens as noted below. There is no expectation that any one particular cytotoxic regimen would result in superior outcomes to any other cytotoxic regimen since none have been compared head-to-head in any randomized study. Similarly, there is no expectation of superior outcomes among any of the immunotherapy regimens. Since immunotherapy-containing regimens are expected to have different PFS and OS outcomes versus cytotoxic chemotherapy regimens, the induction/maintenance regimen of choice will be stratified based on the presence or absence of immunotherapy. Selection of regimen is at the discretion of the treating physician in agreement with the patient. These regimens include FDA approved and/or

NCCN recommended therapies.

General Treatment Considerations for All Systemic Therapy Regimens
Agents will be administered per institutional standard.

Agents are either dosed by BSA or flat dose. BSA-based chemotherapy dosing may be modified for changes in weight according to institutional policies for dose rounding.

Premedications should be given according to the package insert and institutional guidelines for each agent.

For all chemotherapy agents, the duration of treatment is until progression or significant toxicity.

For immune therapy agents, the duration of treatment is until progression or significant toxicity, or up to 2 years. The same approved immunotherapy regimen used prior to radiation in induction/first line treatment must be continued following radiation.

The following are recommended dose administration, but agents should be administered per institutional standard. Additionally, refer to the FDA package insert for complete details on safety and treatment information**.**

5.1.2 Pemetrexed or Pemetrexed plus Pembrolizumab

Administration: 500 mg/m^2 administered by IV over 10 minutes on Day 1 of a 21 day cycle. For pemetrexed plus pembrolizumab regimen, both are administered on day 1 of each 21 day cycle. See Section 5.1.4 for pembrolizumab dosing.

NOTE: Pemetrexed administration requires vitamin supplementation with folic acid and vitamin B12 (patients should receive B12 and folate supplementation per package insert).

See section 5.1.4 for pembrolizumab dosing.

5.1.3 Gemcitabine

Administration1250 mg/m^2 over 30 minute IV infusion on Days 1 and 8 of a 21 day cycle is recommended. Lower starting dose of 1000 mg/m^2 allowed per investigator discretion.

5.1.4 Pembrolizumab

Administration: 200 mg as IV infusion over 30 minutes on day 1 of a 21 day cycle. (For sites in Canada, weight-based dosing (2 mg/kg) of pembrolizumab is acceptable if standard of care.)

Note: the regimen of pembrolizumab 400 mg IV every 6 weeks is not permitted on the NRG-LU002 trial.

5.1.5 Atezolizumab

Administration: 1200 mg as IV infusion on day 1 of a 21-day cycle, administered over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Refer to the FDA package insert for administration instructions.

5.1.6 Nivolumab plus ipilimumab:

Administration: nivolumab 3 mg/kg as IV infusion over 30 minutes on days on 1, 15, and 29 of a 42-day cycle plus ipilimumab 1 mg/kg as IV infusion over 30 minutes on day 1 of a 42-day cycle.

OR

Nivolumab 360 mg as IV infusion over 30 minutes on day 1 and 22 of a 42-day cycle plus ipilimumab 1 mg/kg as IV infusion over 30 minutes on day 1 of a 42-day cycle.

5.2 Local Consolidative therapy (LCT): (30-MAR-2021)

Can be in the form of hypofractionated radiation/SBRT to the primary tumor and metastatic sites or surgery of metastatic sites, and is to be determined by the treating institutions using the following caveats:

- Minimally invasive resections of metastatic sites are encouraged.
- At least one site of disease needs to be present after induction systemic therapy (primary or metastasis) for consolidation.
- At least one site (metastatic or primary) must be treated by SBRT/hypofractionated radiation. All sites must be treated by either RT or surgery.
- All LCT should ideally be completed within 5 weeks of randomization for patients who receive radiation alone (detailed in **Section 5.4.7** with acceptable and unacceptable deviations).
- All LCT should ideally be completed within 6 weeks of randomization if surgery is incorporated with the radiation. Acceptable deviation if all LCT (incorporating some form of surgery) completed between 6-8 weeks. Unacceptable deviation beyond 8 weeks.
- Maintenance systemic therapy should begin within 2 weeks after all LCT if no surgery inclusion or within 3 weeks after all LCT if surgery included.

5.3 Surgery (18-MAY-2018)

Questions regarding Surgery should be directed to Dr. Donington (preferably by e-mail or alternatively by phone).

5.3.1 Patients with no radiologic evidence of progression in the chest or elsewhere, including patients who have stable disease on re-evaluation, may proceed to surgery of only metastatic disease.

5.3.2 All surgery should be performed within 6 weeks of randomization. Occasionally, an extra week will be required to recover from toxicity of first line therapy. If longer than a week is deemed necessary, surgical co-chair should be notified. Site will document the reason(s) for delay on the Surgical Evaluation Form.

5.3.3 Surgical Guidelines for Resection for Metastatic Sites

Extra-cranial metastatic sites eligible for resection include: contralateral lung, mediastinal or cervical lymph nodes, liver, spinal/paraspinal masses, bone, adrenal glands, abdomino-pelvic lymph nodes and spleen.

Complete resections with negative margins should be achieved, but anatomic resections are not required. Minimally invasive techniques should be used whenever possible.

The attending thoracic surgeon must review and sign all post-surgical forms. Post-operative complications are reported in the same manner and with the same forms as for resection of primary tumors.

5.3.4 The attending thoracic surgeon must review and sign all post-surgical forms.

5.3.5 The use of video-assisted thoracic surgery (VATS) or robotic assisted thoracic surgery (RATS) are encouraged and should be used at each surgeon's discretion.

5.3.6 Post-Operative Period

Post-operative care is at the discretion of individual institution, with attention to minimal use of IV fluids in perioperative period, early ambulation and aggressive pulmonary toilet.

5.3.7 Surgical Adverse Events

All acute and late adverse events from protocol surgery will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) per Section 7.2.1. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

Peri-Operative Complications

Major morbidities are scored as any event occurring within 30 days or during the same hospitalization as surgery. The complications of surgery will be documented on the Surgical Evaluation Form as part of the secondary objectives of this study. All patients undergoing surgical resection will be included in the analysis of surgical Adverse Events. Data collection also will include Surgical Operative and Surgical Pathology Reports documenting surgical approach, duration of surgery; estimated blood loss; blood transfusions required intra- and perioperatively; and length of hospital stay. The Adverse Events attributed to thoracic surgery will include any of the following complications listed below:

- Pneumonitis/pneumonia/pulmonary infiltrates (includes pneumonia/empyema that was diagnosed during the postoperative period; specify the organism causing the infection).
- Infection (other than pulmonary).
  NOTE: This includes wound infection of surgical incisions. When there is a wound infection, specify the organism causing the infection in the space provided, and record which surgical incision[s] was infected.
- Fistula (includes any fistula that developed within the postoperative period;
  NOTE: A patient with a bronchopleural fistula associated with an intrathoracic infection should be reported as having both the intrathoracic infection and a fistula, pulmonary/upper respiratory).
- Prolonged air leak, defined as air leaks longer than 5 days (includes bronchial stump leak).

- Pleural space issue (non-malignant) [includes any effusion, pneumothorax, and chylothorax within the postoperative period that requires treatment beyond peri-operative chest tube x 5 days or secondary interventions].
- Cardiac ischemia/infarction (includes any myocardial infarction that occurred within the postoperative period).
- Thrombosis/thrombus/embolism (includes any pulmonary embolus that occurred within the postoperative period).
- Supraventricular and nodal arrhythmia (includes any new atrial arrhythmia that developed within the postoperative period that requires treatment).
- Ventricular arrhythmia (includes any new ventricular arrhythmia that developed within the postoperative period that requires treatment).
- Hemorrhage/bleeding associated with surgery, intra-operative or postoperative (Postoperative period is defined as ≤ 72 hours after surgery; includes hemorrhage that required reoperation for control).
- Death.

5.4 Radiation Therapy in the Form of Stereotactic Body Radiation Therapy or Hypofractionation (30-MAR-2021)

Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SAbR), is a treatment strategy used to deliver highly focused and accurate radiation dose to demarcated targets outside of the brain where the entire course of therapy for an individual target is delivered in few fractions (≤5, oligofractionation). The definition of SBRT and its appropriate conduct have been extensively reviewed by several professional radiotherapy societies. For this protocol, the ACR/ASTRO consensus definition of SBRT and the related conduct guidelines for SBRT, along with guidelines from the AAPM Task Group 101, will be used. When and if there is a discrepancy between these professional society guidelines and this protocol, the protocol should be followed.

This trial aims to assess whether LCT can help systemic therapy improve survival in limited metastatic NSCLC. The expectation is that resection or SBRT will be used in part or all of the treatment of metastatic disease or of the primary disease when feasible. If SBRT is not used to treat the primary disease or metastases (when not amenable to SBRT due to normal tissue constraints), a treatment of 45 Gy can be delivered in 15 fractions to the primary (may include mediastinal nodes/hilum) or metastases using IMRT or a 3D Conformal approach. In this trial, with the flexibility offered by the SBRT schemas and by the 45Gy/15fx regimen, stage III like disease intrathoracically should be treatable as primary disease. Earlier radiation sections highlight the rationale for primary disease site treatment with radiation at the same time as SBRT treatment of metastatic disease. We leave to the discretion of the physician of the study participant what defines bulky disease or multistation disease not amenable to radiation treatment on the study. For details refer to Section 3.2.

Some examples of what constitutes specific radiation treatment sites defining distinct metastatic disease sites include:

a) A lesion in each adrenal gland represents 2 of 3 sites of metastatic disease allowed to be treated on protocol;
b) Similarly to NRG study RTOG 0631, disease in 2 contiguous vertebral bodies (with up to 6 cm of paraspinal extension) can represent one site of disease in the spine; non-contiguous lesions in vertebral bodies separated by one vertebral body free of disease should be viewed as 2 sites of treatment; and
c) Two lesions in such close proximity to one another that treatment with one isocenter is more accurate and safer in the liver, lungs, or other similar anatomic locations should be viewed as one site of metastatic disease treatment. Anatomic sites that may be treated with SBRT are listed below.

Please see Section 2.4 for rationale for fractionation strategy for treating metastases.

5.4.1 Treatment Technology Requirements

SBRT is a highly focused technique requiring many facets of modern technology in order to safely treat patients with large fractions of highly conformal doses. To successfully treat an SBRT patient, centers must satisfy a set of minimum technology requirements as well as use appropriate modalities for treatment.

General treatment technology requirements for SBRT are given in Table 5.4.1A. Questions regarding appropriate technology for this protocol can be directed to the protocol PI or medical physics co-chair.

Table 5.4.1A Quick Reference Summary of Treatment Technology Requirements

Technology	Requirement	Comments
Beam Modality	MV Photons	ViewRay & Linac allowed; Charged particle beams (including electrons, protons, and heavier ions) are not allowed
Beam Energy	1 to 10 MV; 10-18 MV may be used in selected cases with >10 cm from skin to target. For targets in the lung, >50 % of target dose should be delivered by beams with energy ≤10 MV	Minimize use of high energy in lung. 6 MV or lower energies should be predominately used in low-density tissue.
Treatment Technique	3DCRT (static, arc) or intensity modulated techniques (IMRT, VMAT)	Tomographic and robotic techniques allowed.
Image Guidance	Treatment Machine must be equipped to provide daily kV or MV image guidance. The minimum requirements for image guidance are given in Section 5.4.10.	Non-ionizing guidance (RF transponders, optical surface imaging) is allowed, but kV or MV image verification is still required.

5.4.2 Simulation

Proper immobilization and assessment and, if necessary, management of internal motion are essential for SBRT treatment. Quick reference guidelines for simulation are given in Table 5.4.2A with additional details below.

Table 5.4.2A Quick Reference Summary of General Simulation Guidelines

Topic/Parameter	Guideline
Immobilization	Proper immobilization with appropriate clinical devices to ensure reproducibility is required. Patient comfort should be prioritized.
Motion Assessment	Ascertain the characteristics of target (and normal tissue) motion with regard to magnitude (amplitude), timing (period), and regularity to determine the need or success of motion control. This is carried out both in simulation and treatment using real time monitoring (e.g., fluoroscopy, 4-D CT, beacon tracking, etc.)
Motion Control	Motion control is strongly encouraged when the GTV excursion is more than 1 cm in any direction. Typical motion control maneuvers include inhibition strategies (e.g., abdominal compression and active breath hold), tracking based on a motion model, and gating to part of the breathing cycle, but others may be applicable. Internal organ management maneuvers must be reliable enough to insure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., < 5%).
CT Slice Thickness	2 mm or less is recommended. Maximum slice thickness should be 5mm when more than 10cm from the target but no more than 3mm shall be used within 10cm of the target. PTV size should be taken into consideration when choosing the slice thickness. Slices of 1-2 mm are recommended for tumors that are 1 cm or less in the largest dimension. IV contrast is recommended but not required. 3D reformatting is permitted as per primary institution. Same slice thickness maximums, contrast recommendations, and 3D reformatting principles hold for PET/CT and MR imaging as well.
Use of Contrast	IV contrast is encouraged for better delineation between tumor, atelectasis, and vascular structures as well as better definition of normal tissue contours. Oral contrast can be used at the clinical discretion of the treating physician. Generally, contrast scans are acceptable for dose calculations, although density overrides may be applied in areas of strong contrast (such as oral contrast in esophagus). For additional information on use of contrast, please see Section 5.4.3.

Immobilization

Patients should be positioned in a stable position capable of allowing accurate reproducibility of the target positions from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides and large, patient contoured rigid pillows (conforming to patients' external contours) with reference to the stereotactic coordinate system. At a minimum, patients should be uniformly supported with large cushions or patient contoured rigid pillows rather than simply lying on the treatment couch, which is uncomfortable for the period of time required for SBRT simulation, setup, and delivery. Arms should be supported and knees elevated. Patients with COPD often

prefer that their head is elevated above their chest. Patient immobilization must be reliable enough to insure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV) with any significant probability (i.e., < 5%) during the treatment.

Assessment and Management of Internal Organ Motion

Special considerations must be made to account for the effect of internal organ motion (e.g., primarily breathing associated motion but also bowel peristalsis motion) on target positioning and reproducibility. As a first step, it is required that the treatment team quantify the specific motion of a target so as to determine if management strategies listed in the next section are required to meet protocol guidelines. The patient should be in normal free breathing at time of initial tumor motion assessment. Deep inspiration or expiration breath hold is not allowed for initial tumor motion assessment as such assessment generally overestimates free breathing tumor motion. Options for motion assessment include real time fluoroscopy and 4-D CT scanning. Any strategy, including 4-D CT should incorporate appropriate image review and quality assurance to ensure suitability for treatment planning and target delineation.

In some tumor locations, assessed tumor motion measurement indicates that tumor motion would exceed the required small tumor expansions per this protocol (resulting in marginal miss or excessive volume of irradiation) unless a motion management strategy is employed. Respiratory motion management (RMM) including abdominal compression, active breathing control, breath hold, end expiratory gating, or fiducial marker tracking, is recommended for any metastasis to be treated with motion ≥ 1 cm. A recommended approach would be to use an IGTV technique for motion <1cm but for motion > 1cm (typically too large for a free breathing IGTV) motion management including but not limited to abdominal compression, active-breathing control (ABC), gating, breath hold, etc. should be used.

Internal organ management maneuvers must be reliable enough to insure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., < 5%).

If a treatment for multiple metastases (i.e., lung and spine) is designed on a CT scan employing motion management (i.e., abdominal compression), all metastases should be treated with the chosen motion management technique in order to generate an accurate composite dose calculation.

Table 5.4.2B highlights the recommended and minimum requirement for motion assessment and treatment planning imaging.

Table 5.4.2B Motion Assessment/Management Guidelines for Simulation

Treatment Technique	Recommended Method for Motion Assessment During Simulation	Minimum Method for Motion Assessment During Simulation	Scan(s) Required for Treatment Planning
Free breathing treatment using an IGTV approach,	4DCT or fluoroscopy as long as tumor can be directly visualized	Repeated slow acquisition CT scanning through the target (to sample	Average scan from a full field of view 4DCT for dose calculations; MIP may be desirable to aid

including abdominal compression		motion) fused to the planning CT dataset	IGTV definition; Free-breathing scans are not recommended for treatment planning.
Gating with a gating window	4DCT	Exhale CT plus fluoroscopy (free-breathing + fluoroscopy strongly discouraged due to baseline shift)	Reconstructed average of gating window scans from 4DCT
Breath hold (i.e. ABC)	Reproducibility of breath hold confirmed (examples: multiple low dose scans over tumor, repeat fluoroscopy or scout images)	N/A	Scan in breath hold position (Inhale recommended since it maximizes lung volume)
Tracking	4DCT or breath hold CT	N/A	4DCT or breath hold CT

5.4.3 Imaging for Structure Definition, Image Registration/Fusion and Follow-up

All patients will undergo CT-based treatment planning in custom made immobilization devices. CT scan range must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting (if used), and be adequate to ensure contouring of all targeted metastases, as well as necessary organs at risk (OAR), defined below. High-resolution CT scans should be obtained with uniform slice thickness of ≤ 3mm throughout. Slices of 1-2 mm are recommended for tumors that are 1 cm or less in the largest dimension. If a single CT scan cannot be obtained due to a large spatial separation between metastases (i.e., cervical and femoral metastases), or planning system slice number limitation, multiple CT scans are allowed provided that OAR are entirely encompassed in a single CT scan. CT imaging should be performed so that a composite dose distribution including all treated metastases can be created. Ideally, all metastases will be treated in one treatment position. When treating multiple metastases such as a lung and extremity, varying the treatment position may be necessary (i.e., simulation with arms up and arms to the side). Thus, more treatment positions can be used at the discretion of the treating oncologist, but every effort should be made to obtain a composite distribution.

For detailed information regarding recommended imaging modalities for specific disease sites, please see Table 5.4.4A.

Use of Contrast Agents

IV contrast is encouraged for better delineation between tumor, atelectasis, and vascular structures as well as better definition of normal tissue contours. The use of IV contrast will be required for liver metastases. For other metastases (central & peripheral lung, cervical/ mediastinal, abdominal-pelvic, and spinal/paraspinal), the use of IV contrast is encouraged but will be left to the discretion of the treating physician. The use of other contrast agents is left to the discretion of the treating oncologist. Oral contrast can be used at the clinical discretion of the treating physician. Generally, contrast scans are acceptable for dose calculations, although

density overrides should be considered in areas of strong contrast (such as oral contrast in esophagus). Or duplicate planning datasets obtained prior to injection of intravenous contrast may be used for dose calculation.

5.4.4 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.

Treatment Sites
The following treatment sites will be allowed on this protocol: All sites that can be treated with SBRT that fulfill normal tissue tolerances as described in this protocol will be permitted.

Metastases should be assigned to one of the following seven metastatic locations to determine the required options available for dosing schedules:
1. Lung Peripheral
2. Lung Central
3. Mediastinal/Cervical Lymph Nodes
4. Liver
5. Spinal/Paraspinal
6. Osseous
7. Abdominal-pelvic (including abdomino-pelvic lymph nodes/adrenal glands)

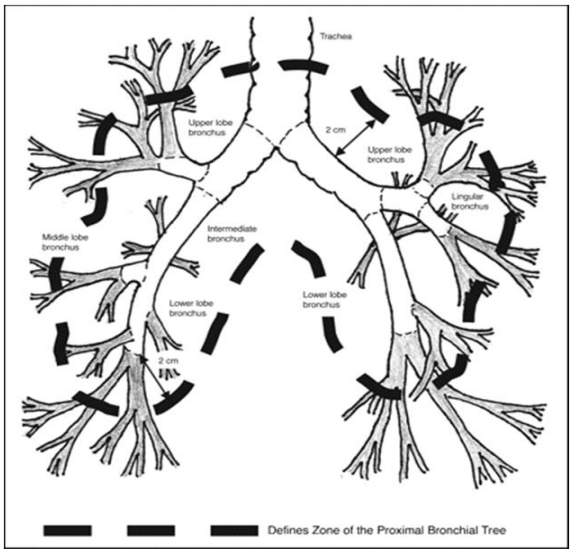
Patients can have up to only 3 (excluding primary site) discrete active extracranial lesions as identified by diagnostic CT or PET/CT which was acquired within 30 days of patient protocol registration. Patients with discrete lesions in very close proximity to one another that can and should be safely incorporated into one SBRT treatment field (e.g. liver lesions, lung lesions, mediastinal lymph nodes) while achieving 1, 3, or 5 fraction dose constraints will be considered one area of potentially 3 anatomic locations (sites) treated. Specific locations not allowed treatment with SBRT on this protocol due to the lack of established tolerance doses of SBRT are described as follows: metastatic disease involving the gastrointestinal tract, i.e. invading the esophagus, stomach, intestines, or mesenteric lymph nodes will not be permitted.

1. *Lung Peripheral*: Metastases within the lung parenchyma with GTV outside of the proximal bronchial tree as described above.

2. *Lung Central*: GTV within 2 cm of proximal bronchial tree as described in RTOG 0813/0915:
   Tumor within or touching the zone of the proximal bronchial tree, defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe

bronchus, lingular bronchus right and left lower lobe bronchi) [See Figure 5.4.4A]. Tumors that are immediately adjacent to mediastinal or pericardial pleura (PTV touching the pleura) also are considered central tumors and are eligible for this protocol. A visual representation is shown below in Figure 5.4.4A.

Figure 5.4.4A Zones of Proximal Bronchial Tree for Central Lung Lesions



3. *Mediastinal/Cervical LN:* Mediastinal: GTV arising within the anatomic space between the lungs, above the diaphragm, and below the thoracic inlet at the level of the top of the sternal notch. Cervical Lymph nodes: GTV occurring within cervical lymph node Levels I-VI and/or retropharyngeal spaces
   - Sternal metastases will be assigned to the mediastinal/cervical lymph node location based on potential for normal tissue toxicity.

4. *Liver:* GTV arising within the liver.
   - Rib metastases immediately adjacent to the liver will be assigned to the liver metastasis location based on potential for normal tissue toxicity.

5. *Spinal/paraspinal:* Metastases will be assigned to the spinal/paraspinal site if the GTV arises within the vertebral bodies expanded by 1 cm. Spinal metastases, shown in Figure 5-4.4B in black, can involve:
   (a) The vertebral body only **OR**
   (b) The vertebral body and pedicle **OR**
   (c) Posterior elements only

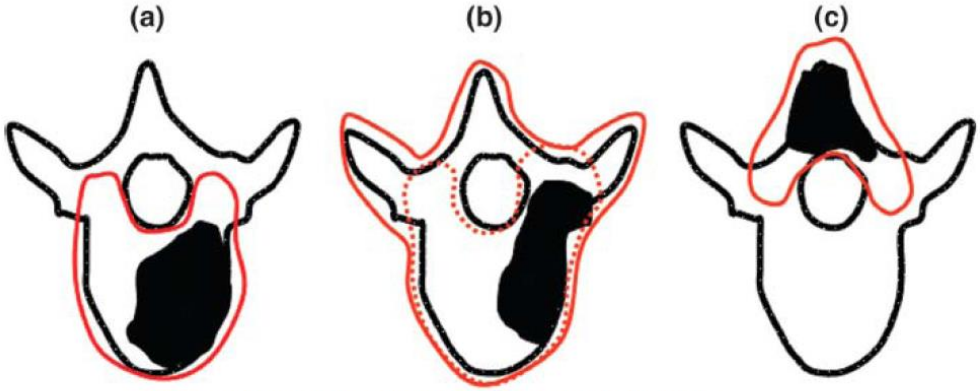


Figure 2: Diagram of Spine Metastasis and Target Volume

Figure 5.4.4B

For each of these metastases, the PTV delineation will include:

(a) the involved vertebral body and both pedicles [solid red line in Figure 5.4.4B-(a)] **OR**

(b) a more generous delineation of the involved vertebral body and both pedicles [dashed red line in Figure 5.4.4B-(b)] **OR**

(c) the involved vertebral body, both pedicles, and the anterior and posterior elements of the spine [solid red line in Figure 5.4.4B-(b)] **OR**

(d) the spinous process and laminae [solid red line in Figure 5.4.4B-(c)]

- The target volume may be chosen at the discretion of the treating Radiation Oncologist based on the extent of tumor involvement.
- Spinal metastases with epidural extension will only be included if there is > 3 mm gap between the edge of the epidural metastasis and edge of the spinal cord.
- Metastases arising in the ribs within 1 cm of the edge of the vertebral body should be included in the spinal metastasis location, but osseous metastases planning guidelines are to be used.
-

6. *Osseous*: GTV arising within an osseous structure, part of the axial skeleton, not included in the spinal definition.

- Rib metastases that are within 1 cm of the vertebral bodies will be classified into the spinal metastasis location given the similar normal tissues at risk.
- Rib/scapular metastases within the thorax adjacent to lung parenchyma will be classified into the lung metastasis location given the similar normal tissues at risk.
- Rib/osseous metastases adjacent (≤ 1cm) to mediastinal or cervical structures will be classified into the mediastinal/cervical lymph node location given the similar normal tissues at risk.

- Rib metastases adjacent (≤ 1cm) to the liver will be classified into the liver location given the similar normal tissues at risk
- Rib metastases adjacent to the stomach/abdominal wall will be classified into the intra-abdominal location given the similar normal tissues at risk
- Sternal metastases will be considered part of the mediastinal/cervical lymph nodes location given the similar normal tissues at risk.

7. *Abdominal-pelvic:* GTV arising within the anatomic space defined by the diaphragm superiorly, the genitourinary diaphragm inferiorly including the peritoneal and retroperitoneal spaces, not including liver, osseous, or spinal metastases.

Target Volume Definition Based on Metastatic Location:

Table 5.4.4A

	Metastatic Location						
	Site 1	**Site 2**	**Site 3**	**Site 4**	**Site 5**	**Site 6**	**Site 7**
Planning Parameter	**Lung Central**	**Lung Peripheral**	**Mediastinal/Cervical**	**Liver**	**Spinal**	**Osseous**	**Abdominal/Pelvic**
CT window/level	Pulmonary/ Mediastinal	Pulmonary/ Mediastinal	Pulmonary/Mediastinal	Hepatic	Bone/Soft Tissue	Bone/soft tissue	Soft Tissue
Additional Studies	PET/CT	PET/CT	PET/CT	PET/CT MRI	PET/CT MRI	PET/CT MRI	PET/CT MRI
Anatomy of focus for multi-modality fusion	Bony Anatomy	Bony Anatomy	Bony Anatomy	Liver	Bony Anatomy	Bony Anatomy	Bony Anatomy
GTV definition	Metastasis	Metastasis	Metastasis	Metastasis	Metastasis	Metastasis	Metastasis
CTV definition	= GTV/IGTV*	= GTV/IGTV*	= GTV/IGTV*	=GTV/IGTV*	=GTV	= GTV	= GTV/ IGTV*
PTV axial expansion	= CTV + 5mm**	= CTV + 5mm**	= CTV + 5mm**	= CTV + 5mm**	= PTV in RTOG 0631** (see Figure 5.4.4)	= CTV + 3-5mm**	= CTV + 5mm**
PTV craniocaudal expansion	= CTV + 5-7mm**	= CTV + 5-7mm**	= CTV + 5-7mm**	= CTV + 5-7 mm**	= PTV in RTOG 0631** (see Figure 5.4.4)	= CTV + 3-5mm**	= CTV + 5-7 mm**

***NOTE:** A GTV to IGTV expansion of greater than 1cm in any one direction is strongly discouraged and alternative respiratory management technique is suggested.

**__NOTE:__ When osseous/rib metastases are classified into other specific metastatic locations, the planning guidelines for that metastatic location should be used. If rib metastases are grouped into the spinal metastasis location, then the metastasis should be contoured as defined for osseous metastases, but the prescription doses for the spinal region should be used.

+__NOTE:__ Mediastinal lymph nodes should undergo motion assessment and an IGTV should be generated to account for motion.

Target Volume Definition For The Primary Disease if Included in Treatment or Metastases (not amendable to SBRT) Treated with Hypofractionation:

For the treatment of the primary disease or metastases with a hypofractionated approach of 45 Gy in 15 fractions, the GTV will be contoured as above and an IGTV will be created from all phases. An expansion of 5-8 mm for CTV is expected, with a PTV expansion of 5 mm at minimum with daily imaging but no more than 1 cm.

Table 5.4.4B Description and Naming of Required Target Volumes

Standard Name	Description
GTVXY_2400	GTV receiving 1 fraction with site "X" *, number Y of site X
IGTVXY_2400	IGTV receiving 1 fraction with site "X" *, number Y of site X
PTVXY_2400	PTV receiving 1 fraction with site "X" *, number Y of site X
GTVXY_3000	GTV receiving 3 fraction with site "X" *, number Y of site X
IGTVXY_3000	IGTV receiving 3 fraction with site "X" *, number Y of site X
PTVXY_3000	PTV receiving 3 fraction with site "X" *, number Y of site X
GTVXY_3400	GTV receiving 5 fraction with site "X" *, number Y of site X
IGTVXY_3400	IGTV receiving 5 fraction with site "X" *, number Y of site X
PTVXY_3400	PTV receiving 5 fraction with site "X" *, number Y of site X
GTV_4500	GTV of primary site/metastases IF treated with conventional fractionation
IGTV_4500	IGTV of primary site/metastases IF treated with conventional fractionation
CTV_4500	CTV of primary site/metastases IF treated with conventional fractionation

PTV_4500	PTV of primary site/metastases IF treated with conventional fractionation

* For the Standard Names above, X equals 1-7, dependent on anatomic treatment site listed in Sec. 5.4.4, Y equals a, b, c…

All structures listed in this table are required when applicable and must be labeled as indicated.

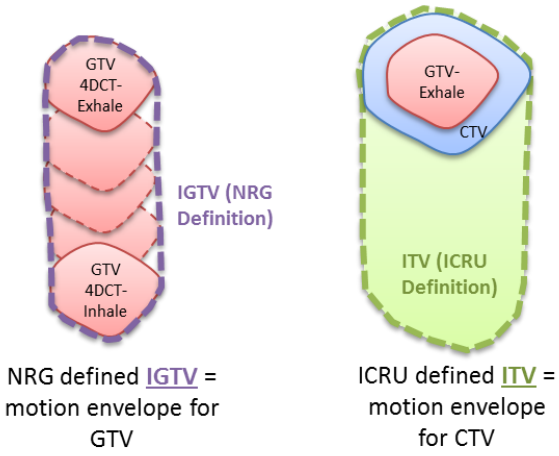
Each lesion should be labeled by their anatomic treatment site, with exception of the primary site or metastases if they are receiving conventional fractionation. They should also be distinguished by adding a letter after the site number, *a* for the 1st lesion, *b* for the 2nd and *c* for the third. An example of this would be PTV1a_2400, PTV1b_2400 and PTV4a_3000, which would correspond with having two peripheral lung lesions (sites 1a and 1b) receiving 1 fraction, and one liver lesion (site 4a) receiving three fractions.

Detailed Specifications
Note: Instructions on IGTV and PTV creation based on treatment technique is given at the end of this section.

Specific SBRT planning parameters depend on the location of the treated metastasis as well as the mechanism used for motion management/evaluation. The table below defines appropriate planning CT window/leveling, recommended additional modality scans to be fused, as well as how to define the GTV, IGTV, CTV, and PTV for each metastatic location. Only rigid registration will be permitted for multi-modality fusion. In general, the GTV is defined as the entirety of the metastasis as seen on planning CT scan aided by additional diagnostic imaging studies (i.e., PET/CT or MRI). Use of additional diagnostic studies is left to the discretion of the treating physician. The CTV=GTV; there is no margin added for microscopic extension. In general, either a helical CT or 4DCT will be used for defining the GTV/IGTV depending upon the tumor motion encountered, although both scans may be acquired at the time of simulation.

Targets in lung will generally be drawn using CT pulmonary windows; however, soft tissue windows, ideally with contrast, should be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. Information from fusion of multimodality imaging (e.g. PET) may be helpful in delineating tumor from normal tissue. For example, in the presence of large amounts of atelectasis or fibrotic changes, PET may be necessary to aid in GTV definition. IV contrast used with the planning CT is useful to differentiate more subtle atelectasis from tumor since atelectasis does not enhance. When a multimodality image serves as the primary image for GTV delineation, an additional margin to account for registration uncertainty should be considered when transferring the GTV to the primary image.

The motion encompassing GTV will be defined at the IGTV. Note that the term “ITV” is explicitly avoided to prevent confusion between a motion encompassing CTV and GTV:



The PTV shall be defined as the IGTV (or GTV when strict motion control is applied) plus an uncertainty/set-up error margin. That uncertainty/set-up margin shall be 5 +/- 2 mm in all directions. If institutional interfraction uncertainties suggest that this would not be a sufficient PTV margin for the workflow and equipment involved, please contact the protocol PIs and physics co-chair for additional guidance. Note that PTV margins are not to account for internal motion uncertainty (which is accounted for within the definition of the IGTV). The addition of an inverse planning optimization "helper" structure can be made to increase coverage to account for dose gradients (i.e. for coplanar VMAT in the cranial/caudal direction) as deemed necessary by the treating institution. General guidelines for IGTVs and GTVs, based on treatment technique, are summarized below in Table 5.4.4C.

Table 5.4.4C Guidelines for Definition of IGTV and PTV corresponding to Treatment Technique

Treatment Technique	Definition of IGTV	Definition of PTV
IGTV using 4DCT (includes abdominal compression)	Boolean union of GTV defined on all phases of 4DCT or a maximum intensity projection image (1)	Refer to Table 5.4.4A
Gating with a gating window	Boolean union of GTV defined on the gated phases of 4DCT	
Breath hold (i.e. ABC)	An appropriate margin (2-5 mm) to account for breath hold reproducibility or uncertainty is recommended	
Tracking	An appropriate margin (2-5 mm) to account for tracking reproducibility or uncertainty is recommended	

(1) If a Maximum Intensity Projection dataset is used for IGTV delineation, care must be taken to verify the IGTV against the GTV defined above on each individual phase. In addition, the MIP is not appropriate for tumors located near boundaries with soft tissue density, such as near the diaphragm or mediastinum.

5.4.5 Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the table below.

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.

The following table outlines the naming of the various normal and critical structures for submission to TRIAD.

Table 5.4.5A
Note: X represents the anatomic treatment site 1-7 as listed in Sec. 5.4.4.

Standard Name	***Description***
PTV as listed in Table 5.4.4B above	See Table 5.4.4B above
PTV20	PTV expanded by 20mm
E-PTVX	All tissue excluding the PTV. Generated by subtracting the PTV receiving a dose of xxxx cGy from the external contour. External minus PTV with site "X" *(including all subsites “Y), with dose (e.g. E-PTV2_2400)
E-PTVX_Ev20	All tissue excluding the 20 mm expanded PTV. Generated by subtracting the 20 mm expanded PTV receiving a dose of xxxx Gy from the external contour. (External minus PTV20mm)
BileDuct_Common	Common Bile duct
Bladder	Bladder
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
BrachialPlexus	Total Brachial plexus
Bronchus	Bronchial tree

Bronchus+20	Proximal bronchial tree expanded by 2cm
CaudaEquina	Cauda equina
Chestwall	Chest wall
Colon	Colon
Duodenum	Duodenum
Esophagus_NAdj	Esophagus Non-Adjacent Wall
Jejunum_Ileum	Both ileum and jejunum
Esophagus	Esophagus
External	Body surface
Femur_L	Left whole Femur
Femur_R	Right whole Femur
Femurs	Combined Left and Right Femurs
GreatVes	Great Vessels Great Vessels of the heart (aorta, vena cava S&I, pulmonary A&V)
GreatVes_NAdj	Great Vessels Non-Adjacent Wall
Heart	Heart
Larynx	Larynx
Liver	Liver
Liver-GTV	Liver minus GTV
Lung_L	Left Lung
Lung_R	Right Lung
Lungs	Combined Left and Right Lungs
Lungs-GTV	Combined Left and Right Lungs minus GTV
Rectum	Rectum
Kidney_Cortex	Renal cortex for both Kidneys
Rib	Ribs within 10 cm of the PTV should be contoured by outlining the bone and marrow
SacralPlex	Sacral plexus

Skin	Outer 0.5 cm of the body surface (rind)
SpinalCord	Spinal cord
Stomach	Stomach
Trachea	Trachea
Trachea_NAdj	Trachea non-adjacent wall
Ureter	Ureter

* X equals 1-7, dependent on anatomic treatment site (1 – 7) described in Section 5.4.4
General, critical structures should be contoured if they are found within an axial slice within 10 cm in the craniocaudal.

Critical structure contours will be drawn in axial planes of the primary planning dataset. In general, critical structures should be contoured if they are found within an axial slice within 10 cm in the craniocaudal direction of any PTV slice treated on protocol. As such, they may be further than 10 cm direct separation and still required to be contoured. If a named critical structure is further than 10 cm from any PTV, then it need not be contoured or submitted.

All metastases-specific organs at risk (OAR) must be contoured. The specific OAR to be contoured will depend on the location of metastases to be treated. The contour of structures that have a lumen (bronchus, trachea, esophagus, etc.) will include both the "wall" and the "lumen" to result in a cylindrical structure. In general, OAR within 10 cm of any single metastasis should be contoured. To identify these OARs, all PTVs will be expanded by 10 cm and any OAR that overlaps with PTV + 10 cm must be contoured. Structures must be labeled as shown above in Tables 5.4.4B and 5.4.5 or resubmission may be required.

Spinal Cord
The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of any PTV and continuing on every CT slice to at least 10 cm below the inferior extent of any PTV. **NOTE: For the spinal cord, constraints are absolute limits, and treatment delivery that exceeds defined limits will constitute a major protocol violation.**

Cauda Equina
Starting at the conus (end of spinal cord, typically around L1 or L2) include the entire spinal canal into the sacrum to the filum.

Esophagus
The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of any PTV and continuing on every CT slice to at least 10 cm below the inferior extent of any PTV.

Brachial Plexus
The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured. The brachial plexus will

be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib. If any PTV is more than 10 cm away from the brachial plexus, this structure does not need to be contoured.

Sacral Plexus
Include the nerve roots from L5 to S3 on each side from the neuroforamina to the coalescing of the nerves at the obturator internus muscle.

Heart
The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aorto-pulmonary window) and extend inferiorly to the apex of the heart.

Trachea and Proximal Bronchial Tree
The trachea and proximal bronchial tree will be contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. For this purpose, the trachea will be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree.

Proximal Trachea
Contouring of the proximal trachea should begin at least 10 cm superior to the extent of the PTV or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.

Proximal Bronchial Tree
The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides as indicated in the diagram in above. The following airways will be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.

Whole Lung
Both the right and left lungs should be contoured individually (**Lung_L**, **Lung_R**) and also combined as one structure (**Lungs**). Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included for the structure created and -labeled as **Lungs-GTV**.

PTV + 2 cm (PTV20)
As part of the QA requirements for "low dose spillage" listed above, a maximum dose to any point 2 cm away in any direction is to be determined (D2cm). To facilitate this QA requirement,

an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. If possible this structure should be constructed as a single contour that is 2 cm larger than the PTV.

Skin
The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

Rib
Ribs within 10 cm of the PTV should be contoured by outlining the bone and marrow. Typically, several portions of adjacent ribs will be contoured as one structure. Adjacent ribs, however, should not be contoured in a contiguous fashion (i.e., do not include the inter-costal space as part of the ribs).

Stomach
The entire stomach and its contents should be contoured as a single structure as a continuation of the esophagus and ending at the first part of the duodenum.

Duodenum
The wall and contents of the 1st, 2nd, and 3rd parts of the duodenum will be contoured as one structure beginning where the stomach ends and finishing as the superior mesenteric artery crosses over the third part of the duodenum.

Jejunum/Ileum
As a conglomerate of bowel loops within the abdomen distinguished from stomach, duodenum, and colorectum.

Colon
From the ileocecal area to include the ascending, transverse, descending and sigmoid colon as one structure.

Rectum
The entire rectum with contents from the peritoneal reflection of the sigmoid to the anus.

Bladder
The entire bladder wall without urine.

Renal Cortex (right and left combined as one)
Specifically, the parallel functioning nephrons of the renal cortices of the kidneys (not the hilum).

Liver

The entire liver as well as an additional structure created to exclude the GTV targets where applicable. (Liver – GTV).

Bile ducts
May use the portal vein from its juncture with the splenic vein to its right and left bifurcation in the liver as a surrogate to identify the bile ducts.

Femur
Individual left and individual right femur as well as a combined structure (Femur_L, Femur_R, Femurs).

Other Structures
The constraints tables above contain other structures. These are required if the structure is within 10 cm of the PTV.

5.4.6 Treatment Planning Guidelines for radiation administration

Treatment planning for SBRT should be approached with care and experience is recommended for sites enrolling on an SBRT protocol. Table 5.4.6A summarizes the general planning guidelines for this protocol.

Table 5.4.6A General Treatment Planning Guidelines

Topic/Parameter	Guidelines
Planning Technique	3DCRT, conformal arc, and intensity-modulated techniques (IMRT, VMAT) allowed. Tomographic and robotic techniques also allowed with appropriate credentialing having been completed. See Section 8.2 for further details.
Number of Beams	As planning dictates although ≥10 beams are recommended for static beam plans due to skin toxicity considerations. Similarly, arcs should cover an appropriate range so as to deliver a safe dose to the skin.
Beam Arrangement	Coplanar or non-coplanar (non-coplanar are encouraged), non-overlapping, non-opposing beams or arc therapy (non-coplanar arcs encouraged). Combination of static and arc beams allowed. Gantry clearance verification prior to treatment should be a mandatory part of patient specific QA.
Beam Energy	As planning dictates although lower energies preferred for lung (see 5.4.1A)
Block Margin (for 3DCRT)	Generally 0 +/- 2 mm, but iterated to achieve coverage specifications. Negative margin blocks are frequently useful to create steep gradients along the axial limits of the PTV while positive margin (e.g., +2 mm) are often needed on the cranial and caudal limits of the PTV

Minimum Field Size	As planning dictates although only the smallest field size accurately commissioned (e.g. small field output factors are within 5% of published standards or values) at the institution should be used. Because of concerns with small field dosimetry, field sizes above 2 cm x 2 cm are preferable.
Dataset for Dose Calculation	IGTV Approach – Average CT (AveIP) from 4DCT or a slow acquisition CT which captures motion if 4DCT not available (Free breathing CT is not appropriate) Breath Hold – CT taken at treatment breath hold Gated – Average from gating window phases from 4DCT or the median phase in the gating window Tracking – 4DCT or breath hold CT Scans with contrast are generally acceptable for dose calculations. However, density/material overrides are recommended in areas of strong contrast when dose calculation accuracy may be affected (such as oral contrast in the esophagus).
Dose Calculation Algorithm	Modern algorithms that accurately handle tissue heterogeneity and scatter should be used. IROC maintains an updated list of approved algorithms. Density corrections must be applied. Density overrides of the GTV are not recommended for photon treatment.
Dose Grid Resolution	3 mm x 3 mm dose grid resolution or smaller is required. Use of 2 mm x 2 mm is recommended, especially for targets less than 2 cm in diameter.

Protocol specific fractionation details as well as prescription definition and compliance guidelines are given in Tables 5.4.6B and 5.4.6C.

Table 5.4.6B Protocol Specific Fractionation Details

Item	**Details**			
	1 Fraction SBRT	**3 Fraction SBRT**	**5 Fraction SBRT**	**Primary Site/ Metastases Not Amenable to SBRT**
Number of Fractions	1	3	5	15
Dose Per Fraction (Gy)	24	10	6.8	3
Total Treatment Duration	See section 5.4.7			

Table 5.4.6C Protocol Specific Target Dose Details and Recommendations

Metric	Guideline Value			
	1 Fraction SBRT	**3 Fraction SBRT**	**5 Fraction SBRT**	**Primary Site/ Metastases Not Amenable to SBRT**
D95% [Gy] for PTV (ie. Dose covering 95% of PTV)	24	30	34	45
D99% [Gy] for PTV (ie. Dose covering 99% of PTV)	21.6	27	30.6	40.5
Dose Heterogeneity within PTV	Typical normalization 60-90% with hotspot within GTV.			A volume of no more than 0.03 cc inside the PTV exceeds 110%, The minimum PTV dose to a volume of 0.03 cc falls below 90%
R100% (Rx Isodose volume/PTV)	<1.2 Desired. Exceptions can be made for small PTVs requiring a block margin to satisfy field size criteria. Effort should be made to avoid dose > 105% of the prescription dose outside of the PTV.			N/A
R50% (50% Rx Isodose volume/PTV)	Effort should be made to have the 50% isodose surface be as small as possible. Detailed tables of recommendations are given below for single targets.			N/A

Table 5.4.6D Recommendations for Allowable Dose Spillage

PTV Volume (cc)	Ratio of 50% Isodose Volume to the PTV, R50%		Maximum Dose at 2 cm from PTV in any direction as % of nominal Rx dose D2cm[%]	
	Per Protocol	Variation Acceptable	Per Protocol	Variation Acceptable
1.8	<5.9	<7.5	<50.0	<57.0
3.8	<5.5	<6.5	<50.0	<57.0
7.4	<5.1	<6.0	<50.0	<58.0
13.2	<4.7	<5.8	<50.0	<58.0
22.0	<4.5	<5.5	<54.0	<63.0

34.0	<4.3	<5.3	<58.0	<68.0
50.0	<4.0	<5.0	<62.0	<77.0
70.0	<3.5	<4.8	<66.0	<86.0
95.0	<3.3	<4.4	<70.0	<89.0
126.0	<3.1	<4.0	<73.0	<91.0
163.0	<2.9	<3.7	<77.0	<94.0

5.4.7 Compliance criteria

Treatment Duration

Interfractional Interval must be no less than 36 hours and no greater than 8 days.

Treatment duration will be defined per metastatic site treated with SBRT and treatment of primary disease and/or metastases requiring hypofractionated 15 fraction regimen.

Per Protocol:

- Single Fraction Treatment: SBRT should be completed within 2 weeks of randomization
- 3 fraction treatment: All 3 fractions of SBRT should be completed within 2 weeks of first SBRT dose and within 4 weeks of randomization
- 5 fraction treatment: All 5 fractions of SBRT should be completed within 3 weeks of first SBRT dose and within 5 weeks of randomization
- 15 fraction treatment: All 15 fractions of radiation should be completed within 3 weeks of first hypofractionated dose, ideally within 4 weeks of randomization and at the latest within 5 weeks of randomization

Variation Acceptable:

- All SBRT treatment completing > 3 but < 4 weeks
- Primary site hypofractionated RT completing >3 weeks but <5 weeks

Deviation Unacceptable:

- All SBRT treatment completed > 4 weeks
- Primary site hypofractionated RT completed >5 weeks

If the primary disease and/or metastases not amenable to SBRT is treated with 45 Gy in 15 fractions, this treatment should ideally be completed over 21 days and any metastatic areas needing treatment with SBRT can be given on the appropriate days within that three week period. For a given lesion (target) treated with SBRT, a minimum of 36 hours and a maximum of 8 days should separate consecutive treatments of that same lesion. While up to 2 metastatic lesions may be treated on the same day with SBRT, the treating physician may choose to separate treatments to alternating lesions by one or more days so long as all treatment is completed per protocol. All SBRT treatments should ideally be completed within 21 days of first treatment and no later than 28 days.

Ample time should be scheduled for each treatment to insure careful execution of the SBRT for each lesion. No more than 2 anatomic sites should be treated with SBRT on any given day. Try to avoid long treatment sessions (e.g., treating 3 anatomic sites in one day with SBRT or hypofractionated treatment of primary plus 2 sites of metastases with SBRT) as the resulting discomfort for the patient from prolonged immobilization may confound accuracy. If there are multiple metastatic sites (2 or 3) being treated with 5 fraction SBRT regimens in addition to a primary disease site treated with the hypofractionated regimen, there may be a necessity to treat that primary disease and both metastatic sites on the same day as a means of getting the patient to maintenance systemic therapy in a clinically appropriate time frame. Ideally, radiation and surgery should be completed within 5 weeks of start of local treatment.

Treatment Plan Compliance

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended. Institutions are encouraged to contact the PI or medical physics co-chair prior to submitting a case with a known unacceptable deviation.

PTV Dosimetry Compliance for SBRT

Tables in Section 5.4.7 describe acceptable variations in the protocol dosimetric parameters. These criteria should be evaluated for each metastasis independently (i.e., while suppressing dose from all other metastases), particularly for metastases treated on separate days. This may not be possible for metastases treated on the same day using a single plan (e.g., VMAT). Dosimetric parameters outside of the variation acceptable range will be scored as Deviation Unacceptable. Please refer to Table 5.4.6B above for allowable prescription and fractionation options.

Table 5.4.7A

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
PTVXY_2400	D95%[Gy]	24	16-27 Excluding 24
PTVXY_3000	D95%[Gy]	30	24.5-33 Excluding 30
PTVXY_3400	D95%[Gy]	34	28-37.5 Excluding 34

Note: X equals the Treatment Site number 1 (1-7) and Y is the sequence of lesion if multiple are in one area (a, b, c)

PTV Dosimetry Compliance for Primary Site/Metastases Not Amendable to SBRT
Table 5.4.7B

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
PTV_4500	D95%[Gy]	45	42-48 (excluding 45)

Organ at Risk Dosimetry Compliance for SBRT

Table 5.4.7C Normal Structure Constraints and Compliance Criteria

		1 Fraction	3 Fractions	5 Fractions	
Serial Tissue	**Volume**	**Per Protocol (Gy)**	**Per Protocol (Gy)**	**Per Protocol (Gy)**	**Endpoint (≥Grade 3)**
Optic Pathway	D0.03cc[Gy]	10	17.4	25	neuritis
	D0.2cc[Gy]	8	15.3	23	
Cochlea	D0.03cc[Gy]	9	14.4	22	hearing loss
Brainstem (not medulla)	D0.03cc[Gy]	15	23.1	31	cranial neuropathy
	D0.5cc[Gy]	10	15.9	23	
Spinal Cord and medulla	D0.03cc[Gy]	14	22.5	28	myelitis
	D0.35cc[Gy]	10	15.9	22	
	D1.2cc[Gy]	8	13	15.6	
Cauda Equina	D0.03cc[Gy]	16	22.5	31.5	neuritis
	D5cc[Gy]	14	21.9	30	
Sacral Plexus	D0.03cc[Gy]	16	22.5	31.5	neuropathy
	D5cc[Gy]	14.4	22.5	30	
Esophagus*	D0.03cc[Gy]	15.4	25.2	35	stenosis/fistula
	D5cc[Gy]	11.9	17.7	19.5	
Brachial Plexus	D0.03cc[Gy]	16.4	26	32.5	neuropathy
	D3cc[Gy]	13.6	22	27	
Heart/Pericardium	D0.03cc[Gy]	22	30	38	pericarditis
	D15cc[Gy]	16	24	32	
Great vessels	D0.03cc[Gy]	37	45	53	aneurysm
	D10cc[Gy]	31	39	47	

Trachea and Large Bronchus*	D0.03cc[Gy]	20.2	30	40	stenosis/fistula
	D4cc[Gy]	17.4			
	D5cc[Gy]		25.8	32	
Bronchus-smaller airways	D0.03cc[Gy]	13.3	23.1	33	stenosis with atelectasis
	D0.5cc[Gy]	12.4	18.9	21	
Rib	D0.03cc[Gy]	33	50	57	Pain or fracture
	D5cc[Gy]	28	40	45	
Skin	D0.03cc[Gy]	27.5	33	38.5	ulceration
	D10cc[Gy]	25.5	31	36.5	
Stomach	D0.03cc[Gy]	22	30	35	ulceration/fistula
	D5cc[Gy]	17.4	22.5	26.5	
Bile duct	D0.03cc[Gy]	30	36	41	stenosis
Duodenum*	D0.03cc[Gy]	17	22.2	26	ulceration
	D5cc[Gy]	11.2	15.6	18.5	
	D10cc[Gy]	9	12.9	14.5	
Jejunum/Ileum*	D0.03cc[Gy]	22	27	32	enteritis/obstruction
	D30cc[Gy]	12.5	17.4	20	
Colon*	D0.03cc[Gy]	29.2	34.5	40	colitis/fistula
	D20cc[Gy]	18	24	28.5	
Rectum*	D0.03cc[Gy]	44.2	49.5	55	proctitis/fistula
	D3.5cc[Gy]	39	45	50	
	D20cc[Gy]	22	27.5	32.5	
Ureter	D0.03cc[Gy]	35	40	45	stenosis
Bladder wall	D0.03cc[Gy]	25	33	38	cystitis/fistula
	D15cc[Gy]	12	17	20	

Penile bulb	D3cc[Gy]	16	25	30	impotence
Femoral Heads	D10cc[Gy]	15	24	30	necrosis

		1 Fraction	3 Fraction	5 Fraction	
Parallel Tissue	**Constraint****	**Per Protocol (cc or %)**	**Per Protocol (cc or %)**	**Per Protocol (cc or %)**	**Endpoint (≥Grade 3)**
Lungs-GTV	CV7Gy[cc]	>1500			Basic Lung Function
	CV10.5Gy[cc]		>1500		
	CV12.5Gy[cc]			>1500	
	V8Gy[%]	<37			Pneumonitis
	V11Gy[%]		<37		
	V13.5Gy[%]			<37	
Liver	CV11Gy[cc]	>700			Basic Liver Function
	CV17.1Gy[cc]		>700		
	CV21Gy[cc]			>700	
Renal cortex (Right & Left)	CV9.5Gy[cc]	>200			Basic Renal Function
	CV15Gy[cc]		>200		
	CV18Gy[cc]			>200	

*Avoid circumferential irradiation

** A complementary volume (CV) or "cold volume" is the volume of tissue receiving the indicated dose or less. CVxGy[cc] are complementary or cold volume objectives for parallel tissues, where "xGy" is the threshold dose and the critical volumes are displayed in the table. To use these objectives as conventional DVH-based inverse planning objectives, the planner can convert using the total structure volume and the equation $V_{\text{threshold dose}}[\%] < [1 - (V_{\text{critical}} / V_{\text{total}})] \times 100\%$ (note the change to "less than"). For example, for the CV12.5Gy[cc] metric and a total lung volume of 4000cc, the corresponding maximum volume objective V12.5Gy[%] should be kept less than [1 - (1500 / 4000)] x 100%, or < 62.5%.

NOTE: For the spinal cord, these are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation. For the non-spinal cord tissues, acceptable deviation following the planning priorities allows a maximum point dose no more than 105% of the prescription dose while fully respecting the defined volume constraint (for serial tissues) OR exceeding the parallel tissue critical volume dose maximum by no more than 5%. Unacceptable deviation exceeds the volume constraint for serial tissues, exceeds the maximum point dose for serial tissues by more than 105% of the prescription dose, or exceeds the parallel tissue critical volume dose maximum by more than 5%.

Organ at Risk Dosimetry Compliance for Primary Site for Primary Site/Metastases Not Amenable to SBRT

Table 5.4.7D

Structure	Constraint	Per Protocol (Gy or %)	Variation Acceptable*
Lungs minus primary GTV	V18Gy[%]	37	40 *
	Mean[Gy]	18	19.7
Great Vessels	D0.03cc[Gy]	54.3	59.6
	D10cc[Gy]	48.9	53.7
Skin	D0.03cc[Gy]	55	60.8
	D10cc[Gy]	49	53.8
Esophagus (non-adjacent wall)	D5cc[Gy]	45	51.3
	D0.03cc[Gy]	54	59.4
Brachial Plexus	D0.03cc[Gy]	50.6	52.5
	D3cc[Gy]	44.5	48.0
Spinal Cord	D0.03cc[Gy]	42	46
	D5cc[Gy]	39.0	42.8
Bronchus_Main	D0.03cc[Gy]	45.6	50.1
	D5cc[Gy]	39.5	43.4

Rib	D0.03cc[Gy]	52.2	57.3
	D5cc[Gy]	48.9	53.7
Heart	D0.03cc[Gy]	48.9	53.7
	D15cc[Gy]	39.5	42.0

CAUTION: If a primary site is adjacent to the one of the metastatic SBRT sites, please contact the Study PI for further instructions.

5.4.8 Treatment Planning Priorities and Instructions

Successful treatment planning criteria are listed in the previous section. In general, attempts should be made to successfully satisfy all of the criteria without deviation. In some circumstances, improvements can be made to the dosimetry plan beyond simply meeting the specified goals. In other circumstances, clinicians are faced with the prospect of not ideally meeting one or more of the criteria (i.e., accepting an acceptable deviation). In this section, we provide priorities in which a most ideal plan for protocol purposes is realized. Figure 5.4.8A demonstrates these priorities graphically. Suggested priority of planning goals in order of importance is:

Table 5.4.8A Treatment Planning Priorities

Planning Priority	Instructions
1	Respect spinal cord, cauda equina, sacral plexus, brachial plexus, luminal GI structures (esophagus, stomach, duodenum, jejunum, ileum, colon) dose constraints in Table 5.4.7C.
2	Meet dose "compactness" constraints including the prescription isodose surface coverage, high dose spillage (location and volume), and intermediate dose spillage (D2cm, and R50) as these define the "essence" of SBRT.
3	Meet critical structure constraints other than those listed in 1.

NOTE: No studies of OAR limits for multiple metastases have been reported in the literature. Thus, organ limits from previously developed protocols, as shown in Tables 5-7, 5-8 and 5-9 below, will be utilized.

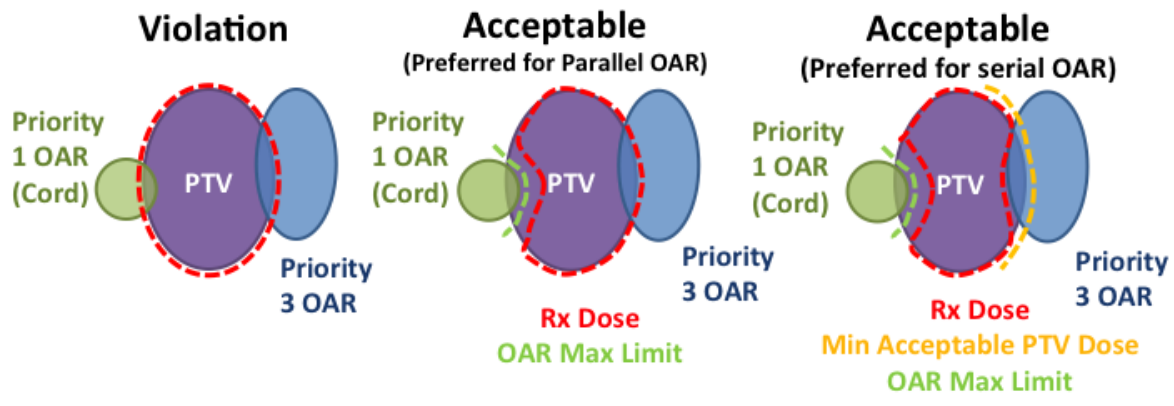


Figure 5.4.8A Graphical representation of preferred planning tradeoffs in areas of overlap. See Table 5.4.8A for more detail.

5.4.9 Patient specific QA

Any patient-specific QA that needs to be acquired should follow institutional guidelines. For intensity-modulated techniques, patient specific QA is required.

5.4.10 Daily Treatment Localization/IGRT

Daily image guidance is required for all SBRT treatments. Table 5.4.10A lists details of IGRT and the minimum requirements for IGRT in lung. Techniques should be consistent with Tables 5.4.2B and 5.4.4B. It is very strongly recommended that all calculated IGRT shifts of 1 mm and greater (using primary localization imaging) be applied.

Table 5.4.10A Guidelines/Instructions for Acceptable IGRT

Treatment Technique	Acceptable Methods for Daily Image Guidance	Matching Instructions
IGTV/free breathing (includes abdominal compression)	**Volumetric Imaging** Volumetric Imaging (i.e. CBCT or CT on rails) is strongly recommended	Initial rigid alignment followed by soft tissue match with average CT and slow CBCT 4DCT to 4D-CBCT can be used when capability exists
	Planar Imaging If volumetric imaging is not available, then an appropriate tumor surrogate (i.e. implanted fiducials) must be able to be accurately imaged in the treatment position with 2D imaging. The patient surface is not an appropriate surrogate for tumor setup although surface based imaging may be used during treatment to assess unexpected patient motion. Note that when orthogonal 2D imaging (with or without implanted fiducials) is employed for sites where respiratory motion is expected and not controlled via motion management techniques, care must be taken to ensure accurate targeting of the IGTV within the treatment. For example, static kV imaging at an undetermined breath hold position would not be adequate IGRT for treating a free-breathing lung tumor. Repeat imaging during treatment is	1. Rigid alignment to bony anatomy 2. Repeat imaging to ensure tumor surrogate is within IGTV 3. Repeat imaging at each treatment port to ensure tumor surrogate remains within the IGTV is very strongly recommended

	recommended to verify that the tumor is in the IGTV If any significant baseline shifts are noted, resimulation should be strongly considered	
Gating with a gating window	The baseline gating position/phase should be verified using appropriate imaging techniques Volumetric Imaging (i.e. CBCT or CT on rails) is strongly recommended for the initial localization to verify isocenter and tumor trajectory	Initial rigid alignment followed by soft tissue match for baseline gating position
Breath hold (i.e. ABC)	Volumetric imaging recommended; planar at breath hold position acceptable – repeated imaging recommended to ensure reproducibility of breath hold All imaging should be done at breath hold treatment position	Initial rigid alignment followed by soft tissue match of tumor or surrogate
Tracking	Volumetric imaging or real-time fluoroscopic imaging of tumor surrogate required based on treatment machine capabilities.	Initial rigid alignment followed by soft tissue match of tumor or surrogate in baseline position

5.4.11 Case Review

NOTE: PRE-TREATMENT REVIEWS are required for the first patient enrolled from each institution. The first case enrolled at each institution case will require approval prior to administering any protocol RT.

The Principal Investigators, Dr. Iyengar, and/or designated Radiation Oncology Co-Chairs, will perform ongoing remote RT Quality Assurance Review after cases enrolled have been received at IROC Philadelphia-RT. The Pre-Treatment review process requires three (3) business days to complete a pre-treatment review once all complete and correct data is received at IROC Philadelphia-RT. If an unacceptable deviation occurs, the next case may require a Pre-Treatment Review.

After institutions have passed the pre-treatment review of the first patient enrolled, review of all other cases will be ongoing and performed remotely.

5.5 General Concomitant Medication and Supportive Care Guidelines

5.5.1 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. Palliative and supportive care for disease-related symptoms will be offered to all patients.

In addition, the following standard treatments are allowed for concurrent medical conditions:

- Epoetin alfa (Epogen, Procrit). Please follow guidelines of the American Society of Clinical Oncology and the American Society of Hematology for the use of epoetin in subjects with cancer and FDA alert on March 09, 2007.
- Hematopoietic growth factors, including filgrastim (Neupogen), or other granulocyte colony stimulating factors (G-CSF). Please follow American Society of Clinical Oncology (ASCO) guidelines for the use of white blood cell growth factors. http://jco.ascopubs.org/content/24/19/3187.
- Prophylactic antiemetics may be administered according to standard practice.
- Megestrol acetate (Megace) may be administered for treatment of cachexia or unexplained, significant weight loss.
- Supportive therapy for toxicities associated with pemetrexed, or gemcitabine therapy, according to the FDA approved label or institutional practice.
- Use of topical corticosteroids, topical antibiotics, and systemic antibiotics, according to standard of care (SOC) or institutional guidelines.
- Bisphosphonates, according to SOC or institutional guidelines.

5.5.2 Prohibited Therapies

Filgrastim, sargramostim or pegfilgrastim are not allowed during radiation treatment. During maintenance therapy, defer to institutional standard and the FDA package insert for contraindicated therapies.

5.5.3 Participation in Other Trials

Patients will not be allowed to participate in other therapeutic trials unless there is evidence of progression on maintenance systemic therapy.

5.6 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 6
- 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

6.1 Systemic Therapy Dose Modifications (30-MAR-2021)

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

There are no dose reductions for immune checkpoint inhibitors (atezolizumab, ipilimumab, nivolumab, pembrolizumab). These agents are either administered at full dose, temporarily withheld, or permanently discontinued.

For patients receiving combination maintenance therapy, if toxicity is reasonably attributed to a single agent, one agent may be modified and the other administered as previously.

If clinically appropriate, dose may be re-escalated in future cycles after dose reduction. Similarly, for combination maintenance therapy (eg, pemetrexed plus pembrolizumab; nivolumab plus ipilimumab), if one agent is withheld, it may be re-introduced in future cycles.

Please refer to package insert for details on dosing and supportive care and other guidelines

6.2 Management of Toxicity Related to Systemic Therapy (18-OCT-2023)

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.

6.2.1 MK-3475 (pembrolizumab) Dose Modification and Toxicity Management Table

Pembrolizumab-related toxicity can be managed and treatment can be held, per investigator discretion, in accordance with package insert guidance and the table below.

General instructions:

1. For non-endocrine-related severe and life-threatening irAEs, investigators should consider the use of IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. Some non-endocrine irAEs do not require steroids. For example, celiac disease induced by pembrolizumab can be controlled by diet alone.
2. For non-endocrine-related toxicities, pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab-treatment.
3. Generally, when corticosteroids are used, investigators should begin a taper when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld due to a non-endocrine irAE, pembrolizumab may generally resume after the irAE has decreased to ≤Grade 1 after a corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up

Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or	Monitor participants for signs and symptoms

	Recurrent Grade 3 or Grade 4	Permanently discontinue	equivalent) followed by taper Patients who do not respond to corticosteroids should be seen by a gastroenterologist for confirmation of the diagnosis and consideration of secondary immune suppression	of enterocolitis (*i.e.*, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (*i.e.* peritoneal signs and ileus) Specifically assess for celiac disease serologically, and exclude *Clostridium difficile* infection Participants with ≥Grade 2 diarrhea suspecting enterocolitis should consider GI consultation and performing endoscopy to rule out enterocolitis and assess mucosal severity Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient

AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Grade 1 or 2	Continue		Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence, any grade hyperglycemia may be an indication of beta-cell destruction and pembrolizumab-induced diabetes akin to type 1 diabetes. This should be treated as a Grade 3 event. Given this risk, exercise caution in utilizing non-insulin hypoglycemic agents in this setting. After a thorough investigation of other potential causes, which may involve a referral to an endocrinologist, follow institutional guidelines. Monitor glucose

	New onset T1DM (evidence of β-cell failure) or Grade 3 or 4 hyperglycemia	Withhold [d] Resume pembrolizumab when symptoms resolve and glucose levels are stable	Initiate treatment with insulin If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g.* anion gap, ketones, blood pH, *etc*.) reported	Monitor for glucose control Strongly consider referral to endocrinologist Obtain C-peptide level paired with glucose, autoantibody levels (*e.g.* GAD65, islet cell autoantibodies), and hemoglobin A1C level
Hypophysitis	Grade 2	Withhold	Administer corticosteroids	Monitor for signs and

	Grade 3 or 4	Withhold or permanently discontinue [d]	and initiate hormonal replacements as clinically indicated	symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) Provide adrenal insufficiency precautions including indications for stress dose steroids and medical alert jewelry Strongly consider referral to endocrinologist
Hyperthyroidism	Grade 2	Consider withholding. Resume pembrolizumab when symptoms are controlled, and thyroid function is improving	Treat with nonselective beta-blockers (*e.g.*, propranolol) or thionamides as appropriate Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed	Monitor for signs and symptoms of thyroid disorders Strongly consider referral to endocrinologist
	Grade 3 or 4	Withhold or permanently discontinue [d]		

Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (*e.g.*, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function Strongly consider referral to nephrologist
	Grade 3 or 4	Permanently discontinue		
Cardiac Events (including myocarditis, pericarditis, arrhythmias, impaired ventricular function, vasculitis)	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1), or Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month

	Grade 2, 3 or 4	Permanently discontinue	Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent Initiate treatment per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or pericardiocentesis as appropriate	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE	Ensure adequate evaluation

	Confirmed SJS, TEN, or DRESS	Permanently discontinue	administer corticosteroids	to confirm etiology or exclude other causes Strongly consider referral to dermatologist Consider skin biopsy for evaluation of etiology
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Infusion-Related Reactions

Infusion Reactions	**NCI CTCAE Grade**	**Treatment**	**Premedication at subsequent dosing**
Mild reaction; infusion interruption not indicated; intervention not indicated	Grade 1	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (*e.g.*, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Grade 2	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (*e.g.* from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Prolonged (*i.e.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Grade 3	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids (*e.g.* methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing.
Life-threatening; pressor or ventilator support indicated	Grade 4	Admit participant to intensive care unit (ICU) and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. Follow Grade 3 recommendations as applicable.	No subsequent dosing.

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; ECMO=extracorporeal membrane oxygenation; GI=gastrointestinal; ICU=intensive care unit; IO=immuno-oncology; ir=immune related; IV=intravenous; MRI=magnetic resonance imaging; PO=per os; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal; VAD=ventricular assist device.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

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

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

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

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

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (*e.g*. vasculitis and sclerosing cholangitis).

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

6.2.2 Atezolizumab Dose Modification and Toxicity Management

Atezolizumab-related toxicity can be managed and treatment can be held, per investigator discretion, in accordance with institutional standards and the FDA package insert, and the following table for additional guidance:

Atezolizumab Toxicity Management Guidelines

Refer to the atezolizumab FDA label for toxicity management information. In addition to the FDA label, NCCN immunotherapy-related toxicity guidelines, and institutional standards, the following are recommended toxicity management guidelines for certain AEs of concern, including immune-related pneumonitis, hepatitis, colitis, endocrinopathies, pancreatitis, neuropathies, meningoencephalitis, and potential ocular toxicities, as well as guidelines for the management of Infusion Related Reactions and Anaphylaxis.

General AE Management and Dose Modification Guidelines

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

Patients may temporarily suspend study treatment for up to 84 days (12 weeks) beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If atezolizumab is held because of AEs for >84 days beyond the scheduled date of

infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in this protocol. If the AE resolves within 84 days and the patient is receiving corticosteroid therapy for the event, atezolizumab may be held for longer than 84 days (up to 4 weeks) in order to allow tapering of the steroid dose to ≤10 mg oral prednisone or equivalent.

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

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

Management of Specific AEs

Management of certain AEs of concern, including immune-related pneumonitis, hepatitis, colitis, endocrinopathies, pancreatitis, neuropathies, meningoencephalitis, and potential ocular toxicities are presented in the Atezolizumab Investigator's Brochure. See **the Agent Administration Guidelines** in this document, including the "**Administration of First and Subsequent Atezolizumab Infusions**" table for guidelines for the management of Infusion Related Reactions and Anaphylaxis.

Atezolizumab has been associated with risks such as the following: IRRs and immune–related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. **Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome.**

Pleural and pericardial effusion

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

Pulmonary events

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

symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

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

Event	Management
Pulmonary event, Grade 1	● Continue atezolizumab and monitor closely. ● Re-evaluate on serial imaging. ● Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. ● Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. ● For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	● Permanently discontinue atezolizumab. ● Bronchoscopy or BAL is recommended. ● Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Hepatic events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in the table below.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of >5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Gastrointestinal events

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in the table below.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (*e.g*., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab. • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (*i.e*., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

Event	Management

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Endocrine disorders

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in the table below.

Patients experiencing one or more unexplained AEs possibly indicative of endocrine dysfunction (including headache, fatigue, myalgias, impotence, mental status changes, and constipation) should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid stimulating hormone (TSH) and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests [*e.g.*, TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone (ACTH) levels, and ACTH stimulation test] and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency. The table below describes dose management guidelines for hyperthyroidism, hypothyroidism, symptomatic adrenal insufficiency, and hyperglycemia.

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab.
Symptomatic adrenal	• Withhold atezolizumab for up to 12 weeks after event onset. [a]

Event	Management
insufficiency, Grade 2–4	• Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab.
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Consider referral to endocrinologist, particularly if patient is deemed to have atezolizumab-induced diabetes; if so, obtain C-peptide level paired with glucose, autoantibody levels (e.g. GAD65, islet cell autoantibodies), and hemoglobin A1C level. • If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g.* anion gap, ketones, blood pH, *etc*.) reported. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab. • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.

Event	Management
	• Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Ocular events

An ophthalmologist should evaluate visual complaints (*e.g.*, uveitis, retinal events). Management guidelines for ocular events are provided in the table below.

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Immune-mediated Cardiac Events

Immune-mediated myocarditis and pericarditis have been associated with the administration of atezolizumab. Management guidelines for cardiac events are provided in the table below.

Immune-mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab.

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (*e.g.*, B-NP [B-Natriuretic Peptide]) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on pericardial disorders below) and should be managed accordingly.
Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, *e.g.*, in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy. All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an electrocardiogram (ECG), a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

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

Event	Management
Immune-related myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a]. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If symptoms resolve to below Grade 2 (*i.e.* patient is completely asymptomatic), resume atezolizumab. [b] • If symptoms do not resolve to below Grade 2 while withholding atezolizumab, permanently discontinue atezolizumab.
Immune-related myocarditis, Grade 3-4	• Permanently discontinue atezolizumab. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If symptoms resolve to below Grade 2, taper corticosteroids over ≥1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be documented by the

Event	Management

investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Immune-mediated Pericardial Disorders

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Event	Management
Immune-mediated myocarditis, Grade 2–4 Immune-mediated pericardial disorders, Grade 2–4	• Permanently discontinue atezolizumab. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

Infusion-Related Reactions and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS)

with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (*e.g.*, acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee *et al*., 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz *et al*., 2017; Adashek and Feldman 2019) including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in the table below.

Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	● Immediately interrupt infusion. ● Upon symptom resolution, wait 30 minutes and then restart infusion at half the rate being given at the time of event onset. ● If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. ● If symptoms recur, discontinue infusion of this dose. ● Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. ● In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. ● For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2[a] Fever[b] with hypotension not requiring vasopressors **and/or** Hypoxia	● Immediately interrupt atezolizumab infusion. ● Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. ● If symptoms recur, discontinue infusion of this dose. ● Administer symptomatic treatment.[c] ● For hypotension, administer IV fluid bolus as needed. ● Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage

requiring low-flow oxygen[d] by nasal cannula or blow-by	constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● Consider IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] ● Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. ● If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. ● If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Principal Investigator.
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	● Permanently discontinue atezolizumab. ● Administer symptomatic treatment.[c] ● For hypotension, administer IV fluid bolus and vasopressor as needed. ● Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] ● Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.
<u>Grade 4</u>[a] Fever[b] with hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia	● Permanently discontinue atezolizumab. ● Administer symptomatic treatment.[c] ● Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or

requiring oxygen by positive pressure (*e.g.*, CPAP, BiPAP, intubation and mechanical ventilation)	dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[f] may be considered at the discretion of the investigator. ● Hospitalize patient until complete resolution of symptoms.

ASTCT= American Society for Transplantation and Cellular Therapy; BiPAP= bi-level positive airway pressure; CAR= chimeric antigen receptor; CPAP= continuous positive airway pressure; CRS= cytokine-release syndrome; HLH= hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS= macrophage activation syndrome.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

a. Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
b. Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
c. Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
d. Low flow is defined as oxygen delivered at ≤6 L/min, and high flow is defined as oxygen delivered at >6 L/min.
e. There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz *et al*. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
f. Refer to Riegler *et al*. for information on experimental treatments for CRS.

Pancreatic events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in the table below.

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase >1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (*e.g.*, >3 weeks), consider treatment

Event	Management
	with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase >2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab.
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. • For recurrent events, permanently discontinue atezolizumab.
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab. • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Dermatologic events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate

persistent and/or severe rash or pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in the table below.

Event	Management
Dermatologic event, Grade 1	● Continue atezolizumab. ● Consider treatment with topical corticosteroids and/or other symptomatic therapy (*e.g.*, antihistamines).
Dermatologic event, Grade 2	● Continue atezolizumab. ● Consider patient referral to dermatologist for evaluation and if indicated, biopsy. ● Initiate treatment with topical corticosteroids. ● Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to dermatologist for evaluation and if indicated, biopsy. ● Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Dermatologic event, Grade 4	● Permanently discontinue atezolizumab.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** ● Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. ● Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. ● Follow the applicable treatment and management guidelines above. ● If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Neurologic disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders and specific guidelines for myelitis, are provided in the tables below.

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: o If event resolves to Grade 1 or better, resume atezolizumab. [b] o If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For facial paresis: o If event resolves fully, resume atezolizumab. [b] o If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Event	Management
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

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

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

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab. • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

Renal events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should

be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

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

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Immune-Mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

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

Event	Management

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (*e.g.*, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (*e.g.*, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over

Event	Management
	≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2017). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count < 100×10^9/L (100,000/mcL)
  - ANC < 1.0×10^9/L (1000/mcL)
- Fasting triglycerides >2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin >500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli *et al*. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin >684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤ 181×10^9/L (181,000/mcL)
  - AST ≥48 U/L
  - Triglycerides >1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in below.

Event	**Management**
Suspected HLH	● Permanently discontinue atezolizumab and contact Medical

Event	Management
or MAS	Monitor. ● Consider patient referral to hematologist. ● Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. ● Consider initiation of IV corticosteroids and/or an immunosuppressive agent. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH= hemophagocytic lymphohistiocytosis; MAS= macrophage activation syndrome.

6.2.3 Nivolumab Dose Modification and Toxicity Management

Nivolumab and ipilimumab-related toxicity can be managed and treatment can be held, per investigator discretion, in accordance with institutional standards and the FDA package insert, and the following table for additional guidance:

All dose modifications apply to both ipilimumab AND to nivolumab.

Decisions to delay nivolumab dose must be made on specified safety criteria. Treatment with nivolumab will be delayed (or discontinued) if the subject experiences at least one adverse event, specified below, considered by the investigator to be **"possibly," probably," or "definitely" related to nivolumab treatment.**

All Other Events	Management/Next Dose for Nivolumab/Ipilimumab
≤ Grade 1	No change in dose.
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below).
Grade 3	Hold until ≤ Grade 1 OR baseline and patient no longer on steroid treatment if initiated (exceptions as noted below). Permanently discontinue for events with a high likelihood of morbidity or mortality with recurrent events.
Grade 4	Discontinue nivolumab.
Recommended management: As clinically indicated	

o Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should discontinue nivolumab

o Any Grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ

pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment **does not** require discontinuation.

o Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should discontinue nivolumab/ipilimumab.

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab/Ipilimumab**
≤ Grade 1	No change in dose*.
Grade 2	Hold* until 1≤ Grade resolved. Resume dose.
Grade 3	Hold* until ≤ Grade 1. Resume dose at investigator discretion
Grade 4	Discontinue nivolumab/ipilimumab
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, toxic epidermal necrolysis (TEN), and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	

Liver Function: AST, ALT, Bilirubin	**Management/Next Dose for Nivolumab/Ipilimumab**
≤ Grade 1	Hold at investigator discretion until ULN or baseline. Resume dose.
Grade 2	Grade 2 (3X UNL to 5X UNL): Hold until grade 1 (UNL-3X UNL) or baseline. Resume dose at investigator discretion.
Grade 3	Grade 3 (5X UNL to 20X UNL) Hold until grade 1 or baseline. Resume at same dose at investigator discretion with return to grade 1 or baseline within 7 days without steroids. If persistent or steroids are required, discontinue nivolumab/ipilimumab.
Grade 4	Discontinue nivolumab/ipilimumab.
Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate liver function test (LFT) changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis. Please note: Grades for liver function follow UNL rather than multiples of baseline.	

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab/Ipilimumab**
≤ Grade 1	Hold until baseline. Then resume dose.
Grade 2	Hold until baseline. Then resume dose.
Grade 3	Resume at same dose level at investigator discretion if resolved to grade 1 within 7 days without steroids and no evidence of colitis. If persistent or steroids are required discontinue nivolumab.

Grade 4	Discontinue nivolumab/ipilimumab.
Patients with Grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require systemic steroids should discontinue nivolumab/ipilimumab. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	

Pancreatitis Amylase/Lipase	**Management/Next Dose for Nivolumab/Ipilimumab**
≤ Grade 1	Continue dose if asymptomatic at investigator discretion.
Grade 2	Continue dose if asymptomatic at investigator discretion. If symptomatic, resume at same dose when resolved
Grade 3	Continue at same dose if asymptomatic at investigator discretion. Patients should have imaging study when clinically indicated (grade 3 symptomatic pancreatitis) before resuming treatment. Patients who develop diabetes mellitus should discontinue nivolumab/ipilimumab.
Grade 4	Hold until grade 2. Resume dose if asymptomatic. Patients who are symptomatic should have imaging study prior to resuming treatment and when clinically indicated. Patients who develop grade 4 symptomatic pancreatitis or diabetes mellitus should discontinue nivolumab/ipilimumab.
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as diabetes mellitus and diabetic ketoacidosis (DKA). Lipase elevation may occur during the period of steroid withdrawal and with other immune-mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated.	

Pneumonitis	**Management/Next Dose for Nivolumab/Ipilimumab**
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO_2. Resume dose after pulmonary and/or infectious disease (ID) consultation excludes lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Resume dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required.
Grade 3	Hold dose pending evaluation. Resume dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis Discontinue nivolumab/ipilimumab
Grade 4	Discontinue nivolumab/ipilimumab.
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified, including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed	

vaccine for all patients.

Other GI NauseaVomiting	**Management/Next Dose for Nivolumab/Ipilimumab**
≤ Grade 1	Continue dose.
Grade 2	Hold pending evaluation for gastritis, duodenitis, and other immune AEs or other causes. Resume at same dose after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume dose. If symptoms do not resolve within 7 days with symptomatic treatment, patients should discontinue nivolumab/ipilimumab.
Grade 4	Discontinue nivolumab/ipilimumab
Patients with Grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 2	Continue dose.
Grade 3	Hold until ≤ Grade 2. Resume at same dose.
Grade 4	Discontinue nivolumab/ipilimumab.
Fatigue is the most common AE associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation.	

Neurologic events	**Management/Next Dose for Nivolumab/Ipilimumab**
≤ Grade 1	Hold dose pending evaluation and observation. Resume dose when resolved to baseline.
Grade 2	Hold dose pending evaluation and observation. Hold until ≤ Grade 1. Discontinue nivolumab/ipilimumab if treatment with steroids is required. Resume at same dose level for peripheral isolated n. VII (Bell's palsy).
Grade 3	Discontinue nivolumab/ipilimumab
Grade 4	Discontinue nivolumab/ipilimumab
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, and myasthenia gravis should be off study.	

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab/Ipilimumab**
≤ Grade 1	*Hold pending evaluation for evidence of adrenal insufficiency or hypophysitis. Asymptomatic thyroid stimulating hormone (TSH) elevation may continue treatment while evaluating the need for thyroid replacement.
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume dose.
Grade 3	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume dose.
Grade 4	Discontinue nivolumab/ipilimumab.
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered Grade 3 events. Isolated thyroid or testosterone deficiency may be treated as Grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement. Patients with grade 3 thyroiditis and skin rash may continue therapy as for grade 2 events with resolution and stable replacement treatment. Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses of corticosteroids. <u>Please note that grading and for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.</u> Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 must be obtained to document baseline.	

Renal	**Management/Next Dose for Nivolumab/Ipilimumab**
≤ Grade 1	Monitor closely and continue therapy.
Grade 2	Hold until ≤ Grade 1. Resume dose.
Grade 3	Hold until ≤ Grade 1. Resume dose.
Grade 4	Discontinue nivolumab
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	

Infusion reaction	**Management/Next Dose for Nivolumab/Ipilimumab**
≤ Grade 1	Monitor closely and continue therapy.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Discontinue nivolumab/ipilimumab
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	

Fever	**Management/Next Dose for Nivolumab/Ipilimumab**
≤ Grade 1	Evaluate and continue at dose.
Grade 2	Hold until ≤ Grade 1. Resume at dose.
Grade 3	Hold until ≤ Grade 1. Resume at dose.
Grade 4	Discontinue nivolumab/ipilimumab
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	
See section 6.4.1 – Treatment of Nivolumab/Ipilimumab -Related Infusion Reactions.	

Cardiac *	**Management/Next Dose for Nivolumab + Ipilimumab Cardiac Toxicities**
Less than grade 2	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize without evidence of myocarditis may resume therapy. If labs worsen or symptoms develop then treat as below.
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone and immune suppression as clinically indicated. If no improvement within 24 hours consider adding either infliximab, ATG or tacrolimus.. May resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Discontinue nivolumab and ipilimumab. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone Add ATG or tacrolimus if no improvement. Discontinue nivolumab and ipilimumab.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

Treatment of Nivolumab/Ipilimumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, urticaria, angioedema, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 5.0 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as medically appropriate:

Remain at bedside and monitor subject until recovery from symptoms.

For Grade 1 symptoms

(Mild reaction; infusion interruption not indicated; intervention not indicated)

Infusion rate may be slowed or interrupted and restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab and ipilimumab administrations, slowing infusion rate as above.

For Grade 2 symptoms

(Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [*e.g*., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; close observation for recurrence and treatment medications may need to be continued for 24-48 hours).

Stop the nivolumab and ipilimumab infusions, begin an IV infusion of normal saline, and reat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, re administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and (acetaminophen) (or paracetamol) 325 to

1000 mg should be administered at least 30 minutes before additional nivolumab and ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms:
(Severe reaction)

Grade 3 symptoms: prolonged [*i.e.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [*e.g.*, renal impairment, pulmonary infiltrates]).

Grade 4 symptoms: (life threatening; pressor or ventilatory support indicated). Nivolumab and ipilimumab will be permanently discontinued

Immediately discontinue infusion of nivolumab and ipilimumab. Begin an IV infusion of normal saline, and bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

Other guidance:
In the case of late-occurring hypersensitivity symptoms (*e.g.*, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (*e.g.*, oral antihistamine, or corticosteroids). Additional treatment prior to next dose as per guidelines above.

Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents (30-MAR-2021)

Commercial Agents

The commercial agents in NRG-LU002 are pemetrexed, gemcitabine, atezolizumab, ipilimumab, nivolumab, and pembrolizumab.

7.2 Adverse Events and Serious Adverse Events (18-MAY-2018)

7.2.1 The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS, and case report forms. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms

will continue to use CTCAE version 4.0 through the broadcast of Amendment 1, at which point adverse event reporting in case report forms will be collected in CTCAE version 5.0.

All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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.

7.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for MK-3475 (pembrolizumab, NSC 776864) (22-FEB-2023)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system.

Version 2.7, December 13, 2022[1]

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

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Abdominal pain	
	Colitis[2]	
	Diarrhea[2]	
	Mucositis oral[2]	
	Nausea	
	Pancreatitis[2]	
	Small intestinal mucositis[2]	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills[2]	
Fatigue		
	Fever[2]	
HEPATOBILIARY DISORDERS		
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]	
		Hepatobiliary disorders - Other (sclerosing cholangitis)
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis[2]
		Cytokine release syndrome[2]
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]
	Immune system disorders - Other (sarcoidosis)[2]	
		Serum sickness[2]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Infusion related reaction
INVESTIGATIONS		
	Alanine aminotransferase increased[2]	

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased[2]	
	Blood bilirubin increased	
		GGT increased
		Serum amylase increased
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyponatremia	
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia[2]	
	Arthritis[2]	
	Back pain	
	Joint range of motion decreased	
	Myalgia[2]	
	Myositis[2]	
NERVOUS SYSTEM DISORDERS		
		Guillain-Barre syndrome[2]
		Nervous system disorders - Other (myasthenic syndrome)[2]
		Nervous system disorders - Other (neuromyopathy)[2]
		Nervous system disorders - Other (non-infectious encephalitis)[2]
		Nervous system disorders - Other (non-infectious meningitis)[2]

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Nervous system disorders - Other (non-infectious myelitis)
		Nervous system disorders - Other (optic neuritis)
		Nervous system disorders - Other (polyneuropathy)[2]
		Paresthesia
		Peripheral motor neuropathy[2]
RENAL AND URINARY DISORDERS		
		Renal and urinary disorders - Other (autoimmune nephritis)[2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Bullous dermatitis[2]	
		Erythema multiforme[2]
	Erythroderma	
		Palmar-plantar erythrodysesthesia syndrome
	Pruritus[2]	
	Rash acneiform[2]	
	Rash maculo-papular[2]	
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]	
	Skin hypopigmentation[2]	
		Stevens-Johnson syndrome[2]
		Toxic epidermal necrolysis
	Urticaria[2]	
VASCULAR DISORDERS		

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Vasculitis[2]

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

[2]Immune-mediated adverse reactions have been reported in patients receiving Pembrolizumab (MK-3475). Adverse events potentially related to Pembrolizumab (MK-3475) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of Pembrolizumab (MK-3475), administration of corticosteroids and supportive care.

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - CPK increased; Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia;

Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Joint effusion[2]; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pleuritic pain[2]; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: Pembrolizumab (MK-3475) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.4 Comprehensive Adverse Events and Potential Risks (CAEPR) List for Atezolizumab (MPDL3280A, NSC 783608) (18-OCT-2023)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3097 patients.* Below is the CAEPR for Atezolizumab (MPDL3280A).

Version 2.4, September 14, 2023[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
CARDIAC DISORDERS		
		Heart failure[2]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]		
		Myocarditis[2]
		Pericardial effusion[2]
		Pericardial tamponade[2]
		Pericarditis[2]
ENDOCRINE DISORDERS		
		Adrenal insufficiency[2]
		Endocrine disorders - Other (diabetes)[2]
	Hyperthyroidism[2]	
		Hypophysitis[2]
	Hypothyroidism[2]	
EYE DISORDERS		
		Eye disorders - Other (ocular inflammatory toxicity)[2]
		Uveitis[2]
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
		Colitis[2]
	Diarrhea	
	Dysphagia	
	Nausea	
		Pancreatitis[2]
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue		
	Fever[3]	
	Flu like symptoms[3]	
HEPATOBILIARY DISORDERS		
		Hepatic failure[2]
		Hepatobiliary disorders - Other (hepatitis [immune related hepatitis])[2]
IMMUNE SYSTEM DISORDERS		
	Allergic reaction[3]	
		Anaphylaxis[3]
		Cytokine release syndrome[3]
		Immune system disorders

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]		
		- Other (hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS))[2]
		Immune system disorders - Other (systemic immune activation)[2]
INFECTIONS AND INFESTATIONS		
Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction[3]	
INVESTIGATIONS		
	Alanine aminotransferase increased[2]	
	Alkaline phosphatase increased[2]	
	Aspartate aminotransferase increased[2]	
	Blood bilirubin increased[2]	
		Creatinine increased
	GGT increased	
	Lipase increased[*]	
		Platelet count decreased
	Serum amylase increased[*]	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
		Hyperglycemia[2]
	Hypokalemia	
	Hyponatremia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia[2]	
	Back pain	
		Generalized muscle weakness
	Myalgia	
		Myositis[2]
NERVOUS SYSTEM DISORDERS		

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]		
		Ataxia[2]
		Encephalopathy[2]
		Guillain-Barre syndrome[2]
		Myasthenia gravis[2]
		Nervous system disorders - Other (meningitis non-infective)[2]
		Nervous system disorders - Other (facial paresis)[2]
		Nervous system disorders - Other (encephalitis non-infective)[2]
		Nervous system disorders - Other (immune-mediated myelitis)[2]
		Paresthesia[2]
		Peripheral motor neuropathy[2]
		Peripheral sensory neuropathy[2]
RENAL AND URINARY DISORDERS		
		Acute kidney injury
		Renal and urinary disorders - Other (nephritis)[2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Hypoxia	
	Nasal congestion	
		Pleural effusion[2]
		Pneumonitis[2]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		Bullous dermatitis[2]
		Erythema multiforme[2]
	Pruritus	
	Rash acneiform	
	Rash maculo-papular	
		Skin and subcutaneous

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]		
		tissue disorders - Other (Drug reaction with eosinophilia with systemic symptoms [DRESS])[2]
		Skin and subcutaneous tissue disorders - Other (Exanthematous pustulosis)[2]
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]	
		Stevens-Johnson syndrome[2]
		Toxic epidermal necrolysis[2]

*Denotes adverse events that are <3%.

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia
CARDIAC DISORDERS - Cardiac arrest; Ventricular tachycardia

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

Note: Atezolizumab (MPDL3280A) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.5 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Nivolumab (NSC 748726) (18-OCT-2023)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for Nivolumab.

Version 2.5, June 10, 2023[1]

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
		Blood and lymphatic system disorders - Other (lymphatic dysfunction)
CARDIAC DISORDERS		

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Cardiac disorders - Other (cardiomyopathy)
		Myocarditis
		Pericardial tamponade[2]
		Pericarditis
ENDOCRINE DISORDERS		
	Adrenal insufficiency[3]	
	Hyperthyroidism[3]	
	Hypophysitis[3]	
	Hypothyroidism[3]	
EYE DISORDERS		
		Blurred vision
		Dry eye
		Eye disorders - Other (diplopia)[3]
		Eye disorders - Other (Graves opthalmopathy)[3]
		Eye disorders - Other (optic neuritis retrobulbar)[3]
		Eye disorders - Other (Vogt-Koyanagi-Harada)[3]
	Uveitis	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis[3]	
		Colonic perforation[3]
	Diarrhea	
	Dry mouth	
		Enterocolitis
		Gastritis
		Mucositis oral
	Nausea	
	Pancreatitis[4]	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue		
	Fever	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Injection site reaction	
HEPATOBILIARY DISORDERS		
		Hepatobiliary disorders - Other (Immune-related hepatitis)
IMMUNE SYSTEM DISORDERS		
		Allergic reaction[3]
		Autoimmune disorder[3]
		Cytokine release syndrome[5]
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]
		Immune system disorders - Other (sarcoid granuloma, sarcoidosis)[3]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction[7]	
INVESTIGATIONS		
	Alanine aminotransferase increased[3]	
	Aspartate aminotransferase increased[3]	
	Blood bilirubin increased[3]	
	CD4 lymphocytes decreased	
	Creatinine increased	
	Lipase increased	
	Lymphocyte count decreased	
	Neutrophil count decreased	
	Platelet count decreased	
	Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Hyperglycemia
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
		Musculoskeletal and connective tissue disorder - Other (polymyositis)
		Myositis
		Rhabdomyolysis
NERVOUS SYSTEM DISORDERS		
		Encephalopathy[3]
		Facial nerve disorder[3]
		Guillain-Barre syndrome[3]
		Myasthenia gravis[3]
		Nervous system disorders - Other (demyelination myasthenic syndrome)
		Nervous system disorders - Other (encephalitis)[3]
		Nervous system disorders - Other (meningoencephalitis)
		Nervous system disorders - Other (meningoradiculitis)[3]
		Nervous system disorders - Other (myasthenic syndrome)
		Peripheral motor neuropathy
		Peripheral sensory neuropathy
		Reversible posterior leukoencephalopathy syndrome[3]
RENAL AND URINARY DISORDERS		

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Acute kidney injury[3]
		Renal and urinary disorders - Other (Immune-related nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Pleural effusion[3]	
	Pneumonitis[3]	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia (BOOP))[3]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		Erythema multiforme[3]
	Pruritus[3]	
	Rash maculo-papular[3]	
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]	
	Skin hypopigmentation[3]	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis

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

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3]Nivolumab being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune

response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving Nivolumab. These complications may occur despite intervening therapy between receiving Nivolumab and allo-SCT.

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

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

7.6 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipilimumab, (MDX-010, NSCs 732442 and 720801) (30-MAR-2021)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

Version 2.10, March 29, 2019[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
		Blood and lymphatic system disorders - Other (acquired hemophilia)
CARDIAC DISORDERS		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Atrial fibrillation	
		Myocarditis[2]
		Pericardial effusion
EAR AND LABYRINTH DISORDERS		
	Hearing impaired	
ENDOCRINE DISORDERS		
	Adrenal insufficiency[2]	
	Hyperthyroidism[2]	
	Hypophysitis[2]	
	Hypopituitarism[2]	
	Hypothyroidism[2]	
	Testosterone deficiency[2]	
EYE DISORDERS		
	Eye disorders - Other (episcleritis)[2]	
	Uveitis[2]	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis[2]	
		Colonic perforation[3]
	Constipation	
Diarrhea		
	Enterocolitis	
	Esophagitis	
		Ileus
Nausea		
	Pancreatitis[2]	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
Fatigue		
	Fever	
		General disorders and administration site conditions - Other (Systemic inflammatory response syndrome [SIRS])

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Multi-organ failure
HEPATOBILIARY DISORDERS		
	Hepatobiliary disorders - Other (hepatitis)[2]	
IMMUNE SYSTEM DISORDERS		
	Autoimmune disorder[2]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]
INFECTIONS AND INFESTATIONS		
		Infections and infestations - Other (aseptic meningitis)[2]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
		Lymphocyte count decreased
	Neutrophil count decreased	
	Weight loss	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Dehydration	
	Hyperglycemia	
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Arthritis	
		Generalized muscle weakness

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]	
NERVOUS SYSTEM DISORDERS		
		Ataxia
	Facial nerve disorder[2]	
	Guillain-Barre syndrome[2]	
	Headache	
	Myasthenia gravis[2]	
		Nervous system disorders - Other (immune-mediated encephalitis)[2]
		Peripheral motor neuropathy
		Peripheral sensory neuropathy
	Trigeminal nerve disorder	
PSYCHIATRIC DISORDERS		
		Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS		
	Acute kidney injury	
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Pneumonitis	
		Respiratory failure
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)
		Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Erythema multiforme
	Pruritus	
Rash maculo-papular		
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
	Urticaria	
VASCULAR DISORDERS		
	Hypotension	

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

[2]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

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

Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia
CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure[2]
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[7]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the

other agent, or the combination may result in events never previously associated with either agent.

7.7 Adverse Events for Commercial Study Agents (30-MAR-2021)

All systemic agents used in NRG-LU002 are commercially supplied. Refer to the package insert for detailed pharmacologic and safety information.

7.8 Expedited Reporting of Adverse Events (18-MAY-2018)

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.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Biostatistical/Data Management Center by phone, (number to be provided). An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.8.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS24-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. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. For guidance to submit supporting documentation contact NRG Oncology at 1-215-574-3191.
- 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.

7.8.2 Expedited Reporting Requirements for Adverse Events For Arm 1 and Arm 2 Maintenance Therapy Any Phase Study Utilizing a Commercial Agent[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.

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 protocol treatment 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

For Arm 2: Local Consolidative Therapy
Any Phase Study Utilizing Radiation Therapy (including chemoRT studies) and Surgery[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.

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

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 have an attribution of possible, probable, or definite require reporting as follows:

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

Expedited 10 calendar day reports for:
- Grade 3 adverse events

Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements - None

7.8.3 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.

7.8.4 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or systemic therapy). 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 under an NCI IND/IDE 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 systemic therapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

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

Second Malignancy:

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

8. REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES (18-OCT-2023)

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability. RCR utilizes five person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (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)	✓	✓	✓		

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;
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

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. Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the ***RCR Help Desk*** by email at < RCRHelpDesk@nih.gov>.

8.1 Cancer Trials Support Unit Registration Procedures (18-OCT-2023)

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update

Management System (RUMS) on the Cancer Trials Support System Unit (CTSU) members' website.

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

8.1.1 IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (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. 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 for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;

- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements for Protocol NRG-LU002 Site Registration
Additional 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);
- 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).

Protocol-Specific Requirements for NRG-LU002

- IRB/REB approved consent (International and Canadian sites only: English and native language versions*. The English version must be submitted to NRG Regulatory prior to IRB review: regulatory-phl@NRGOncology.org).

*Note: International and Canadian Institutions must provide certification/verification of IRB/REB consent translation to NRG Oncology (described below).

- 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.
- 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 of the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Site 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 members' website.

*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.

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 15 years following the completion of the trial at the participating site (15years 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].

Downloading Site Registration Documents:

Download the site registration forms from the NRG-LU002 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log on to the CTSU members' website (https://www.ctsu.org)
- 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* and protocol number *NRG-LU002*
- 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 the 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, go 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 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 shown 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 the NCI or their affiliated networks.

8.2 RT-Specific Pre-Registration Requirements (18-OCT-2023)

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. 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.

RT Credentialing Requirements	Web Link for Procedures and Instructions: http//irochouston.mdanderson.org		
	Treatment Modality		Key Information
	SBRT	IMRT	
Facility Questionnaire	✓	✓	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ go to http://irochouston.mdanderson.org/questionnaires.
Credentialing Status Inquiry Form	✓	✓	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Phantom Irradiation	✓	✓	An IROC Houston anthropomorphic phantom must be successfully completed (if the institution has not previously met this credentialing requirement) if the institution plans to deliver SBRT or IMRT. Credentialing for IMRT allows the institution to also use 3D-CRT SBRT, but credentialing for 3D-CRT SBRT does not allow the institution to use IMRT. Flattening-filter-free (FFF) photon beam delivery, Tomotherapy and Cyberknife treatment delivery modalities must be credentialed individually. Instructions for requesting and irradiating the phantom are available on the IROC Houston website under credentialing (http//irochouston.mdanderson.org).
IGRT Verification Study	✓	✓	Institutions must be credentialed for soft tissue IGRT by IROC Houston. Find details on the IROC Houston QA Center website (http://irochouston.mdanderson.org) Institutions that have previously been approved for IGRT may not need to repeat credentialing.
Pre-Treatment Review	✓	✓	Pre-treatment review of first case per institution by Study Co-Chairs.
Credentialing Issued to:			
Institution			IROC Houston QA Center will notify the institution and NRG Oncology Headquarters that all desired credentialing requirements have been met. The site will need to upload a PDF of approval email from IROC Houston to the CTSU Regulatory Portal for RSS to be updated.

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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- 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; and

- TRIAD Site User role on an NCTN, ETCTN, or other relevant 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 username and password 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 (18-OCT-2023)

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.

Informed Consent: Patients must be aware of the neoplastic nature of their disease and informed of the procedure(s) to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts prior to signing the informed consent in accordance with institutional and federal guidelines. Current IRB/REB/REC approval of this protocol and a consent form is required prior to patient consent and registration. The model consent form created for this study adheres to the NCI informed consent template requirements.

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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems.To perform enrollments or request slot reservations: 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;
- 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.

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration: websupport@acr.org or call the NRG Registration Desk at 215-574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

9.0 DRUG INFORMATION (18-AUG-2023)

General Patient Care Implications

Patients must use highly effective contraception, including men with vasectomies if he is having sex with a woman of childbearing potential or with a woman who is pregnant while on study drug, for 6 months following the last dose of study drug because the study treatment may be teratogenic. Highly effective contraception is defined as hormonal contraceptives (oral contraceptives, Nuvaring, Depo Provera), intrauterine device, true abstinence, two barrier methods of birth control including condoms with cervical cap or diaphragm, patient has received surgical sterilization, patient is monogamous with a post-menopausal partner.

9.1 Commercial Agent: Pemetrexed (30-MAR-2021)

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 5.1 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: Gemcitabine (30-MAR-2021)

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 5.1 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.

9.3 Commercial Agent: Pembrolizumab (30-MAR-2021)

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 and the Comprehensive Adverse Events and Potential Risks (CAEPR) in section 7.3.

9.3.2 Availability/Supply

Please see Section 5.1 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.

9.4 Commercial Agent: Atezolizumab (30-MAR-2021)

US sites must refer to the package insert and sites in Canada must refer to the product monograph for detailed pharmacologic and safety information.

9.4.1 Adverse Events

Please refer to the package insert and the Comprehensive Adverse Events and Potential Risks (CAEPR) in section 7.4.

9.4.2 Availability/Supply

Please see Section 5.1 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.

9.5 Commercial Agent: Nivolumab (30-MAR-2021)

US sites must refer to the package insert and sites in Canada must refer to the product monograph for detailed pharmacologic and safety information.

9.5.1 Adverse Events

Please refer to the package insert and the Comprehensive Adverse Events and Potential Risks (CAEPR) in section 7.5.

9.5.2 Availability/Supply

Please see Section 5.1 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.

9.6 Commercial Agent: Ipilimumab (30-MAR-2021)

US sites must refer to the package insert and sites in Canada must refer to the product monograph for detailed pharmacologic and safety information.

9.6.1 Adverse Events

Please refer to the package insert and the Comprehensive Adverse Events and Potential Risks (CAEPR) in section 7.6.

9.6.2 Availability/Supply

Please see Section 5.1 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.

10. PATHOLOGY/BIOSPECIMEN

10.1 Biospecimen Submission Tables

10.1.1 Optional Specimen Submissions

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.

10.2 Tissue Selection for Exploratory Marker Testing: (30-MAR-2021)

For patients who have consented to participate in the tissue/blood component of the study the following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.2.1 Marker to be tested and its usage

Circulating tumor DNA (ctDNA) will be an exploratory biomarker in this study. It is possible that only a subgroup of patients who meet trial eligibility will benefit from the addition of SBRT to maintenance chemotherapy and ctDNA will be evaluated as a potential strategy for identifying this subgroup for the purposes of selecting patients for future studies. We hypothesize that levels of ctDNA levels at enrollment will predict outcomes. Specifically, we hypothesize that patients with low levels ctDNA after completion of first-line/induction systemic therapy will have significantly better PFS than patients with high levels of ctDNA. To explore this hypothesis we will perform NGS-based ctDNA detection using CAPP-Seq on the pre-treatment plasma samples in order to quantify the amount of ctDNA in haploid tumor genome equivalents/ml of plasma as previously described (Newman 2016). Additionally we will also analyze the first on-treatment plasma sample (~3 months from initiation of maintenance chemotherapy) by CAPP-Seq. The absolute concentration at the 3 month time point and the change between the pre-treatment and 3 month time point will be explored for association with PFS and OS.

10.2.2 Testing requirements and reporting:

Testing will be performed retrospectively after completion of the trial.

10.2.3 Method of testing:

Testing for ctDNA will be performed using CAPP-Seq which was designed specifically for NSCLC and can detect the presence of ctDNA with high sensitivity and specificity

(Newman 2014, Newman 2016). Cell-free DNA will be isolated from plasma and all samples with at least 5ng of cell-free DNA will be analyzed using CAPP-Seq. Results will be reported as percent and absolute concentration of ctDNA.

10.2.4 Location of testing:
Biospecimens will be stored in the NRG Oncology Biospecimen Bank (see address and contact information below). Testing will be performed centrally in Dr. Max Diehn's lab after completion of the trial.

10.2.5 Tissue Submission for testing: See Biospecimen Submission tables below.

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

Specimen Collection for Banking for Future Research
Specimens are being collected for future translational research projects.

- 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 NRGBB-SF. Sites should include the following information in their email: their 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 bank 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 LU002 kits provided to the site for batch shipping frozen biospecimens to the NRGBB-SF. Ship all Biospecimens for Optional Study #3 for banking 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	Shipping

		Requirements/Instructions for Site	
H&E slide(s) of Primary tumor if available. If primary is not available then an H&E from the metastasis is acceptable	Pre-treatment: 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 - same block as H&E slide submitted above	Pre-treatment: 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. Note: Unstained slides are not an acceptable alternative for tissue/punch blocks for banking studies.	Ship to NRGBB-SF (use cold packs during warm weather)
Serum- Red top tube	Pre-treatment: Any time prior to start of protocol treatment During treatment: Once approximately 3 months after the initiation of maintenance systemic therapy Post treatment: At the time of first progression	Process serum and aliquot minimum of 0.5ml per vial into 5 cryovials. Store at -80°C (-70°C to -90°C) until ready to batch ship on Dry ice. Forms: ST form	Ship on Dry Ice by Overnight Courier to NRGBB-SF
Plasma- 2 Purple Top EDTA tubes (10 mls each, centrifuged and processed for plasma collection)	Pre-treatment: Any time prior to start of protocol treatment During treatment: Once approximately 3 months after the initiation of maintenance systemic therapy	Process plasma and aliquot a minimum of 1.8 ml plasma into each of five 2 ml cryovials. Place into biohazard bag and immediately freeze tubes upright at -70 to -90º C. Store frozen until ready to ship. Forms: ST form	Ship on Dry Ice by Overnight Courier to NRGBB-SF

	Post treatment: At the time of first progression		
Whole Blood-EDTA tube	Pre-treatment: Any time prior to start of protocol treatment	Collect blood, mix and aliquot 1 ml of whole blood per vial into three (3) 2 ml cryovials. Store at -80°C (-70°C to -90°C) until ready to batch ship on Dry ice. Forms: ST form	Ship on Dry Ice by Overnight Courier to NRGBB-SF

11 SPECIAL STUDIES (NON-TISSUE)

11.1 Patient-Reported Outcomes (PROs) and Health-Related Quality of Life (QOL) (22-June-2018)

Objective:

- To evaluate the effect of adding LCT to systemic therapy in limited stage IV NSCLC on QOL

Hypotheses:

The primary HRQOL hypothesis is that QOL using FACT-TOI at 3-month (from study registration) will be superior in the LCT + systemic therapy arm compared to the systemic therapy alone arm as the addition of SBRT is expected to improve tumor response and improve disease-related QOL.

Secondary exploratory objectives are:

- To describe the levels and change in baseline at each assessment of the EQ-5D index and EQ-5D VAS in each of the study arms
- To analyze the effect of smoking status on outcome using the Cancer Patient Tobacco Use Questionnaire (C-TUQ)

11.2 Background (18-MAY-2018)

Health related quality-of-life (QOL) is an important endpoint in clinical trials to assess the overall disease burden and treatment effect from the patient's perspective using patient reported outcomes (PROs). In this study, if the SBRT arm shows superior OS compared to systemic therapy alone, a new standard of care will be defined for limited metastatic NSCLC, provided that the QOL and toxicity profiles are acceptable to the patient. Especially in the setting of metastatic disease, in which patients have a difficult prognosis, it is critical that trials investigating further refinement of therapeutic strategies factor in QOL in addition to overall survival. Obtaining QOL data at baseline, during treatment, and follow up after treatment provides baseline prognostic data as well as reporting the effect of treatment on HRQOL from the patient's perspective. Baseline QOL data was found to be a prognostic variable in addition to clinical factors in predicting survival in cancer patients (Quinten 2014, Urba 2012) in a pooled analysis of 7417 cancer patients entered on randomized trials. These data suggest that obtaining baseline QOL data are of superior prognostic significance than obtaining physician graded performance scale scores such as Karnofsky performance scales or ECOG scales prior to initiation of treatment.

The primary QOL objective in this study is to measure functional, physical and lung cancer specific QOL in lung cancer patients using the change from baseline (at study registration) of FACT-TOI at 3 months (using each patient as his or her own control). A clinically meaningful between-group change from baseline is defined as FACT-TOI of ≥5 points between arms. The FACT-TOI instrument will also measure longitudinal QOL in both arms and will be administered at the following time points: baseline (prior to registration), and within 2 weeks of each of the following time points: 1, 3, 6, 9 and 12 months following study registration.

11.3 FACT-TOI

In order to analyze the difference in QOL between all arms, we plan to use a brief, validated instrument that is user friendly and has clinical relevance. FACT-TOI is a measure that sums the functional well-being (FWB), physical well-being (PWB), and the lung cancer subscale (LCS) of the Functional Assessment of Cancer Therapy – Lung (FACT-L) QOL instrument, which has been extensively used for measuring QOL in patients with lung cancer. In a review of literature reported that the FACT-L scale has been used in more than 5,000 patients and has been found to be sensitive to changes in performance status, treatment response. FACT has been translated into many languages. NRG Oncology has obtained permission to use the FACT for this study in English, Spanish, and French. The full FACT-L questionnaire can be completed in less than 10 minutes. This instrument has not only been shown to be prognostic for survival, but also sensitive to changes in QOL on serial evaluations throughout treatment. Importantly, the FACT-TOI has been associated with clinically meaningful changes in patients with lung cancer. The lung cancer sub-scale (LCS) consists of 9 items, involving lung cancer specific symptoms. All items are rated on a 5-item (point) Likert Scale, from 0 (not at all) to 4 (very much). It has been determined that a 5-point difference on the FACT-TOI is associated with a meaningful difference in clinical and subjective indicators. Thus, a difference of 5 points will be considered clinically significant. Handling of missing data will be in accordance with the FACIT Administration and Scoring Guidelines, described at www.facit.org.

11.4 QUALITY-ADJUSTED SURVIVAL, EUROQOL (EQ-5D-5L) (18-MAY-2018)

The EuroQol (EQ-5D) is a well-accepted instrument to measure general QOL and cost-utility analysis (Pickard 2007) and will be used to assess quality-adjusted survival for this study. It is a two-part questionnaire that the patient can complete in 5 minutes (Schulz 2002) and has been translated into multiple languages. NRG Oncology has obtained permission to use the EQ-5D for this study in English, Spanish, and French. The first part consists of 5 items covering 5 dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels including: 1-no problem, 2-moderate problems, and 3-extreme problems. There are 243 potential health states. The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20 cm, 10 point-interval scale. Either the index score or the VAS score can be used in the quality-adjusted survival analysis (Wu 2002). The benefit of measuring quality-adjusted survival is that the product, quality-adjusted survival, can be compared to the outcomes of other interventions across disease sites and can be used by

health policy makers to rank interventions. The EQ5D will be used to evaluate the effect of adding SBRT to systemic therapy on quality-adjusted survival.

Protocol-eligible patients will be included in the quality-adjusted survival analysis only if they have provided baseline and at least 1 subsequent measurement.

Patients will complete the EQ-5D-5L version within 2 weeks of each of the following time points: Baseline (prior to registration), and at 3, 6 and 12 months following study registration.

11.5 CANCER PATIENT TOBACCO USE QUESTIONNAIRE (C-TUQ) (18-MAY-2018)

There is much evidence that smoking is associated with poorer outcomes, including survival, in patients with cancer (Land 2016a). However, tobacco use has not been uniformly assessed in clinical trials. The NCI-AACR Cancer Patient Tobacco Use Assessment Task Force recently developed and tested a Cancer Patient Tobacco Use Questionnaire (C-TUQ). Revisions to item wording, response options, etc, resulted in a questionnaire that showed navigational ease as well as good question comprehension and response accuracy (Land 2016b). Thus, the NCI-AACR Task Force recommends that C-TUQ be used as a standardized instrument in clinical trials. In this study, we plan to use the core items (1,4, 5 and 6) plus the following extension items (7 and 11-14). Items 4 and 5 are only needed at baseline. C-TUQ will be collected within 2 weeks of each of the following time points: baseline, 3 months, 6 months, and 12 months. As continued smoking has been associated with worse survival in lung cancer patients undergoing treatment, the C-TUQ will be important to better understand the results of this study.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

A pre-treatment review for the first patient registered at each institution must be submitted to TRIAD for review PRIOR TO DELIVERY of radiation treatment. The plan(s) will be reviewed centrally by the Radiation Oncology Study Chair/Co-Chair and feedback regarding protocol compliance will be forwarded to the participating institution. Based on the results of any of the reviews described above, a request for additional pre-treatment reviews might be necessary. In general, the treatment plan for subsequent patients enrolled at a site will not be required to be centrally reviewed prior to treatment, but will be reviewed for protocol compliance at a later date. Allow 3 business days for the results of the pre-treatment review process. The pre-treatment review process will not start until all required data is submitted to TRIAD.

RT Quality Assurance Review

For those cases enrolled after the pre-treatment review requirement has been met, the Radiation Oncology Co-Chair will perform an RT Quality Assurance Review after IROC Philadelphia-RT has received complete data for the first 20 cases enrolled. The review team will perform the next review after IROC Philadelphia-RT has received complete data for the next 20 cases enrolled. The final cases will be reviewed within 3 months after this

study has reached the target accrual or as soon as IROC Philadelphia-RT has received complete data for all cases enrolled, whichever occurs first.

12.2 Medical Oncology Modality Quality Assurance Reviews

The Medical Oncology Co-Chair, David Gerber, MD or Saiama N. Waqar, MD, MSCI, will perform a Systemic Therapy 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 systemic therapy treatment data as specified in Section 14.2. The scoring mechanism is: 1) Per Protocol, 2) Acceptable Variation, 3) Unacceptable Deviation, and 4) Not Evaluable.

The Medical Oncology Co-Chairs will perform a Quality Assurance Review after NRG Headquarters has received complete data for the first 20 cases enrolled. The Medical Oncology Co-Chairs will perform the next review after NRG Headquarters has received complete data for the next 20 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 (18-MAY-2018)

The surgical co-chair, Dr. Donington will perform a Quality Assurance Review for verification of protocol compliance on a continuous basis. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

Goals of Surgical Quality Assurance:

1. to assure correct appropriate staging and evaluation of patients following first line therapy,
2. to assure safety of patients undergoing resection,
3. to assure adequate resection of metastatic sites

Deviations Minor:

1. Resections outside the defined window (unless prior approval from the Surgery Co-Chair was obtained),
2. Wedge resection of metastatic tumor with inadequate tumor to closest surgical margin distance

Deviations Unacceptable:
Those deviations that affect patient safety/outcome, which will result in an institutional suspension and mediation prior to further participation in the study.

13. ASSESSMENT OF EFFECT

Not Applicable

14. DATA QUALITY PORTAL (18-OCT-2023)

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. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

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

14.1 Data Management/Collection (18-OCT-2023)

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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; 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 have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or an Investigator (IVR); and
- Rave Read Only or RAVE SLA 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 the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email 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 eLearning 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 who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application 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 or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

14.2 Summary of Data Submission

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 7.4 to 7.4.3 for information about expedited and routine reporting.

Summary of Data Submission: Refer to CTSU website.

See Section 8 for TRIAD account access and installation instructions.

14.3 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

15. STATISTICAL CONSIDERATIONS

15.1 Study Design (18-MAY-2018)

The study is an open-label, randomized, integrated phase II/III trial to evaluate maintenance systemic therapy with and without LCT for limited metastatic non-small cell lung cancer. Patients will be enrolled and randomized 2:1 between LCT + maintenance systemic therapy arm and maintenance systemic therapy alone arm.

15.2 Study Endpoints (18-MAY-2018)

15.2.1 Primary Endpoints

Phase II: The primary endpoint is progression-free survival (PFS). PFS is defined as the time from randomization to any documented progression or death due to any cause, whichever occurs first.

Phase III: 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.

15.2.2 Secondary Endpoints

- Time to in-field local failure, defined as the time from randomization to in-field failure or marginal failure (evidence of tumor viability);
- Time to development of new lesions, defined as the time from randomization to the first occurrence of any new lesions that have not been treated with local consolidative therapy;
- Toxicities (CTCAE v5);
- Duration of maintenance systemic therapy usage;
- Quality of life as measured through FACT-TOI, EQ-5D and C-TUQ instruments;
- Association between progression-free survival and ctDNA

15.3 Primary Objective and Study Design (19-JUL-2021)

15.3.1 Primary Hypothesis and Endpoints

The primary hypothesis of this study is that LCT and maintenance systemic therapy (Arm 2) will improve the progression-free survival (phase II) and overall survival (phase III), compared to the maintenance systemic therapy alone (Arm 1) for limited metastatic NSCLC patients. This study population does not have reliable historical data in the contemporary era of immunotherapy. Based on published data including KEYNOTE 021, KEYNOTE 024G, KEYNOTE 407, plus findings from Socinski 2018, we assume the NRG-LU002 cohorts to approximate the following groups of treatments: 1) pembrolizumab monotherapy based on FDA-approved indications; 2) pembrolizumab and pemetrexed based on FDA-approved indications; 3) cytotoxic chemotherapy based on FDA-approved indications; 4) atezolizumab monotherapy based on FDA-approved indications; and 5) ipilimumab and nivolumab based on FDA-approved indications. We therefore project that, for the standard maintenance systemic therapy, the 6 month and 12 month rates of PFS are approximately 60% and 39%, and 12 month and 24 month rates of OS are 68% and 47%, respectively.

For the phase II portion, we consider a hazard reduction of 40% in PFS (HR_{PFS} =0.6) with LCT to warrant a phase III study. For the entire study, we aim to demonstrate a hazard reduction of 32% in OS (HR_{OS} = 0.68) with LCT.

Assuming PFS and OS follow approximately exponential distributions, the HR_{PFS} of 0.6 target corresponds to improving 12-month PFS rate from 39% to 57%, or from 45% to 62%; the HR_{OS} of 0.68 target corresponds to improving 24-month OS from 47% to 60%, or from 54% to 66%. Meanwhile, we recognize that the changing landscape of systemic therapies and inclusion of immunotherapy in the induction regimen make it extremely challenging to accurately project the potential benefits in the scale of rates of OS and PFS, so the aforementioned improvements in PFS and OS rates are just for illustrations. The sample size calculation is based on HR, which is robust to the underlying assumptions for the control arm. We also have stratified patients based on inclusion of immunotherapy in the induction regimen to mitigate this issue.

15.3.2 Statistical Analysis Plan for Primary Endpoints

For both phase II and phase III portions of this study, the respective primary analyses for PFS and OS will be performed on a modified intent-to-treat (mITT) basis, such that all randomized eligible 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, protocol deviations, baseline characteristics, and efficacy outcome research.

The primary analysis for the phase II portion based on PFS is to be conducted when at least 138 PFS events are available. We will compare the distributions of PFS between treatment arms using a one-sided log-rank test stratified by histology and systemic therapy type in all randomized eligible patients. The rates at various timepoints (e.g., every 6 months after randomization) and medians of 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. Results from an unstratified analysis will also be provided.

At the time of phase II primary analysis, we will also estimate the HR_{OS} and use it as a parallel criterion to determine if the experimental regimen is worth continuing to a phase III analysis. In particular, we consider the experimental regimen is likely to be safe with respect to OS if the estimated $HR_{OS} \leq 1.53$ (control is reference) when at least 70 deaths are available. This criterion is motivated by the futility monitoring rule proposed by Freidlin et al. (2010). Considering the data are not mature enough for any reliable inefficacy evaluation on OS at the time of phase II primary analysis based on PFS, to avoid substantial accrual suspension, we plan to perform this early "harm" look of OS when 25% of the full OS information, i.e., at least 70 deaths, have been observed.

In summary, the primary phase II analysis will be conducted when at least 138 PFS events and 70 deaths are both available. The accrual for the trial is to be suspended if 216 eligible patients have been randomized in the event that we have not observed either 138 PFS events or 70 deaths. Contingent upon the primary phase II analysis the accrual will proceed into the phase III portion, i.e., if the estimated $HR_{PFS} \leq 0.83$ (equivalently, $Z \geq 1.036$) and $HR_{OS} \leq 1.53$ (equivalently, $Z \leq 1.645$), based on stratified Cox PH model.

The primary analysis for the entire phase III trial, if applicable, will be conducted when at least 278 deaths are available. OS will be analyzed using the same methods as the primary phase II analysis for PFS. The study will be interpreted as positive if the one-sided p-value from the stratified log-rank test is less than 0.025, with proper adjustments based on group sequential method per the planned interim analysis plan (see Section 15.4). In an exploratory nature, the analysis for PS may be updated at the time of conducting phase III analysis, if applicable.

15.3.3 Sample Size and Power Calculations:

The overall sample size of this phase II/III study is 378 eligible patients (125 patients in the maintenance systemic therapy arm and 253 patients in the LCT + maintenance systemic therapy arm), and the final analysis for OS will occur when at least 278 deaths (full OS information) have been observed. This design will provide at least 85% power to detect a hazard ratio for OS (HR_{OS}) of 0.68 (approximately) at a 0.025 significance level (1-sided) using the stratified log-rank test. Guarding against ineligibility or lack-of-data of up to 5%, the targeted accrual of randomized patients for the entire phase II/III study is 400.

The phase II portion is meant to provide at least 95% power to detect a hazard ratio for PFS (HR_{PFS}) of 0.60 (approximately) at a significance level (1-sided) of 0.15. We consider this phase II portion as a randomized phase II screening design (Rubinstein 2005) to justify the choice of type 1 and type 2 errors for PFS analysis. Based on the aforementioned assumptions, at least 138 PFS events will be needed to detect a HR_{PFS} of 0.6, and the estimated HR_{PFS} using Cox model needs to be less than 0.83 to be considered promising enough for a further study.

The sample size and power calculation were performed based on software EAST and Monte Carlo simulations using R.

15.3.4 Sample Size and Power Calculations for Quality-of-Life (QOL) Research

The primary QOL endpoint is the clinically meaningful deterioration of FACT-TOI at 3 months from baseline. A clinically meaningful deterioration is defined as a decline of 5 points or more in FACT-TOI. The primary QOL hypothesis is that fewer patients in the experimental arm will experience clinically meaningful deterioration at 3 months than those in the control arm.

We project that about 70% of all randomized patients (~264 eligible patients) will be available for evaluation at both baseline and 3 months. Power analysis suggests that 264 evaluable patients at both baseline and 3 months will provide about 90% power to detect about a 20% difference in deterioration rate in control and experimental arms at a two-sided alpha of 0.05.

15.3.5 Power Calculations for Translational Research

The translational research objectives are considered exploratory in nature. While the predictive and prognostic potential for ctDNA remains to be of primary interest, the assay technology may evolve over time. As such, no marker assays will be conducted on the

collected specimens until sufficient clinical outcome data is ready for statistical analysis. When this information is available from the parent study, a full correlative study protocol for the marker studies detailing the scientific hypothesis, research plan, clinical outcome, assay methods for each biomarker, and a more complete statistical section (with adequate power justification and analysis plan) will be submitted and subjected to CTEP review in accordance with National Clinical Trials Network (NCTN) policies.

To determine if the study may offer exploratory yet still meaningful findings whether a to-be-determined cutoff of ctDNA may predict PFS changes in patients treated with RT, we provide the following table as a preliminary evaluation for the interaction effects between "marker" status and treatment assignments. Based on the design parameters and the method proposed by Peterson and George [Peterson 1993], and using all patients to be available at the end of study, we summarize the statistical power to detect interaction effects (ratio of hazard ratios) of 0.33, at 2-sided significance level of 0.05. We denote monthly hazard rates as λ, expected number of events of respective subgroups as E[N], and the hazard ratio between marker + and - as Δ. The subscripts indicate the corresponding treatment arms. The assumed monthly hazard rates and associated expected number of events are listed in the following Table accordingly.

Prevalence of Marker +/-		Arm 1			Arm 2			Interaction	
		Marker -	Marker +	Δ_1	Marker -	Marker +	Δ_2	$\Delta_{21}=\Delta_2/\Delta_1$	Power
0.2	λ	0.085	0.085	1.0	0.059	0.0194	0.33	0.33	79.1%
	E[N]	66	17		109	13			
	λ	0.0788	0.118	1.5	0.055	0.027	0.5	0.33	84.1%
	E[N]	64	19		105	16			
	λ	0.075	0.150	2.0	0.052	0.035	0.67	0.33	88.4%
	E[N]	62	21		102	20			
0.33	λ	0.085	0.085	1.0	0.059	0.0194	0.33	0.33	91.9%
	E[N]	55	27		99	23			
	λ	0.0788	0.118	1.5	0.055	0.027	0.5	0.33	94.5%
	E[N]	52	31		93	29			
	λ	0.075	0.150	2.0	0.052	0.035	0.67	0.33	95.5%
	E[N]	50	33		88	33			

Based on the table above, the proposed study will have a reasonably good power to detect a strong predictive (interaction) effect (HR=0.33) with marker prevalence as low as 20%.

15.4 Study Monitoring of Primary Objectives (30-MAR-2021)

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, patient exclusion rates and reasons following registration, compliance rate of treatment delivery, 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 efficacy endpoint. The DMC also will review the study on an "as needed" basis.

For the phase II portion with respect to its primary endpoint PFS, one interim futility analysis will be conducted based on Freidlin (2010) when 69 PFS events (50% of full PFS information for phase II) are available. If the observed $HR_{PFS}>1$, the two-sided 95% confidence interval for HR_{PFS} (on the scale of $logHR_{PFS}$) would not contain the alternative hypothesis that $HR_{PFS}=0.6$. In this case we would consider terminating the study as the experimental regimen will be viewed as ineffective. The final analysis of PFS for phase II portion will occur when at least 1) 138 PFS events are available and 2) 70 deaths are both available.

For the phase III portion with respect to its primary endpoint OS, two interim analyses for futility and efficacy are planned prior to its final analysis when at least 278 deaths are available. They will be conducted approximately when we observe 50% (139 deaths) and 75% (209 deaths) of the full OS information (278 deaths). Based on the proportion of information available, the Lan-DeMets implementation of O'Brien-Fleming boundary is used to determine the critical value for the interim analyses for efficacy, and a Linear 20% Inefficacy Boundary (LIB20), as proposed by Freidlin (2010), is used for interim analyses for futility. All interim analyses will be based on mITT population.

The following Table summarizes the interim efficacy/futility monitoring schedule with respect to OS for the entire phase III study:

Interim and Final Analysis for OS

Analysis	Projected Time (month) under H1**	Percent Information	Number of Events	Efficacy boundary Z>	Futility boundary Z<
Interim 1	48	50%	139	2.963	0.055
Interim 2	63	75%	209	2.356	0.298
Final	87	100%	278	2.015	-

* Early look for detriment in experimental arm, left-tail $p<0.05$ will prompt stopping.

** Including the 6 months accrual bump-up period (see details in Section 15.5).

At each protocol-planned interim analysis, the results from the test assessing the treatment efficacy and futility will be reported to the NRG Oncology Data Monitoring Committee (DMC). The responsible senior statistician may recommend early reporting of the results and/or stopping accrual (if applicable) of the trial if the critical value exceeds the specified boundary in a sequential design for either efficacy or futility. The accrual rate, treatment compliance, treatment safety, and the importance of the study are also considered in making such a recommendation. The DMC will then make a recommendation about the trial to the NRG Oncology leadership and study team.

15.5 Accrual/Study Duration Considerations (18-MAY-2018)

The study is event-driven and plans to randomize up to 378 eligible patients with 2:1 ratio into the experimental and control arms. Guarding against ineligibility or lack-of-data rate of up to 5%, the targeted accrual of randomized patients for the entire phase II/III study is 400. During the first 6 months following activation, little accrual is anticipated while the trial is being approved by institutional review boards (IRBs). Assuming a uniform monthly accrual rate of 9.5 patients (9 eligible patients to be randomized) and minimal accrual in the first 6 months for ramp-up, the accrual for the phase II portion is projected to last approximately 30 months (2.5 years). Another 18 months (1.5 years) will be needed to complete the entire phase III accrual. The entire phase III study is projected to last approximately 87 months (7.2 years) since the phase II portion initiation to reach the required 278 deaths, without accounting for the accrual suspension for conducting the phase II analysis.

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.

15.6 Secondary Endpoints and Statistical Analysis Plans (18-MAY-2018)

15.6.1 Statistical Analysis Plan for Safety Endpoints

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 eligible subjects based on the treatment they actually received.

For each patient, the maximum severity reported will be used in the summaries. Adverse events will be summarized regardless of relationship to protocol treatment as assessed by the investigator. 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. Treatment-related adverse events using NCI Common Terminology Criteria for Adverse Events per Section 7.2.1 will be presented in statistical analysis reports/publications in CTCAE, v. 5. AE rates will be reported with the frequency and severity (e.g., type, grade, and attribution) by arm, the analysis will be performed at the time of both phase II and phase III (if applicable) primary endpoint analyses.

15.6.2 Statistical Analysis Plan for Efficacy Endpoints

The analyses for all efficacy secondary endpoints will be performed on a modified intent-to-treat (mITT) basis. Statistical inferences will be conducted in an exploratory nature and for hypothesis generating purposes.

Times to in-field/local failure and new lesions will be analyzed as competing risks data, where deaths without respective failures will be considered as competing events. Rates at various timepoints (i.e., every 6 months after randomization) for each arm will be estimated using the cumulative incidence function. The associated 95% confidence interval (CI) will be calculated using the Delta method and based on a log-log transformation applied on the estimated cumulative incidence functions.

Statistical inferences of the development of each failure between arms will be based on cause-specific hazards using the log-rank test and Cox proportional hazard model. Gray's test and the Fine-Gray model will also be used to provide statistical inferences between arms based on cumulative incidence functions and subdistribution hazards.

15.6.3 Statistical Analysis Plan for Quality-of-Life (QOL) Endpoints

The QOL analyses will be performed based on all randomized patients. FACT-TOI completion rates will be summarized at each assessment point as the proportion of assessments actually received out of the expected number (i.e., the number of subjects still in follow-up).

The primary QOL endpoint, FACT-TOI deterioration rate at 3 months, is defined as the proportion of randomized subjects who have a 5 point or greater decrease from baseline in FACT-TOI at 3 months from baseline. FACT-TOI deterioration rates at 3 months and associated 95% confidence interval will be calculated for each treatment group, based on all randomized subjects. Clopper-Pearson method will be used for calculating 95% CI. The deterioration rates of each arm will also be compared using Cochran-Mantel-Haenszel Test, stratified by histology.

FACT-TOI at baseline and at each subsequent assessment, as well as their change from baseline will be summarized using descriptive statistics by treatment group as randomized. The summary at baseline and at each time point is based on all randomized subjects with a measurement at respective time point. The change from baseline analysis will only include subjects who have an assessment at baseline and at the subsequent time point.

The scores at baseline and subsequent time points, as well the changes from baseline at each time point for each treatment group will be compared using the two-sample t-test. If the parametric assumptions are not met, then the Mann-Whitney test will be used. Effect size of FACT-TOI changes at different time points will be calculated based on Cohen's d, i.e., dividing the difference between arms in mean score changes by the pooled standard deviation of the baseline score means.

Longitudinal data analysis will also be performed to characterize the trend of scores over time across the two treatment groups using hierarchical formulation of the linear mixed model. The model will include treatment groups, stratification factors and time.

EQ-5D consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The EQ VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state.

Subjects' overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics by treatment group, as randomized. Proportion of subjects reporting problems for the five EQ-5D dimensions at each assessment time point will be summarized by level of problem and by treatment group, as randomized. Percentages will be based on number subjects assessed at assessment time point.

C-TUQ will be summarized using descriptive statistics by treatment group, as randomized. The core items (1, 4, 5 and 6) plus the following extension items (7 and 11-14) are of primary interest in this analysis. Items 4 and 5 are only analyzed at baseline. Proportions of patients who changed their smoking behavior after diagnosis, as collected in item 7, will be summarized at the different timepoints (treatment completion, 3, 6 and 12 months). In addition, if there are reasonably sufficient compliant cases in each arm, the association between active smoking status and FACT at 3 months by arms will be explored. Likewise, the prognostic value (with respect to survival) of active smoking status at baseline, during and end of treatment will be explored if there are a reasonable number of compliant cases. We anticipate more experiences will be shared across the clinical oncology community with the increasing utility of C-TUQ in the course of this trial. If needed and applicable, additional details may be specified in Statistical Analysis Plan or amended in the protocol prior to conducting the primary analysis of quality of life component.

15.6.4 Statistical Analysis Plan for Translational Research Endpoints

The translational research will be performed among all randomized patients with usable specimens. All translational research analyses are exploratory in nature.

The association between baseline ctDNA concentration and efficacy outcome, e.g., progression-free survival, will be assessed using the Cox proportional hazard model stratified by ≤1 vs. > 1 haploid tumor genome equivalent/ml of plasma. Proper assessments for the chosen functional form of ctDNA concentration and model assumption will be applied. Analyses will be performed both separately for each arm, and jointly across all patients with an interaction term (if applicable). In addition, the absolute concentration at the 3 month time point and the change between the pre-treatment and 3 month time point will be summarized descriptively, and will be explored

for association with landmark PFS and OS at 3 months using a Cox proportional hazard model.

15.7 Gender/Ethnicity/Race Distribution (18-MAY-2018)

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	3	3	0	0	6
Asian	3	5	0	0	8
Native Hawaiian or Other Pacific Islander	3	3	0	0	6
Black or African American	19	21	0	0	40
White	133	149	6	12	300
More Than One Race	0	0	0	0	0
Total	161	181	6	12	360

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	3	3	0	0	6
White	11	13	4	6	34
More Than One Race	0	0	0	0	0
Total	14	16	4	6	40

REFERENCES (30-MAR-2021)

Ashworth AB, Senan S, Palma DA, et al.An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* 2014 Sep; 15(5):346-55.

Bartlett EK, Simmons KD, Wachtel H, Roses RE, Fraker DL, Kelz RR, Karakousis GC. The rise in metastasectomy across cancer types over the past decade. *Cancer*. 2015 Mar 1;121(5):747-57.

Behera M, Owonikoko TK, Chen Z, et al.Single agent maintenance therapy for advanced stage non-small cell lung cancer: a meta-analysis. *Lung Cancer* 77(2), 331-338 (2012).

Bonnette P, Puyo P, Gabriel C, Giudicelli R, Regnard JF, Riquet M, Brichon PY; Groupe Thorax. Surgical management of non-small cell lung cancer with synchronous brain metastases. *Chest*. 2001 May;119(5):1469-75.

Brahmer JR, Rodriguez-Abreu D, Robinson AG, et al. Progression After the Next Line of Therapy (PFS2) and Updated OS Among Patients with Advanced NSCLC and PD-L1 TPS >=50% enrolled in KEYNOTE-024. *J Clin Oncol* 35, 2017 (suppl; abstr 9000).

Brodowicz T, Krzakowski M, Zwitter M, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. *Lung Cancer* 52(2), 155-163 (2006).

Burt M, Wronski M, Arbit E, Galicich JH.Resection of brain metastases from non-small-cell lung carcinoma. Results of therapy. Memorial Sloan-Kettering Cancer Center Thoracic Surgical Staff. *J Thorac Cardiovasc Surg*. 1992 Mar;103(3):399-410.

Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *The Lancet Oncology* 11(6), 521-529 (2010).

Chaudhuri AA, Binkley MS, Osmundson EC, et al. Predicting Radiotherapy Responses and Treatment Outcomes Through Analysis of Circulating Tumor DNA. *Semin Radiat Oncol*. 2015 Oct;25(4):305-12.

Cheruvu P, Metcalfe SK, Metcalfe J, et al. Comparison of outcomes in patients with stage III versus limited stage IV non-small cell lung cancer. *Radiation Oncology* 6, 80 (2011).

Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet*. 2009 Oct 24; 374(9699):1432-40.

Collen C, Christian N, Schallier D, et al. Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients. *Ann Oncol.* 2014 Oct; 25(10):1954-9.

De Ruysscher 2012 - De Ruysscher D, Wanders R, van Baardwijk A, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (NCT01282450). *J Thorac Oncol*. 2012;7(10):1547-1555.

Diaz, LA & Bardelli, A. Liquid biopsies: genotyping circulating tumor DNA. *Journal of Clinical Oncology*. 2014 Feb 20; 32(6): 579-586.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009 Jan;45(2):228-47.

Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with *gemcitabine plus carboplatin in advanced non-small-cell lung cancer. Journal* of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2009 Feb 1; 27(4):591-8.

Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Annals of Surgery* 230(3), 309-318; discussion 318-321 (1999).

Freidlin B, Korn EL, & Gray R (2010). A general inefficacy interim monitoring rule for randomized clinical trials. *Clinical Trials*, 7(3), 197-208.

Furák J, Troján I, Szöke T, Agócs L, Csekeö A, Kas J, Svastics E, Eller J, Tiszlavicz L. Lung cancer and its operable brain metastasis: survival rate and staging problems. *Ann Thorac Surg*. 2005 Jan;79(1):241-7.

Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. *New Engl J Med* 2018; April 16, 2018.

Garon EB, Gandhi L, Rizvi N, et al. Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced Non–Small Cell Lung Carcinoma (NSCLC). *Annals of Oncology* 2014; 25: 1-41 and http://accc-iclio.org/wp-content/uploads/2015/07/ICLIO-01-Webinar-irRC-Slides.pdf).

Gerber DE: Maintenance therapy for advanced lung cancer: who, what, and when? *Journal of Clinical Oncology*: Official Journal of the American Society of Clinical Oncology 31(24):2983-90, 2013.

Gerber DE, Dahlberg SE, Sandler AB, et al. Baseline tumour measurements predict survival in advanced non-small cell lung cancer. *Br J Cancer*. 2013 Sep 17;109(6):1476-81.

Girard N, Mornex F. Stage IIIB non-small cell lung cancer. Optimization of radiotherapy in lung cancer: some interesting questions to be solved. *Rev Mal Respir*. 2006 Nov;23(5 Pt 3):16S61-16S67.

Gomez, DR. A Randomized Phase II Study Assessing the Efficacy of Local Consolidative Therapy for Non-Small Cell Lung Cancer Patients With Oligometastatic Disease. NCT01725165.

Gomez DR, Blumenschein GR Jr, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol*. 2016 Oct 24. pii: S1470-2045(16)30532-0).

Gomez DR, Tang C, Zhang J, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. *J Clin Oncol*. 2019 Jun 20;37(18):1558-1565.

Granone P, Margaritora S, D'Andrilli A, Cesario A, Kawamukai K, Meacci E.Non-small cell lung cancer with single brain metastasis: the role of surgical treatment. *Eur J Cardiothorac Surg*. 2001 Aug;20(2):361-6.

Hasselle MD, Haraf DJ, Rusthoven KE, et al. Hypofractionated image-guided radiation therapy for patients with limited volume metastatic non-small cell lung cancer. *Journal of Thoracic Oncology*: Official Publication of the International Association for the Study of Lung Cancer 7(2), 376-381 (2012).

Hellman S, Weichselbaum RR. Oligometastases. *Journal of Clinical Oncology*: Official Journal of the American Society of Clinical Oncology 13(1), 8-10 (1995).

Hellmann MD, Paz-Ares L, Caro RB, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. *N Engl J Med*. 2019 Nov 21;381(21):2020-2031. doi: 10.1056/NEJMoa1910231. Epub 2019 Sep 28.

Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. *N Engl J Med* 2020; 383:1328-1339 DOI:10.1056/NEJMoa1917346.

Iyengar P, Kavanagh B, Wardak Z, et al. A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) Combined with Erlotinib for Patients with Limited but Progressive Metastatic Non-small Cell Lung Cancer (NSCLC). *Journal of Clinical Oncology*: Official Journal of the American Society of Clinical Oncology, 2014 Dec 1; 32(34):3824-30.

Iyengar, P. Maintenance Chemotherapy Versus Consolidative Stereotactic Body Radiation Therapy (SBRT) Plus Maintenance Chemotherapy for Stage IV Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II Trial. NCT02045446.

Kozower BD, Larner JM, Detterbeck FC, Jones DR.Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013 May;143(5 Suppl):e369S-e399S.

Land SR, Toll BA, Moinpour CM, et al. Research Priorities, Measures and Recommendations for Assessment of Tobacco Use in Clinical Cancer Research. *Clin Cancer Res*. 22(8):1907-13, 2016a.

Land SR, Warren GW, Crafts JL, et al. Cognitive testing of tobacco use items for administration to patients with cancer and cancer survivors in clinical research. Cancer. 122(11):1728-34, 2016b.

Lewis SL, Porceddu S, Nakamura N, et al. Definitive Stereotactic Body Radiotherapy (SBRT) for Extracranial Oligometastases: An International Survey of >1000 Radiation Oncologists. Am J Clin Oncol. 2015 Feb 2.

Lucchi M, Dini P, Ambrogi MC, Berti P, Materazzi G, Miccoli P, Mussi A.Metachronous adrenal masses in resected non-small cell lung cancer patients: therapeutic implications of laparoscopic adrenalectomy. Eur J Cardiothorac Surg. 2005 May;27(5):753-6.

Magilligan DJ Jr, Rogers JS, Knighton RS, Davila JC.Pulmonary neoplasm with solitary cerebral metastasis. Results of combined excision. J Thorac Cardiovasc Surg. 1976 Nov;72(5):690-8.

Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg. 1975 Oct;70(4):606-12.

Mehta N, Mauer AM, Hellman S, et al. Analysis of further disease progression in metastatic non-small cell lung cancer: implications for locoregional treatment. Int J Oncol. 2004 Dec; 25(6):1677-83.

Mercier O, Fadel E, de Perrot M, Mussot S, Stella F, Chapelier A, Dartevelle P. Surgical treatment of solitary adrenal metastasis from non-small cell lung cancer. J Thorac Cardiovasc Surg. 2005 Jul;130(1):136-40.

Milano MT, Katz AW, Zhang H, et al. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. International journal of radiation oncology, biology, physics 83(3), 878-886 (2012).

Modi A, Vohra HA, Weeden DF.Does surgery for primary non-small cell lung cancer and cerebral metastasis have any impact on survival? Interact Cardiovasc Thorac Surg. 2009 Apr;8(4):467-73.

Mok, TS, Wu Y-L, Kudaba I et al. Pembrolizumab versus chemotherapy for previously

untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019; 393: 1819–30 Published Online April 4, 2019 http://dx.doi.org/10.1016/ S0140-6736(18)32409-7.

National Cancer Institute SEER Cancer Statistics Review 2016.

Newman AM, Bratman SV, To J, et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. Nat Med. 2014 May;20(5):548-54. doi: 10.1038/nm.3519. Epub 2014 Apr 6.

Newman AM, Lovejoy AF, Klass DM, et al. Integrated digital error suppression for improved detection of circulating tumor DNA. Nat Biotechnol. 2016 May;34(5):547-55. doi: 10.1038/nbt.3520. Epub 2016 Mar 28.

Palma D. Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET). NCT01446744.

Papadimitrakopoulou V, Gadgeel SM, Borghaei H, et al (2017). First-line carboplatin and pemetrexed (CP) with or without pembrolizumab (pembro) for advanced nonsquamous NSCLC: Updated results of KEYNOTE-021 cohort G. Journal of Clinical Oncology, 35(15_suppl), 9094-9094. doi:10.1200/JCO.2017.35.15_suppl.9094.

Papadimitrakopoulou V, Cobo M, Bordoni R, et al. IMpower132: PFS and Safety Results with 1L Atezolizumab + Carboplatin/Cisplatin + Pemetrexed in Stage IV Non-Squamous NSCLC. IASLC 19th World Conference on Lung Cancer, September 23-26, 2018.

Park C, Papiez L, Zhang S, et al. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy.
Int J Radiat Oncol Biol Phys. 2008 Mar 1;70(3):847-52.

Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. The International Registry of Lung Metastases. The Journal of Thoracic and Cardiovascular Surgery 113(1), 37-49 (1997).

Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, Markesbery WR, Macdonald JS, Young B. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med. 1990 Feb 22;322(8):494-500.

Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2012 Mar; 13(3):247-55.

Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Nov 22;379(21):2040-2051.

Porte H, Siat J, Guibert B, Lepimpec-Barthes F, Jancovici R, Bernard A, Foucart A, Wurtz A. Resection of adrenal metastases from non-small cell lung cancer: a multicenter study. Ann Thorac Surg. 2001 Mar;71(3):981-5.

Potters L, Kavanagh B, Galvin JM et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. International Journal of Radiation Oncology, Biology, Physics 76(2), 326-332 (2010).

Quinten C, Martinelli F, Coens C, et al. A global analysis of multitrial data investigating quality of life and symptoms as prognostic factors for survival in different tumor sites. Cancer. 120(2):302-11, 2014.

Ramalingam S, Belani C. Systemic chemotherapy for advanced non-small cell lung cancer: recent advances and future directions. The Oncologist 13 Suppl 1, 5-13 (2008).

Raz DJ, Lanuti M, Gaissert HC, Wright CD, Mathisen DJ, Wain JC. Outcomes of patients with isolated adrenal metastasis from non-small cell lung carcinoma. Ann Thorac Surg. 2011 Nov;92(5):1788-92.

Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Oct 8).

Reck M, Ciuleanu T-E, Dols MC, et al. Nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA.DOI: 10.1200/JCO.2020.38.15_suppl.9501 *Journal of Clinical Oncology* 38, no. 15_suppl (May 20, 2020) 9501-9501. Published online May 25, 2020.

Rubinstein LV, Korn EL, Freidlin B, et al (2005). Design issues of randomized phase II trials and a proposal for phase II screening trials. Journal of Clinical Oncology, 23(28), 7199-7206.

Rusch VW, Asamura H, Watanabe H, et al. The IASLC Lung Cancer Staging Project. J Thorac Oncol 4:5 568-577 (2009)

Rusthoven KE, Hammerman SF, Kavanagh BD, et al. Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis. Acta 0ncologica 48(4), 578-583 (2009). PMID: 19373699.

Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 27(10), 1579-1584 (2009).

Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 27(10), 1572-1578 (2009).

Salama JK, Hasselle MD, Chmura SJ, et al. Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. Cancer 118(11), 2962-2970 (2012).

Schild S. Radiation Therapy or Observation After Chemotherapy in Treating Patients With Stage IV Non-Small Cell Lung Cancer. NCT00776100 (2008).

Socinski MA, Jotte RM, Cappuzzo F, et al. IMpower150 Study Group Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med. 2018 Jun 14;378(24):2288-2301.

Strong VE, D'angelica M, Tang L, et al. Laparoscopic adrenalectomy for isolated adrenal metastasis. Annals of Surgical Oncology 14(12), 3392-3400 (2007).

Tsuruzono K, Kodama K, Higashiyama M, Doi O, Hayakawa T. Nakagawa H, Miyawaki Y, Fujita T, Kubo S, Tokiyoshi K. Surgical treatment of brain metastases of lung cancer: retrospective analysis of 89 cases. J Neurol Neurosurg Psychiatry. 1994 Aug;57(8):950-6.

Urba S, Gatz J, Shen W, et al. Quality of life scores as prognostic factors of overall survival in advanced head and neck cancer: analysis of a phase III randomized trial of pemetrexed plus cisplatin versus cisplatin monotherapy. Oral Oncol. 2012;48(8):723-9. doi: 10.1016/j.oraloncology.2012.02.016. Epub 2012 Mar 11.

Urbanic J. Stereotactic Body Radiation Therapy (SBRT) in Metastatic Non-small Cell Lung Cancer. NCT01185639.

Vokes E. The Synergistic Metastases Annihilation With Radiotherapy and Docetaxel (Taxotere) [SMART] Trial for Non-Small Cell Lung Cancer (NSCLC). NCT00887315.

Weichselbaum RR, Hellman S. Oligometastases revisited. Nature Reviews Clinical Oncology 8(6), 378-382 (2011).

Welsh JW, Tang C, de Groot P, et al. 2017 ASTRO Abstract LBA-5: Phase II 5-arm trial of ipilimumab plus lung or liver stereotactic radiation for patients with advanced malignancies.

West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019 Jul;20(7):924-937. doi: 10.1016/S1470-2045(19)30167-6. Epub 2019 May 20.

Wroński M, Arbit E, Burt M, Galicich JH.Survival after surgical treatment of brain metastases from lung cancer: a follow-up study of 231 patients treated between 1976 and 1991. J Neurosurg. 1995 Oct;83(4):605-16.

Wu AW, Jacobson KD, Frick DL, et al. Validity and responsiveness of the EQ-5D as a measure of health-related quality of life in people enrolled in an AIDS clinical trial. Qual Life Res. 2002; 11(3):273-82.

Xanthopoulos EP, Handorf E, Simone CB 2nd, et al. Definitive dose thoracic radiation therapy in oligometastatic non-small cell lung cancer: A hypothesis-generating study. Pract Radiat Oncol. 2015 Jan 31.

APPENDIX I: RETIRED STUDY CHAIRS (22-FEB-2023)

NRG Oncology acknowledges the following study chair who participated in the development and recruitment for this trial until retirement:

Radiation Oncology Co-Chair
Hak Choy, MD
UT Southwestern Medical Center
5801 Forest Park Rd.
Dallas, TX 75390
214-645-7600/Fax: 214-645-9193
Hak.Choy@UTSouthwestern.edu