RTOG Foundation Collaboration with Bristol-Myers Squibb

RTOG 3505

A Limited Participation Study

RANDOMIZED, DOUBLE BLINDED PHASE III TRIAL OF CISPLATIN AND ETOPOSIDE PLUS THORACIC RADIATION THERAPY FOLLOWED BY NIVOLUMAB/PLACEBO FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

Sponsor: RTOG Foundation

Principal Investigator/Medical Oncology	David E. Gerber, MD

Study Co-Chairs

Medical Oncology	Corey Langer, MD
Radiation Oncology	James J. Urbanic, MD
Medical Physics	Robert Jeraj, PhD
Quality of Life	Ben Movsas, MD
Translational Science	Bo Lu, MD
Pathology	Kirk Jones, MD
Senior Statistician	Chen Hu, PhD

Closure Date: **November 11, 2017**
Termination Date: **January 23, 2019**

Protocol Acceptance
On behalf of the RTOG Foundation, Inc.

Walter J. Curran, Jr., MD
RTOG Foundation Chairman

Date: January 29, 2019

RTOG Foundation Collaboration with Bristol-Myers Squibb

RTOG 3505

A Limited Participation Study

RANDOMIZED, DOUBLE BLINDED PHASE III TRIAL OF CISPLATIN AND ETOPOSIDE PLUS THORACIC RADIATION THERAPY FOLLOWED BY NIVOLUMAB/PLACEBO FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

Sponsor: RTOG Foundation

Principal Investigator/Medical Oncology	David E. Gerber, MD

Study Co-Chairs

Medical Oncology	Corey Langer, MD
Radiation Oncology	James J. Urbanic, MD
Medical Physics	Robert Jeraj, PhD
Quality of Life	Ben Movsas, MD
Translational Science	Bo Lu, MD
Pathology	Kirk Jones, MD
Senior Statistician	Chen Hu, PhD

Protocol Acceptance
On behalf of the RTOG Foundation, Inc.

Walter J. Curran, Jr., MD
RTOG Foundation Chairman

Date: January 30, 2017

RTOG 3505
***(ClinicalTrials.gov NCT #* NCT02768558)(5/10/16)**

A Limited Participation Study

RANDOMIZED, DOUBLE BLINDED PHASE III TRIAL OF CISPLATIN AND ETOPOSIDE PLUS THORACIC RADIATION THERAPY FOLLOWED BY NIVOLUMAB/PLACEBO FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

Principal Investigator/Medical Oncology David E. Gerber, MD Harold C. Simmons Cancer Center 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	Translational Science Co-Chair Bo Lu, MD Thomas Jefferson University 111 South 11th Street Philadelphia, PA 19107 215-955-6705/FAX 215-955-0310 bo.lu@jefferson.edu
Radiation Oncology Co-Chair James J. Urbanic, MD University of California, San Diego 1200 Garden View Road, Suite 210 Encinitas, CA 92024 858-246-0500/FAX 858-246-0501 jurbanic@ucsd.edu	Medical Physics Co-Chair Robert Jeraj, PhD University of Wisconsin Carbone Cancer Center 7033 WIMR, 1111 Highland Ave Madison, WI 53705 608-263-8619/FAX 608-262-2413 rjeraj@wisc.edu
Medical Oncology Co-Chair Corey Langer, MD 6 PCAM 3400 Civic Center Blvd University of Pennsylvania Philadelphia, PA 19104 215-615-5888/FAX 215-615-5122 corey.langer@uphs.upenn.edu	Pathology Co-Chair Kirk Jones, MD Department of Pathology Box 0102 505 Parnassus Ave, Moffitt Room M565 UCSF San Francisco, CA 94115 415-476-7864/FAX 415-476-5271 kirk.jones@ucsf.edu

Study Team continued on next page

Study Team (continued)

Quality of Life/PRO Co-Chair Ben Movsas, MD 2799 West Grand Blvd Henry Ford Hospital Detroit MI 48202 313-916-5188 /FAX 313-916-3264 Bmovsas1@hfhs.org	**Senior Statistician** Chen Hu, PhD Johns Hopkins Sidney Kimmel Comprehensive Cancer Center/RTOG Foundation 1818 Market Street, Suite 1720 Philadelphia, PA 19103 215-928-0153 chu@acr.org

RTOG Foundation Headquarters Contact Information	
Data Managers: For questions concerning eligibility or data submission	Jeff Serianni, jserianni@acr.org Amy Krystkiewicz, akrystkiewicz@acr.org
ACR Core Laboratory/RTQA: For questions concerning RT planning or RT data requirements	Jennifer Presley, jpresley@acr.org
ACR Core Laboratory/RTQA: For questions concerning data submission to TRIAD	Triad-Support@acr.org
ACR Diagnostic Imaging For questions concerning central imaging review	Emilie Connors, 215-574-3201, econnors@acr.org
Serious Adverse Event Coordinator For questions concerning serious adverse event reporting procedures, timelines, and queries	Sara McCartney, 267-940-9404, smccartney@acr.org
Project Manager: For questions concerning regulatory documentation, investigational drug supply and/or shipment issues.	Erin Cunningham, 215-717-0831, ecunningham@acr.org
Membership: For questions concerning contracts and reimbursement	RTOG-Membership@acr.org
For Code Breaks, 8:30 a.m. to 5 p.m. ET	215-574-3150, ask for the Supporting Statistician
For Code Breaks after business hours or on weekends or holidays	215-459-3576

RTOG FOUNDATION
RTOG 3505

RANDOMIZED, DOUBLE BLINDED PHASE III TRIAL OF CISPLATIN AND ETOPOSIDE PLUS THORACIC RADIATION THERAPY FOLLOWED BY NIVOLUMAB/PLACEBO FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

Participating Sites: A list of participating sites can be accessed on the RTOG website.

Protocol Agents

Agent	Supply	IND #	IND Sponsor
Cisplatin	Commercial	Exempt	N/A
Etoposide	Commercial	Exempt	N/A
Nivolumab/Placebo	Bristol-Myers Squibb	130197	RTOG Foundation, Inc.

Document History

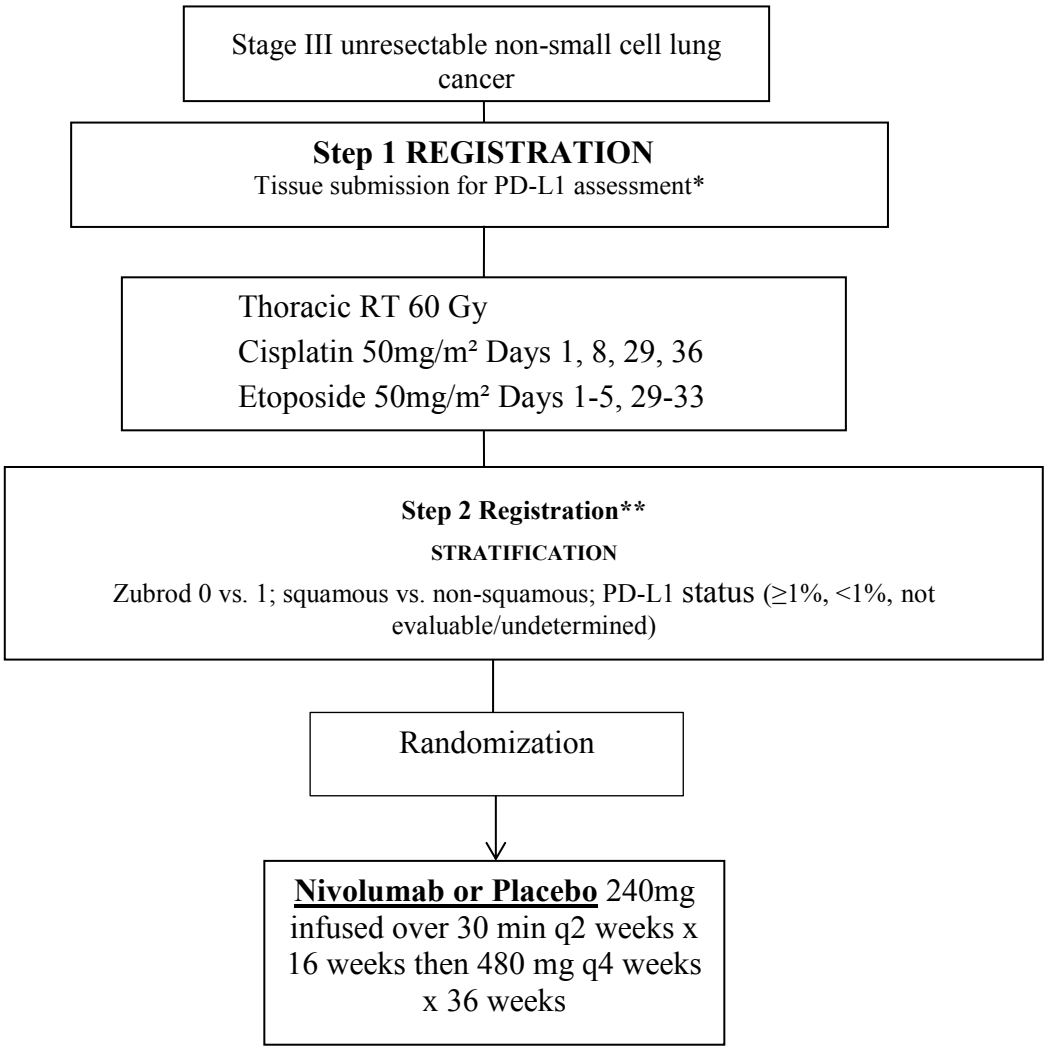
	Version Date	Release Date
Amendment 2	**January 30, 2017**	**February 22, 2017**
Amendment 1	**May 27, 2016**	**June 6, 2016**
Approved Only	**April 25, 2016**	

TABLE OF CONTENTS

RTOG 3505

Randomized, Double Blinded Phase III Trial of Cisplatin and Etoposide plus Thoracic Radiation Therapy Followed by Nivolumab/Placebo for Unresectable Locally Advanced Non-Small Cell Lung Cancer

SCHEMA



*** Verification that archived tissue block is available for submission as the completed submission will be required at least 5 weeks prior to Step 2 Registration**

****Assessment for progression after chemoRT; if evidence of distant metastases or local disease progression, will not be randomized**

1. OBJECTIVES

1.1 Primary Objective

- To compare the overall survival (OS) for patients with Stage III unresectable non-small lung cancer treated with or without nivolumab following concurrent chemoradiation.
    - Overall survival is defined as the time from randomization to death due to any cause.
- To compare progression-free survival (PFS) based on an assessment by an Independent Radiology Review Committee (IRRC) according to RECIST 1.1 criteria for patients with Stage III unresectable non-small lung cancer treated with or without nivolumab following concurrent chemoradiation.
    - PFS is defined as the time from randomization to documented progressive disease or death due to any cause, whichever occurs first;
    - PFS will be determined by IRRC per guidelines of Section 4.3.

1.2 Secondary Objectives

- To compare toxicities in the control and experimental arms;
- To compare Functional Assessment of Cancer Therapy - Trial Outcome Index for lung cancer (FACT-TOI) at 15 months;
- To evaluate OS and PFS in patients with (1) PD-L1-positive, (2) PD-L1-negative and PD-L1 not evaluable/undetermined tumors;

1.3 Exploratory Objectives

- To evaluate biomarkers and biomarker correlatives;
- To determine the proportion of patients alive at 12 and 24 months;
- To determine the proportion of patients progression free at 12 and 24 months according to RECIST 1.1;
- To evaluate PROMIS fatigue at 3 months, EQ-5D utilities and EQ-VAS before and after progression;
- To evaluate PFS based on investigator assessment

2. BACKGROUND

We have reached a plateau in outcomes for locally advanced non-small cell lung cancer (LA-NSCLC). Despite aggressive therapy with concurrent chemoradiation, fewer than 20-25% of patients with stage III NSCLC achieve 5-year survival and are presumably cured. To date, modifications of chemotherapy have not improved these outcomes. The addition of 3 cycles of consolidation docetaxel after concurrent cisplatin-etoposide with thoracic radiation had no impact on overall survival compared to chemoradiation alone (Hanna 2008). A similar, much larger trial performed in Southeast Asia showed no survival advantage whatsoever for consolidative docetaxel/cisplatin after definitive chemoradiation compared to chemoradiation alone (Ahn JS 2015). Finally, a study of maintenance gefitinib after completion of cisplatin-based concurrent chemoradiation in unselected patients with LA-NSCLC demonstrated a decrease in survival (Kelly 2008). The addition of the anti-EGFR monoclonal antibody cetuximab to chemoradiation did not extend survival (Bradley 2015).

Furthermore, in 2015, there is no evidence that achievable radiotherapy (RT) doses above 60 Gy using standard 3D technology are better than 60 Gy, suggesting that opportunities exist

for outcome improvement lie in modification of medical components of chemoradiation regimens. In an interim analysis of the Radiation Therapy Oncology Group (RTOG) 0617 clinical trial, patients receiving a radiation dose of 74 Gy had a median progression-free survival of 9.8 months, compared to 11.8 months for patients receiving 60 Gy. The high-dose RT arms were closed after overall survival results crossed the futility boundary (Bradley 2015).

2.1 There is a strong rationale to combine immunotherapy and radiation therapy (RT).
While NSCLC is typically considered relatively non-immunogenic, RT is thought to augment tumor immunogenicity (Iyengar 2013). The abscopal effect refers to the observation that RT to a local area results in an antitumor effect distant to the radiation site. One proposed mechanism for this phenomenon is inducing the release of circulating tumor antigen or inflammatory factors that could then mediate an augmented immune response against distant malignant lesions expressing similar tumor antigens. Supporting this hypothesis, local RT has been shown to increase the activity of natural killer cells (Uchida 1989).

Conversely, the therapeutic effects of ablative RT on local tumors are dependent on anti-tumor immune responses (Iyengar 2013). Of note, Formenti and colleagues demonstrated that the abscopal effect of radiotherapy is in part immune mediated and that T cells are required to mediate distant tumor effects of radiotherapy (Demaria 2004). In a preclinical model, ablative RT dramatically increased T-cell priming in draining lymphoid tissues, leading to reduction of the primary tumor or distant metastases in a CD8+ T-cell-dependent fashion. In the same model, these RT-initiated immune responses were greatly amplified by local immunotherapy (Lee 2009). Particularly relevant to the current proposal, RT has been shown to increase tumor expression of PD-L1, and combined RT plus PD-1-pathway targeting results in synergistic suppression of tumor-infiltrating myeloid-derived suppressor cells (MDSCs), thereby promoting anti-tumor immunity (Deng 2014).

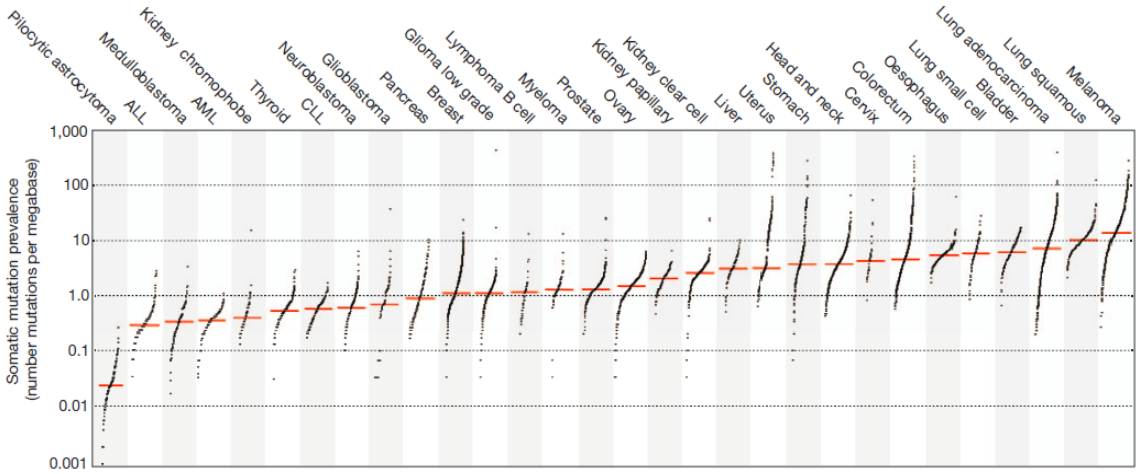
To date, the most extensive experience combining immune modulating therapies with radiation therapy for lung cancer has been with L-BLP25 (Tecemotide), a mucin-1 (MUC1) antigen specific cancer vaccine. In a phase 3 trial, 1513 patients with stage III NSCLC previously treated with chemotherapy and radiation (either concurrent or sequential) were randomized to L-BLP25 (Tecemotide) or placebo. Approximately 65% of patients received concurrent chemoradiation, and 35% received sequential chemoradiation. 274 patients were excluded from the primary analysis population as a result of a clinical hold, resulting in analysis of 829 patients in the tecemotide group and 410 in the placebo group in the modified intention-to-treat population. Although the study failed to meet its primary endpoint of improved OS in the overall study population, a pre-planned subgroup analysis demonstrated an improvement in median OS from 20.6 months to 30.8 months (HR 0.78; 95% CI, 0.64-0.95; P=0.016) in those patients who had received concurrent chemoradiation prior to randomization (Butts 2014, Mitchell 2015). Although no firm conclusions can be drawn from this experience, these results suggest that concurrent chemoradiation may provide the optimal platform on which to add immunotherapies.

With the availability of immunotherapies such as the anti-Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) monoclonal antibody ipilimumab (FDA approved for melanoma) and agents

targeting the programmed death-1 (PD-1) pathway, the potential benefit of combining these agents with RT has become evident clinically. For instance, a recent case report described a patient with metastatic melanoma had evidence of slow progression of a paraspinous mass, hilar lymph nodes, and a liver lesion while receiving ipilimumab. The patient received palliative RT to the paraspinous mass. There was no radiographic improvement noted 6 weeks later. However, after re-initiation of ipilimumab, the paraspinous mass resolved completely. Furthermore, the hilar lymph nodes and liver metastasis (both of which had previously progressed during ipilimumab treatment but had not been irradiated) also responded (Postow 2012).

Among cancer types, lung cancer may be a particularly attractive setting to incorporate immunotherapy into treatment paradigms. A number of studies have suggested that tumor mutational burden is associated with benefit from immunotherapy (Rizvi 2015, Le 2015). Presumably, increased mutational burden results in increased tumor antigenicity, thereby priming the tumor for immune attack. As shown in Figure 1 below, lung cancer carries one of the highest mutational burdens of any malignancy. In this figure, each dot represents a sample, the red horizontal lines represent median numbers of mutations, and the vertical axis (log scale) shows the number of mutations per megabase.

Figure 1. Mutational burden by malignancy



2.2 The PD-1/PD-L1 immune regulatory checkpoint represents a new and effective target for cancer treatment

In contrast to CTLA-4 (which exerts its regulatory effects in the priming phase of the immune response in regional lymph nodes), the negative regulatory effects of the PD-1 pathway occur in the effector phase of the immune response in peripheral tissues. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2, resulting in dephosphorylation of multiple effector molecules involved in the CD3 T-cell signaling cascade (Talmadge 2007). PD-1 is expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regulatory cells (Tregs), and natural killer (NK) cells (Hodi 2010). Although healthy organs express little (if any) PD-L1, numerous cancers are

known to express abundant levels of PD-L1. PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with melanoma, suggesting that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and therefore represents an attractive target for therapeutic intervention. Indeed, no fewer than six monoclonal antibodies targeting this pathway have entered clinical development for the treatment of various malignancies (BMS-936558/MDX1106/nivolumab [Opdivo; Bristol-Myers Squibb]; CT-011 [CureTech]; MK-3475/pembrolizumab [Keytruda; Merck]; BMS-936559/MDX-1105 [Bristol-Myers Squibb]; Medi-4736/durvalumab [MedImmune]; MPDL-3280A/atezolizumab [Genentech]), of which nivolumab and pembrolizumab have been approved for melanoma and NSCLC.

2.3 Nivolumab (BMS-936558, previously MDX-1106 and ONO-4538), an anti-PD-1 monoclonal antibody, has emerged as one of the most promising immunotherapies for lung cancer.

Nivolumab is a fully human, IgG4 (kappa) monoclonal antibody that binds PD-1 on activated immune cells to disrupt engagement of receptor with ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). This action results in counteracting inhibitory signals and augmenting host antitumor responses. In early clinical trials, nivolumab monotherapy demonstrated clinical activity in multiple tumor types, including melanoma, renal cell carcinoma, and NSCLC (Brahmer 2010). In a multicenter phase I trial enrolling NSCLC, melanoma, renal cell carcinoma, castration-resistant prostate cancer, and colorectal cancer, radiographic response rate in advanced, previously treated NSCLC was 18% (14 of 76 patients) (Topalian 2012). In some cases, these responses were prolonged. For 8 of the 14 responding cases, responses lasted ≥ 24 weeks; in 2 cases, responses lasted more than one year. In 7% of cases, stable disease lasted ≥ 24 weeks.

Response rates varied according to treatment dose, histology, and biomarkers. In the 1.0 mg/kg cohort, response rate was 6%. In the 3.0 mg/kg arm, response rate was 27%. In the 10.0 mg/kg arm, response rate was 20%. For squamous cases, response rate was 17% (9/54) [22% at the 3.0 mg/kg level], compared to 18% (13/74) [26% at the 3.0 mg/kg level] in non-squamous cases. For tumors negative for PD-L1 by immunohistochemistry, there were no radiographic responses (0/17). For PD-L1-positive tumors, response rate was 36% (9/25; P=0.006) (Brahmer 2013).

While treatment in this study was overall well tolerated, there were instances of immune-related adverse events. The most common treatment-related adverse events included fatigue, rash, diarrhea, pruritus, decreased appetite, and nausea. Apparent immune-related adverse events included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis. In total, grade 3 or 4 treatment-related adverse events occurred in 14% of patients. Pneumonitis occurred in 3% of patients (1% grade 3-4). There were 3 deaths attributed to pneumonitis (2 NSCLC, 1 colorectal cancer). In many cases, early pneumonitis was reversible with stopping treatment, initiating glucocorticoids, or both.

Nivolumab has also been given in combination with platinum doublet chemotherapy for advanced NSCLC. In a phase I trial dose de-escalation trial, 43 patients were treated with nivolumab plus either gemcitabine-cisplatin, pemetrexed-cisplatin, or carboplatin-paclitaxel (Rizvi 2013). No DLTs were observed with any combination when nivolumab was

administered 10 mg/kg every 3 weeks. Grade 3 pneumonitis developed in 3 patients (7%). Other apparent immune-related grade 3-4 toxicities included rash, nephritis, and colitis.

More recently, two phase 3 clinical trials (Checkmate 057 and Checkmate 017) comparing nivolumab to single-agent docetaxel chemotherapy in previously treated advanced NSCLC have been conducted (see Table 1). Both trials have demonstrated improved overall survival with nivolumab compared to docetaxel.

Table 1. Checkmate 057 and Checkmate 017 Summary of Results

Table 5.4.1.1-1: Summary of Key Efficacy Results - All Randomized Subjects in CA209057 and CA209017

	CA209057 (NSQ NSLC)		CA209017 (SQ NSCLC)	
Efficacy Parameter	**Nivolumab N=292**	**Docetaxel N=290**	**Nivolumab N=135**	**Docetaxel N=137**
PRIMARY ENDPOINT				
Overall Survival				
Hazard Ratio[a]	0.73 (0.59, 0.89)[b]		0.59 (0.43, 0.81)[c]	
Median (95% CI) (Months)[d]	12.2 (9.7, 15.0)	9.4 (8.1, 10.7)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
Rate at 12 Months (95% CI)	50.5 (44.6, 56.1)	39.0 (33.3, 44.6)	42.1 (33.7, 50.3)	23.7 (16.9, 31.1)
SECONDARY ENDPOINTS				
Objective Response Rate				
n (%)	56 (19.2)	36 (12.4)	27 (20.0)	12 (8.8)
95% CI[e]	(14.8, 24.2)	(8.8, 16.8)	(13.6, 27.7)	(4.6, 14.8)
Progression-free Survival				
Hazard Ratio (95% CI)[a]	0.92 (0.77, 1.11)		0.62 (0.47, 0.81)	
Median (95% CI) (Months)[d]	2.3 (2.2, 3.3)	4.2 (3.5, 4.9)	3.5 (2.1, 4.9)	2.8 (2.1, 3.5)
Rate at 12 Months (95% CI)	18.5 (14.1, 23.4)	8.1 (5.1, 12.0)	20.8 (14.0, 28.4)	6.4 (2.9, 11.8)

Source: CA209057 CSR[60] and CA209017 CSR[59]

[a] Stratified Cox proportional hazards model. The hazard ratio is nivolumab over docetaxel.

[b] 95.92% CI

The Checkmate 057 trial enrolled patients with non-squamous NSCLC; the trial met its primary endpoint of improving OS. In the unselected population, for patients receiving nivolumab (N=287), median overall survival (OS) was 12.2 months compared with 9.4 months for docetaxel (N=268) (HR 0.73, HR 0.59-0.89, p=0.0015) (Figure 2). Fewer grade 3 to 5 adverse events were reported for nivolumab (10%) when compared with docetaxel (54%) in the Checkmate 057 trial. Clinical benefit was particularly evident for patients whose tumors had PD L1 staining of 1% or more, with OS of 17.2 to 19.4 months compared with 8-9 months for docetaxel (HR 0.59) (Borghaei H 2015). Conversely, there did not appear to be a benefit for nivolumab over docetaxel in the PDL1-negative population (HR 0.9).

In the Checkmate 057 trial, treatment-related select adverse events observed included infusion-related reactions (3%; no grade 3-4), rash (9%; <1% grade 3-4), pneumonitis (3%; 1% grade 3-4), ALT/AST increased (3%; <1% grade 3-4), diarrhea (8%; 1% grade 3-4), and hypothyroidism (7%; no grade 3-4) (Borghaei H 2015).

Currently, the National Comprehensive Cancer Network (NCCN) guidelines (version

7.2015) recommend nivolumab as subsequent therapy for PS 0-2 patients with metastatic nonsquamous NSCLC who have progressed on or after platinum-based chemotherapy (category 2A). The NCCN panel does not recommend testing for PD L1, because many patients with metastatic NSCLC benefit from nivolumab including PD L1 negative population.

Checkmate 017 enrolled patients with squamous NSCLC and also met its primary endpoint of improving OS (Brahmer 2015). Patients were randomized to nivolumab (3 mg/kg IV over 60 minutes every 2 weeks) (n=135) versus standard of care docetaxel (75 mg/m^2 IV every 3 weeks) (n=137). In a prespecified interim analysis, compared to docetaxel, nivolumab resulted in a 41% reduction in the risk of death (HR 0.59; 95% CI, 0.44-0.79; *P*=0.00025). Median OS was 9.2 months in the nivolumab arm (95% CI, 7.3-13.3 months) and 6 months in the docetaxel arm (95% CI, 5.1-7.3 months). As shown in Figure 2, there is early and persistent separation of survival curves, with suggestion of a "tail" that may represent longer-term survival in approximately 20% of patients. Notably, the trial included patients regardless of tumor PD-L1 status.

In the nivolumab arm, the most common adverse reactions (reported in ≥20% of patients) were fatigue (50%), dyspnea (38%), musculoskeletal pain (36%), decreased appetite (35%), cough (32%), nausea (29%), and constipation (24%). Serious adverse events occurred in 59% of patients receiving nivolumab. The most frequent serious adverse events reported in ≥2% of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain. Pneumonitis occurred in 7 patients (6%). There were five grade 3 cases, and two grade 2 cases. All patients discontinued nivolumab and experienced complete resolution following high-dose corticosteroids. Median time to onset of pneumonitis was 3.3 months (range 1.4-13.5 months). Overall, nivolumab was discontinued due to adverse events in 27% of patients, and 29% of patients receiving nivolumab had a drug delay for an adverse event.

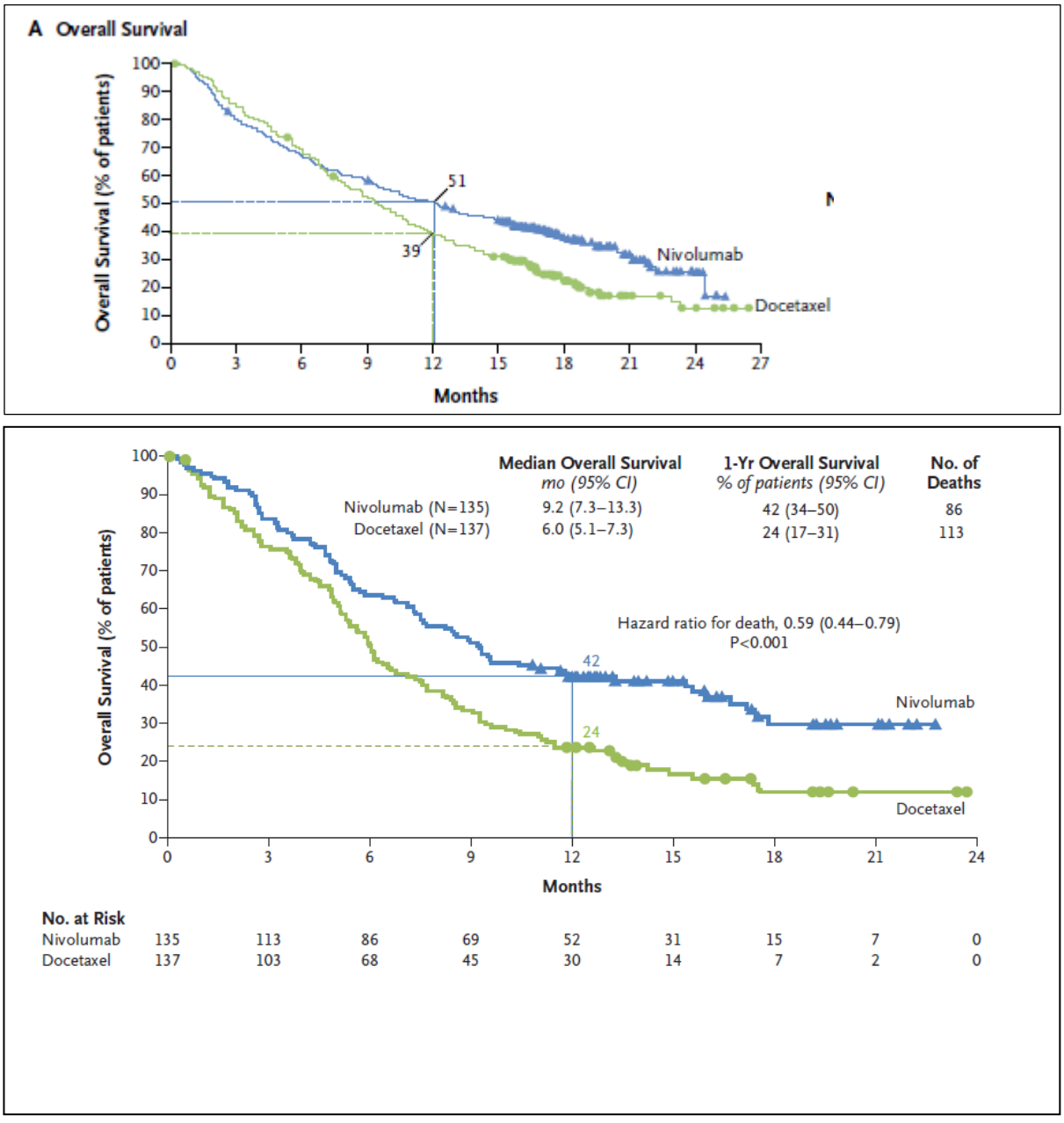
With at least 10 months of minimum follow up for all patients, the confirmed objective response rate (ORR), the study's primary endpoint, was 15% (95% CI, 9-22%), of which all were partial responses. Median time to onset of response was 3.3 months (range 1.7-8.8 months) after treatment initiation. Among responders, 67% had ongoing responses with durability of response ranging from 1.9+ to 11.5+ months. Among this cohort, 59% had durable responses of ≥6 months.

Currently, the NCCN guidelines (version 7.2015) recommend nivolumab as subsequent therapy for PS 0-2 patients with metastatic squamous NSCLC who have progressed on or after platinum-based chemotherapy (category 1).

More recently, nivolumab was compared to chemotherapy in the first-line setting. The CheckMate 026 trial randomized patients with previously untreated advanced NSCLC with ≥1% PD-L1 positive cells to nivolumab or histology-dependent platinum-doublet therapy. There was no significant difference in the primary endpoint of PFS in the PD-L1 ≥5% population. Median PFS was 4.2 months with nivolumab and 5.9 months with chemotherapy (HR 1.15; 95% CI, 0.91-1.45; *P*=0.25) (Socinski 2016). Importantly, these results are not

directly relevant to the present trial because of differences in (1) the clinical setting and (2) the control arm.

Figure 2. Overall survival in the Checkmate 057 (top) and 017 (bottom) trials.



Safety Summary of CheckMate 017 presented at ASCO 2015

	Nivolumab n = 131		Docetaxel n = 129	
	Any Grade	Grade 3–5[a]	Any Grade	Grade 3–5
Treatment-related AEs, %	58	7	86	57
Treatment-related AEs leading to discontinuation, %	3[b]	2	10[c]	7
Treatment-related deaths, %	0		2[d]	

No grade 5 events were reported with nivolumab. [b]1% pts had increased ALT/AST, increased lipase, myasthenic syndrome, or rash, and 2% pts had pneumonitis. [c]Peripheral neuropathy (3%) and fatigue (2%). [d]Interstitial lung disease, pulmonary hemorrhage, and sepsis (1 pt each).

Treatment-related AEs (≥10% of patients) in CheckMate 017 presented at ASCO 2015

	Nivolumab n = 131		Docetaxel n = 129	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Total patients with an event, %	**58**	**7**	**86**	**55**
Fatigue	16	1	33	8
Decreased appetite	11	1	19	1
Asthenia	10	0	14	4
Nausea	9	0	23	2
Diarrhea	8	0	20	2
Vomiting	3	0	11	1
Myalgia	2	0	10	0

Anemia	2	0	22	3
Peripheral neuropathy	1	0	12	2
Neutropenia	1	0	33	30
Febrile neutropenia	0	0	11	10
Alopecia	0	0	22	1

Treatment-related Select AEs of CheckMate 017 presented at ASCO 2015

	Nivolumab n = 131		Docetaxel n = 129	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Endocrine, %	4	0	0	0
Hypothyroidism	4	0	0	0
Gastrointestinal, %	8	1	20	2
Diarrhea	8	0	20	2
Colitis	1	1	0	0
Hepatic,[a] %	2	0	2	1
ALT increased	2	0	1	1
AST increased	2	0	1	1
Pulmonary, %	5	1	1[b]	0
Pneumonitis	5	1	0	0
Lung infiltration	1	0	0	0
Interstitial lung disease	0	0	1[b]	0
Renal,[c] %				
Blood creatinine increased	3	1	2	0
	3	0	2	0
Tubulointerstitial nephritis	1	1	0	0
Skin,[d] %	9	0	9	2
Hypersensitivity/Infusion reaction, %	1	0	2	1
Hypersensitivity	0	0	2	1
Infusion-related reaction	1	0	1	0

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 4,000 subjects treated to date. For

monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation adverse events (AEs), which may be numerically greater in subjects with NSCLC. This may be because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. There is no pattern in the incidence, severity, or causality of AEs related to nivolumab dose level (Investigator Brochure, version 14).

To date, across the clinical trial experience in 691 patients with solid tumors, fatal immune-mediated pneumonitis has occurred in 0.7% (5/691) of patients receiving nivolumab. All five fatal cases occurred in a dose-finding study with nivolumab doses of 1 mg/kg (2 patients), 3 mg/kg (2 patients), and 10 mg/kg (1 patient). Perhaps reflecting cumulative experience with and knowledge of this potential toxicity, there were no fatal cases of pneumonitis in the phase 3 Checkmate 017 and Checkmate 057 trials. In the Checkmate 017 trial in previously treated advanced squamous NSCLC, pneumonitis occurred in 5% of patients receiving nivolumab, of which there was only one Grade 3 case and no Grade 4 cases. The median time to onset of treatment-related pulmonary events was 15.1 weeks (range, 2.6 to 85.1). All but one patient with pulmonary events received corticosteroids. All cases resolved, with median time to resolution of 5.0 weeks (range 0.6 to 12.1). Among these resolved cases, one patient experienced subsequent recurrence of pneumonitis, which responded to corticosteroid treatment. A total of 4/131 (3%) patients discontinued nivolumab due to pneumonitis. In the Checkmate 057 trial, any grade pneumonitis was 3% and grade 3 and above pneumonitis was 1%. The low rate of pneumonitis and the good response to supportive therapy seen in the most recent nivolumab trials suggests that, with appropriate monitoring and precautions, this agent could be studied in combination with thoracic radiation therapy.

Although nivolumab has not yet been studied in combination with RT, data are available for nivolumab-treated patients who previously received RT. While the precise timing and nature of treatments were not captured, of the 129 patients with NSCLC treated on the phase 1, dose-escalation, cohort expansion trial (CA209-003), 75 (58%) had previously received RT. In the overall patient population of 129 NSCLC cases, there were 9 cases of pneumonitis (7.0%) and three cases of grade 3-4 pneumonitis (2.3%), suggesting that the overwhelming majority of NSCLC patients treated with nivolumab after prior RT do not develop pneumonitis. There also is limited experience for patients receiving RT during or after nivolumab therapy. Among approximately 3,000 patients across tumor types (NSCLC, renal cell carcinoma, melanoma) treated with nivolumab to date, approximately 50 were treated with palliative RT during or immediately following nivolumab therapy. Sites of palliative RT included brain (whole brain RT as well as stereotactic radiation), bone, and thorax (for obstructive lesions). No serious adverse events were associated with these cases of palliative RT administration.

2.4 Rationale for the Study Design

Study population**:** Enrollment is not restricted to patients with PD-L1-positive tumors for numerous reasons. Despite early reports suggesting that PD-L1-positive patients appear to derive particular benefit from PD-1- and PD-L1-targeted therapies, the definition of PD-L1-positivity remains unclear. Furthermore, in preclinical models, RT has been shown to

increase tumor expression of PD-L1 (Deng 2014), which would limit the correlation of outcomes with pre-RT tissue biomarkers. The observation that tumor PD-L1 expression may be prognostic in general lung cancer populations—but not among cases treated with radiation or chemotherapy (Sun 2014)—further suggests that baseline assessment of this biomarker may not adequately define the target population most likely to benefit. Finally, in the CheckMate 017 and 057 trials, nivolumab was associated with improved OS in an unselected population. Notably, in the CheckMate 057 trial (non-squamous NSCLC), there was no benefit for nivolumab over docetaxel in the PDL1-negative population (HR 0.90; 95% CI, 0.66-1.24). Nevertheless, these results cannot be extrapolated to this clinical trial due to important clinical and biologic differences between populations and treatment paradigms. For these reasons, this trial does not restrict enrollment to PD-L1-positive NSCLC. To investigate the association between this biomarker and clinical outcomes, we will correlate baseline tumor PD-L1 expression with clinical outcomes in this trial.

Chemotherapy regimen: Concurrent cisplatin-etoposide (EP) plus thoracic RT to 60 Gy is an established and proven therapy for stage III NSCLC, with clinical outcomes superior to sequential regimens or to RT alone. This regimen has been successfully combined with "consolidation" chemotherapy, such as docetaxel 75 mg/m^2 q21d with acceptable toxicity profiles (Hanna 2008). In a randomized phase 2 trial, the regimen had improved outcomes compared to a carboplatin-paclitaxel-based regimen (3-year OS 33% vs 13%) (Wang 2012), although survival differences between the regimens have not been noted in population-based observational studies (Ezer 2014, Santana-Davila 2015). This regimen (EP-RT) is ideally suited to combination with consolidation nivolumab because, in contrast to carboplatin-paclitaxel chemoradiation regimens, (a) the entire chemotherapy course is administered during the 6 to 7 weeks of thoracic radiation and (b) the steroid requirement (which could hypothetically reduce the efficacy of nivolumab) is lower. Finally, rates of radiation pneumonitis—a toxicity that could hypothetically be exacerbated by immunotherapy—may be lower with concurrent cisplatin-etoposide than with concurrent carboplatin-paclitaxel (approximately 5% versus 15%) (Hanna 2008, Belani 2005).

Immunotherapeutic agent: Compared to anti-CTLA-4 antibodies (eg, ipilimumab, tremelimumab), anti-PD-1 antibodies such as nivolumab appear to have greater anti-tumor effect in NSCLC, as evidenced by the unprecedented overall survival results in previously treated advanced NSCLC seen in the Checkmate 017 and Checkmate 057 studies. They also appear to result in substantially lower rates of certain autoimmune toxicities, including colitis and hypophysitis. As of October 2015, nivolumab has been U.S. FDA approved for the treatment of both squamous and non-squamous previously treated advanced NSCLC.

Timing, duration, dose, and schedule of nivolumab: There is preclinical evidence supporting the administration of immunotherapy before, during, and after RT. However, administration of immunotherapy before chemoradiation could delay potentially curative treatment for this aggressive disease. Furthermore, several clinical and laboratory observations support the evaluation of a sequential (consolidation) approach. Administration of the immunotherapeutic L-BLP25 vaccine after completion of concurrent chemoradiation was found to be well tolerated and have efficacy in stage III NSCLC (Butts 2014). In a 3-arm phase II study in advanced NSCLC, the anti-CLTA-4 antibody ipilimumab yielded the

greatest benefit in a phased approach (ie, starting with chemotherapy Cycle #3 rather than Cycle #1), suggesting that tumor debulking prior to immunotherapy may enhance efficacy (Lynch 2012). Furthermore, as no chemotherapy will be given with nivolumab, no steroid premedication will be administered, thereby theoretically optimizing immune stimulation. Patients with severe toxicities from concurrent chemoradiation will be identified prior to administration of nivolumab and will have additional time to recuperate from their toxicities. Finally, clinical observations of anti-CTLA-4 antibodies suggest that immunotherapy administration following RT may provide synergistic effects (Postow 2012).

The initiation of nivolumab 4-12 weeks after completion of chemoradiation reflects previous experience with combined modality regimens for locally advanced disease, prior experience with nivolumab and palliative radiation therapy, and optimization of potential synergistic effects. In concurrent chemoradiation regimens that continue chemotherapy after completion of thoracic radiation, the first post-radiation chemotherapy cycle is commonly given 3-4 weeks after thoracic radiation has ended (Hanna 2008, Belani 2005). In the START phase 3 trial of tecemotide (MUC1 vaccine) after chemoradiotherapy, vaccine was initiated 4-12 weeks after chemoradiotherapy completion and was well tolerated (Butts 2014). As described above, administration of palliative RT with at least a 14-day window between RT and nivolumab dosing in multiple disease settings has not been associated with increased toxicity. Finally, relatively early initiation of immunotherapy may also capitalize on residual and ongoing radiation-induced tumor antigenic stimulation (Iyengar 2013, Uchida 1989).

The administration of nivolumab for up to 1 year is based on theoretical rationale, selected cases of apparent clinical benefit, experience in advanced NSCLC, and tolerability. This duration covers the time period when patients are at greatest risk of recurrence or progression. Furthermore, preclinical studies have demonstrated that continued stimulation of the immune system contributes to the anticancer effects of CTLA-4 blockade. The potential value of repeated dosing also has been seen in human studies of the anti-CTLA-4 antibody ipilimumab. In one dramatic and illustrative case, a heavily pretreated patient with ovarian cancer and increasing CA-125 (GVAX vaccine refractory) was enrolled onto a monotherapy ipilimumab (MDX-010) study (Hodi 2008). After the first dose of ipilimumab (MDX-010), her CA-125 decreased dramatically. Re-dosing at the time of CA-125 increase resulted in an even more rapid decline in her CA-125. Repeated dosing following CA-125 increases occurred 4 times to date and with clear and dramatic reductions in CA-125.

There are also data on the tolerability of prolonged anti-PD-1 therapy from phase 1 trials in advanced NSCLC. A number of patients who continued nivolumab beyond 6 months (and a smaller number beyond 12 months) due to prolonged radiographic response or stable disease were able to do so without apparent cumulative toxicity (Topalian 2012).

Finally, disease-related considerations suggest that a one-year duration of nivolumab is optimal. Among patients with stage 3 NSCLC who achieve disease control after chemoradiation, approximately 75% of cases that eventually progress will do so within the first 12 months after completion of chemoradiation, suggesting that this is the highest risk period (Butts 2013). Post-treatment fluorodeoxyglucose (FDG) uptake not representing disease recurrence or progression has been reported up to 15 months after completion of

chemoradiation (Larici 2011). If such radiographic findings correspond to physiologic effects related to tumor antigenic stimulation, then this period of time might represent the optimal period to capitalize on the abscopal effect.

Nivolumab dose, infusion time, and schedule: In this trial, patients assigned to the nivolumab arm will receive a fixed dose of 240 mg IV infused over 30 minutes every two weeks for 16 weeks, followed by nivolumab 480 mg IV infused over 30 minutes every 4 weeks for 36 weeks (52 weeks total).

Nivolumab monotherapy has been extensively studied in NSCLC populations in studies CA209003, CA209063, CA209017, and CA209057 with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of subjects in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected in these studies, together with PK data from several Phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab clearance and volume of distribution were found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Conversely, given the relationship between nivolumab PK and body weight, a flat-dose is expected to lead to lower exposures in heavier subjects, relative to the exposures in lighter subjects. Table 2 presents summary statistics of the estimated nivolumab steady-state trough, peak and time-averaged concentration (Cminss, Cmaxss, and Cavgss, respectively; document on file) in NSCLC subjects receiving 3 mg/kg, together with corresponding statistics of exposures predicted for a flat nivolumab dose of 240 mg. It should be noted that a dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight of NSCLC subjects in the three Phase 2 and 3 clinical studies of nivolumab monotherapy in NSCLC subjects (CA209017, CA209057, and CA209063). As evident from the data presented below, the geometric mean values of Cminss, Cmaxss, and Cavgss with flat dosing are slightly (< 15%) higher than that produced by a 3 mg/kg dose, and the coefficient of variation (cv%) in these measures of exposure are only slightly (< 10%) greater than that of 3 mg/kg dosing. Nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3mg/kg and efficacy has been found to be relatively flat.

The summary statistics of nivolumab steady state exposure are listed in below Table 2.

Table 2. Nivolumab steady state exposure

Nivolumab Dose	C_{minss} Geo. Mean [ug/mL] (cv%)	C_{maxss} Geo. Mean [ug/mL] (cv%)	C_{avgss} Geo. Mean [ug/mL] (cv %)
240 mg	61.5 (44.6)	133.7 (35.0)	82.4 (38.2)
3 mg/kg	54.7 (41.9)	118.9 (31.8)	73.3 (35.6)

Rationale for 480mg Q4W Dosing

Nivolumab 480 mg every 4-week schedule (Q4W) will be more convenient for subjects. Based on pharmacokinetic modeling, the 480 mg Q4W (after steady state is reached with 240 mg every 2 weeks) will provide steady-state average concentrations similar to 3 mg/kg or 240 mg Q2W, which has been shown to provide longer survival in NSCLC patients. However, 480 mg Q4W is expected to result in higher (approximately 20%) steady-state maximum concentration (peaks), and lower (approximately 10%) steady-state trough concentrations compared to steady state of 3 mg/kg Q2W. Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose was identified. In addition, the exposure-response relationship for safety is flat. Thus, a slight increase in the steady-state maximum concentration is not expected to increase the safety risk of nivolumab. Furthermore, a marginal decrease in steady-state trough concentration is not expected to reduce the efficacy as high trough concentrations and > 90% intra-tumoral receptor occupancy are still maintained at 480 mg Q4W dose. Nivolumab 480 mg Q4W is expected to have similar efficacy and safety profile to 240mg Q2W.

Rationale for Shorter Infusion Times for Nivolumab
Prolonged infusion times place a burden on patients and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of 30 minutes duration for nivolumab in subjects will diminish the burden provided no change in safety profile.

Previous clinical studies of nivolumab monotherapy have used a 60-minute infusion duration for nivolumab. However, nivolumab has been administered at up to 10 mg/kg with the same infusion duration: nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg safely over long treatment duration. In Study CA209010, (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were grade 1-2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical studies. Overall, a change in safety profile is not anticipated with 30-minute infusion of nivolumab.

Radiotherapy credentialing and review. Across studies and disease types, there has been no pattern to suggest that prior RT predisposes patients to recall reactions or other toxicities in the prior radiation field, nor does pneumonitis appear to be associated with the presence of intra-thoracic malignancy.
However these data-sets are quite limited and largely related to patients treated in the metastatic setting with the thoracic radiotherapy having occurred at some time prior to the nivolumab using a variety of radiotherapy doses and techniques but often in the palliative range. Definitive chemoradiotherapy carries a real risk for lung injury. Therefore, this trial testing adjuvant nivolumab will require substantial radiotherapy treatment credentialing/benchmarking and periodic case review of the radiotherapy dosimetry. Through an active quality assurance program, we hope to minimize the chance for increased toxicity related to sub-optimal radiotherapy techniques.

Additionally, central review of follow-up imaging will occur. This is being required for three main reasons: 1) Co-primary end-point of PFS; 2) Correlation with any potential increase in lung toxicity; 3) Scientific understanding of potential differences in imaging changes that could occur in immunotherapy cohort compared to placebo cohort.

2.5 Biomarker Studies

2.5.1 Tumor PD-L1 Expression

The effect of tumor PD-L1 expression on treatment response to anti-PD-1 targeted immunotherapy is a key focus of ongoing investigation. Identification of predictive biomarkers of response to therapy protects patients from exposure to risks of ineffective therapies and improves cost-effectiveness. Submission of formalin-fixed and paraffin embedded tumor samples (blocks) from core or excisional biopsy is required for all patients at the time of study enrollment. Preferably, an archived tumor block sample should be shipped for this study. If an archived tumor block sample is not available, then two 2mm punches from the core needle biopsy blocks may be provided for analysis. If punches are not available, at a minimum, one H&E and 5 positively charged unstained slides may be sent (see details in Section 3.2.15). NOTE: core or excisional biopsy is required. Fine needle aspirates (FNA) and cytology specimens are not adequate for PD-L1 analysis.

Analysis of PD-L1 expression will be performed by use of the 28-8 antibody to PD-L1 (BMS) using the Dako IHC platform (Taube 2012). PD-L1 membrane staining will be assessed by light microscopy. Either complete circumferential or partial linear plasma membrane staining will constitute positive PD-L1 staining. While cytoplasmic staining may be observed, it will not be used in the evaluation of tissue sample status. Alternative biomarkers may be evaluated as determined by additional data associated with disease progression or response to nivolumab.

2.5.2 Optional tumor tissue collection and studies

An optional image-guided core needle (at least 18 gauge) tumor biopsy upon evidence of progressive disease (PD) after step 2 registration, may be performed according to institutional practice, provided it is not associated with unacceptable clinical risk. If a standard-of-care diagnostic biopsy to confirm recurrence is obtained, at least two core biopsies, minimum, should be obtained as part of this recurrence biopsy. Paraffin embedded tissue from this biopsy will be used for confirmation of recurrence and for additional research by the RTOG. Patients consenting to have their tissue submitted at recurrence will have a tube of whole blood collected.

These samples will be shipped and stored at the Biospecimen Bank at UCSF.

Optional Tumor samples (immune-related or response-related markers)

The remaining tumor samples after the PD-L1 staining will be shipped back and stored at UCSF. They will be used for the following studies: The expression and spatial distribution of immune-related or response-related markers by Multiplex immunohistochemistry may also include, but may not be limited to, PD-L1, CTLA-4, CD3, CD4, CD8, CD45RO, forkhead box P3, granzyme B, OX40, PD1, cleaved caspase 3 and Ki67. Archived material (or biopsies if available) may also be analyzed for the presence of key mutations which

may include but are not limited to: EGFR, K-ras, N-ras, B-raf, anaplastic lymphoma kinase and the met proto oncogene to evaluate their potential relevance and correlations with response to nivolumab.

2.5.3 Optional blood collection for Blood borne biomarkers

Blood samples will be analyzed to evaluate protein, nucleic acid, and cellular biomarkers that relate to nivolumab. PBMC will also be isolated from whole blood and will be preserved, and may be used for subsequent flow cytometry or assessment of the diversity of the immune cell repertoire based on VDJ coding region analysis, the relationship to clinical responses, and changes in response to treatment with nivolumab. Blood collected for analysis of immune cell gene expression profiles within the peripheral compartments will be evaluated for any relationship with efficacy endpoints. Serum samples will also be collected for analysis of circulating soluble factors in relation to immune status at baseline and in response to treatment. Factors to be analyzed may include but are not limited to: the presence of IFN-γ tumour necrosis factor-α, interleukin (IL)-2, IL-6, IL-10, IL-8, IL-12, and levels of soluble PD-L1 using Luminex platform.

Autoantibody profiles

Recent studies have found that more than 25% of healthy individuals have strong IgG humoral immune responses to a variety of self-antigens, indicating that a "benign" form autoimmunity is much more common than autoimmune disease (Wandstrat 2006, Li 2011, Tan 1997). This autoimmunity is directed against a variety of self-antigens. These findings indicate that many healthy individuals exhibit significant autoimmunity that is regulated in the peripheral immune system by pathways such as those triggered by CTLA-4 and PD1. Consistent with this, CTLA-4 and PD1 are both known to potentiate autoimmune disease, suggesting that the inhibition of these regulatory pathways aggravates pre-existing autoimmunity. Based on this, we hypothesize that checkpoint therapy immune-related adverse events often result from the activation of pre-existing autoimmunity.

We will test this hypothesis by utilizing a variety of novel technologies developed in the Department of Immunology at UT Southwestern to quantify autoimmune responses. Specifically, the UT Southwestern core facility has the ability to measure IgG autoantibody reactivity against more than 120 antigens simultaneously with as little as 5 μl of serum or plasma. We will screen the autoantibodies in sera from individuals before, during, and after nivolumab therapy using this system.

The protein array system that we have developed for autoantibody screening can also be used to assess antibodies against any antigen. Consequently, a panel of tumor-type-specific antigens will also be incorporated into these arrays so that we can follow the level and specificity of anti-tumor humoral immunity elicited by checkpoint therapy in individual patients and correlate this with disease progression.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: 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 RTOG website). For radiation therapy-related eligibility questions, please contact ACR Core Laboratory/RTQA (via the contact list on the RTOG website).

This does not include diagnostic imaging questions as described in Section 2.

3.1 Patient Selection Guidelines

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 (WOCBP) and men who are sexually active should be willing and able to use medically acceptable forms of *(*hormonal or barrier method of birth control; abstinence*)* contraception prior to study entry and for the duration of study participation. WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug/placebo. Men who are sexually active with WOCBP should use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab/placebo and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception

3.1.3 Submission of tumor tissue for PD-L1 expression analysis is required for all patients. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. (See details of tumor tissue submission in Section10.)

3.2 Eligibility Criteria

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

Step 1 Registration Prior to Chemoradiation

3.2.1 Pathologically (histologically or cytologically) proven diagnosis of NSCLC with unresectable, medically inoperable disease, or patients who refuse resection stage IIIA or stage IIIB disease (AJCC 7th edition)

- Unresectable stage IIIA disease is defined by multiple and/or bulky N2 mediastinal lymph nodes on computed tomography (CT) scan such that, in the opinion of the treating investigator, the patient was not a candidate for surgical resection.
- N2 disease must have been documented by biopsy, or at a minimum by fluorodeoxyglucose positron emission tomography (PET) or CT if nodes were more than 2 cm.
- T4 disease is often considered resectable at the discretion of a thoracic surgeon. Patients with T4N0 or T4N1 disease can be enrolled if their case is reviewed by a thoracic surgeon and felt to be unresectable or if they are either medically inoperable or refuse surgery.
- Stage IIIB patients have N3 or T4N2 status. N3 status must have been documented by the presence of a contralateral (to the primary tumor) mediastinal lymph node or

supraclavicular or scalene lymph node proven by biopsy, or at a minimum by fluorodeoxyglucose PET or more than 2 cm on CT scan. Patients with disease extending into the cervical region (defined as disease extending above cricoid cartilage) are not eligible.

- Patients with either N2 or N3 adenopathy and Tx disease will be eligible and categorized as Stage IIIA or IIIB based on their nodal status.

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

- History/physical examination, including documentation of height, weight, BSA, and vital signs, within 30 days prior to registration;
- CT scan with IV contrast (CT scan without contrast acceptable if IV contrast is medically contraindicated) of the lung and upper abdomen through the adrenal glands within 60 days prior to registration (recommended within 30 days prior to registration);
- MRI of the brain with contrast (or CT with contrast if MRI is medically contraindicated) within 60 days prior to registration; **note**: the use of intravenous contrast is required for the MRI or CT (unless medically contra-indicated).
- Whole-body FDG-PET/CT within 60 days prior to registration; **note**: patients do not need to have a separate CT of chest and upper abdomen with contrast if PET/CT imaging includes a high quality CT chest with contrast.

3.2.3 Age ≥ 18 years;

3.2.4 The trial is open to both genders;

3.2.5 Zubrod Performance Status of 0-1 within 30 days prior to registration;

3.2.6 Adequate hematologic function within 14 days prior to registration defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- Hemoglobin ≥ 9.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥9.0 g/dl is acceptable.);

3.2.7 Adequate renal function within 14 days prior to registration defined as follows:

- Serum creatinine within normal institutional limits or creatinine clearance ≥60 ml/min

3.2.8 Adequate hepatic function within 14 days prior to registration defined as follows:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for the institution (except subjects with Gilbert Syndrome, who can have total bilirubin <3.0 mg/dL);
- ALT, AST ≤ 3.0 x ULN for the institution;

3.2.9 Adequate respiratory function within 180 days prior to registration defined as follows:

- FEV1 > 1.2 liters; DLCO ≥ 50% predicted;

3.2.10 Patients with post-obstructive pneumonia are eligible provided they no longer require intravenous antibiotics at registration;

3.2.11 Patients must be at least 3 weeks from prior thoracotomy (if performed); if prior thoracotomy then measurable disease on imaging must be present

3.2.12 A pleural effusion, which is a transudate, cytologically negative and non-bloody, are eligible if the radiation oncologist feels the tumor can be encompassed within a reasonable field of radiotherapy; if pleural fluid is too small a volume to effectively sample by thoracentesis and does not show increased metabolic activity on CT/PET imaging, the patient will be remain eligible.

3.2.13 Negative serum pregnancy test within three days prior to registration for women of childbearing potential

3.2.14 The patient must provide study-specific informed consent prior to study entry. Patients who lack the psychological or intellectual capacity to consent for themselves are excluded.

3.2.15 Sites must verify that archived tissue will be available prior to Step 1 registration to the trial although the actual submission can be immediately after Registration Step 1 but at least 5 weeks prior to Registration Step 2.

Recognizing the difficulties obtaining adequate tissue for analysis from locally advanced lung cancer patients, there are three options available. We would encourage investigators to provide the preferred amount of samples to assist in the greatest scientific yield. NOTE: core or excisional biopsy is required for this study. Fine needle aspirates (FNA) and cytology specimens are not adequate for PD-L1 analysis.

Preferred: H&E slide and archived tissue tumor block. If sites wish the block to be returned they may submit the block and the Biospecimen Bank will cut the unstained for the required study and then punch and return the block

Alternative: If an archived tumor block sample cannot be shipped for this study, then two 3mm punches from the core needle biopsy blocks may alternatively be provided for analysis in addition to the H&E slide.

Minimum: One (1) H&E stained slide (required) and five positively charged unstained slides cut at 3-4 microns from the same block as the H&E. Unstained slides must be stored at 4°C same day as being cut and shipped with a cold pack at 4°C within 5 business days after being cut. Do NOT store or ship unstained slides at room temperature.

Step 2 Registration (after completion of chemoradiation, before randomization)

3.2.16 Zubrod performance Status of 0 or 1.

3.2.17 Must be randomized less than 12 weeks following completion of chemoradiotherapy to ensure nivolumab/placebo begins no later than 12 weeks following completion of chemoradiotherapy.

3.2.18 Laboratory values must meet the following criteria *and must be obtained within 21 days prior to randomization*

- WBC ≥ 2000/μL
- Neutrophils ≥ 1000/μL
- Platelets ≥ 50 x10^3/μL
- Hemoglobin > 9.0 g/dL (Note: The use of transfusion or other intervention to achieve Hgb ≥9.0 g/dl is acceptable.)
- Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

- AST/ALT ≤ 3 x ULN
- Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)

3.2.19 All toxicities attributed to prior chemoRT therapy other than alopecia, fatigue, or peripheral neuropathy must have resolved to ≤Grade 2 (NCI CTCAE version 4) before administration of nivolumab or placebo.

3.2.20 Negative serum pregnancy test for women of childbearing potential within 7 days of randomization

3.2.21 Agreement of women of childbearing potential to use highly effective contraception during receipt of study drug and up to 161 days (23 weeks) from the last dose of nivolumab/placebo and men receiving nivolumab/placebo who are sexually active with women of childbearing potential to use highly effective contraception during receipt of study drug for 31 weeks from the last dose of nivolumab/placebo.

3.2.22 Mandatory submission per 3.2.15 is required for PD-L1 and other biomarker analysis.

3.3 Ineligibility Criteria

Patients with one or more of the following conditions are NOT eligible for this study.

Step 1 Registration (prior to chemoradiation):

3.3.1 Definitive clinical or radiologic evidence of metastatic disease;

3.3.2 Prior or current invasive malignancy (except non-melanomatous skin cancer, localized bladder and prostate cancer) unless disease free for a minimum of 2 years (for example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);

3.3.3 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields. For example, patients with prior breast radiotherapy treatments would likely be excluded;

3.3.4 Prior systemic treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways;

3.3.5 A condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease;

3.3.6 Severe, active co-morbidity defined as follows:

- An active, known or suspected autoimmune disease. Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger;
- Known immunosuppressive disease, for example HIV infection or history of bone marrow transplant or CLL;
- Chronic Obstructive Pulmonary Disease (COPD) exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration. COPD requiring chronic oral steroid therapy;

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
- Transmural myocardial infarction within the last 6 months;
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- History of symptomatic or previously established interstitial lung disease;
- Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection;
- History of severe hypersensitivity reaction to any monoclonal antibody or allergy to study drug components;
- As there is potential for hepatic toxicity with nivolumab, drugs with a predisposition to hepatotoxicity should be used with caution in patients treated with nivolumab-containing regimen;

3.3.7 Pregnancy, nursing females, or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

Step 2 Registration (after completion of chemoradiation, before randomization):

3.3.8 Failure to complete minimum required amounts of chemoradiation (defined as at least 50% of intended days of chemotherapy administration and at least 54 Gy total dose of radiation)

3.3.9 Bilateral lung V20 >37% on radiation therapy treatment plan used for concurrent chemoradiotherapy

3.3.10 Grade 3 and above pulmonary toxicity of dyspnea, hypoxia, or pneumonitis experienced during chemoradiation

3.3.11 Evidence of disease progression after chemoradiation or evidence of metastastic disease

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

4.1 Assessment tables at registration, treatment, and follow-up time points:

Concurrent ChemoRT PRE-TREATMENT ASSESSMENTS REGISTRATION STEP 1

Assessments	Prior to Registration Step 1 (calendar days)	Prior to Treatment (calendar days)
Mandatory tissue submission for PD-L1 analysis (see note)	Verify available	
History and physical exam	30	
Zubrod performance status	30	
Tumor measurements	30	
Rad Onc exam	30	
Med Onc exam	30	
CBC/differential; ANC, platelets; hemoglobin	14	
Na, K, CO2, Cl,	14	
Mg, Ca, LDH	14	
Serum creatinine	14	
Total bilirubin, AST, ALT, Alk Phos	14	
Serum pregnancy test	3	
Cytology/Pathology Report confirming NSCLC	90	
Whole body FDG-PET/CT (base of skull to mid thigh)	60	
CT chest with contrast and include adrenals*	60	
MRI of brain (CT if MRI contraindicated)	60	
Pulmonary function testing (PFTs/DLCO)	90	
Informed consent	Within 30 days including Day of registration	
FACT-L, PROMIS, EQ-5D-5L		X[1]
Specimen collection for banking		If patient consents: 14. See Section 10.

* Patients do not need to have a separate CT of chest and upper abdomen with contrast if FDG-PET/CT imaging includes a high quality CT chest with contrast

[1]After consent, prior to initiation of chemoRT

Notes for Pre-Treatment Assessment

Mandatory submission: Preferred: H&E slide and archived tissue tumor block. If sites

wish the block to be returned they may submit the block and the Biospecimen Bank will cut the unstained for the required study and then punch and return the block

Alternative: If an archived tumor block sample cannot be shipped for this study, then two 3mm punches from the core needle biopsy blocks may alternatively be provided for analysis in addition to the H&E slide.

Minimum: One (1) H&E stained slide (required) and five positively charged unstained slides cut at 3-4 microns from the same block as the H&E. Unstained slides must be stored at 4°C same day as being cut and shipped with a cold pack at 4°C within 5 business days after being cut. Do NOT store or ship unstained slides at room temperature.

Sites must verify that tissue is available prior to Step 1 registration to the trial although the actual submission can be immediately after Registration Step 1 but at least 5 weeks prior to Registration Step 2.

NOTE: core or excisional biopsy is required for this study. Fine needle aspirates (FNA) and cytology specimens are not adequate for PD-L1 analysis.

Concurrent Chemo RT ASSESSMENTS DURING TREATMENT

Assessments	**Weekly during Concurrent Treatment**	**At week 1 and 5 only during concurrent chemoRT**
Performance status	X	
Rad Onc Evaluation	X	
Med Onc evaluation		X[1]
CBC/differential; platelets	X[1]	
Na,K,CO2, Cl,	X[1]	
Mg, Ca, LDH	X[1]	
Total bilirubin, ALT, AST		X[1]
Serum creatinine *or* creatinine clearance	X[1]	
Adverse event evaluation	X	
Specimen collection for banking		X[2]

[1] C1D1 testing does not need to be repeated if performed within 7 days of starting protocol therapy.
[2]Day 1 and Day 42

Nivolumab/Placebo PRE-TREATMENT ASSESSMENTS REGISTRATION STEP 2

Assessments	Prior to Registration Step 2 (calendar days)	Prior to Treatment with nivolumab/placebo -14 days
Medical history and height	21	
Physical examination including vital signs (blood pressure, weight)	21	
Zubrod performance status	21	
Na, K, CL, Mg, Phos, Ca, LDH	21	
Total bilirubin, AST, ALT, Alk Phos, amylase, lipase, glucose, albumin	21	
BUN; Serum creatinine	21	
CBC/differential; platelets	21	
Thyroid function (TSH, free T3 and free T4), fasting am cortisol	21	
Serum pregnancy test	X[1]	
AE evaluation		X
CT of chest with contrast and include adrenals	30 (and at least 14) after chemoRT completed	
Mandatory Tissue Submission for PD-L1 Analysis	35 and ideally immediately after Registration Step 1	
FACT-L, PROMIS, EQ-5D-5L		X[2]

[1]Within one week of study randomization

[2]After Step 2 registration, prior to initiation of nivolumab/placebo

ASSESSMENTS DURING NIVOLUMAB/PLACEBO TREATMENT (1 YEAR)

Assessments	On Day 1 of each Cycle	Every 3 months
Physical examination including vital signs (blood pressure, weight)	X	
Zubrod performance status	X	
Na, K, CL, Mg, Phos, Ca, LDH	X	
Total bilirubin, AST, ALT, Alk Phos, amylase, lipase, glucose, albumin	X	
CBC/differential; platelets	X	
BUN, creatinine	X	
TSH	X[1]	
AM cortisol		As needed if symptomatic
Serum or urine Pregnancy test	X[2]	
AE evaluation	X	
CT of chest with contrast and include adrenals		X[3]
Specimen collection for banking		X
FACT-L, PROMIS, EQ-5D-5L		X[4]

[1] Every 6 weeks during q2 week dosing, then every 8 weeks during q4 week dosing; assess free T3 and free T4 if clinically indicated (e.g. abnormal TSH or symptomatic)

[2]Every 4 weeks[3]After completion of chemoradiotherapy, radiographic assessment with CT chest with contrast including adrenals will occur prior to starting nivolumab/placebo as a component of Step 2 Registration. Further radiographic assessment will occur every 3 months for 2 years (including the year of nivolumab/placebo). The first day of nivolumab/placebo will be used for calculation of the 3 month intervals. After 2 years, radiographic disease assessment should be performed every 6 months during year 3-5 then annually thereafter. FDG-PET/CT should be done to confirm clinically uncertain progression or treatment related effects at the discretion of the treating investigator. This imaging may be done locally.

[4]At 3, 6, 9 and 12 months; should be collected regardless of disease status of the patient

ASSESSMENTS IN FOLLOW UP POST NIVOLUMAB/PLACEBO

Assessments	**Every 3 mos until 2 years post chemoRT then every 6mos until 5 years post chemoRT, then yearly**
History and physical exam	X
Zubrod performance status	X
Tumor status	X
Med Onc exam	X
AE Evaluation	X
CBC with diff, Plts	X[1]
Na, K, CL, Mg, Phos, Ca, LDH, glucose	X[1]
Total bilirubin, ALT, AST, Alk Phos, albumin	X[1]
Serum creatinine, BUN	X[1]
TSH*	X[1]
Serum or Urine Pregnancy test	X[1]
CT Chest with contrastand include adrenals	X[2]
FACT-L, PROMIS, EQ-5D-5L	X[3]

* Assess free T3 and free T4 if clinically indicated (e.g. abnormal TSH or symptomatic)

[1] At 35 days from the last dose (± 7 days) or coinciding with the date of discontinuation of study drug (± 7 days) if the date of discontinuation is greater than 42 days from the last dose. Repeat in 80 days (from first follow-up assessment) only if study drug related toxicity persists. Pregnancy test must be performed at both time points. Assess free T3 and free T4 if clinically indicated.

[2]After completion of chemoradiotherapy, radiographic assessment with CT chest with contrast including adrenals will occur prior to starting nivolumab/placebo as a component of Registration Step 2. Further radiographic assessment will occur every 3 months for 2 years (including the year of nivolumab/placebo). The first day of nivolumab/placebo will be used for calculation of the 3 month intervals. After 2 years, radiographic disease assessment should be performed every 6 months during year 3-5 then annually thereafter. FDG-PET CT should be done to confirm clinically uncertain progression or anatomic changes in the thorax likely due to the effects of chemoradiotherapy, at the discretion of the treating investigator. This imaging may be done locally.

[3]FACT-L, PROMIS, and EQ-5D-5L are collected at 15 and 18 months from start of nivolumab/placebo; should be collected regardless of disease status of the patient. EQ-5D-5L is collected at 2, 3, 4, and 5 years from start of nivolumab/placebo.

Follow-up of Patients Discontinuing Therapy Early
After completion of study treatment, subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed for overall survival until death, withdrawal of consent, or the end of the study (whichever occurs first).

4.2 Definition of Disease Assessments

Tumor assessments will be made using modified RECIST 1.1 criteria. The same measurable and non-measurable lesions will be followed from baseline across on-study time points using RECIST 1.1 guidelines. A RECIST 1.1 tumor assessment will be derived for each on-study time point for each enrolled subject, from which the primary objective of the trial will be determined. In subjects whose in-field disease status is ambiguous, but who have not developed systemic progression, treatment may continue. Follow-up scans will be reviewed by ACR Diagnostic Imaging Core Lab in consultation with the study PIs, if necessary to determine status based on the below guidelines. Patients with uncertain progression may require repeat imaging at 6 weeks rather than 3 months if disease status remains uncertain.

Refer to Appendix II for detailed definitions of RECIST v1.1 response assessment

4.3 Central Image Collection and Review

4.3.1 Imaging Schedule

Imaging exams will be collected at the following time points. Images must be submitted in digital format to the ACR DI Core Lab for archiving:

- Baseline (prior to study treatment)
- Post-chemoRT
- All mandated follow-up imaging: every 3 months for 2 years; every 6 months for years 3-5; then yearly
- At disease progression
- And at request when treatment occurs beyond progression and subsequent tumor evaluations

Imaging studies (defined in Section 4.1) as well as the Image Transmittal Worksheet will be submitted to the ACR DI Core Lab within 2 weeks of image acquisition for all image data sets, excluding imaging visits where disease progression is suspected. Where disease progression is suspected, all imaging studies performed from baseline to date of progression must be submitted to ACR DI Core Lab within 3 business days of the date progression is determined.

4.3.2 Independent Review of Progression

At the time of investigator-assessed progression, sites must request an Independent Review of Progression from the ACR DI Core Lab. This Independent Review of Progression at the time of investigator-assessed progression is a separate process from the IRRC review to assess the primary endpoint. All subjects who are assessed to have RECIST 1.1 progression by the treating investigator must have all available tumor assessments submitted for an Independent Review of Progression. The Independent Review of Progression will be conducted by a blinded, third party, independent radiologist contracted by ACR DI who will assess the scans for RECIST 1.1 progression. When the review is complete, results from the central radiology review and local interpretation will be compared. If the central reviewer agrees with the local assessment of progression, subsequent therapy may be initiated per investigators' clinical decision, and protocol therapy may be discontinued or continued based on the guidelines in section 6.3.5 (Treatment Beyond Disease Progression).

If there is discordance between the local and central reviews (central review does not confirm progression), a central adjudicator from the imaging committee organized by the ACR DI Core Lab will review both the local and central results and determine which interpretation (local or central) with which they agree. The adjudicator's decision is then the final decision of the ACR DI committee on the progression review.

If the adjudicator agrees with the local assessment of progression, subsequent therapy may be initiated per investigators' clinical decision, and protocol therapy may be discontinued or continued based on the guidelines in section 6.3.5 (Treatment Beyond Disease Progression).

If the adjudicator agrees with the central reviewer and does not confirm progression, these cases will be discussed with the individual sites and a consensus decision will be made as to the participation of the patient on the trial therapy. The adjudicator's decision will become the interpretation which must be used by the local site's treating physician if the patient is to remain on protocol therapy. It is the local site treating physician's responsibility to determine whether to base clinical decisions on the local read or the central read if there is discordance; however, if the patient is to remain on protocol therapy, interpretation from the centralized review must be used.

In those cases when the site investigators disagree with final adjudicated central review interpretation, subsequent therapy may be initiated per investigators' clinical decision, and protocol therapy may be discontinued. The local site investigators also have the option of continuing therapy beyond their local interpretation of progression based on section 6.3.5. If treating the patient beyond progression with nivolumab the unusual situation is created in which the local site has reported progression, the central review with adjudication disagrees and the patient is continuing on nivolumab. In this specific situation the patient remains on study and continues tumor assessments outlined by protocol until central review determines RECIST 1.1 progression.

For any patient being treated beyond progression based on the criteria outlined in Section 6.3.5, central imaging review must occur again at the time further progression is documented by the local site. This further progression is defined as an additional 10% increase in tumor

burden volume from time of initial PD. This includes an increase in the sum of all target lesions and/ or the development of new measurable lesions. If this further progression is confirmed by central review treatment should be discontinued permanently.

If clinically acceptable, subsequent therapy should begin only after RECIST 1.1 progression has been assessed by the central reviewers. The independent review of progression will occur within 5-7 working days of receipt of all needed imaging at ACR. Subjects who start subsequent therapy without prior assessment of RECIST 1.1 progression by the central review process must continue tumor assessments (if clinically feasible) according to the protocol-specified schedule and submit them for central review. When RECIST 1.1 progression is assessed by the investigator (whether assessed before or after the start of palliative local therapy or subsequent therapy), the central review center must be notified. Tumor assessments may be discontinued when the independent central radiologist assesses the subject to have met RECIST 1.1 criteria for progression.

4.3.3 Independent Radiology Review Committee (IRRC)

For all randomized subjects with Baseline imaging and at least one on-study time-point, a timepoint-by-timepoint imaging evaluation will be performed by an Independent Radiology Review Committee (IRRC), consisting of two (2) trained radiologist reviewers and an adjudicator, if warranted. The two primary reviewers will determine time point and cross time point response assessments. Neither primary reviewer will have access to the other primary reviewer's annotations or tumor response data. Upon completion of both reviewers' read, comparison of key adjudication variables for each of the independent reviewers is performed and if warranted, adjudication is conducted.

The IRRC review is not subject to input from clinical sites or imaging facilities. All tumor assessments will be provided by ACR DI Core Lab for statistical analysis as described in the protocol. Dosimetry information from the radiation therapy treatment plan may be requested and used to better understand the imaging changes seen. This is particularly critical due to the possibility of evolving radiation lung fibrosis during the time period of nivolumab/placebo treatment.

At the time of the final analysis for PFS, the IRRC will review tumor assessments in all randomized subjects to determine RECIST 1.1 response for the analyses of PFS. This IRRC review for the final PFS analysis will be a separate process from the blinded independent radiology review at the time of investigator-assessed progression.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

This will be a randomized, double-blind, placebo-controlled phase 3 clinical trial. Patients will be treated with standard concurrent chemoradiation (thoracic radiation to 60 Gy plus cisplatin-etoposide), followed by randomization to nivolumab or placebo, which will be started 4-12 weeks after completion of concurrent chemoradiation administered every 2 weeks as an intravenous infusion over 30 minutes for up to a total of 1 year.

Concurrent chemoradiation: Chemotherapy and radiotherapy are to begin within 48 hours of each other. Day 1 of radiotherapy must be Monday, Tuesday, or Wednesday, but no later in the week. Treatment must begin within 14 days after registration.

5.1 Chemotherapy/Other Agent-Based Therapy

5.1.1 Concurrent Chemotherapy

Concurrent chemoradiation must begin within 14 days after step 1 registration.
Consists of one treatment course

Cisplatin Dose Administration
Cisplatin 50mg/m^2 is given intravenously on days 1 and 8, and days 29 and 36 of concurrent therapy.
After administering appropriate antiemetics, cisplatin will be infused over 1-2 hours along with vigorous hydration.

Cisplatin Supportive Care Guidelines
Patients must receive intravenous hydration and and polyantiemetics on day 1, day 8, day 29, and day 36 cisplatin therapy. These should be administered according to institutional practice and the patient's baseline electrolyte levels. As an example, one commonly employed regimen is as follows: prior to cisplatin, begin intravenous hydration with 1,000 ml NS + 20 meq KCL + 4 gms MgSO4 at 250 cc/hr over two hours. The cisplatin may be preceded and followed by 12.5 grams of mannitol, IV push. After cisplatin infusion, complete the remaining 500 cc of hydration fluid over two hours. The patient should be encouraged to drink as much liquid as possible overnight if an outpatient; otherwise, an additional two liters of fluid should be given IV over the next 12 hours if the patient is an inpatient.

Appropriate polyantiemetic regimens must be used prior to and following the administration of cisplatin *(e.g., phenothiazine, antihistamine, benzodiazepine plus dexamethasone - OR - ondansetron or 5HT3 antagonist with or without dexamethasone and PRN benzodiazepines, as well as neurokinin/substance P inhibitors)*.
Etoposide Dose Administration
Etoposide 50mg/m^2 is given intravenously on days 1-5, and days 29-33 of concurrent therapy.
Infuse etoposide over at least 45-60 minutes. Infusions of 30 minutes or less greatly increase the risk of hypotension.

5.1.2 Nivolumab/placebo

Nivolumab is approved in US and Europe to treat metastatic melanoma. On March 5, 2015, nivolumab was US FDA approved for the treatment of patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy. Subsequently, nivolumab was also approved in Europe for this indication in NSCLC. On October 9, 2015, nivolumab was US FDA_approved for the treatment of patients with metastatic non-squamous NSCLC with progression on or after platinum-based chemotherapy.

Nivolumab/placebo must begin within 4-12 weeks after completion of chemoradiation
If subjects meet all eligibility criteria and have recovered sufficiently from treatment with chemoradiation, initial consolidation therapy with nivolumab/placebo will be started a

minimum of 4 weeks and a maximum of 12 weeks after chemoradiation is complete. Treatment with a dose of nivolumab/placebo 240 mg IV will occur on day 1 of each 2 week cycle for 16 weeks followed by 480 mg on day 1 of each 4 week cycle until progressive disease or unacceptable toxicity develop or until the subject has completed 52 weeks of therapy with nivolumab/placebo. Nivolumab should be dosed no sooner than 12 days during the every 2 week administration and no sooner than 26 days during the every 4 week administration.

Nivolumab/Placebo Dose Administration
Nivolumab/placebo 240 mg is given intravenously every 2 weeks for 16 weeks then dosed 480 mg every 4 weeks for 36 weeks for a total of 52 weeks (1 year).
For both the 240 mg and the 480 mg doses, nivolumab/placebo is to be administered as a 30-minute IV infusion and diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

Patients may be dosed no less than 12 days from the previous dose of drug; and dosed up to 3 days after the scheduled date if necessary.

There will be no dose modifications for nivolumab/placebo

See Section 6.0 for nivolumab/placebo dose delay and management

5.2 Radiation Therapy

Protocol treatment must begin within 14 days after Step 1 registration.

Note: All participating institutions will be credentialed for lung photons 3DCRT or IMRT prior to registering patients to the study.

For detailed information on the specific technology requirement required for this study, please refer to the study specific guide on the RTOG Foundation 3505 protocol page of the RTOG website, www.rtog.org

Protocol treatment will be scored according to the Compliance Criteria table in Section 5.2.8.

It is recommended that radiation therapy be delivered after chemotherapy per Section 5. Day 1 of radiotherapy must be Monday, Tuesday, or Wednesday, but no later in the week.

5.2.1 Treatment Technology

This protocol requires the use of photons delivered either using 3D-CRT or IMRT techniques. Tomotherapy is allowed if appropriately credentialed for its use. Use of CyberKnife is not permitted for this trial.

The use of IGRT is highly encouraged but not required. No margin reduction will be allowed whether IGRT is used or not, and separate IGRT credentialing will not be required.

Institutions must complete the pre-registration credentialing requirements before registering patients on this study.

5.2.2 Immobilization and Simulation

Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices.

Simulation Imaging

Contiguous CT slices of maximum 3 mm slice thickness should be obtained starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume. I.V. contrast-enhanced CT- simulation is recommended but not required in this study.

CTs and PET/CTs should be used to guide tumor and normal organ volume definition. In the event that contrast-enhanced datasets are used for treatment planning, the density of the contrast should be overridden to a representative background electron density.

Motion Management Technique

Motion management is highly recommended for this protocol. In instances in which motion management is not possible, larger expansion volumes will be used to adequately cover the motion-related uncertainties. The types of motion management allowed on this study are 4DCT with ITV, active breath-hold, gated treatment, and abdominal compression. IMRT will be restricted to patients with less than 1cm of tumor motion on 4D imaging or utilizing of gating, ABC, or breath hold methods. Abdominal compression as a method of minimizing respiratory motion is allowed.

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

A whole-body FDG-PET/CT and an IV contrast enhanced CT scan or MRI exam (if CT scan with contrast is medically contraindicated, when MR of the chest is submitted, a non-contrast chest CT should also be submitted) of the lung and upper abdomen through the adrenal glands are required within 60 days prior to registration. These exams will be used for disease staging and to assist in volume delineation in all eligible patients (see Section 4.0).

The ACR Imaging Core Lab group will collect the pre-chemoradiation treatment FDG-PET/CT and dedicated contrast enhanced chest CT. ACR Imaging Core Lab will also collect all mandated follow-up CT (and/or MRI) scans of the chest and upper abdomen post-treatment, at the time of progression, and at the time point immediately prior to progression. See Section 8.2.1 for digital data imaging submission details. If FDG-PET/CT is obtained at any of the above time points including at time of progression, this should be should be submitted as well.

ACR Imaging Core Lab also will be involved in the analysis of submitted imaging data as part of the confirmation of local progression review and central review of radiographic response/recurrence.

5.2.4 Accounting for Tumor Motion Approaches and Internal and Setup Margins

Internal margin (IM): The IM used will be dictated by the motion management decision made at time of simulation. It is required for all cases, with the exception of instances in which simulation is done with 4DCT to develop a MIP of tumor volume (see number 4 below).

1. If the simulation is done with a free-breathing CT only, the IM will be 1 cm in the superior- inferior direction and 0.5 cm in the axial direction.

2. If simulation is done with abdominal compression, the IM will be 0.7 cm in the superior-inferior direction and 0.5 cm in the axial direction.

3. If simulation is done using an active breath-hold or gated breathing technique, the IM will be 0.5 cm in all directions.

4. If simulation is done using a 4DCT to develop a maximum intensity projection of the tumor volume based on the entire tumor motion, no IM is needed. **(This is the encouraged and preferred method)**

Setup Margin (SM): The SM will be 0.5 cm in all directions. No margin reduction will be allowed, even when using IGRT. The final PTV is constructed by expanding the just ITV or sum of the CTV + IM by the SM based on the definitions from Table A or B in section 5.2.5.

5.2.5 Definition of Target Volumes and Margins

All structures must be labeled for digital RT data submission as listed in the table below. Capital letters, spacing and use of underscores must be applied exactly as indicated. Resubmission of data may be required if labeling of structures does not conform to the DICOM standard name listed.

The structures marked as "Required" in the table must be contoured and submitted with the treatment plan.

There are two tables below. The first table applies to patients being treated using method 1, 2, or 3 from section 5.2.4. The second table applies only to patients being treated with method 4 of section 5.2.4 (4DCT with maximum intensity projection of the tumor volume based on the entire tumor motion)

Contouring of the ITV_6000 is necessary only when the ITV approach is used.

TABLE A: FREE BREATHING / ABDOMINAL COMPRESSION / ACTIVE BREATH HOLD / GATING MOTION MANAGEMENT TECHNIQUES

DICOM Standard Name	Description	Detailed Specification
GTV_6000	GTV to receive 60 Gy **Required for free breathing, active breath hold or gating motion management techniques**	The primary tumor and clinically positive lymph nodes seen on the planning CT (> 1cm short axis diameter) and pre-treatment PET scan (SUV > 3) will constitute the GTV. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged. An ITV is defined at this point as the enveloping GTV motion over the course of a respiratory cycle.

CTV_6000	CTV to receive 60 Gy **Required**	The CTV is defined to be the GTV plus a 0.5 cm margin to account for microscopic tumor extension. If an ITV is used then a 0.5 cm margin is added to the ITV to form a CTV. The CTV should be adjusted to not expand into other organs such as esophagus, major blood vessels, or bone.
PTV_6000	PTV to receive 60 Gy **Required**	The PTV will be equal to the CTV+IM+SM. IM and SM are defined in Section 5.2.4 above. In cases in which the PTV expansion extends outside of the skin, towards the spinal cord or into the spinal canal, it can be assumed that tumor motion will not occur in this direction, and the PTV margin in this direction can be limited. PTV margin can be limited up to 0.5 cm towards this particular dimension (skin or spinal cord).

TABLE B: 4D CT WITH MAXIMAL INTENSITY TUMOR VOLUME TECHNIQUE (PREFERRED METHOD)

DICOM Standard Name	Description	Detailed Specification
iGTV_6000	Defined as the enveloping GTV motion over the course of the entire respiratory cycle **Required** when a 4DCT is used to encapsulate entire breathing cycle volume	The primary tumor and clinically positive lymph nodes seen on the planning CT (> 1 cm short axis diameter) and pre-treatment PET scan (SUV > 3) over the course of a respiratory cycle. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged.
ITV_6000	ITV to receive 60 Gy **Required** when iGTV is drawn	The ITV will be equal to the iGTV plus a 0.5 cm clinical margin as appropriate to account for microscopic tumor extension.

PTV_6000	PTV to receive 60 Gy **Required**	The PTV will be equal to the ITV+SM. SM is defined in Section 5.2.4 above. In cases in which the PTV expansion extends outside of the skin, towards the spinal cord or into the spinal canal, it can be assumed that tumor motion will not occur in this direction, and the PTV margin in this direction can be limited. PTV margin can be limited up to 0.5 cm towards this particular dimension (skin or spinal cord).

5.2.6 Definition of Critical Structures and Margins

Note: All required structures must be labeled for digital RT data submission exactly as listed in the first column of the table below. Capital letters and spacing must be used exactly as indicated. Resubmission of data may be required if labeling of structures does not conform to the DICOM Standard Name listed.

DICOM Standard Name	**Description**	**Detailed Specification**	
SpineCanal	Spinal Canal **Required**	Boundaries: The bony limits of the spinal canal	
		Cranial	Top of C1 (or first CT slice)
		Caudal	Bottom of L2 (or last slice of CT)
Lungs	**Both Lungs minus GTV_6000 (or iGTV_6000)** **Required**	Boundaries: Use Lung OAR Atlas*	
		Other notes: Both lungs merged into 1 structure and excluding the overlap with GTV_6000/iGTV_6000	
Esophagus	**Required**	Boundaries: The esophagus contour should include the mucosa, submucosa, and all muscular layers out to the fatty adventitia. Cranial: Bottom of cricoid cartilage Caudal: GE junction	
BrachialPlexus	**Required for upper lobe tumors**	The ipsilateral brachial plexus should be contoured for upper lobe tumors	
Heart	**Required**	Cranial: Ascending Aorta Caudal: Apex	
External	**Required**	External contour of patient encompassing all internal organs on each slice	
NonPTV	**Required**	External (as described above) minus PTV	

*Investigators can access the Lung OAR Atlas at http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx

5.2.7 Dose Prescription

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priorities in Section 5.2.9 should be used during dose optimization. It is important to

remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here. Cases will be scored using the Compliance Criteria table.

Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Dose specification technique**
PTV_6000	60	2.0	30	Covering exactly 95% of PTV

5.2.8 Compliance Criteria

The compliance criteria listed below 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.

Target Volume Constraints and Compliance Criteria

Name of Structure	**Dosimetric parameter**	**Per Protocol**	**Variation Acceptable**
PTV_6000	$D_{95\%}$(Gy)	60	58.8 to 61.2Gy (excluding 60 Gy)
	*D_{min}(Gy)	≥ 57	≥54 Gy
	*D_{max}(Gy)	≤ 72	≤75 Gy

*** Dmin and Dmax values are for a volume of 0.03 cc.**

Normal Structure Constraints and Compliance Criteria

Name of Structure	**Dosimetric parameter**	**Per Protocol**	**Variation Acceptable**
SpineCanal	$D_{0.03cc}$(Gy) (max)	≤ 50	none
Lungs	V_{5Gy}(%)	≤ 65	≤ 70
	V_{20Gy}(%)	≤ 35	≤ 37
	D_{mean}(Gy)	≤ 20	≤ 22
Esophagus	V_{35Gy}(%)	≤ 50	≤ 55
	V_{70Gy}(%)	≤ 20	≤ 25
	D_{mean}(Gy)	≤ 34	≤ 37
BrachialPlexus	D_{max}(Gy)	≤63	≤ 66
Heart	V_{30Gy}(%)	≤ 50	≤ 55
	V_{45Gy}(%)	≤ 35	≤ 40
	$D_{0.03cc}$(Gy) (max)	≤ 70 Gy	≤ 75 Gy **

***The Variation Acceptable category extends the Per Protocol category numbers to allow**

for more challenging treatment planning problems. The Variation Acceptable range does not include the Per Protocol values. Plans will be scored as Deviation Unacceptable when Per Protocol and Variation Acceptable constraints are not met.
** When this value cannot be achieved, treatment plans must be modified to move dose distribution hotspots away from the heart to avoid having the case scored as a Deviation Unacceptable.

Delivery Compliance Criteria

	Per Protocol	Variation Acceptable
Start date (days after step 1 registration)	14 days	15-30 days
RT Elapsed Days	< 45 days	46-51 days
Interruptions (other than holidays or weekends)	0-2 days	3-7 days

Note: Cases will be scored as Deviation Unacceptable when the time limits given above are not met.

5.2.9 Treatment Planning Priorities and Instructions

Critical Structure and Target priorities are listed in order of decreasing importance:

SpineCanal
PTV
Lungs
Esophagus
Heart
BrachialPlexus

If lung dose constraints are exceeded, several solutions can be entertained:

- For 3D-CRT: Increase the weighting of AP/PA treatments by 1, and reduce the obliques. This can be done as long as the cord dose, which takes precedence, is not exceeded.
- For 3D-CRT or IMRT: Reduce the CTV to the minimum range suggested above and/or reduce the PTV by choosing another motion management option with smaller internal margins.

It is recommended that the esophagus not be circumferentially irradiated with > 60 Gy (i.e. the 60 Gy isodose line should not encompass the entire axial cross-section of the esophagus at any level).

5.2.10 Dose Calculations

Required algorithms

Acceptable choices of algorithm are listed at http://irochouston.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf. Any algorithm used for this study must be credentialed by MD Anderson Dosimetry Lab.

Primary dataset for dose calculation

The primary dataset for dose calculation must be a free-breathing CT that was

acquired along with 4DCT, an average intensity pixel CT (AveIP) generated from the 4DCT, the breath- hold/gated CT, or the free-breathing CT acquired with no other motion management. Maximum Intensity Pixel (MIP) generated images from 4DCTs may not be used as the primary dose calculation dataset.

Dose matrix resolution

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

5.2.11 Patient-Specific QA

Any patient-specific QA that needs to be acquired should follow institutional guidelines.

5.2.12 Daily Treatment Localization/IGRT

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

A reliable method of daily image guidance will be utilized. This can include but is not limited to daily conebeam imaging, fiducial marker tracking systems, kV – kV matching. Daily conebeam imaging aligned to the tumor and soft-tissue anatomy is considered the preferred approach.

5.2.13 R.T. Quality Assurance Reviews

The Radiation Oncology Principal Investigator, James Urbanic, MD, and appointed delegates will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at ACR Core Laboratory/ RTQA. Dr Urbanic and delegates will perform additional reviews after complete data for the next 20 cases enrolled has been received at ACR Core Laboratory/ RTQA. This pattern will occur throughout the study accrual period. These 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 ACR Core Laboratory/ RTQA, whichever occurs first.

5.2.14 Radiation Therapy Adverse Events

Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy.

Cardiac Toxicity

Radiation-induced myocarditis rarely occurs at doses lower than 50 Gy.

Neurologic Toxicity

Radiation-induced transverse myelitis rarely occurs at doses lower than 50 Gy.

Esophagitis

Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous Xylocaine, Carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required.

It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may

persist for 4-6 weeks. If Grade 4 (CTCAE, v. 4) esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to ≤ 3 treatment days. Patients requiring hospitalization because of esophagitis may have their treatment interrupted.

Pulmonary Toxicity

Pneumonitis is possible in the later weeks of chemoradiotherapy and during the weeks that follow. In general, pneumonitis is a diagnosis of exclusion and is treated with a combination of corticosteroids and supportive care at the discretion of the treating physician. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving ≥ 20 Gy, usually within the first 6 months after initiation of treatment. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 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.
Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Steroids are also permitted for the prevention/treatment of nausea/vomiting during chemoradiation and are permitted, as indicated, for treatment of toxicities such as radiation pneumonitis.

Other permitted supportive/ancillary medications include but are not limited to the following:

- Anticonvulsants
- Antiemetics
- Anticoagulants
- Antidiarrheals
- Analgesics
- Hematopoietic Growth Factors
- Nutritional supplementation
- Highly active antiretroviral therapy (HAART)

5.3.2 Prohibited Therapies

The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in above *Permitted Therapy for Nivolumab)*
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of NSCLC
- Myeloid growth factors

5.3.3 Participation in Other Trials

Patients may not participate in other clinical trials that are intended to treat the diagnosed lung cancer or intended to reduce toxicity of therapy.

5.4 Emergency Unblinding Procedure

The decision to break the unblinding code must be based on an extraordinary clinical circumstance for which knowledge of drug assignment will affect clinical judgment.

Sites can call RTOG Foundation Headquarters during business hours (8:30 AM to 5 PM ET), at 215-574-3150 and ask to speak to the Supporting Study Statistician. For after hours, weekends, and holidays, call 215-459-3576.

5.5 Duration of Therapy

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

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- 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.
- Sponsor discontinuation of study

6. TREATMENT MODIFICATIONS/MANAGEMENT

There are no dose modifications for nivolumab/placebo. Instead, the dose will be delayed or discontinued as specified below

6.1 Chemoradiotherapy Dose Modifications

Key to the successful and safe administration of nivolumab/placebo will be close monitoring of toxicities arising from the antecedent concurrent chemoradiation. Treatment modifications for in-field toxicities will be as follows:

Toxicity	CTCAE grade	XRT	Cisplatin	Etoposide
Esophagus/pharynx	4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Esophagus/pharynx	3	No change or hold ≤ 5 days	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Esophagus/pharynx	2	No change	No change	No change
Pulmonary	4	Discontinue	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Pulmonary	3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Skin	4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Skin	3	No change	No change	No change

Radiation therapy is held for neutropenia (ANC < 500/mcl); radiation therapy may be restarted when the ANC ≥ 500/mcl.

If treatment is interrupted ≥ 3 weeks for pneumonitis discontinue all protocol therapy

6.2 Cisplatin and Etoposide Dose Modifications

Concurrent chemoradiotherapy consists of a single, 8 week treatment course.
The grades of adverse events below refer to CTCAE, v. 4.

Cisplatin (50 mg/m^2) is administered intravenously on days 1 and 8, and days 29 and 36 of concurrent chemoradiation. Etoposide (50 mg/m^2) is administered intravenously on days 1-5 and days 29-33 of concurrent chemoradiation.

If cisplatin and/or etoposide are held for greater than 2 consecutive weeks, the drugs will be held permanently for the duration of concurrent therapy.

The following dose levels are used for dose modifications during both the concurrent chemoradiation phase. There will be no dose reduction below level -1.

Dose Level	Cisplatin	Etoposide
0	50 mg/m^2	50 mg/m^2
-1	40 mg/m^2	40 mg/m^2

Hematologic Toxicity

Dose modification on Day 1 and Day 29 during concurrent chemoradiation

ANC		Platelet	Cisplatin and Etoposide Dose
≥ 1,500/mcl	and	≥ 100,000/mcl	Continue w/ previous dose
< 1,500/mcl	or	< 100,000/mcl	Hold*

*Check weekly and resume therapy at previous dose (no dose reduction) when counts recover to ANC ≥ 1,500 and platelets ≥ 100,000/mcl.

Febrile neutropenia occurring during chemoradiation will result in a decrease of the cisplatin and etoposide dose level by –1. Febrile neutropenia occurring despite dose reduction during chemoradiation will result in discontinuation of chemotherapy. Radiation therapy is held for neutropenia (ANC < 500/mcl); radiation therapy may be restarted when the ANC ≥ 500/mcl.

The use of myeloid growth factors **will be prohibited** during the entire treatment due to potential interaction with concurrent or previous RT.

Renal Toxicity

Dose modification on Day 1 and Day 29 of cisplatin and etoposide:

CrCl < 50 ml/min	Hold therapy. Administer fluids and repeat creatinine in one week.

If after one week CrCl ≥ 50 ml/min	Administer both cisplatin and etoposide at full dose, but increase pre- and post-cisplatin hydration.
If after one week CrCl < 50 ml/min	Discontinue chemotherapy.

Day 8 and Day 36 cisplatin modifications

- Omit cisplatin if grade 4 neutropenia on day 8 or day 36; no modification for grades 1-3 myelotoxicity
- Omit cisplatin if patient develops ≥ Grade 2 renal toxicity, Grade 4 esophagitis, or febrile neutropenia
- If cisplatin omitted on day 8, it should not be given again until day 29; if cisplatin omitted on day 36, it should not be given again

Hepatic Toxicity

Give the following doses for etoposide only:

Bilirubin	**Etoposide**
< 1.5 mg/dl	Same dose level
1.5 -3.0 mg/dl	↓ 1 dose level
≥ 3.0 mg/dl	Hold*

*Hold until <3.0 mg/dl then resume with one level dose reduction

Gastrointestinal Toxicity

Nausea/Vomiting: For ≥ grade 3 nausea or vomiting despite maximum antiemetics, decrease cisplatin by one dose level for the next dose. If nausea and vomiting improve, cisplatin dose should be re-escalated to the previous dose, if possible.

Neurotoxicity (Peripheral)

Cisplatin doses should be modified for neurologic toxicity (see below). Serum magnesium and calcium levels should be checked; vitamin B12 levels may need to be evaluated especially in older patients.

Grade 1: Give cisplatin at full dose.

Grade ≥ 2: Hold cisplatin until neurotoxicity resolves to ≤ grade 1, then resume with one dose level reduction. Continue treatment with etoposide. If cisplatin is held for ≥ 21 days, discontinue cisplatin.

Ototoxicity: Discontinue cisplatin for ≥ grade 3 ototoxicity.

Hypomagnesemia and Hypokalemia: is not an indication for stopping therapy. Oral and parenteral supplementation is indication for serum levels < LLN.

All Other Treatment-Related Toxicities that Exceed grade 2: (except alopecia, nausea, vomiting, fatigue and anorexia, and grade 3 myelosuppression on days 8 and 36), hold cisplatin and etoposide until the toxicities have resolved to grade 2 or less and resume cisplatin and etoposide with one dose level reduction.

6.3 Nivolumab/Placebo Dose Modifications

There are no nivolumab/placebo dose modifications. Depending on toxicities, nivolumab/placebo is either given at full dose, withheld, or discontinued.

6.3.1 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, and Neurological. See the nivolumab Investigator Brochure for the treatment algorithms.

Early recognition and intervention are recommended according to the management algorithms found in the Investigator Brochure. In addition, the Investigator Brochure (IB) includes ophthalmologic evaluations for any visual symptoms in order to evaluate for nivolumab related uveitis. Investigators should follow the algorithms for immune-related events.

Note: The algorithms are essential guides for AE management, but the guidance provided in these algorithms should not replace the investigator's medical judgment but should complement it.

For patients expected who require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider the following recommendations:

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.
- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.
- In patients who develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Additional details on the safety of nivolumab, including results from clinical studies, are available in the IB.

6.3.2 Dose Delay Criteria

Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories. [see the nivolumab Investigator Brochure]

Nivolumab/placebo administration should be delayed for CTCAE, v. 4 toxicities as indicated in the management algorithms that in the opinion of the treating physician are **related to the study drug**. Nivolumab/placebo administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event

- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
    - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the principal investigator for Grade 3 amylase or lipase abnormalities.
    - If a patient has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
    - If a patient has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

6.3.3 Criteria to Resume Treatment

Patients may resume treatment with nivolumab/placebo when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue
- Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

If the criteria to resume treatment are met, the patient should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes. Cycle number is to be counted continuously (without skipping numbers) in case the nivolumab/placebo dose is delayed or interrupted.

If treatment is delayed > 6 weeks the subject must be permanently discontinued from study therapy, except as specified in discontinuation section.

For patients treated with corticosteroids:
Grade 2 events must resolve to ≤ Grade 1 before considering retreatment.

All patients treated with steroids for grade ≥2 drug related immune mediated adverse events should have nivolumab/placebo held until resolution to ≤ Grade 1 for at least 2 weeks following complete removal from steroid treatment except for maintenance replacement doses for adrenal insufficiency (preferably no greater than 10mg prednisone

equivalent daily).

All patients treated with steroids for grade ≥3 events should have nivolumab/placebo discontinued. Patients with grade 3 thyroiditis and skin rash may continue therapy as for grade 2 events with resolution and stable replacement treatment.

Patients with hepatitis, pancreatitis, pneumonitis, and colitis are at risk for exacerbation with retreatment if there is residual inflammation and should resolve to Grade 0 or baseline before retreatment. Baseline can mean the initial grade *i.e.* grade <2 where permitted on study.

Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses only of corticosteroids.

Please note that grading 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.

New immune-related events or exacerbation of existing events during steroid treatment or taper suggest the presence of ongoing immune activation and should require permanent discontinuation of nivolumab.

A patient who is treated with steroids, evaluated, and found to not have an autoimmune or inflammatory event requiring steroid treatment, may be restarted if asymptomatic off steroids for 2 weeks and other restarting criteria are met.

6.3.4 Discontinuation Criteria

Treatment should be permanently discontinued for the following:

- 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
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reactions, and infusion reactions
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below
- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation

- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 8 x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a patient with a dosing interruption lasting > 6 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a patient with a dosing interruption lasting > 6 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued nivolumab/placebo dosing

6.3.5 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Patients will be permitted to continue treatment beyond initial RECIST 1.1 defined progressive disease (PD) as long as the following criteria are met:

1. Investigator-assessed clinical benefit and do not have rapid disease progression
2. Tolerance of study drug
3. Stable performance status
4. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression
5. Patient provides written informed consent prior to receiving additional nivolumab/placebo treatment, using the ICF addendum describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The decision to continue treatment beyond initial progression should be discussed with the Principal Investigator and documented in the study records. A radiographic assessment/ scan should be performed within 4-6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. If PD is not confirmed on the 4-6 week

imaging after initial progression, the patient should then revert to imaging on the 12 week cycle with the timing to start from the scan of initial disease progression. The assessment of clinical benefit should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab. If the investigator feels that the patient continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the assessment schedule.

Further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions and/ or the development of new measurable lesions. Treatment should be discontinued permanently upon documentation of further disease progression.

Patients with global deterioration of health status who require discontinuation of treatment without objective evidence of disease progression at the time of treatment discontinuation should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression (i.e. radiographic confirmation) even after discontinuation of treatment.

6.3.6 Treatment of Nivolumab/Placebo-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, 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 v. 4.0 guidelines.

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

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor the patient until recovery from symptoms. 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/placebo administrations.

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]; prophylactic medications indicated for 24 hours).

Stop the nivolumab/placebo infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg; 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 the patient closely. If symptoms recur then no further nivolumab/placebo will be administered at that visit. 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/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab/placebo 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: 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: life threatening; vasopressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab/placebo. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend 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. The patient should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab/placebo will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor the patient until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agent administered in RTOG 3505 is being made available under an IND sponsored by RTOG Foundation and distributed by a third party drug distributor. The placebo will be prepared by an unblinded pharmacist on site. For nivolumab/placebo, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.4 of the protocol.

Commercial Agents

The commercial agents in RTOG 3505 are cisplatin and etoposide.

7.1.1 Adverse Events for Investigational Study Agents

Investigators must obtain the current version of the BMS-936558 (nivolumab) Investigator Brochure (IB) for comprehensive pharmacologic and safety information. The IB can be accessed on the RTOG Foundation 3505 protocol page of the RTOG website, www.rtog.org. Sites must use their username and password to access the protocol page and the IB.

7.1.2 Adverse Events for Commercial Study Agents

Refer to the package insert for detailed pharmacologic and safety information

7.2 Adverse Events (AEs)

This study will use the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

7.2.1 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.

AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 13).

All nonserious adverse events (not only those deemed treatment-related) are to be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF.

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page and SAE Report Form if they meet seriousness criteria:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

Definition of Immune-Mediated Adverse Events (IMAES)

IMAEs include events, regardless of causality, occurring within 100 days of the last dose. IMAEs are specific events (that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine [adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis]) for which patients received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism,

hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression. The table below provides a summary of the IMAEs category and their respective preferred terms.

Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions	
IMAE Category	**PTs included under IMAE Category**
Pneumonitis	Pneumonitis, Interstitial lung disease
Diarrhea/Colitis	Diarrhea, Colitis, Enterocolitis
Hepatitis	Hepatotoxicity, Hepatitis, Hepatitis acute, Autoimmune hepatitis, AST increased, ALT increased, Bilirubin increased, ALP increased
Adrenal insufficiency	Adrenal insufficiency
Hypothyroidism/Thyroiditis	Hypothyroidism, Thyroiditis Thyroiditis acute (collapsed with thyroiditis for frequency), Autoimmune thyroiditis (collapsed with thyroiditis for frequency)
Hyperthyroidism	Hyperthyroidism
Hypophysitis	Hypophysitis
Diabetes mellitus	Diabetes mellitus, Diabetic ketoacidosis
Nephritis and renal dysfunction	Nephritis, Nephritis allergic, Tubulointerstitial nephritis, Acute renal failure, Renal failure, Increased creatinine
Rash	Rash, Rash maculopapular

NOTE: If the event is a Serious Adverse Event (SAE) (see next section), further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.3 Serious Adverse Events (SAEs)

Serious Adverse Events that meet expedited reporting criteria defined in the table below will be reported via the SAE report form in RAVE. SAEs that require 24h notification are defined in the expedited reporting table.

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Other serious/important medical events;

- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

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

7.4 Serious Adverse Event (SAE) Reporting Requirements

It is the responsibility of the investigator to document all adverse events which occur during the study. All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the RTOG SAE Report Form in RAVE. RTOG will report SAEs to Bristol-Myers Squibb within 24 hours of awareness. RTOG will report unexpected and related SAEs to the FDA and Bristol-Myers Squibb via the MedWatch Form per the requirements set forth in the Code of Federal Regulations, Section 312.32.

7.4.1 Reporting SAEs

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. **All SAEs must be reported per the reporting table below that occur from time of consent and within 100 days of the last dose of study drug.** Subjects who are randomized and never receive treatment must have SAEs collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

The SAE report should comprise a full written summary, detailing relevant aspects of the SAE in question. The SAE summary also must include the investigator's assessment of relatedness to all components of protocol treatment. Amend the SAE report with follow-up information, when it becomes available. In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to RTOG Operations Office by phone, 215-574-3191. An electronic report must be submitted immediately upon re-establish of the Internet connection.

SAEs that occur during the follow-up period beginning 100 days after end of treatment and are considered by the investigator to be related to protocol treatment must be reported expeditiously via the SAE Report Form.

All SAEs must be reported in RAVE within the designated timeframe outlined in the reporting table below. RTOG will complete a preliminary review of the SAE details and will contact the site with queries, as applicable. RTOG will report the SAE to Bristol-Myers Squibb within 24 hours of notification of the event. RTOG will report to the FDA per 21 CFR 312.

Pregnancy

Patients who become pregnant during the study should discontinue the study immediately. Investigators should report a pregnancy, including a male participant's impregnation of his partner, expeditiously as a grade 3 SAE coded in the CTCAE v.4 as "pregnancy, puerperium and perinatal conditions, other—pregnancy" on the SAE report form (in RAVE) and submit the Pregnancy Report Form in Rave within 14 days of notification. RTOG will report the pregnancy to Bristol-Myers Squibb within 24 hours of notification of the event. Patients should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant, including a male participant's impregnation of his partner, either during the treatment phase of the study or within 100 calendar days after the end of treatment. The pregnancy outcome for patients on study should be reported to RTOG. RTOG will report the status to Bristol-Myers Squibb.

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 RTOG via the SAE Report Form 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 the SAE Report Form within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of protocol treatment and are related to protocol treatment 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

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur within 100 Days of the Last Administration of the Investigational Agent/Intervention [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 RTOG via the SAE Report Form within the timeframes detailed in the table below.

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via the SAE Report Form 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 100 days after the last administration of investigational agent/intervention and are considered related to protocol treatment require reporting as follows:

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

- Grade 3 adverse events

Specific Protocol Inclusions and Exceptions to Expedited Reporting:

Hemophagocytic lymphohistiocytosis is an ***inclusion*** to expedited reporting. Hemophagocytic lymphohistiocytosis is a rare but potentially fatal disease of normal but overactive histiocytes and lymphocytes. It is a manifestation of cytokine release syndrome. Occurring at any grade, hemophagocytic lymphohistiocytosis must be reported in an expedited manner as a serious adverse event.

8. REGISTRATION AND STUDY ENTRY PROCEDURES

8.1 Regulatory Requirements

Please refer to the study-specific guide for investigators and research staff for detailed procedures regarding the following: requirements for regulatory collection and RT credentialing. The RTOG Foundation 3505 Study Guide is posted on the RTOG website https://www.rtog.org/clinicaltrials/rtogfoundationstudies/rtogfoundationstudy3505.aspx .

8.2 RT Registration Requirements

For detailed information on the specific technology requirement required for this study, please refer to the study specific guide on the RTOG Foundation 3505 protocol page of the RTOG website, www.rtog.org.

8.2.1 Pre-Registration Credentialing Requirements for IMRT/3DCRT

See the study-specific guide on the RTOG Foundation 3505 protocol page of the RTOG website, www.rtog.org, for details of RT pre-registration credentialing requirements for IMRT/3DCRT.

8.2.2 Pre-Registration Requirements for TRIAD Installation

See the study-specific guide on the RTOG Foundation 3505 protocol page of the RTOG website, www.rtog.org, for details on TRIAD installation requirements needed prior to patient enrollment.

8.3 Patient Enrollment

See the study-specific guide on the RTOG Foundation 3505 protocol page of the RTOG website, www.rtog.org**.**

9.0 DRUG INFORMATION

9.1 Investigational Study Agent

Nivolumab, IND # 130197

To supplement the toxicity information contained in this document, investigators must obtain the current version of the BMS-936558 (nivolumab) Investigator Brochure (IB) for comprehensive pharmacologic and safety information. Also see Appendix I.

The IB can be accessed on the RTOG Foundation 3505 protocol page of the RTOG website, www.rtog.org. Sites must use their username and password to access the protocol page and the IB.

Table	Product Description				
Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Secondary Packaging (Qty) /Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab BMS-936558-01 Solution for Injection*	100 mg/vial (10 mg/mL)	Carton of 5 or 10 vials	10cc Type 1 flint glass vial	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8 degreesC. Protect from light, freezing, and shaking

*Nivolumab/placebo may be labeled as BMS-936558-01 Solution for Injection

0.9% Sodium Chloride Injection solution is to be used as nivolumab/placebo. Placebo (0.9% Sodium Chloride Injection) and diluent solutions (0.9% sodium chloride injection, 5% dextrose injection) should also be sourced by investigative sites if available and permitted by local regulations.

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to Appendix I and the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions"

9.1.1 Drug Ordering and Accountability

Bristol-Myers Squibb will supply Nivolumab free of charge to patients on study in the U.S. and Canada. An on-site unblinded pharmacist will be responsible for mixing placebo per instructions provided in Appendix I. The drug will be distributed by a third party vendor under contract to RTOG Foundation. Drug accountability records must be maintained at all sites according to good clinical practices.

See the study-specific guide on the RTOG Foundation 3505 protocol page of the RTOG website, www.rtog.org , for details of drug shipment.

9.2 Commercial Agent

Cisplatin and Etoposide

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.2.1 Availability/Supply

Please see Section 5 for administration instructions. 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.

10. PATHOLOGY/BIOSPECIMENS

10.1 Tissue/Specimen Submission

In this study, it is **required** that tissue be submitted to the Biospecimen Bank at UCSF for PD-L1 expression analysis for all patients. It is highly recommended (but optional for the patient) that if any tissue remains after analysis, it will be stored at the Biospecimen Bank at UCSF for future research.

In addition, it is highly recommended (but optional for the patient) that serum and peripheral blood specimens be submitted for the two tests described in Section 10.3, Peripheral blood for phenotyping the lymphocytes and serum for banking at UCSF for future translational research.

Tissue from a biopsy or surgical specimen will be obtained from formalin fixed and paraffin embedded (FFPE) in tissue blocks. Sites must verify that an archived tumor block is available prior to Step 1 registration to the trial although the actual submission can be immediately after Step 1 registration but at least 5 weeks prior to Registration Step 2. Institutions must ship FFPE tissue as outlined in Section 10.2 to the Biospecimen Bank at UCSF by overnight courier.

As noted in section 3.2.15, we recognize the difficulty in submitting tissue from stage 3 lung cancer patients in which the total available tissue may be small. We have designed three possibilities:

Preferred: H&E slide and archived tissue tumor block. If sites wish the block to be returned they may submit the block and the Biospecimen Bank will cut the unstained for the required study and then punch and return the block.

Alternative: If an archived tumor block sample cannot be shipped for this study, then two 3mm punches from the core needle biopsy blocks may alternatively be provided for analysis in addition to the H&E slide.

Minimum: One (1) H&E stained slide (required) and five (5) positively charged unstained slides cut at 3-4 microns from the same block as the H&E. Unstained slides must be stored at 4C same day as being cut and shipped with a cold pack at 4C within 5 business days after being cut. The date that the unstained slides were cut must be noted on the ST form. Do NOT store or ship unstained slides at room temperature as they will not be able to be used for the mandatory testing. Please pack slides well to avoid breakage. If any slides are received broken the site must resubmit additional slides before the biobank can send for mandatory PDL1 testing.

Ship FFPE biospecimens for mandatory central review and whole blood and serum samples for banking to:
(do NOT ship fresh peripheral blood to this address)
Biospecimen Bank at UCSF
2340 Sutter Street, Room S341
San Francisco, CA 94115

415-476-7864; RTOG@ucsf.edu

Ship all fresh peripheral blood in heparin tubes to:
Hooper Laboratory
Attn.: Rhonda Kean (laboratory manager) or Craig Hooper, PhD
JAH 454
1020 Locust Street
Philadelphia, PA 19107
Phone: 215-503-1559

See the tables below for mandatory and optional specimen collection.

See further details of specimen collection/processing/shipping on the RTOG web site, http://www.rtog.org/LinkClick.aspx?fileticket=1SFlEVxSui4%3d&tabid=281.

10.2 Mandatory Studies

Mandatory Study: Tumor PD-L1 Expression for All Patients

Specimens are being collected to determine if patients with PD-L1 positive tumors will have an improved PFS when treated with nivolumab in comparison to patients with PD-L1 negative tumors (see Section 2.7 for further details).

- Required Form: ST form and Pathology report- must have all PHI redacted except date of procedure and pathology accession number.
- Shipping costs: Paid for by sites. Return labels are provided for frozen biospecimens only. International sites are encouraged to have a Fed Ex Customs Broker to help with any custom issues.
- At least 5 weeks prior to Registration Step 2.
- H&E slide and residual FFPE material will remain at the bank for all patients who consent to banking. Blocks can be returned upon request but will be punched prior to returning.

Ship specimens to:
Biospecimen Bank at UCSF
2340 Sutter Street, Room S341
San Francisco, CA 94115

For questions, contact:
Biospecimen Bank at UCSF; RTOG@ucsf.edu; 415-476-7864/FAX 415-476-5271

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide (must match the block being submitted). Can be a duplicate cut	Slide shipped ambient to the Biospecimen Bank

		slide, does not have to be the diagnostic slide.	
A corresponding paraffin embedded tissue block, OR two 3mm embedded punches of the primary tumor OR 5 unstained slides as specified in section 10.1	Pre-treatment	Paraffin-embedded tissue block or punch biopsies from the block. If embedded punches are submitted the H&E from the punch block must also be submitted. If 5 unstained slides are being provided instead of the block they must be stored at 4°C and shipped at 4°C within 5 business days after being cut. The date that the slides were cut must be noted on the ST form. See Section 10.1 for details.	Block or punches shipped ambient (ship with a cold pack during warm weather) to the Biospecimen Bank. NOTE: Unstained slides must be shipped with cold pack by overnight courier. Pack slides well to avoid breakage, If slides are received broken this will delay testing and site will have to resubmit the slides.

10.3 Optional Specimen Collection for RTOG 3505 Research and Banking

Optional Study #1: SNP analyses and Serum for immune phenotype
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 in the protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent. Specimens are being collected to determine immune phenotype, and co-stimulatory/co-inhibitory receptors with clinical response. • Required Form: ST form • Biospecimen Kits: Available from the Biospecimen Bank at UCSF. • Shipping days for frozen specimens: Monday-Wednesday (U.S. sites); Monday-Tuesday (Canada and Non-North American). • Shipping costs: Return labels are provided for peripheral blood or frozen biospecimens only. Batch shipping is encouraged for all sites with access to a -70°C to -90° Freezer. Canada and International sites will be required to have access to a -70°C to -90°Freezer to batch ship samples and may have to provide

their own outer shipping containers. International sites are encouraged to have a Fed Ex Customs Broker to help with any custom issues.

Ship specimens to:
Biospecimen Bank at UCSF
2340 Sutter Street, Room S341
San Francisco, CA 94115

For questions, contact:
Biospecimen Bank at UCSF; RTOG@ucsf.edu; 415-476-7864/FAX 415-476-5271

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
Whole blood for DNA- collected in EDTA tube	**Pre-treatment only**	Invert tubes several times, then aliquot 1ml per aliquot into 1 ml cryovials (3-5 per tube drawn). Store at -70°C to -90° until shipped.	Sent frozen on dry ice via overnight carrier to the Biospecimen Bank Batch shipping of multiple cases in one shipment is encouraged.
Serum: One 5 mL red top (clot) tube	• Pre-treatment; • Post-chemoradiation/ before nivolumab/ placebo • 60days after nivolumab/placebo • at study discontinuation for either toxicity or progression	Serum centrifuged and aliquotted. Frozen serum samples containing minimum of 0.5mL per aliquot in 1 mL cryovials (5 per tube drawn). Samples should be frozen and stored at a -70°C to -90°; see Appendix III for processing instructions.	Serum sent frozen on dry ice via overnight carrier to the Biospecimen Bank Batch shipping of all time points or multiple cases in one shipment is encouraged.

Optional Study #2: Peripheral blood for immune phenotype
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 in the protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

Specimens are being collected to determine immune phenotype, and co-stimulatory/co-inhibitory receptors with clinical response.

- Required Form: Special Study specific ST form
- Shipping days: Sites should only draw blood samples on Monday-Wednesdays and only ship Monday-Thursdays.
- Shipping labels will be provided with kits for peripheral blood. Canada and International sites may have to provide their own outer shipping containers.
- Sites must notify Rhonda Kean at Rhonda.Kean@jefferson.edu when they are shipping these samples

Ship specimens to:
Hooper Laboratory
Attn.: Rhonda Kean (laboratory manager) or Craig Hooper, PhD
JAH 454
1020 Locust Street
Philadelphia, PA 19107

For questions, contact: 215-503-1559

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
Peripheral Blood Mononuclear Cells (PBMC) – 5 Green top (heparin) tubes	• Pre-treatment (day -14 to day 0) • After ChemoRT/before nivolumab/placebo • During nivolumab/placebo: Day 60 • at study discontinuation for either toxicity or progression	See Appendix IV for processing and shipping information	Ship fresh at room temperature overnight for morning delivery to the Hooper Laboratory. Ship Monday-Thursday

Optional Study #3: Tumor tissue for future research
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 in the protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent. • Required Form: ST form and Pathology report- must have all PHI redacted except date of procedure and pathology accession number • Shipping costs: Paid for by sites. Return labels are provided for frozen

biospecimens only. International sites are encouraged to have a Fed Ex Customs Broker to help with any custom issues.

Ship specimens to:
Biospecimen Bank at UCSF
2340 Sutter Street, Room S341
San Francisco, CA 94115

For questions, contact:
Biospecimen Bank at UCSF; RTOG@ucsf.edu; 415-476-7864/FAX 415-476-5271

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
Representative H&E stained slides of the primary tumor	At progression	H&E stained slide (must match the block being submitted)	Slide shipped ambient to the Biospecimen Bank
A corresponding paraffin-embedded tissue block or two 3 mm embedded punches of the primary tumor taken before initiation of treatment	At progression	Paraffin-embedded tissue block or punch biopsies from the block. If embedded punches are submitted the H&E from the punch block must also be submitted	Block or punches shipped ambient (ship with a cold pack during warm weather) to the Biospecimen Bank

11. SPECIAL STUDIES (NON-TISSUE)

11.1 Toxicity, Patient-Reported Outcomes (PROs), and Health-Related Quality of Life (QOL)

Objectives

- To characterize immune mediated toxicity from nivolumab following chemoradiation (CRT) for locally advanced NSCLC;
- To evaluate the effect of immune mediated toxicity from nivolumab following CRT on QOL and patient reported fatigue.

Hypotheses

The primary HRQOL endpoint will be to determine if 15-month QOL (from start of nivolumab/placebo) using the Functional Assessment of Cancer Therapy - Trial Outcome Index for lung cancer (FACT-TOI) is correlated with overall survival (OS). The hypothesis is that long-term QOL using FACT-TOI at 15-month (from start of nivolumab/placebo) will be superior in the CRT followed by nivolumab arm compared to the CRT followed by placebo arm as the addition of nivolumab is expected to improve tumor response to CRT and improve disease-related QOL.

Secondary exploratory objectives are:

- To compare patient reported fatigue using the PROMIS fatigue short form between the consolidative nivolumab arm compared to placebo. The hypothesis is that acute fatigue at 3 months (from start of nivolumab/placebo) will be greater in the nivolumab arm compared to the placebo arm but will not impact long-term QOL outcome at 15 months (from start of nivolumab/placebo).
- 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

Background

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, consolidative nivolumab/placebo will follow CRT. If the consolidative nivolumab arm shows superior OS compared to placebo, a new standard of care will be defined for locally advanced NSCLC, provided that the QOL and toxicity profiles are acceptable to the patient. Past efforts at treatment intensification such as concurrent chemotherapy cetuximab plus platinum-based CRT or induction chemotherapy regimens, have failed to improve survival yet have shown substantial increases in toxicity, unplanned treatment breaks or delays in therapy, all of which can lead to inferior QOL outcome and potential decreased efficacy, such that trials investigating further refinement of concurrent CRT regimens need to factor in QOL with toxicity outcome.

The effects of nivolumab immunotherapy following standard CRT in lung cancer on QOL are currently unknown. Hence, this study will provide a unique and critical opportunity to characterize the effects of this novel treatment on QOL. It is anticipated consolidative nivolumab will improve OS with minimal overlapping acute toxicities of nivolumab and CRT. 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 and PRO objective in this study is to measure functional, physical and lung cancer specific QOL in lung cancer patients using the change from baseline of FACT-TOI at 15 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 nivolumab/placebo, at 3, 6, 9 and 12 months during nivolumab/placebo treatment, and at 15 and 18 months from start of nivolumab/placebo.

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 and is available free of charge to institutions with the completion of an agreement to share data, accessible at http://www.facit.org/translation/licensure.aspx. 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.

Fatigue in NSCLC

Fatigue in lung cancer patients receiving consolidative nivolumab is caused by immune mediated effects combined with RT dose volume factors and chemotherapy toxicities.

In melanoma studies investigating nivolumab, the most common toxicity described is fatigue. Other toxicities include dermatologic toxicity, gastrointestinal, symptoms (diarrhea/colitis, decreased appetite). Rare immunologic mediated toxicities from immunotherapy including nivolumab and ipilumumab have been described and include pneumonitis and endocrinopathies (pituitary, hypothalamus, thyroid, and adrenal disease). These immune-mediated toxicities may present with nonspecific symptoms such as fatigue, headache, mental status changes, abdominal pain, change in bowel habits, or hypotension. In lung cancer, fatigue is one of the most common and distressing symptoms affecting up to 60% of patients. With concurrent chemoradiation, the majority of patients experience fatigue usually peaking during the first and second weeks after completion of CRT, which can remain higher than baseline in approximately half of patients long-term (Spratt 2012). Because approximately 25% of patients undergoing nivolumab monotherapy experience fatigue, the effect of consolidative nivolumab following CRT on patient-reported fatigue warrants study.

Hence an exploratory objective is to evaluate patient reported fatigue using the PROMIS fatigue short form in patients receiving nivolumab following chemoradiation for lung cancer.

PROMIS-Fatigue: A Novel Short Form Fatigue Scale

The National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) Roadmap initiative (www.nihpromis.org) was initiated. PROMIS is a 5-year cooperative group program of research designed to develop, validate, and standardize item banks to measure patient-reported outcomes (PROs) relevant across common medical conditions, including cancer [Cella, 2007; Garcia, 2007]. Integral to the work of this group, includes the creation of a PROMIS-derived fatigue short form (using limited questions to minimize patient burden) that was developed for ease of use in oncology populations. While the psychometric properties of this 7-question short fatigue scale have been validated in the general population [Garcia, 2007; Lai, 2008], validation in patients with cancer is ongoing. A "cross-walk" has been successfully developed between the PROMIS fatigue item bank and the PROMIS-Cancer fatigue item bank that produced the short form measure. These two item banks, sharing 54 common items, were linked by equating item parameters using items that held stable psychometric properties between the cancer and general population populations in which they were tested. Results showed that cancer patients reported more severe fatigue (1/3 standard deviation more severe, but the same scale characteristic curve slope) than the general population, which matches clinical expectations [Cella, 2008].

The PROMIS fatigue will be completed at baseline, prior to nivo/placebo, at 3, 6, 9 and 12 months during nivolumab/placebo treatment, and at 15 and 18 months from start of nivolumab/placebo.

Quality-adjusted Survival, EuroQol (EQ-5D-5L)

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. 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 nivolumab to chemoradiation 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 at the following time points:
baseline, prior to starting nivolumab/placebo phase, at 3, 6, 9 and 12 months during nivolumab/placebo treatment, and at 15 and 18 months, 2, 3, 4, and 5 years from start of nivolumab/placebo.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

The Radiation Oncology Co-Chair, James Urbanic, M.D. and delegates, will perform an RT Quality Assurance Review after the ACR Core Laboratory/RTQA has received complete data for the first 20 cases enrolled. Dr. Urbanic will perform the next review after the ACR Core Laboratory/RTQA has received complete data for the next 20 cases enrolled. Subsequent reviews will continue in a periodic and timely fashion. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as the ACR Core Laboratory/RTQA has received complete data for all cases enrolled, whichever occurs first.

The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of radiotherapy treatment data as specified in Section 13.2. The scoring mechanism is: Per Protocol, Variation Acceptable, and Deviation Unacceptable.

12.2 Drug Quality Assurance Reviews

The Principal Investigator/Medical Oncology, David Gerber, MD and Medical Oncology Co-Chair, Corey Langer, M.D., will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 13. The scoring mechanism is: **Per Protocol, Acceptable Variation, Unacceptable Deviation, and Not Evaluable**.

Drs. Gerber and Langer will perform a Quality Assurance Review after RTOG Headquarters has received complete data for the first 20 cases enrolled. Drs. Gerber and Langer will perform the next review after RTOG 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 RTOG Headquarters has received complete data for all cases enrolled, whichever occurs first.

13. DATA AND RECORDS

This study will utilize Medidata Rave. See the Data Management Plan in the study-specific guide on the RTOG Foundation 3505 protocol page of the RTOG website, www.rtog.org, for further details.

13.1 Summary of Dosimetry Digital RT Data Submission (Submit to ACR Core Laboratory/RTQA see the study-specific guide on the RTOG Foundation 3505 protocol page of the RTOG website, www.rtog.org, for details of TRIAD.)

ALL DIGITAL RT DATA MUST BE IN DICOM FORMAT

Item	Due
Treatment Planning Data exported from planning system and uploaded to TRIAD	**Within 1 week of start of RT**

will include the following:	
• **Planning CT**	**Indicate "RT Digital Data" in Submission Type in TRIAD for all planning files**
• **RT Structure File – all required structures included and labeled per tables in Section 5.2.5 and 5.2.6**	
• **RT Dose File (one file for total prescription dose)**	
• **RT Plan File**	
• **PET Scan – if used to aid contouring for treatment plan**	**Indicate "Imaging-Baseline" in Submission Type in TRIAD**

Notes:

- **Upon submission of all digital RT data via TRIAD, complete an online Digital Data transmission form (DDSI) located on the RTOG Foundation 3505 website**https://www.rtog.org/clinicaltrials/rtogfoundationstudies/rtogfoundationstudy3505.aspx
- **RTOG 3505 DVH Analysis Worksheet**
- **Note: Data will not be processed until DDSI form is received**
- **Please include motion management technique in Comment section of DDSI Form**

13.2 Summary of Diagnostic Imaging Digital Data Submission (Submit to ACR Imaging Corelab; see the study-specific guide on the RTOG Foundation 3505 protocol page of the RTOG website, www.rtog.org, for details of TRIAD.))

ALL DIGITAL DIAGNOSTIC IMAGING DATA MUST BE IN DICOM FORMAT

Item	Due (via TRIAD)[1]
Contrast-enhanced CT of the Chest to include liver and adrenals (Baseline)[2]	**Within two weeks of acquisition**
Contrast-enhanced CT/MRI of the Brain (Baseline)	**Within two weeks of acquisition**
FDG-PET/CT Whole-Body (Baseline)	**Within two weeks of acquisition**
Contrast-enhanced CT of the Chest to include liver and adrenals (post-chemoRT)[2]	**Within two weeks of acquisition**
Contrast-enhanced CT of the Chest to include liver and adrenals (Follow-Up)[2]	**Within two weeks of acquisition** • **Every three months for the first two years (e.g., Months 3, 6, 9, etc.)** • **Every six months for years 3-5** • **Annually thereafter**

Contrast-enhanced CT of the Chest to include liver and adrenals *in timepoints of site-determined PD*[2]	**Within 3 days of acquisition**
FDG-PET/CT Whole-Body (Follow-up; perform as clinically indicated)[3]	**Within two weeks of acquisition**
Contrast-enhanced CT/MRI of the Brain (Follow-up; perform as clinically indicated)[3]	**Within two weeks of acquisition**
Notes: *[1]All images should be accompanied by an Image Transmittal Worksheet (ITW).* *[2]If IV contrast is contraindicated, MRI Chest may be submitted in place of a contrast-enhanced CT Chest, along with a non-contrast-enhanced CT Chest.* *[3] Patients with uncertain progression may require repeat imaging at 6 weeks rather than 3 months if disease status remains uncertain.*	

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

Patients will be enrolled and randomized 1:1 between two arms. The treatment allocation scheme described by Zelen (1974) will be used. Patients will be stratified by Zubrod Performance Status (0 vs. 1); histology (squamous vs. non-squamous), as there may be a trend toward greater benefit of nivolumab in squamous histology (Topalian 2012); and tumor PD-L1 status.

14.2 Study Endpoints

14.2.1 Primary endpoints:

- Overall survival (OS)
  OS is defined as the time between the date of randomization and the date of death due to any cause. OS will be censored on the last date a subject is known to be alive.
  Progression free survival (PFS) based on Independent Radiology Review Committee (IRRC) according to RECIST 1.1
- PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by IRRC according to RECIST 1.1, or death due to any cause, whichever occurs first. Please refer to Section 4 "Central Imaging Review" for details on IRRC PFS data generation and collection, and Section 14.3.2 for detailed definition of PFS events and censoring.

14.2.2 Secondary endpoints:

- Toxicities
- Functional Assessment of Cancer Therapy - Trial Outcome Index for lung cancer (FACT-TOI) at 15 months
- OS and PFS in patients with (1) PD-L1-positive, (2) PD-L1-negative and PD-L1 not evaluable/undetermined tumors

14.2.3 Exploratory endpoints

- biomarker and biomarker correlatives
- proportion of patients alive at 12 and 24 months
- proportion of patients progression free at 12 and 24 months using investigational site assessments according to RECIST 1.1

- PROMIS fatigue at 3 months
- Descriptive analysis of the EQ-5D utilities and the EQ-VAS by study arm before and after progression.
- PFS based on investigator assessment.

14.3 Primary Objectives Study Design

14.3.1 Primary Hypotheses and Endpoints

The primary hypotheses of this study are (1) nivolumab increases OS with a hypothesized hazard ratio of 0.7; (2) nivolumab increases IRRC-determined PFS with a hypothesized hazard ratio of 0.667 (control arm is the reference level). In particular, assuming OS and PFS are exponentially distributed (at least approximately), the alternative hypothesis for OS is that patients receiving the experimental regimen will have a median survival time of at least 34.3 months, while those receiving the control regimen will have a median survival time of 24 month. Similarly, the alternative hypothesis for PFS assumes the median times for PFS will be 12 and 18 months for the control and experimental arms, respectively.

14.3.2 Statistical Analysis Plan for Primary Endpoints

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

The study accounts for two primary endpoints: OS and PFS. Overall (2-sided) alpha is 0.05, which is split with 0.01 for evaluating PFS and with 0.04 for evaluating OS.

The primary OS analysis will be conducted using a two-sided log-rank test stratified by histology, Zubrod and PD-L1 status in all randomized patients. Hazard ratio (HR) and corresponding two-sided 96% confidence interval (CI) will be estimated using a Cox proportional hazard model, with treatment group as a single covariate, stratified by the above stratification factors. The stratification factors will be obtained at the time of randomization. Results from an unstratified analysis will also be provided. The rates at various timepoints (i.e., every 6 months after randomization) and medians of OS 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.

The primary PFS analysis will be conducted using the same methods and stratification factors as OS analysis, except that the hazard ratio (HR) and corresponding two-sided 99% confidence interval (CI) will be estimated using a stratified Cox proportional hazard model.

PFS is defined as the time between the date of randomization and the first date of documented progression, regardless of discontinuation of study drug, or death due to any cause, whichever occurs first. Progressive disease (PD) is determined by IRRC

according to RECIST 1.1. Subjects who die without a reported progression will be considered to have the PFS event on the date of their death. Subjects who do not progress or die will be censored on the date of their last evaluable tumor assessment as determined with radiographic evidence. Subjects who do not have any on-study tumor assessments and do not die will be censored on their date of randomization. For the primary PFS analysis, subjects who have palliative local therapy or initiate systematic anti-cancer therapy (aka new therapy) without a prior reported progression or a progression confirmed by IRRC, whichever occurs first, will be censored on the date of their last evaluable tumor assessment as determined with radiographic evidence prior to the permanent discontinuation of treatment or the initiation of subsequent anti-cancer therapy or palliative local therapy.

Two sensitivity analyses will be performed to assess the robustness of the primary PFS analysis:

1. Sensitivity analysis 1 is the same as the primary analysis except that for patients with a PFS event who miss two or more scheduled assessments immediately prior to the PFS event, data will be censored at the last tumor assessment as determined with radiographic evidence prior to the missed visits.
2. Sensitivity analysis 2 is the same as the primary analysis except that it considers permanent discontinuation of study treatment (per Section 6.4) or initiation of palliative local therapy or systematic anti-cancer therapy, whichever occurs earlier, to be a PD event for subjects without a documented PD or death.

The censoring rules for primary and sensitivity analyses are summarized in Table 3.

Table 3: Censoring rules for Primary and Sensitivity Analyses of PFS

Situation	**Primary Analysis**	**Sensitivity Analysis 1**	**Sensitivity Analysis 2**
No PD and no death; new therapy is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; otherwise progressed at treatment discontinuation
No PD and no death; new therapy is initiated	Censored at last disease assessment prior to new therapy	Censored at last disease assessment prior to new therapy	Progressed at date of new therapy or treatment discontinuation
PD or death documented after ≤1 missed disease assessments	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥2 missed disease	Progressed at date of documented PD or death	Censored at last disease assessment immediately prior	Progressed at date of documented PD or death

assessments		to the ≥2 missed disease assessments	

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of the following classification variables:

- Age category (≤65, >65 years)
- Sex (female, male)
- Race (white, non-white)
- ECOG status (0, 1)
- Histology (squamous, non-squamous)
- Smoking status (never, former, current)

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

14.3.3 Sample Size and Power Calculations:

The study accounts for two primary endpoints: OS and PFS. Overall (2-sided) alpha is 0.05, which is split with 0.01 for evaluating PFS and with 0.04 for evaluating OS. The study is event-driven and plans to randomize 550 patients with 1:1 ratio into the experimental and control arms. Assuming a rate of 16.7% due to ineligibility and drop-out between initial registration and randomization, a total of 660 patients will be enrolled to ensure 550 patients will be randomized after completion of chemoradiation. Assuming a uniform monthly accrual rate of 14.4 patients (12 eligible patients to be randomized), and minimal accrual in the first 6 months for ramp-up, the accrual is projected to last 52 months (4.3 years) with additional 25 months follow up. The overall study is projected to last 71 months (5.9 years) since the first patient first visit (FPFV), or 77 months (6.4 years) since the study activation to reach the required number of events. If a higher rate of ineligible and drop-out is observed during the study conduct, the protocol may be amended to ensure at least 550 eligible patients to be randomized.

The null hypothesis for IRRC-assessed PFS is that both arms will have a median survival time of 12 months. The alternative hypothesis for PFS is that patients receiving the experimental regimen will have a median survival time of at least 18 months, corresponding to a 33% relative hazard reduction (HR=0.667). There is only one (final) PFS analysis planned and will be conducted after at least 363 PFS events are observed between the experimental and control arms. The analysis is projected to occur after 50 months from first patient first visit (FPFV) and 4 months after the completion of planned accruals. If the initial accruals are slower than expected such that 363 PFS events are observed prior to the completion of planned patient accruals, then the analysis may be delayed for 6 months to allow all randomized subjects to have a reasonable amount of follow-up information for the primary PFS analysis. With at least 363 PFS events, the study has ≥90% power to detect a hazard ratio of 0.667 for PFS at alpha=0.01 (2-sided) at this planned final PFS analysis. A p-value less than 0.01 (1-sided 0.005) using stratified log-rank test for PFS approximately corresponds to an empirical hazard ratio of 0.763 (or approximately at least 15.7 months of median PFS in experimental vs. 12 months in

control, if PFS in both arms follow exponential distributions approximately).

The null hypothesis for overall survival is that both arms will have a median survival time of 24 months. The alternative hypothesis for overall survival is that patients receiving the experimental regimen will have a median survival time of at least 34.3 months, corresponding to a 30% relative hazard reduction (HR=0.7). Using a 2-sided test with alpha of 0.04 and two planned OS analyses, a total of 355 deaths (complete information of OS) and 550 analyzable patients are required to detect the hypothesized survival difference with 90% power. There is one interim OS analysis and one final OS analysis is planned. The interim analysis will be conducted at the same time of the final PFS analysis. Based on the proportion of information available at the interim OS analysis, the Lan-DeMets implementation of O'Brien-Fleming boundary will be used to determine the critical value for the interim analysis. It is projected at the time of PFS final analysis, projected to occur after 50 months from first patient first visit (FPFV) and 4 months after the completion of planned accruals, approximately 230 OS events or 65% cumulative information for OS will be observed.

The final OS analysis will occur when complete information for overall survival, i.e., observing at least 355 deaths, is available. The final OS analysis is projected to occur after 71 months from first patient first visit (FPFV).

The trial will be declared positive if either the overall or progression-free survival comparison of the treatments is statistically significant favoring the experimental arm at 0.04 and 0.01 (2-sided), respectively. For OS analysis, the boundary for statistical significance at the interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of O'Brien-Fleming use function. For example, with 2-sided alpha of 0.04 and using stratified log-rank test, if 230 deaths have occurred at the time of the interim analysis, the statistical significance will be declared $p \leq 0.008$ (1-sided 0.004, approximately corresponds to an empirical hazard ratio of 0.704); and if 355 deaths have occurred at the time of the final OS analysis, statistical significance will be declared if $p \leq 0.0376$ (1-sided 0.0188, approximately corresponds to an empirical hazard ratio of 0.802).

If the long-term clinical effect ("cure rate") is present around 3 to 3.5 years since randomization, the study is anticipated to last 2 additional years of follow-up to observe the required number of events, i.e., the entire study duration may be 101 months (8.4 years) or longer.

The sample size and power calculation were performed in the software EAST.

14.4 Study Monitoring

14.4.1 Interim Analysis for the DMC

The RTOG Foundation Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and safety after enrollment of the first patient. 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.

14.4.2 Interim Analysis for Safety

To ensure the safety of this trial, the rates of protocol-specified adverse events between the arms will be compared after 13.3% and 26.7% of the eligible and evaluable patients who receive any protocol treatment (40 and 80 on each arm) have been accrued to the trial and observed for at least 180 days after the end of chemoradiation treatment (or die within 180 days). The As-Treated (AT) patient population will be used for the analysis of safety data in this study. The AT population consists of all randomized subjects who received at least one dose of study treatment (nivolumab or placebo). Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data.

With a total of 160 patients approximately evenly receiving nivolumab and placebo, we will have at least 85% power to detect the following difference in the rates of protocol-specified AE occurring within 180 days after the end of concurrent chemoradiation treatment at the significance level of 0.05 (2-sided): 5% vs.25%, 10% vs. 30%, and 15% vs. 35%. Using the Lan-DeMets implementation of O'Brien-Fleming boundary, if the p-value related with this comparison is less than 0.003 and 0.049 (2-sided) the trial accrual (if applicable) will be suspended due to safety concerns. In the event of excessive protocol-specified adverse events such that the trial accrual suspension is warranted, RTOG Foundation DMC will hold a special meeting to review the study data and provide a recommendation as to whether the study may continue, whether amendment(s) to protocol should be implemented, or whether the study should be stopped.

The difference in rates between the two treatment arms and their two-sided 95% CI, as well as associated odds-ratios will be estimated using the Cochron-Mantel-Haenszel (CMH) method of weighting (Agresti 2002), adjusting for the stratification factors. The difference in rate will also be compared using Cochron-Mantel-Haenszel (CMH) test, adjusting for the stratification factors, when 80 and 160 eligible and evaluable AT patients available from both treatments.

Protocol-specified adverse events are defined as following:

The development of grade 3 or higher adverse events definitely, probably, or possibly related to treatment for the following adverse events within 180 days after the end of concurrent chemoradiation treatment:

ChemoRT Toxicity	**Notes**
Cardiac Disorders	Grade 3 or higher: Acute coronary syndrome, Atrial fibrillation, Atrial flutter,

	Conduction disorder, Pericardial effusion, Pericarditis, Restrictive cardiomyopathy
Gastrointestinal Disorders	Grade 4 or higher: Dysphagia, Esophagitis, Esophageal fistula, Esophageal obstruction, Esophageal perforation, Esophageal stenonsis, Esophageal ulcer, Esophageal hemorrhage
Injury, Poisoning, and Procedural Complications	Grade 3 or higher: Dermatitis radiation, Fracture (limited to rib fractures only)
Nervous System Disorders	Grade 3 or higher: Brachial plexopathy, Recurrent laryngeal nerve palsy, Myelitis
Respiratory, Thoracic, and Mediastinal Disorders	Grade 3 or higher: Atelectasis (grade 4-5 only), Bronchopulmonary hemorrhage, Mediastinal hemorrhage, Pleural hemorrhage, Tracheal hemorrhage, Bronchial fistula, Pulmonary fistula, Bronchopleural fistula, Tracheal fistula, Hypoxia (provided gr.3 is worse than baseline), Bronchial obstruction, Tracheal obstruction, Pleural effusion, Pneumonitis, Pulmonary fibrosis
Skin and Subcutaneous Disorders	Grade 3 or higher: Skin ulceration (thorax only)
Changes in PFTs per the RTOG Pulmonary Toxicity Scale (see Section 5.2.14)	Grade 3 or higher: FEV1 decline, Forced Vital Capacity decline, DLCO decline
IMMUNE-MEDIATED Toxicity	**Notes**
Skin Rash and Oral Lesions	Grade 3 or higher: Bullous dermatitis, Erythema multiforme, Erythroderma, Palmar-plantar erythrodysesthesia syndrome, Papulopustular rash, Pruritus, Purpura, Rash acneiform, Rash maculo-papular, Skin ulceration, Stevens-Johnson syndrome, Toxic epidermal necrolysis,
Liver Function, AST/ALT/T. Bili	Grade 3 or higher
Renal Function, Serum Creatinine	Grade 3 or higher
Diarrhea/Colitis	Grade 3 or higher;

Pancreatitis, Amylase/Lipase	Grade 3 with development of symptomatic pancreatitis or DM; Grade 4 or higher
Pneumonitis	Grade 3 or higher
Other GI (including N-V)	Grade 3 and symptoms not resolving within 7 days with symptomatic treatment; Grade 4 or higher
Neurologic Events	Grade 3 or higher; any CNS events including aseptic meningitis, encephalitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis
Endocrine, Hypophysitis, Adrenal Insufficiency	Grade 3 or higher
Uveitis/Ocular	Grade 3
Infusion Reaction	Grade 3 or higher
All Other Immune-Mediated Events	Grade 3 or higher

14.4.3 Interim Analysis for Efficacy

The RTOG Foundation Data Monitoring Committee (DMC) will review the interim analysis for superiority based on OS and the primary analysis of PFS. Both analyses are planned to occur and the results will be reviewed by DMC at the same time. If either the primary PFS analysis or the interim OS analysis is deemed to be positive per the respective rules, the study results will be unblinded and reported. Otherwise, the study will remain open and the results will continue to remain blinded.

The primary PFS analysis is planned after 363 PFS events are observed between the experimental and control arms. The analysis is projected to occur after 50 months from first patient first visit (FPFV) and 4 months after the completion of planned accruals. If the initial accruals are slower than expected such that 363 PFS events are observed prior to the completion of planned patient accruals, then the analysis may be delayed for 6 months to allow all subjects to have a reasonable amount of follow-up for PFS analysis. The interim OS analysis will be based on the proportion of complete OS information available at the time of primary PFS analysis. It is projected that approximately 230 OS events or 65% cumulative information for OS (355 deaths) will be observed.

14.5 Accrual/Study Duration Considerations

The study is event-driven and plans to randomize 550 patients with 1:1 ratio into the experimental and control arms. Assuming a uniform monthly accrual rate of 14.4 patients (12 eligible patients to be randomized), and minimal accrual in the first 6 months for ramp-up, the accrual is projected to last 52 months (4.3 years), and the study is projected to last 77 months (6.4 years) to reach the required number of events.

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

14.6 Dose Level Guidelines

NA

14.7 Secondary Endpoints

14.7.1 Toxicities

The As-Treated (AT) patient population will be used for the analysis of safety data in this study. The AT population consists of all randomized subjects who received at least one dose of study treatment (nivolumab or placebo). Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data.

Exposure to nivolumab treatment and length of safety follow-up will be summarized. For each patient, the maximum severity reported will be used in the summaries. Adverse events will be summarized regardless of relationship to study drug as assessed by the investigator. All adverse events, adverse events leading to withdrawal of study drug, adverse events leading to dose reduction or interruption, Grade ≥ 3 adverse events, serious adverse events, and adverse events of special interest will be summarized. Deaths and cause of death will be summarized. The rate of treatment-related adverse events using NCI Common Terminology Criteria for Adverse Events (CTCAE, v. 4) 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 primary endpoint analysis.

14.7.2 Functional Assessment of Cancer Therapy - Trial Outcome Index for lung cancer (FACT-TOI) at 15 months

The QOL analyses will be performed based on all randomized patients. FACT-TOI complete 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 on treatment in follow-up).

Baseline and FACT-TOI 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.

FACT-TOI deterioration rate at 15 months is defined as the proportion of randomized subjects who had 5 points or more decrease from baseline in FACT-TOI. FACT-TOI deterioration rate at 15 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.

Based on prior trials in locally-advanced NSCLC, we expect about 40% patients will remain for evaluation at 15 months. Based on RTOG 0617, the deterioration rate at 1 year was about 50%. Therefore, assuming a 60% deterioration rate 15 months in control arm, about 220 evaluable patients at 15 months will detect a 20% difference (e.g., 60% vs. 40%) in deterioration rate with about 85% power at a two-sided alpha of 0.05, after taking account of the potential treatment effects which may result in unequal number of patients between arms.

The scores at baseline and subsequent time points, as well the associated changes from baseline 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.

14.7.3 OS and PFS in patients with 1. PD-L1-positive, 2. PD-L1-negative tumors and 3. PD-L1 undetermined tumors

If the trial is declared positive based on either OS or PFS in the overall ITT population, a step-down procedure will be applied to OS and PFS in the ITT subgroups in the following order: (1) PD-L1 positive (both ≥1% and ≥50% will be assessed); (2) PD-L1 negative, (3) PD-L1 undetermined, and the overall 2-sided alpha 0.05 is recycled for each subgroup analysis. Within each PD-L1 status group, OS and PFS will be analyzed using a 2-sided log-rank test stratified by histology and Zubrod in all randomized patients. Hazard ratio (HR) and corresponding two-sided 95% confidence interval (CI) will be estimated using a Cox proportional hazard model, with treatment group as a single covariate, stratified by histology and Zubrod. Results from an unstratified analysis will also be provided. The rates at various timepoints (i.e., every 6 months after randomization) and medians of OS 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.

In the event that study is not declared positive based on either OS or PFS in the ITT population, the presence of qualitative interactions between PD-L1 status and nivolumab will be assessed by analyzing OS and PFS within each PD-L1 positive and negative subgroups separately for exploratory purposes. The statistical analysis plan will be same except that no formal hypothesis testing will be performed. In addition, when assessing the presence of quantitative interactions is warranted based on exploratory subgroup analyses, an overall global interaction test for OS and PFS will be conducted. This will be performed in the overall ITT population by comparing the fit of a Cox proportional hazards model including treatment, PD-L1 status, and treatment-by-PD-L1 status

interaction terms, stratified by histology and Zubrod, with one that excludes the interaction terms at the 2-sided 10% significance level. If the fit of the model is not significantly improved with including the global interaction terms, then it will be concluded that the overall treatment effect is consistent across the PD-L1 status subgroups.

If there are too few OS events and PFS events available for a meaningful analysis of a particular subgroup, e.g., less than 20 events in a subgroup, the aforementioned subgroup statistical analysis plan will not be performed for statistical inferences, and only descriptive summaries of OS and PFS will be provided.

14.8 Exploratory Hypothesis and Endpoints

14.8.1 Biomarker analysis

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response, including efficacy and/or adverse events. The predictive and prognostic potential for the proposed biomarkers may become scientifically obsolete or the assay technology may evolve over time, making the technology outlined in the current protocol obsolete when the study is finished. As such, no marker assays will be conducted on the collected specimens. When sufficient 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 available.

14.8.2 Proportion of patients alive and progression-free at 12 and 24 months

The proportion of patients alive and progression-free at 12 and 24 months will be estimated by the Kaplan-Meier methodology for each arm, and the 95% CI will be calculated using Greenwood's formula and based on a log-log transformation applied on the survival function in the ITT population.

14.8.3 PROMIS fatigue

Baseline and PROMIS 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. Changes in PROMIS fatigue at 3 months are of particular interest.

14.8.4 EQ5D

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.

14.8.5 PFS based on investigator assessment

PFS based on investigator assessment (inv-PFS) is defined similarly to the co-primary endpoint, IRRC-PFS, except that progressive disease (PD) is determined by investigator's assessment based on RECIST criteria. The intention of this analysis is to illustrate if the estimation and inferential results based on inv-PFS are concordant with those based on IRRC-PFS in order to reassure the applicability of the study results in clinical practice. The analysis will be considered as exploratory and descriptive in nature. In addition to analyzing inv-PFS using the methods described in Section 14.3.2 for PFS primary analysis, the source of PFS events (PD vs. death) based on investigators' assessment and IRRC will be summarized separately, and the censoring times distributions of inv-PFS and IRRC-PFS will be summarized separately.

REFERENCES

Ahn JS, Ahn YC, Kim JH, et al. Multinational randomized phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small-cell lung cancer: KCSG-LU05-04. *J Clin Oncol*. 33(24):2660-6, 2015.

Anscher MS, Kong FM, Andrews K, et al. Plasma transforming growth factor beta1 as a predictor of radiation pneumonitis. *IJROBP*. 41:1029-35, 1998.

Anscher MS, Marks LB, Shafman TD, et al. Using plasma transforming growth factor beta-1 during radiotherapy to select patients for dose escalation. *J Clin Oncol*. 19:3758-65, 2001.

Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol*. 23:5883-91, 2005.

Borghaei H, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015 Sep 27. Epub ahead of print: http://www.ncbi.nlm.nih.gov/pubmed/26412456

Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncology*. 16(2):187-199, 2015.

Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol*. 28:3167-75, 2010.

Brahmer JR, Hom L, Antonia SJ, et al. Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in patients with non-small cell lung cancer (NSCLC): overall survival and long-term safety in a phase 1 trial. International Association for the Study of Lung Cancer 15th Annual World Conference on Lung Cancer. Abstract MO18.03. 2013.

Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small cell lung cancer. *N Engl J Med* 373:123-35, 2015.

Butts CA, Socinski MA, Mitchell PL, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small cell lung cancer (START): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 15:59-68, 2014.

Carthon BC, Wolchok JD, Yuan J, et al. Preoperative CTLA-4 blockade: Tolerability and immune monitoring in the setting of a presurgical clinical trial. *Clin Cancer Res*. 16:2861-71, 2010.

Cella D, Yount S, Rothrock N, et al. PROMIS Cooperative Group. The Patient-Reported Outcomes Measurement Information System (PROMIS): Progress of an NIH Roadmap cooperative group during its first two years. *Med Care*. 2007; 45(5 Suppl 1):S3-S11.

Cella D, Lai J, Garcia SF, et al. The Patient Reported Outcomes Measurement Information System-Cancer (PROMIS-Ca): Cancer-specific application of a generic fatigue measure. [Abstract]. J Clin Oncol. 2008; 26, 6537.

Chen Y, Hyrien O, Williams J, et al. Interleukin (IL)-1A and IL-6: Applications to the predictive diagnostic testing of radiation pneumonitis. *IJROBP*. 62:260-6, 2005.

Demaria S, Ng B, Devitt ML, Babb JS, Kawashima N, Liebes L, Formenti SC. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *IJROBP*. 58:862-70, 2004.

Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest*. 2014 Jan 2. Epub ahead of print: http://www.jci.org/articles/view/67313

Ezer N et al. Cisplatin vs. carboplatin-based chemoradiotherapy in patients >65 years of age with stage III non-small cell lung cancer. *Radiother Oncol*. 2014;112: 272-8.

Fu XL, Huang H, Bentel G, et al. Predicting the risk of symptomatic radiation-induced lung injury using both the physical and biologic parameters V(30) and transforming growth factor beta. *IJROBP*. 50:899-908, 2001.

Garcia SF, Cella D, Clauser SB, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative.*J Clin Oncol*. 2007;25(32): 5106-12. Review. Erratum in: *J Clin Oncol*. 2008; 26(6):1018.

Glasziou PP, Simes RJ, Gelber RD. Quality adjusted survival analysis. *Stat Med*. 1990; 9(11):1259-76.

Hanna N, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: The Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol*. 26:5755-60, 2008.

Hara R, Itami J, Komiyama T, et al. Serum levels of KL-6 for predicting the occurrence of radiation pneumonitis after stereotactic radiotherapy for lung tumors. *Chest*. 125:340-4, 2004.

Hodi FS, Butler M, Oble DA, et al. Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients. *Proc Natl Acad Sci U S A*. 105:3005-10, 2008.

Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. *J Cutan Pathol*.

2010; 37(Suppl 1): 48-53.

Investigator Brochure: Nivolumab (v.14). Bristol-Myers Squibb. 30 June 2015.

Ivanova A, Qaqish BF, and Schell MJ. Continuous toxicity monitoring in phase II trials in oncology. *Biometrics*. 61: 540-545, 2005.

Iyengar P, Gerber DE. Locally advanced lung cancer: An optimal setting for vaccines and other immunotherapies. *Cancer J.* 19:247-62, 2013

Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol*. 26:2450-6, 2008.

Ku GY, Yuan J, Page DB, et al. Single-institution experience with ipilimumab in advanced melanoma patients in the compassionate use setting: lymphocyte count after 2 doses correlates with survival. *Cancer*. 116:1767-75, 2010.

Lai J-S, Cella D, Choi SW, et al.Developing a fatigue item bank from the patient-reported outcomes measurement information system (PROMIS FIB version 1). Presented at the International Conference on Survey Methods in Multinational, Multiregional, and Multicultural Contexts (3MC). June 25-28, 2008.

Larici AR, del Ciello A, Maggi F, et al. Lung abnormalities at multimodality imaging after radiation therapy for non-small cell lung cancer. *Radiographics*. 31:771-89, 2011. PMID 21571656

Le DT, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *NEJM*. 372: 2509-20, 2015.

Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. *Blood*. 114:589-95, 2009.

Li QZ, Karp DR, Quan J, et al. Risk factors for ANA positivity in healthy persons. *Arthritis Research & Therapy.* 27 :153-60, 2011.

Liakou CI, Kamat A, Tang DN, et al. CTLA-4 blockade increases IFNgamma-producing CD4+ICOShi cells to shift the ratio of effector to regulatory T cells in cancer patients. *Proc Natl Acad Sci U S A*. 105:14987-92, 2008.

Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. *J Clin Oncol*. 30:2046-54, 2012.

Mitchell P, et al. Tecemotide in unresectable stage III non-small cell lung cancer in the phase III START study: Updated overall survival and biomarker analyses. *Ann Oncol*. 26:1134-1142, 2015.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*.35:549–556, 1979.

Pickard AS, et al. Health utilities using the EQ-5D in studies of cancer. *Pharmacoeconomics.* 25(5):365-84, 2007.

Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *NEJM*. 366:925-31, 2012.

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..

Rizvi NA, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 348: 124-8, 2015.

Rizvi NA, Antonia SJ, Chow LQM, et al. A phase I study of nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus platinm-based doublet chemotherapy (PT-doublet) in chemotherapy-naive non-small cell lung cancer (NSCLC) patients (pts). *J Clin Oncol*. 31 (suppl; abstract 8072), 2013.

Rubinstein LV, Korn EL, Freidlin B, et al. Design issues of randomized phase II trials and a proposal for phase II screening trials. *J Clin Oncol.* 23(28): 7199-7206, 2005.

Santana-Davila R et al. Cisplatin and etoposide versus carboplatin and paclitaxel with concurrent radiotherapy for stage III non-small-cell lung cancer: an analysis of Veterans Health Administration data. *J Clin Oncol.* 2015;33: 567-74.

Santin AD, Hermonat PL, Ravaggi A, et al. Effects of concurrent cisplatinum administration during radiotherapy vs. radiotherapy alone on the immune function of patients with cancer of the uterine cervix. *IJROBP*. 48:997-1006, 2000.

Socinski M, et al. CheckMate 026: A phase 3 trial of nivolumab vs investigator's choice (IC) of platinum-based doublet chemotherapy (PT-DC) as first-line therapy for stage iv/recurrent programmed death ligand 1 (PD-L1)-positive NSCLC. *Ann Oncol*. 27 (suppl_6):552-587, 2016.

Schulz MW, et al. A comparison of techniques for eliciting patient preferences in patients with benign prostatic hyperplasia. *J Urol.* 168(1):155-9, 2002.

Sun J-M, Zhou W, Choi Y-L et al. PD-L1 expression and survival in patients with non-small cell lung cancer (NSCLC) in Korea. *J Clin Oncol* 32:5s (abstr 8066), 2014.

Talmadge JE, et al. Inflammatory cell infiltration of tumors: Jekyll or Hyde. *Cancer Metastasis Rev.* 2007; 26: 373-400.

Tan EM, Feltkamp TI, Smolen JS, et al. Range of antinuclear antibodies in "healthy" individuals. *Arthritis Rheum*. 40:1601-11, 1997.

Taube JM, Anders RA, Young GD, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med.* 4(127):127ra37, 2012.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *NEJM*. 366:2443-54, 2012.

Uchida A, Mizutani Y, Nagamuta M, et al. Effects of X-ray irradiation on natural killer (NK) cell system. I. Elevation of sensitivity of tumor cells and lytic function of NK cells. *Immunopharm Immunotoxicol*. 11:507-19, 1989.

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.

Wandstrat AE, Carr-Johnson F, Branch V, et al. Autoantibody profiling to identify individuals at risk for systemic lupus erythematosus. *Journal of Autoimmunity*. 27:153-60, 2006.

Wang L et al. Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer. *Lung Cancer*. 2012;1: 89-96.

Weber JS, O'Day S, Urba W, et al. Phase I/II study of ipilimumab for patients with metastatic melanoma. *J Clin Oncol*. 26:5950-6, 2008.

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.

Yuan J, Gnjatic S, Li H, et al. CTLA-4 blockade enhances polyfunctional NY-ESO-1 specific T cell responses in metastatic melanoma patients with clinical benefit. *Proc Natl Acad Sci U S A*.105:20410-5, 2008.

Zelen H. The randomizatino and stratification of patients to clinical trials (MI#7506064). *J Chronic Disease*. 27:365-375, 1974.

Zhang L, Wang L, Yang M, et al. Association of DNA repair and inflammatory cytokines gene polymorphisms with radiation-induced toxicity in lung cancer. *IJROBP*. 69:S60-61, 2007.

APPENDIX I
Nivolumab (BMS-936558) Pharmacy Reference Manual

1 OBJECTIVE

The objective of this procedure manual is to provide the study site with clear and detailed information for the storage, handling, preparation and administration of Nivolumab used in the RTOG 3505/CA209-333 study

2 BMS CLINICAL PRODUCT CONTACT

If concerns regarding the quality or appearance of the study drug, or questions regarding administration arise, do not dispense the study drug and contact the Bristol-Myers Squibb immediately:

Questions with regard to drug preparation and pharmacy manual content:

Peter Trimboli, RPh
Pharmacy Services, Drug Supply Management
Bristol-Myers Squibb Research and Development
Telephone: 609-252-4862
Email: pharmacyservices@bms.com

3 NIVOLUMAB INJECTION

3.1 DESCRIPTION

Product Name	Nivolumab Injection (BMS 936558), 100 mg/vial (10 mg/mL)
Product description and Packaging	*Packaging:* Vials assembled into white dispensing boxes containing 100 mg vials. *Vials:* 10 cc Type I glass vial. 20 mm stopper and seal, respectively. *Appearance:* Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present.
Product Ingredients	Each vial contains 100 mg Nivolumab

Continued on next page

3.2 *Handling and Dose Preparation*

As with all injectable drugs, care should be taken when handling and preparing Nivolumab. Whenever possible, Nivolumab infusions should be prepared in a laminar flow hood, glovebox, or safety cabinet using standard procedures for the safe handling of intravenous agents applying aseptic techniques. Gloves are required. If nivolumab solution comes in contact with the skin or mucosa, immediately and thoroughly wash with soap and water.

Dose Preparation and administration

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

Preparation

- Withdraw the required volume of Nivolumab and transfer into an intravenous container.
- Dilute Nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL (see example below)
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of Nivolumab.

Storage of Infusion

The product does not contain a preservative. After preparation, store the Nivolumab infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion

or

- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.

  Do not freeze.

Administration

Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not coadminister other drugs through the same intravenous line. **Flush the intravenous line at end of infusion with appropriate amount of diluent (e.g. 15-20 ml) to ensure that the total dose is administered. Total infusion and flush time should equal to 30.**

Dose selection for Nivolumab should be assigned per subject as outlined in the clinical protocol study drug dosing section of the clinical protocol. *The examples below use a total volume of 60*

ml to allow for a practical administration rate, however other volumes may be used for Nivolumab preparation so as long as the final concentration remain between 1 - 10 mg/ml (e.g. 100 ml).

NOTE: When Nivolumab Placebo is required, placebo shall be considered an equal volume of drug diluent alone (NS, D5W) which is standard to site practice for mixing active Nivolumab (60 ml, or 100 ml) and should be infused at the same rate (30 minutes).

Preparation example 240 mg dose;

Nivolumab 240 mg (24 ml Nivolumab 10mg/ml solution, local rounding rules applicable) may be mixed with 36 ml NS or D5W to a total volume = 60 ml which can be infused over 30 minutes at 2 ml/min followed by flush.

Preparation example 480 mg dose;

Nivolumab 480 mg (48 ml Nivolumab 10mg/ml solution, local rounding rules applicable) may be mixed with 12 ml NS or D5W to a total volume = 60 ml which can be infused over 30 minutes at 2 ml/min followed by flush.

3.3 *Product Storage and Stability*

Nivolumab 100 mg vials for injection should be refrigerated at 2°C to 8°C (36°F to 46°F). Protected from light and **should not be frozen**. Do not use beyond the expiration date on the vial. Protect the vials from light by storing in the original package until time of use. Vials do not contain preservative and thus are intended for single use only and should be discarded after use and product reconciliation.

Nivolumab should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of Nivolumab with other agents.

4 SITE TEMPERATURE EXCUSIONS AND TRANSIT

Drug must be stored under the proper conditions as listed on the clinical supply label. If any temperature excursions are encountered during on site storage, please report these to BMS for assessment as outlined in the Bristol-Myers Squibb, "Investigational Medicinal Product (IMP) handling at Investigational Sites: Shipment, Receipt, Storage, Use Date Extension and Return/Destruction" guideline using the Temperature Excursion Response Form. See Form 1 Proper storage conditions must be maintained during movement of inventory within an

investigational site. Storage conditions for medications requiring storage at 2ºC to 8ºC (36ºF-46ºF) must be maintained throughout the transport with documentation maintained within the site files. Where controlled storage conditions (for example, temperature, relative humidity, light, etc.) are required during transit, the necessary environmental controls must be in place to ensure that the drug product remains within the acceptable temperature range. Temperature monitoring devices such as min max device must be implemented during transit.

5 PRODUCT RECEIPT, ACCOUNTABILITY, AND DESTRUCTION

Drug Receipt

Shipment Inspection Instructions

1. Open box **immediately** upon receipt.
2. Carefully inspect kits ensuring all of the supplies were received in good condition, correct quantity received, and all of the container ID #s were received as noted on packing slip.
3. Sign and date (date of receipt) packing slip and file with study-specific documents.
4. Log in all supplies in each shipment on the appropriate Inventory log Form

Accountability

It is the responsibility of the investigator to ensure that a current disposition record of investigational product accountability and reconciliation is maintained at each study site where study drug is inventoried and dispensed.

In addition, records or logs must comply with local regulations and guidelines for the conduction and handling of clinical supplies should include but not limited too:

- Amount received and placed in storage area
- Amount currently in storage area
- Label ID number or batch number
- Amount dispensed to and returned by subject, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Non-study disposition (e.g. lost, wasted)
- Amount destroyed at study site, if applicable
- Amount returned to the Sponsor, if applicable
- Dates and initials of person responsible for Investigational Product (IP)
- Dispensing/accountability, as per the Site Signature and Delegation Log.

Study Drug Destruction

Study drugs can be destroyed on site if local policies allow to do so. It is the Investigator's

responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented.

Form 1

Bristol-Myers Squibb

Temperature Excursion Response Form for Investigational Medicinal Products

Section A. To be completed by the site at the time of Site Storage Temperature Excursion:

Protocol Number:	**Site Number/Investigator Name/Country:**
Description of Drug Products involved in Excursion:	
Batch number (s) printed on label:	**Container numbers:**
Description of Excursion (temperature highs/lows and duration):	
Below label storage lower limit …...°C Duration:……. Low extreme t°: …..°C **Above label storage upper limit ….. °C Duration:……... High extreme t°: …..°C**	
Reason for excursion:	
Has the issue been resolved?	
Have these specific containers been involved in a previous excursion? NO ☐ YES ☐ **If yes, please provide:**	

Batch number (s):	**Container numbers:**	**Temperature highs/lows and duration**

When is the next planned patient visit when these supplies may be dispensed?

Excursion information submitted by: _____ Date: _____

Print/Signature/Title of site staff

Section B. Usage Decision to be made by Bristol-Myers Squibb:

Temperature excursion details for the products listed above have been evaluated. Usage decision is based on the temperature data that were made available by the investigational site.

Conclusion (and comments):

☐ **All products are suitable for continued use**

_____

_____

☐ **All products are NOT suitable for further dispensation. Please remove supplies from available inventory and work with your Site Manager/Site Monitor to have supplies destroyed and IVRS updated if applicable.**

_____

_____

Assessment completed by:_____ Date _____

Print/Signature/Title

Send completed form to: Peter Trimboli, RPh at pharmacyservices@bms.com

Templates as provided via separate attachment or below may serve as a sample for dosage calculations and may be printed out and used to document any calculations and infusion times as required by the clinical study team. Content in this attachment may be added or omitted.

Drug Dose and Volume Calculator for IV Infusion	
Drug Product :	
Protocol number	
Patient name or ID:	
Preparation date and time:	
Drug Strength (mg/mL)	
Subject body weight (kg)	
[1]Dose in mg	
Volume of Drug (mL)	
Total Volume of infusion (mL)	
Volume of Diluent (mL) NS or D5W	
Infusion duration (min)	
Infusion Rate (mL/min)	
Infusion hang time	
Infusion completion time	

Note: If required, flush line with separate volume of same diluent (e.g. 15-20 ml) as outlined in the study pharmacy manual

APPENDIX II

1.1 Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

1.1.1 Measurable disease

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

1.1.2 Measurable lesions

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

1.1.3 Non-measurable lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.1.4 Malignant lymph nodes

1.1.1.1 To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.5 Baseline documentation of "Target" and "Non-Target" lesions

Target lesions.

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the

sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions.
All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

1.1.6 Response Criteria

Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression of non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

* Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail.

Evaluation of best **overall** response

The best overall response is the best time point response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 3: Response Assignment

Target Lesions	**Non-Target lesion**	**New Lesion**	**Overall response**
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
	Not evaluated	No	PR
PR	Non-CR/ Non-PD/ not evaluated	No	PR
SD	Non-CR/ Non-PD/ not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

APPENDIX II (continued)

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

1.1.7 Definitions for Response Evaluation –RECIST version 1.1

1.1.7.1 First Documentation of Response
The time between initiation of therapy and first documentation of PR or CR.

1.1.7.2 Duration of Response
Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented, taking as reference for progressive disease the smallest measurements recorded since treatment started.

1.1.7.3 Duration of Overall Complete Response
The period measured from the time that measurement criteria are met for complete response until the first date that progressive disease is objectively documented.

1.1.7.4 Objective response rate
The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST v1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

1.1.7.5 Progression Free Survival
A measurement from the start of the treatment until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs, taking as reference the smallest measurements recorded since the treatment started.

Progression free survival will be measured from the date of initial treatment to the earliest date of disease progression, resection of measurable tumor or death for subjects who fail; and to the date of last contact for subjects who remain at risk for failure.

1.2 Methods of Measurement

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and

never more than 28 days before the beginning of the treatment.
Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. The same imaging modality must be used throughout the study to measure disease.

1.2.1 CT and MRI

CT and MRI are the best currently available and most reproducible methods for measuring target lesions. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

1.2.2 Chest X-Ray

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by an aerated lung (CT is preferable).

1.2.3 Clinical Examination

Clinically detected lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained

at the institution.

APPENDIX II (continued)

1.2.4 Cytology and Histology

Cytologic and histologic techniques can be used to differentiate between complete and partial responses in rare cases (e.g. after treatment to differentiate residual benign lesions and residual malignant lesions in germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.

APPENDIX III

Biospecimen Bank at UCSF: Biospecimen Collection, Processing, and Shipping Instructions for FFPE and Serum

- **FFPE Specimens:**
  - Slides should be shipped in plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear slides shaking they can break during shipping.
  - Unstained slides must be stored at 4C after cutting and shipped to the Biospecimen bank with cold packs at 4C within 5 business days from cutting. The date that the slides were cut should be noted on the ST form.
  - FFPE Blocks can be shipped in a plastic block holder or wrapped with paper or placed in a paper envelope, and placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear blocks shaking they may break during shipping. During warm weather months the use of cold packs is recommended to prevent wax from melting.
  - Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.
  - Urgent overnight shipments (central review) should always be sent by Courier.
  - If patients consented to banking DO NOT ship FFPE specimens with a return request. We cannot accept or bank samples that we cannot keep. Always send what can be banked (duplicate H&Es, Blocks or punches as specified in the protocol). We can punch and return blocks if noted in the protocol. Punch kits can be requested from us by email (RTOG@ucsf.edu) for sites that wish to punch the block themselves.

- **Frozen Specimens:**
  - Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs.). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - Send frozen specimens via overnight courier to the address above. Frozen specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80°C until ready to ship.

- **For Questions regarding collection/shipping please contact the Biospecimen Bank at UCSF by e-mail: RTOG@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

Shipping Instructions for FFPE and Serum: (See Appendix III for processing and shipping information for peripheral blood)

US Postal Service Mailing Address: **Use only for non-urgent ambient specimens- FFPEs, slides, blocks:**	**Courier Address (FedEx, UPS, etc.):** **For Frozen, Urgent or Trackable Specimens:**
Biospecimen Bank at UCSF **UCSF- Box 1800** **2340 Sutter St, room S341** **San Francisco, CA 94143-1800**	**Biospecimen Bank at UCSF** **University of California San Francisco** **2340 Sutter St, room S341** **San Francisco, CA 94115**

- Include all required specimen paperwork in pocket of biohazard bag.
- Check that the Specimen Transmittal (ST) Form has been completely filled out
- Check that all samples are labeled with the study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

Blood Collection Kit Instructions

This Kit is for collection, processing, storage, and shipping of serum and whole blood for first 3 timepoints. Recurrence/ toxicity patients- site should request follow-up kits separately for these patients.

Kit contents: For 3 timepoints

• Five 1 ml cryovials per timepoint. (Twenty per kit) • Biohazard bag (4) • ST Form and Kit Instructions Note: sites will have to provide their own EDTA for whole blood and standard Red Top tube for serum blood draw unless specifically requested.	• Absorbent shipping material (4) • 1 Styrofoam container (inner) and Cardboard shipping (outer) box for batch shipping • UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers

Preparation and Processing of Serum

Serum: Red Top Tube

- Label as many 1ml cryovials (5 to 8) for each time point as necessary for the serum collected.
  Label tubes with the RTOG Foundation study and case number, time point, collection date and time, and clearly mark cryovials "serum".

Preparation and Processing of Serum (continued)

Process:

1. Allow one red top tube (not provided in kit) to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. Aliquot 0.5 ml serum into five (5) labeled cryovials. Make sure tubes are labeled as specified above.
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C. Store frozen until ready to ship. See below for storage conditions.

Whole Blood for DNA Purple Top EDTA tube (EDTA tube is not provided)

- Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the RTOG study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many labeled cryovials as are necessary for the blood collected (3 to 5). Make sure tubes are labeled as specified above.
3. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C. Store frozen until ready to ship on dry ice. See below for storage conditions

PLEASE make sure EVERY SPECIMEN IS LABELED and include collection time point on ST Form.

PLEASE make sure EVERY SPECIMEN IS LABELED and include collection time point on ST Form.

Freezing and Storage:

- Freeze Serum and whole blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

- Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all required paperwork in sealed plastic bag taped on outside top of the Styrofoam box.
- Wrap frozen specimens of same time point together in absorbent shipping material and place specimens from separate time points or cases in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs./3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 dry ice stickers to outer cardboard box. Fill out the UN1895 Label COMPLETELY.

Preparation and Processing of Serum

Shipping/Mailing:(Continued)

- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- **For questions regarding collection, shipping or to order a Serum Collection Kit, please e-mail RTOG@ucsf.edu or call (415) 476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
Biospecimen Bank UCSF
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: RTOG@ucsf.edu

Note: See Appendix IV for processing and shipping information for peripheral blood.

APPENDIX IV

Hooper Laboratory: Preparation, Processing and shipping of Peripheral Blood

Kit Contents:
5 Heparin Blood (green top) draw tubes per time point
Tube holder
Outer box for tube holder
Study Specific ST Form
Fed Ex Clinical Pak with label

Processing:

1. Sites should only draw blood samples on Monday-Wednesdays and only ship Monday-Thursdays.
2. Draw blood in 5 green heparin tubes.
3. Mix gently.
4. Place tubes in tube holder and outer box provided with Kit.
5. Seal up tube holder box and place in Fed Ex Clinical Pak provided
6. Ship the blood at room temperature on the same day for overnight delivery if possible.
7. Blood samples drawn too late in the day for overnight shipping, should be refrigerated overnight and shipped the following day for same day delivery.
8. Ship same day to Hooper Laboratory- Label is provided on the Clinical Pak.

Shipping Address: Note: Do NOT ship peripheral blood to Biospecimen Bank at UCSF.
Hooper Laboratory
Attn.: Rhonda Kean (lab manager) or Craig Hooper, PhD
JAH 454
1020 Locust Street
Philadelphia, PA 19107
For questions, contact: 215-503-1559