NRG ONCOLOGY
NRG-LU004
(ClinicalTrials.gov NCT #03801902) (23-JAN-2019)

Phase I Trial of Accelerated or Conventionally Fractionated Radiotherapy Combined With MEDI4736 (durvalumab) in PD-L1 High Locally Advanced Non-Small Cell Lung Cancer (NSCLC) (ARCHON-1)

This trial is sponsored by the National Cancer Institute (NCI) and will be led by NRG Oncology.

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Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
MEDI4736 (durvalumab)	NCI/PMB	778709	[redacted]	DCTD

Participating Sites

☒ U.S.
☐ Canada
☐ Approved International Member Sites

Document History

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Amendment 2	November 25, 2019
Amendment 1	January 23, 2019
Initial	December 4, 2018

This protocol was designed and developed by NRG Oncology. It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by NRG Oncology nor does NRG Oncology assume any responsibility for unauthorized use of this protocol.

CTSU CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and CIRB supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log-in with a CTEP-IAM username and password. Permission to view and download NRG-LU004 supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS). Additional study related documents can be found on the protocol specific page of the NRG website.		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

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SCHEMA (13-JAN-2021)

Registration: Institution-determined PD-L1 expression ***using Dako 22C3 IHC antibody*** platform or the Ventana SP263 assay. The first 6 patients with PD-L1 expression of ≥50% will be registered to Cohort 1 and the following 6 patients with PD-L1 expression of ≥50% will be registered to Cohort 2.

LEAD-IN SCHEMA (Initial Safety Schedules)

Cohort 1, n=6
MEDI4736 (durvalumab)[†] **q4 weeks** (+/- 7 days) x 13 doses
+ ACRT 60 Gy in 15 fractions x 3 weeks (weeks 1-3)

Cohort 2, n=6
MEDI4736 (durvalumab)[†] **q4 weeks** (+/- 7 days) x 13 doses
+ standard RT 60 Gy in 30 fractions x 6 weeks (weeks 1-6)

[†] MEDI4736 (durvalumab) begins 2 weeks (Day -14) before RT (+/- 48 hours); see Section 5.1 for dosing details

EXPANSION COHORTS

After completing one of the Initial Safety Schedules of concurrent RT+MEDI4736 (durvalumab):

- If Cohort 1 only is deemed safe, all patients will be registered to Cohort 3.
- If Cohort 2 only is deemed safe, all patients will be registered to Cohort 4.
- **If both Cohorts 1 and 2 are deemed safe, patients will be randomized to either Cohort 3 or Cohort 4 with 1:1 randomization.**

RANDOMIZE

Cohort 3, n=6	Cohort 4, n=6
MEDI4736 (durvalumab)[†]q4 weeks (+/- 7 days) x 13 doses + ACRT 60 Gy in 15 fractions x 3 weeks (weeks 1-3)	MEDI4736 (durvalumab)[†] q4 weeks (+/- 7 days) x 13 doses + standard RT 60 Gy in 30 fractions x 6 weeks (weeks 1-6)

[†] MEDI4736 (durvalumab) begins 2 weeks (Day -14) before RT (+/- 48 hours); see Section 5.1 for dosing details

1.0 OBJECTIVES

1.1 Primary Objective

1.1.1 To evaluate if the addition of MEDI4736 (durvalumab) to two schedules of radiation therapies (60 Gy in 30 fractions or 60 Gy in 15 fractions) is safe.

1.2 Secondary Objectives

1.2.1 To examine if the addition of MEDI4736 (durvalumab) to radiation therapy is feasible.

1.2.2 To assess toxicities associated with the addition of MEDI4736 (durvalumab) to radiation therapy.

1.2.3 To obtain preliminary estimates of progression-free survival (PFS), using RECIST guidelines, in patients who received MEDI4736 (durvalumab) added to radiation. Although the clinical benefit of MEDI4736 (durvalumab) in combination with radiotherapy has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response.

1.3 Exploratory Objectives

1.3.1 To assess the impact the addition of MEDI4736 (durvalumab) has on progression-free survival, using irRC guidelines.

1.3.2 To assess the changes in circulating tumor cells (CTCs) and various immune parameters during treatment with durvalumab and radiotherapy and changes after completion of treatment.

2.0 BACKGROUND

2.1 Current Management Approach and Rationale for Study (13-JAN-2021)

Initially, the FDA approved the use of frontline pembrolizumab instead of chemotherapy in unresectable metastatic NSCLC patients with high PD-L1 IHC expression (defined as a Tumor Proportion Score (TPS) ≥ 50% using either the Dako 22C3 antibody or the Ventana SP263 antibody platforms) [Reck 2017] based on KEYNOTE-024, which demonstrated an improvement in median PFS (10.3 vs 6 months, $p<0.01$), and improved 6-month overall survival (OS) (hazard ratio (HR) 0.6=0.005). The updated survival results reported at the International Association for the Study of Lung Cancer (IASLC) 2017 meeting demonstrated a HR of 0.63 [95% confidence interval (CI)], 0.47-0.86; P = .002) favoring pembrolizumab. The median OS was 30.2 months for pembrolizumab compared to 14.2 months with chemotherapy. It should be noted that these OS results held up in spite of significant cross-over in the second-line setting to checkpoint inhibitors in the patients who received chemotherapy. Additionally, the overall response rate (ORR) was improved with pembrolizumab (44.8% vs 27.8%) with an increase in duration of response (not reached (NR) vs 6.3 months). Quality of Life (QOL) analysis favored the pembrolizumab arm. In this population of patients, PD-1/PD-L1 inhibitors are superior to systemic chemotherapy in metastatic NSCLC.

The standard of care for local-regionally advanced NSCLC is concurrent chemoradiation. However, 5-year survival rates still hover around 20-25% for stage III NSCLC. Additional advances in treatment options are needed. The results of the PACIFIC trial, a

phase III trial which adds consolidation MEDI4736 (durvalumab) to standard chemoradiation, demonstrated significant improvement in progression free survival (PFS) by 11 months (Antonia 2017). There was not only a significantly longer time to distant metastatic disease or death (median 23.2 months vs. 14.6 months, HR 0.52 [(95% CI, 0.39-0.69)] but there was also a significantly greater overall response rate [(28.4% vs 16%, HR 1.78 (1.27-2.51)] and median duration of response [not reached vs. 13.8 months, HR 0.43 (0.22-0.84)] in the primary disease after chemoradiation. This suggests that immunotherapy alone can exert effects that can maintain local control of disease. This is seen even in patients without selection for PD-L1. It is expected that the PACIFIC regimen will be a new standard of care for unresectable locally advanced NSCLC. However, there is significant toxicity of concurrent chemoradiotherapy, which can significantly impact the patient's quality of life and survival, especially in elderly patients (Stinchcombe 2017). Since the median age of NSCLC is 70 years old, much work is needed for an effective and less toxic treatment regimen for patients.

Conventional radiotherapy (RT) dose regimen of 60 Gy in 30 fractions is the current standard dosing (Perez 1980, Bradley 2015). Accelerated hypofractionated RT (ACRT) increases the biologic equivalent dose and thereby improve disease control. There has been abundant clinical experience using ACRT without concurrent chemotherapy to achieve excellent local control for both early and locally advanced disease (Cheung et al, 2014). ACRT can also synergize with immunotherapy in many preclinical models, showing anti-PD-L1 antibody enhanced the efficacy of radiation through a CD8 T cell dependent mechanism (Deng, Weichselbaum 2014, Deng, Beckett 2014). The anti-tumor effect was seen both locally in the primary tumor, and also contralateral, non-irradiated tumor, supporting the role of radiation inducing an immunologic "distant", or abscopal, anti-tumor effect. Even more important is the demonstration that it was the concomitant administration, and not the sequential administration, of anti-PD-L1 with radiation, that improved tumor control and survival in the mice (Dovedi et al, 2014).

It is for these reasons that we believe that the systemic effects and local control effects of checkpoint inhibitors will even be greater in patients with high expression of PD-L1, as demonstrated in Keynote 024. This is the primary rationale why we are selecting patients with PD-L1 high expressing tumors to replace concurrent chemotherapy for immunotherapy in combination with radiotherapy in our trial. This benefit shouldn't be confined to only the patients who are not eligible for chemotherapy, but all patients who are eligible for chemotherapy will likely benefit more from immunotherapy.

However, ACRT with systemic therapy may cause concerning side effects that will be greater than just ACRT alone. While this is not known if such side effects will be increased with immunotherapies, there is experience with platinum-based doublet chemotherapy that may raise similar concerns. CALGB 31102 (Alliance) was a phase I study to escalate the dose per fraction while keeping the total dose at 60 Gy in order to define the maximally tolerated course of accelerated radiation therapy with concurrent chemotherapy. With 21 evaluable patients, only modest hypofractionation was achieved, with the MTD defined in cohort 2 at 60 Gy in 2.5 Gy/fraction, with 2 patients in cohort 2 sustained grade 5 toxicities (hemoptysis, pneumonitis)(Urbanic et al., 2018). While the

current trial does not combine chemotherapy, which is known as a radiation sensitizer, there are potential hazards of combining with immunotherapy that will require very close monitoring of the potential additive or synergistic toxicities. We are conducting the current study taking those safety concerns into consideration.

MEDI4736 (durvalumab)

Mechanism of action
MEDI4736 (durvalumab) is a human monoclonal antibody (mAb) of the immunoglobulin (Ig) G (IgG) 1 kappa subclass that blocks the interaction of programmed cell death ligand (PD-L) 1 (but not PD-L2) with PD-1 on T cells and cluster of differentiation (CD) 80 (B7.1) on immune cells (IC). It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.). MEDI4736 (durvalumab) has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In vitro studies demonstrate that MEDI4736 (durvalumab) antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFNγ) (Stewart et al, 2015).

2.2 Clinical pharmacokinetics (PK)

As of October 24, 2016, PK data from study CD-ON-MEDI4736-1108 were available for 993 patients following treatment with MEDI4736 (durvalumab) at 0.1 to 10 mg/kg every two weeks (Q2W) and 15 mg/kg every three weeks (Q3W) (dose-escalation), 10 mg/kg Q2W (dose-expansion), and 20 mg/kg every four weeks (Q4W) (dose-exploration), administered as an intravenous (IV) infusion over 60 minutes. The maximum plasma concentration (C_{max}) increased in an approximately dose-proportional manner over the dose range examined. The area under the concentration-time curve from 0 to 14 days (AUC_{0-14}) increased dose-proportionally at doses of 3 to 20 mg/kg and more than dose-proportionally at doses of <3 mg/kg, likely due to saturable target-mediated clearance (CL). The steady state was achieved at approximately Week 16. Accumulation of MEDI4736 (durvalumab) was observed following repeated dosing. Mean accumulation ratio (AR) ranged from 0.64 to 1.87 and 3.16 to 4.93 for C_{max} and (trough plasma concentration (C_{trough}), respectively. Near complete target saturation (sPD-L1 and membrane bound) is expected with MEDI4736 (durvalumab) ≥3 mg/kg Q2W.

Clinical safety summary
As of July 12, 2017, MEDI4736 (durvalumab) 10 mg/kg Q2W has been given to more than 1800 patients from three MEDI4736 (durvalumab) monotherapy studies (CD-ON-MEDI4736-1108, ATLANTIC and PACIFIC). The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see the Dosing Modification and Toxicity Management Guidelines in Section 6). However, life-threatening and fatal events have been reported.

Adverse events (AEs) that were considered by the investigator as related to MEDI4736 (durvalumab) in ≥5% of patients were fatigue (15.8%), diarrhea (8.1%), hypothyroidism (8.0%), nausea (7.2%), pruritus (6.9%), decreased appetite (6.4%), and rash (6.4%). AEs of Grade 3 or higher considered related to MEDI4736 (durvalumab) were reported in 201 patients (10.6%): 177 patients (9.4%) had events of Grade 3, 13 patients (0.7%) had events of Grade 4, and 11 patients (0.6%) had Grade 5 (fatal) events. The only Grade 5 event considered related to MEDI4736 (durvalumab) occurring in ≥2 patients was pneumonitis (5 patients [0.3%]). A total of 108 patients (5.7%) had serious AEs (SAEs) that were considered by the investigator as related to MEDI4736 (durvalumab).

AEs of special interest (AESI)
The AESIs reported in AstraZeneca or MedImmune-sponsored MEDI4736 (durvalumab) studies are defined as AEs that include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism that may require more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy.

Early recognition of signs and symptoms potentially related to an inflammatory or immune-mediated mechanism is important for proper management of toxicities. For guidance on identifying, evaluating, and treating AESIs/imAEs, see the Toxicity Management Guidelines.

AESI/imAEs observed with anti PD-L1/PD-1 agents such as MEDI4736 (durvalumab) include pneumonitis, hepatitis, diarrhea/colitis and intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), nephritis, rash/dermatitis, pancreatitis, myocarditis, myositis/polymyositis and rare/less frequent imAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome.

Other inflammatory responses that are rare with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

The summary information for the AESIs below, unless stated otherwise, are based on the DCO of July 12, 2017.

Pneumonitis
Across the MEDI4736 (durvalumab) monotherapy pooled dataset pneumonitis events observed (pneumonitis, interstitial lung disease (ILD), acute interstitial pneumonitis and pulmonary fibrosis) were reported at a frequency rate of Common (98/1889; 5.2%). Most were Grade 1 or 2 in severity and most were reported as PT pneumonitis (88 patients [4.7%]). CTC Grade 3 pneumonitis (PT) was reported in 15 patients (0.8%);

CTC Grade 4 in 1 patient (<0.1%) and CTC Grade 5 pneumonitis in 5 patients (0.3%). CTC Grade 3 ILD (PT) has been reported from studies outside of the pooled dataset. There were no CTC Grade 4 or 5 events of ILD.

Presentations of pneumonitis can range from asymptomatic lung infiltrates to those that mimic severe bacterial pneumonia (Teply and Lipson 2014). Early consideration of pneumonitis should be realized when patients present with new onset or worsening of respiratory symptoms such as dyspnea or cough. Prompt treatment with steroids is important as per current established Toxicity Management Guidelines.

Hepatitis
Immune-mediated hepatitis/hepatic toxicity is the inflammation of the liver. Hepatic AEs induced by PD-1/PD-L1 inhibitors commonly present as asymptomatic increase of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), rarely total bilirubin. A proportion of patients may be presenting with fatigue, fever and radiologic appearances including hepatomegaly, periportal lymphadenopathy and periportal edema (Zhang et al, 2016).

As a grouped term, selected hepatic events including laboratory abnormalities were reportedly 12.0% (227 patients) across 1889 patients who have received MEDI4736 (durvalumab) monotherapy 10 mg/kg Q2W. Hepatitis events (autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatotoxicity and hepatitis) were reported at a frequency rate of Uncommon (14 patients; 0.7%). Seven of the 14 events of hepatitis were Grade 3. There were no Grade 4 events with the exception of hepatitis acute (1 patient) reported outside of the pooled dataset. One patient experienced a CTC Grade 5 event of autoimmune hepatitis. Other AESIs such as hepatic failure (5 patients), jaundice (5 patients), hyperbilirubinemia (15 patients) and laboratory abnormality AESIs have been observed, 3 of which were CTC Grade 5 (hepatic failure, hyperbilirubinemia and transaminases increased).

Monitoring liver function tests while receiving study medication is important as hepatitis often manifests as asymptomatic elevated levels of hepatic transaminases (ALT, AST, bilirubin; Kim et al, 2013). Prompt treatment with steroids is important as per current established Toxicity Management Guidelines.

Colitis
Diarrhea is the most frequent AESI reported across the Phase I to Phase III clinical studies with MEDI4736 (durvalumab) monotherapy with a frequency of Very common (329/1889; 17.4%) in patients receiving 10 mg/kg MEDI4736 (durvalumab) IV Q2W. Most of these were Grade 1. Treatment-emergent colitis-type AESIs were reported at a frequency of Common (21 of 1889 patients; 1.1%). Most were Grade 2 or 3. CTC Grade 4 colitis was reported in 1 patient (rare; <0.1%).

Patients should be monitored for signs and symptoms of colitis or diarrhea. Investigators are instructed to begin diarrhea management early to minimize the risk of colitis (please refer to the Toxicity Management Guidelines). Early initiation of diarrhea treatment

guidelines has been shown to reduce bowel perforation and colectomy rates, drug-related diarrhea, and serious gastrointestinal imAEs by up to 50% in patients treated with ipilimumab (Tarhini 2013).

Intestinal perforation
Full thickness injury of the bowel wall and subsequent perforation of the gastrointestinal tract can be due to a variety of etiologies, commonly instrumentation, surgery, bowel injury, bowel obstruction, neoplasms (particularly colon carcinoma) and concomitant medications such as prolonged use of non-steroidal inflammatory drugs (NSAIDs). Spontaneous perforation can be related to inflammatory changes or tissues weakened by medications or connective tissue disorders (Cahalane 2016).

Across the MEDI4736 (durvalumab) monotherapy pool of studies, intestinal perforation was reported at a frequency rate of Uncommon (2/1889; 0.1%); Grades 2 and 4. There were no Grade 5 events.

Monitor for symptoms that may be related to bowel perforation such as sepsis, peritoneal signs, and ileus (refer to the Toxicity Management Guidelines for diarrhea/colitis). Investigators should adhere to the overall management for immune-mediated toxicities by performing a thorough evaluation to rule out alternative etiologies and by initiating prompt treatment including steroids.

Endocrinopathies
Immune-mediated endocrinopathy is the inflammation of any organ in the hypothalamic-pituitary-adrenal axis, but is most typically reported to affect the pituitary, thyroid and/or adrenal glands, leading to hypophysitis/hypopituitarism, thyroid dysfunction, and/or adrenal insufficiency (Teply and Lipson 2014). The clinical presentation of immune-mediated endocrinopathies most often include hypothyroidism, hyperthyroidism, and nonspecific symptoms of headache and fatigue, but may also include myalgias, visual field defects, behavioral changes, electrolyte disturbances, loss of appetite and hypotension (Tarhini 2013). Patients with endocrinopathies may present with abnormal endocrine laboratory test results including thyroid-stimulating hormone (TSH), free T4, total and free T3, cortisol, adrenocorticotrophic hormone, luteinizing hormone, follicle-stimulating hormone, and testosterone.

Frequencies for immune-mediated endocrinopathy, as grouped terms of AESIs including laboratory abnormality AEs, are indicated in the table below.

Endocrinopathy AESIs

Endocrinopathy	**MEDI4736 (durvalumab) monotherapy (10 mg/kg Q2W) (N=1889)**	**MEDI4736 (durvalumab) + tremelimumab (20 mg/kg Q4W and 1 mg/kg) (N=1088)**
Hypothyroidism [a]	Very common 206 (10.9%)	Very common 137 (12.6%)

Hyperthyroidism [a]	Common 135 (7.1%)	Common 78 (7.2%)
Adrenal insufficiency [a]	Uncommon 13 (0.7%)	Common 21 (1.9%)
Hypophysitis/Hypopituitarism [a]	Rare 1 (<0.1%)	Uncommon 24 (0.4%)
Type 1 diabetes mellitus	Rare 1 (<0.1%)	0 (0.0%)

[a]Grouped term based on a number of individual MedDRA PTs.
AESI adverse event of special interest; MedDRA Medical Dictionary for Regulatory Activities; N total number of patients; PT preferred term; Q2W every 2 weeks; Q4W every 4 weeks.

Most endocrinopathy events reported were Grade 1 or 2. In the monotherapy pool, Grade 3 events consisted of adrenal insufficiency (2 patients), hypophysitis/hypopituitarism (1 patient), hyperthyroidism (1 patient) and hypothyroidism (2 patients). There were no CTC Grade 4 or 5 events. In the combination, AESIs for hypothyroidism and hyperthyroidism (including laboratory abnormalities) were the most frequently observed events with frequency rates of Very common (12.6%) and Common (7.2%), respectively. The severity of these events are predominantly Grades 1 and 2 with Grade 3 events observed with hyperthyroidism only (0.5%). Adrenal insufficiency was reported as mostly Grades 2/3 with 1 Grade 4 event and no Grade 5 events. Hypophysitis or hypopituitarism was reported as mostly Grade 3 with no Grade 4 or 5 events.

Across the monotherapy pool of studies, 1 patient (<0.1%) experienced Grade 3 Type 1 diabetes mellitus. The patient, a 60 year old Caucasian male with NSCLC without a history of diabetes mellitus or hyperglycemia, developed severe autoimmune-mediated hyperglycemia (blood glucose 458 mg/dL) 43 days after starting MEDI4736 (durvalumab), was tested positive for anti-GAD antibody 322 U/mL (reference range 0 to 5 U/mL) and was negative for B-islet antibody. He was diagnosed with Type 1 diabetes mellitus and was treated with insulin; the DM resolved with sequelae (insulin dependency).

Prompt recognition and management of endocrinopathies is important. Refer to the endocrinology section of the Toxicity Management Guidelines.

Nephritis
The major clinical syndromes produced by immune-mediated renal injury include nephrotic syndrome, rapidly progressive glomerulonephritis, and acute renal failure (Cunard and Kelly 2003). In association to immune-checkpoint inhibitors, two different forms of ipilimumab-induced renal damage are reported, acute kidney injury due to predominant acute granulomatous tubulointerstitial nephritis and nephrotic syndrome in lupus nephritis (Izzedine et al, 2014). Signs and symptoms include increase in serum creatinine, decrease in urine output, peripheral edema, hematuria, loss of appetite.

As a grouped term, selected renal events including laboratory abnormalities were reported at a frequency of 6.3% (119 patients) across the 1889 patients included in the MEDI4736 (durvalumab) monotherapy pool. Blood creatinine was the most common event reported (4.0%), of which the majority were Grade 1 or 2 in severity. Nephritis events were reported at a frequency rate of Uncommon (6 patients [0.3%]) with 1 event

each of Grade 2 autoimmune nephritis, glomerulonephritis, glomerulonephritis membranous, and nephritis and 2 tubulointerstitial nephritis (Grade 2 and 3).

Patients should be monitored for changes in renal function (e.g., that manifest as elevated serum blood urea nitrogen and creatinine, decreased creatinine CL, electrolyte imbalance, decrease in urine output, or proteinuria and any other findings that may be indicative of nephritis) prior to and periodically during treatment. Prompt treatment with steroids is important as per current established Toxicity Management Guidelines.

Rash/dermatitis
Immune-mediated dermatitis is generally mild and presents as mild local or diffuse maculo-papular, erythematous rash on the trunk or extremities, which may be accompanied by pruritus, alopecia, and vitiligo, suggestive of inflammatory response to melanocytes (Lacouture et al, 2014). In rare cases, severe dermatitis has been reported to manifest as Stevens-Johnson syndrome, toxic epidermal necrolysis, or rashes complicated by dermal ulceration or necrotic, bullous, or hemorrhagic manifestations (Tarhini et al, 2013, Kaehler et al, 2010).

AESIs of rash (as a composite term) were reported as Very common in 283 (15.0%) patients receiving MEDI4736 (durvalumab) monotherapy and Very common in 256 (23.5%) patients receiving the combination. The majority of events were CTC Grade 1, with 11 and 7 patients, respectively, experiencing CTC Grade 3 events.

AESIs falling under the grouped term of dermatitis include milder events such as pruritus, eczema and erythema to more specific or severe skin toxicities such as events of dermatitis bullous, dermatitis exfoliative or dermatitis psoriasiform. Overall, these events have been reported as Very common (n=299; 15.8%) in monotherapy. Most events were Grade 1, with 3 patients in the monotherapy group.

Close monitoring, early detection and prompt treatment with steroids (topical or systemic based on severity) is important. Refer to the Toxicity Management Guidelines.

Myocarditis
In the literature for other immune checkpoint inhibitors, a variety of clinical presentations, diagnostic evidence (laboratory, imaging, histopathology), and resulting diagnoses have been described in cases of myocarditis, including heart failure, brady- and tachyarrhythmias, and acute coronary syndrome-like presentations without evidence of ischemia. Treatments are variable, and include immunosuppression and beta blockers, ACE inhibitors, and diuretics. Outcomes can range from rapid response and resolution with immunosuppression to fulminant, fatal events.

Across the MEDI4736 (durvalumab) monotherapy pool of studies, as of the DCO of July 12, 2017, there has been 1 serious report of Grade 3 myocarditis and 2 additional cases (Grade 3 and Grade 4) outside of the pooled dataset. In all cases the patients recovered or were improving with corticosteroid therapy.

Investigators should be aware of such rare, but severe immune-mediated adverse events including myocarditis with its presenting signs/symptoms (e.g., decreased ejection fraction, arrhythmias, in particular occurrences of atrioventricular block).

For patients with suspected myocarditis, investigators should obtain a cardiology consult and institute full diagnostic work-up (that includes exclusion of other alternate causes such as infection) and the appropriate management that includes discontinuing drug (permanently if myocarditis is confirmed) and the prompt use of steroids or other immunsosuppressives. Patients with pre-existing cardiac disorders should be closely monitored for deterioration in their cardiac condition, which could suggest new onset myocarditis.

Myositis/polymyositis
The diagnosis of myositis or polymyositis should be suspected in patients who present with proximal muscle weakness and the evaluation should include an examination of the skin, muscle enzyme measurement, antibody testing, any systemic disease manifestations and exclusion of other diseases including drug-induced myopathy. Cases of myositis have been reported with myocarditis in which immune infiltration has been described in skeletal and cardiac muscle (Johnson et al, 2016).

In the MEDI4736 (durvalumab) pool of studies as of the DCO, 3 patients (0.2%) reported the event of myositis, including 1 Grade 3 in severity. Outside of the pooled dataset, there were 2 fatal events of polymyositis considered as treatment-related by the Investigator.

Investigators should adhere to the Toxicity Management Guidelines by performing a thorough evaluation to rule out alternative etiologies and initiating prompt treatment with steroids and modification of study drug dose regimen depending on the severity of the event. Refer to the Toxicity Management Guidelines.

Pancreatitis
Pancreatitis is an inflammatory condition of the pancreas that typically manifests initially as asymptomatic elevations of amylase and lipase in patients treated with immune checkpoint inhibitors. Clinical presentation frequently includes low-grade abdominal pain with accompanying fever and malaise (Weber et al, 2012, Di Giacomo et al, 2010). Biopsies showed diffuse T-cell infiltrate consistent with immune-mediated pancreatitis (Weber et al, 2012).

Across the 1889 patients in the monotherapy program, events of pancreatitis were Uncommon to Rare. Four patients (0.2%) experienced pancreatitis (Grade 2, Grade 3 and Grade 4 in severity) and 1 patient (<0.1%) with Grade 3 acute pancreatitis. Elevations in amylase and lipase were reported as Uncommon (0.6% and 0.5%, respectively).

Patients should be monitored for signs and symptoms of pancreatitis including Grade 3 or 4 elevations in lipase and/or amylase. Close monitoring, early detection and prompt treatment of these events are important. Refer to the Toxicity Management Guidelines.

Other rare or less frequent AESIs and immune-mediated adverse events
Events with an inflammatory or immune mediated mechanism could occur in nearly all organs. ImAEs that are less frequent with a potential immune-mediated etiology include, but are not limited to: pericarditis, sarcoidosis, uveitis, and other events involving the eye (e.g., keratitis and optic neuritis), skin (e.g., scleroderma and vitiligo), hematological (e.g., hemolytic anemia and, immune thrombocytopenic purpura) and rheumatological events (polymyalgia rheumatic and autoimmune arthritis).

Neuropathy/neuromuscular toxicities such as Guillain-Barre Syndrome and myasthenia gravis have also been observed. One patient receiving MEDI4736 (durvalumab) monotherapy outside of the pooled dataset experienced Grade 4 myasthenia gravis

Prompt treatment of these conditions as per current Toxicity Management Guidelines is required.

Infusion-related reactions, anaphylaxis and allergic reactions
Adverse reactions that occur during or shortly after infusion may include fever, chills, hypotension, dyspnea, tachycardia, cyanosis, respiratory failure, urticarial and pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension rash, headache, flushing, sweating, myalgia, nausea, vomiting, unresponsiveness, and hemodynamic instability. The typical onset can be within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. The majority of reactions occur after the first or second exposure to the agent, but between 10% and 30% occur during subsequent treatments (Lenz 2007).

Anaphylaxis is a systemic, immediate hypersensitivity reaction that is mediated by interactions between factors released from IgE and mast cells; these interactions result in an antigen-antibody reaction. Clinical manifestations of acute allergic reactions may range from localized skin reactions at the injection site to AEs, which can include, but are not limited to, those events similar to infusion-related reactions to severe reactions including anaphylaxis and drug hypersensitivity syndromes. These reactions may be more common with higher rates of infusion, and in patients with a history of allergies.

Patients participating in MEDI4736 (durvalumab) clinical studies should be closely monitored during and after infusions. Severe hypersensitivity reactions should be managed according to standard clinical practice, and medical equipment and staff trained to treat acute anaphylactic reactions must be immediately available at all sites that perform mAb infusions.

Cytokine release syndrome
Certain mAb therapeutics have been shown to induce a range of acute infusion reactions including cytokine-release syndrome that can lead to AEs in patients. As of the DCO date, there have been no reported events of cytokine release syndrome in the ongoing MEDI4736 (durvalumab) studies.

Immune-complex disease
The potential risk of immune complex disease for MEDI4736 (durvalumab) is theoretical based on the known risk associated with mAbs and other proteins. The incidence of MEDI4736 (durvalumab) ADA-positive patients in clinical studies is low, and hence the risk of immune complex disease is likely to be low. Specifically, of 1124 patients treated with MEDI4736 (durvalumab) 10 mg/kg Q2W and evaluable for the presence of ADAs, 3.3% of patients tested positive for treatment-emergent ADAs. Neutralizing antibodies against MEDI4736 (durvalumab) were detected in 0.3% of patients. The presence of ADAs did not have a clinically relevant effect on PK. There have been no reported events of immune complex reactions in patients receiving MEDI4736 (durvalumab).

For guidance on identifying, evaluating, and treating an imAE please see the Toxicity Management Guidelines.

2.2.2 Infections

In addition to infections determined as ADRs, other infections are considered as potential risks based on the potential mechanism of action of checkpoint inhibitors.

Serious and/or ≥Grade 3 infections requiring hospitalization including, but not limited to, sepsis, pneumonia, lung infections, have been reported in clinical studies with MEDI4736 (durvalumab), but are often confounded by underlying disease and use of concomitant medications (e.g., steroids and other immunosuppressives). As of the DCO, events from the MedDRA Infections and Infestations SOC, events with a severity ≥Grade 3 and frequency of ≥1% in the monotherapy pool included lung infection (n=19; 1%), pneumonia (n=51; 2.7%), sepsis (n=35; 1.9%) and urinary tract infection (n=21; 1.1%). Overall, CTC Grade 3 events were reported in 143 patients (7.6%), CTC Grade 4 events were reported in 36 patients (1.9%) and CTC Grade 5 infection events in 18 patients (1.0%).

Non-serious infections have been reported in clinical studies with MEDI4736 (durvalumab). Of the ADRs under the MedDRA Infections and Infestations SOC, events reported as non-serious only and with a frequency of >1% included nasopharyngitis (n=92; 4.9%), oral candidiasis (n=49; 2.6%), pharyngitis (n=20; 1.1%) and rhinitis (n=39; 2.1%).

3.0 PATIENT ELIGIBILITY AND INELIGIBILITY CRITERIA

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

3.1 Eligibility Criteria (13-JAN-2021)

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

3.1.1 Pathologic (cytological or histological) proof of diagnosis of stage II-III (AJCC 8th ed.) unresectable or inoperable, non-metastatic NSCLC within 60 days prior to registration, with no liver or renal end organ damage, as determined by normal laboratory values noted below. Locally recurrent, N1-N3 disease following surgery without prior radiation therapy is eligible. Patients with N1 to N3 and undetectable primary lung tumors (T0) are eligible.

3.1.2 Pathological diagnosis of PD-L1 high expressing tumors (≥50%) within 60 days prior to registration (**using Dako 22C3 IHC antibody or the Ventana SP263 antibody platforms**) performed at a CLIA-certified lab.

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

- History/physical examination within 30 days prior to registration;
- PET/CT scan for staging within 30 days prior to registration (note: if CT portion of PET/CT scan is not of diagnostic quality, then a separate CT scan with contrast is required);
- MRI scan of the brain with contrast; if medically contraindicated, then CT scan of the brain with contrast (unless medically contraindicated) is acceptable, within 30 days prior to registration;
- Sufficient lung function with FEV1 ≥ 0.8 Liter or ≥ 35% predicted and DLCO ≥ 40% with or without bronchodilator within 30 days prior to registration;
- Patients who meet the criterion above without O2, but who need acute (started within 10 days prior to registration) supplemental oxygen due to tumor-caused obstruction/hypoxia are eligible, provided the amount of the O2 needed has been stable.

3.1.4 Age ≥ 18;

3.1.5 Body weight > 30 kg;

3.1.6 ECOG Performance Status of 0-2 within 30 days prior to registration;

3.1.7 Adequate hematologic function within 30 days prior to registration defined as follows:

- ANC ≥ 1500 cells/mm³;
- Lymphocyte count ≥ 500 cells/mm³;
- Platelet count ≥ 100,000 cells/mm³;
- Hemoglobin ≥ 9.0 g/dL (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dl is acceptable).

3.1.8 Adequate renal function within 30 days prior to registration defined as follows: Glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m^2 (See Appendix IV for eGFR calculations).

3.1.9 Adequate hepatic function within 30 days prior to registration defined as follows:

- Total bilirubin ≤ 1.5 x ULN with the following exception:
    - Patients with known Gilbert disease who have serum bilirubin level ≤ 3 x ULN may be enrolled;
- AST and ALT ≤ 2.5 x ULN.

3.1.10 Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients, obtained within 14 days prior to registration. Women

will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

3.1.11 Patients who are human immunodeficiency virus (HIV) positive may participate IF they meet the following eligibility requirements:

- They must be stable on their anti-retroviral regimen, and they must be healthy from an HIV perspective.
- They must have a CD4 count of greater than 250 cells/mcL.
- They must not be receiving prophylactic therapy for an opportunistic infection.

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

3.2 Ineligibility Criteria (25-NOV-2019)

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

3.2.1 Definitive clinical or radiologic evidence of metastatic disease.

3.2.2 Prior invasive malignancy (except those with a negligible risk of metastasis or death and with expected curative outcome [such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent] or undergoing active surveillance per standard-of-care management [e.g., CLL Rai Stage 0, prostate cancer with Gleason score ≤ 6, and PSA ≤ 10 mg/mL]) unless disease free for a minimum of 3 years;

3.2.3 Prior chemotherapy or systemic therapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;

3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields so that cumulative composite dose combining previous plan and current plan to be within 80 Gy to the trachea, major blood vessels, esophagus, and heart, and 55 Gy to the spinal cord (if such patients are being considered, this will need to be centrally reviewed). Prior chest radiation without overlap is permissible;

3.2.5 History of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. Patients with a history of treated autoimmune thyroid disease requiring thyroid replacement but not immunosuppressives, as well as type 1 diabetes, are permitted.

Patients with vitiligo, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.2.6 History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on chest PET/CT or CT scan;

3.2.7 Severe, active co-morbidity defined as follows:

- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, fatty liver, and inherited liver disease;
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications;
- Active tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice);
- Active hepatitis B (chronic or acute) or hepatitis C infection. Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen (HBsAg) test, a positive anti-HBc [antibody to hepatitis B core antigen], and a negative viral DNA test (only obtained if HBsAg is found positive) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

3.2.8 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception during treatment and for 3 months after the last dose of MEDI4736 (durvalumab); this exclusion is necessary because the treatment involved in this study may be significantly teratogenic. Women who are breastfeeding are also excluded.

3.2.9 Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria:

a. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.

3.2.10 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

3.2.11 History of allogenic organ transplantation.

3.2.12 History of leptomeningeal carcinomatosis

3.2.13 History of active primary immunodeficiency

3.2.14 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:

a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection);
b. Systemic corticosteroids at physiologic doses not to exceed <<10 mg/day>> of prednisone or its equivalent;
c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

3.2.15 Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

3.2.16 Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

4.0 REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

PRE-TREATMENT ASSESSMENTS (23-JAN-2019)

Assessments	Prior to Registration (calendar days)	Prior to Treatment (calendar days)
Pathologic proof of NSCLC	60	
History, physical examination, performance status, vital signs*	30	
PD-L1 level	60	
PET/CT for staging (including tumor measurements †)	30	
Brain MRI with contrast or brain CT with contrast if there is contraindication for MRI	30	
Pulmonary Function Tests (FEV1 and DLCO)	30	
Urine or serum pregnancy test (women of childbearing potential)	14	
CMP (Complete Metabolic Panel) and CBC with differential**	30	
TSH***		As clinically indicated
ECG, Troponin****		As clinically indicated
Biospecimen Collection: tissue and blood for integrated CTC and immune biomarker analyses – see Section 10 and Appendices V to VIII for details		Once prior to receipt of durvalumab

* Vital signs to include heart rate and blood pressure, additional baseline cardiac monitoring (e.g. ECG, troponin, BNP) as clinically indicated

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

*** TSH with reflex to T4, then T3 if clinically indicated

**** Cardiac monitoring as clinically indicated based upon relevant past medical history and signs/symptoms

† Radiographic tumor measurements should be obtained via Chest CT. See RECIST 1.1 (Appendix I) for allowable imaging modalities used to assess disease at baseline and subsequent visits.

ASSESSMENTS DURING TREATMENT (23-JAN-2019)

Assessments	**During Radiation Therapy/MEDI4736 (durvalumab) Treatment**	**During Post-Radiation Therapy/MEDI4736 (durvalumab) Treatment**
History and Physical Exam, Vital Signs*, Performance Status and Concurrent Medications	Weekly	Every cycle
Toxicity Assessment Graded per NCI CTCAE, v 5.0	Weekly	Every cycle
TSH**	As clinically indicated	Every 3 cycles unless clinically indicated
CMP and CBC with differential	Weekly	Every cycle
CT scan chest (through adrenals) with contrast (unless contraindicated)		4-6 weeks after conclusion of RT and then every 3 months
Biospecimen Collection: tissue and blood for integrated CTC and immune biomarker analyses – see Section 10 and Appendices V to VIII for details	On Day 15 from start of radiation and Day 30 from start of radiation	At 3 months from start of durvalumab (i.e. cycle 4)
Biospecimen Collection of CTC only	None	At 6 months and 12 months from start of durvalumab (i.e. cycles 7 and 13)

* Vital signs to include heart rate and blood pressure, additional cardiac monitoring (e.g. ECG, troponin, BNP) as clinically indicated; see Section 5.1 for VS assessment during MEDI4736 (durvalumab) infusion

**TSH with reflex to T4, then T3 if clinically indicated

ASSESSMENTS IN FOLLOW UP

Assessments	**q3 months for year 1 from end of MEDI4736 (durvalumab), q4 months for year 2 from end of MEDI4736 (durvalumab)**	**As clinically indicated**
Performance Status	X	
History and Physical Examination	X	
Toxicity Assessment Graded per NCI CTCAE, v 5.0	X	
TSH*	X (Until return to normal limits and then as clinically indicated)	
CT scan of chest (through adrenals)	X (Or to progression, whichever occurs first)	
MRI Brain or CT scan with contrast		X

*TSH with reflex to T4, then T3 if clinically indicated

Definition of Disease Assessments

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eisenhauer 2009] which will be site-reported. Immune-Related Response Criteria (irRC) guidelines for treatment response (ESMO guidelines, Haanen 2017) will also be calculated by NRG Oncology using site-reported tumor measurements. See Appendix I for details.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

Systemic therapy protocol treatment with MEDI4736 (durvalumab) must start within 2 weeks of trial registration and 2 weeks (Day -14) prior (+/- 48 hours) to the start of RT.

5.1 MEDI4736 (durvalumab)

NOTE: Please refer to the Investigator Brochure for complete details on safety and treatment information. [See Section 9.1 for instructions about how to obtain the IB and preparation of MEDI4736 (durvalumab).]

MEDI4736 (durvalumab) will be administered intravenously as a 1500 mg fixed dose over 60 minutes starting 2 weeks (Day -14 +/- 48 hours) prior to starting radiation therapy, for 13 cycles (1 cycle = 4 weeks), until disease progression or toxicity or death, whichever comes first (see Section 5.2.6). Patients must be monitored before and after the infusion with assessment of vital signs at the times specified in Section 4 and as clinically indicated. During the infusion period, patients must be monitored (pulse rate, blood pressure) every 30 minutes (including times where infusion rate is slowed or temporarily stopped).

If RT is held or discontinued, MEDI4736 (durvalumab) may be continued as scheduled. In patients who require dose delays, MEDI4736 (durvalumab) will be continued as soon as the patient meets retreatment criteria, and the full dose of 1500 mg will be administered. If the patient does not meet retreatment criteria before the next scheduled dose, if/when the toxicity resolves to the point where treatment is possible, the doses of MEDI4736 (durvalumab) are applied off schedule q 4 weeks. The missing doses will not be made up.

Cohort 1 & Expansion Cohort 3			
Week	**Days**	**ACRT (4 Gy/fractions)**	**MEDI4736 (durvalumab) 1500 mg IV**
-2	-14 to -8		Day -14
-1	-7 to -1		
1	1 to 7	Day 1 to 5	
2	8 to 14	Day 8 to 12	
3	15 to 21	Day 15 to 19	Day 15
4	22 to 28		
5	29 to 35		
6	36 to 42		
7-47	43 to 329		q 4 weeks X 11 cycles: Days 43, 71, 99, 127, 155, 183, 211, 239, 267, 295, 323

Cohort 2 & Expansion Cohort 4			
Week	**Days**	**Standard RT (2 Gy/fractions)**	**MEDI4736 (durvalumab) 1500 mg IV**
-2	-14 to -8		Day -14
-1	-7 to -1		
1	1 to 7	Day 1 to 5	
2	8 to 14	Day 8 to 12	
3	15 to 21	Day 15 to 19	Day 15
4	22 to 28	Day 22 to 26	
5	29 to 35	Day 29 to 33	
6	36 to 42	Day 36 to 40	
7-47	43 to 329		q 4 weeks X 11 cycles: Days 43, 71, 99, 127, 155, 183, 211, 239, 267, 295, 323

5.2 Radiation Therapy (25-NOV-2019)

Radiation therapy protocol treatment must begin within 2 weeks (Day -14 +/- 48 hours) after start of MEDI4736 (durvalumab) administration. **Pre-treatment review is required for each treatment plan prior to the start of RT.** Three (3) business days are required for the pre-treatment review once all required data is received in completion. Refer to Section 12.1 for submission details. **Daily IGRT will be used for all patients.**

5.2.1 Treatment Technology

Three-dimensional conformal radiation therapy (3D-CRT) or Intensity Modulated Radiation Therapy (IMRT) is allowed. Proton Beam Therapy is not allowed. IMRT delivered from units with capabilities including Tomotherapy, ViewRay and VMAT are permitted. For photons, beam energy of 6-10 MV will be used. Daily image guided radiation therapy (IGRT) using orthogonal X-ray, cone beam CT, CT on rails, or MR guidance must be used for all patients, regardless of radiation techniques. Multi-leaf collimation (MLC) will be used to spare normal tissues outside of the target volume.

5.2.2 Immobilization and Simulation

Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices. Alpha cradles or Vac-Lok devices are used for shoulder immobilization. Arms are abducted bilaterally with hands above the head (preferably in all cases unless patients are incapable of doing so but setup must be reproducible daily and treatment planning will accommodate for the deviation).

Simulation Imaging

Simulation CTs should be CT slices of 3 mm slice thickness starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume. Administration of intravenous (I.V.) contrast during simulation CT is optional provided a diagnostic CT with contrast has been done to help delineate the major blood vessels. If such diagnostic CT is not available, I.V. contrast should be given during the treatment planning CT. In the case in which contrast is present during the treatment planning CT, the density of the contrast should be overridden to a representative background electron density.

Motion Management Technique
The use of four-dimensional radiation treatment planning is highly encouraged to account for respiratory motion in the treatment planning process. Other methods permitted are active breath hold, gated treatment and abdominal compression.

5.2.3 Imaging for Structure Definition and Image Registration

A volumetric treatment planning CT study will be required to define gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV)(see definitions below). Contiguous CT slices, having no more than 3 mm thickness through the regions harboring gross tumor and grossly enlarged lymph nodes and no more than 10 mm thickness of the remaining regions are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume. The GTV, CTV, and PTV and critical structures will be outlined on all appropriate CT slices. A treatment planning FDG PET/CT scan (or FDG-PET alone) with the patient in the treatment position is encouraged for treatment planning. In the case where the PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan. Otherwise, a diagnostic PET/CT used for staging could be used for target delineation with image co-registration with the planning CT.

5.2.4 Definition of Target Volumes and Margins

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

There are two tables below. The first table (Table A) applies to patients being treated using the non-preferred motion management method. The second table (Table B) applies only to patients being planned with 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
CTV_6000	CTV to receive 60 Gy	Required
PTV_6000	PTV to receive 60 Gy	Required

TABLE B: 4D VOLUME TECHNIQUE

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
ITV_6000	ITV to receive 60 Gy	Required when IGTV is drawn
PTV_6000	PTV to receive 60 Gy	Required

Detailed Specifications
Target volumes: The definitions of volumes will be in accordance with the ICRU 50 (1999) for 3D and ICRU 83 (2010) for IMRT.

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.
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 0.8 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, no IM is needed.

Setup margin (SM): Daily IGRT is a requirement for this trial; therefore, the SM will be 0.5 cm in all directions.
GTV_6000: The primary tumor and clinically positive lymph nodes seen either on the planning CT
(> 1cm short axis diameter) or 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.
CTV_6000: The CTV is defined to be the GTV plus a 0.5cm to 1cm margin as appropriate to account for microscopic tumor extension. If an IGTV is used then a 0.5cm to 1cm margin is added to the IGTV to form a CTV. The CTV should be adjusted to not expand into other organs such as esophagus, major blood vessels, or bone.
IGTV_6000: 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. Maximum intensity projection image may be used for contouring, with verification against all breathing phases.

ITV_6000: 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: The PTV will be equal to the ITV+IM+SM. SM is defined in Detailed Specifications paragraph 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 0.5cm towards this particular dimension (skin or spinal canal).

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

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard Name	Description	Validation **Required/Required when applicable/Optional**
SpinalCord	Spinal Cord	**Required**
Lungs-GTV	Combined lungs minus GTV	**Required**
SpinalCord_PRV03	PRV 3 mm expansion to the spinal cord	**Required**
Esophagus	Esophagus	**Required**
Heart	Heart	**Required**
BrachialPlexus	Brachial Plexus	**Required for upper lobe tumors or high mediastinal nodal involvement**
Trachea	Trachea	**Required**
GreatVes	Major blood vessels (aorta, pulmonary trunk)	**Required**

Detailed Specifications

SpinalCord: Boundaries: Cranial: 1st slice of CT; Caudal: last slice of CT
SpinalCord_PRV03: Boundaries: Uniform 3 mm expansion in all directions

Esophagus: Boundaries: Cranial: Bottom of cricoid; Caudal: GE junction

Lungs-GTV: Boundaries: Cranial: From apex bilaterally; Caudal: to bottom of L2; Right + Left Lung Combined but excluding GTV

Heart: Boundaries: Base: Bottom of the aortic arch; Inferior: Apical most of the ventricle

BrachialPlexus: C5, C6, C7, C8, T1 nerve roots and cord extensions

Trachea: Bottom of cricoid to mainstem bronchi

GreatVes: Arch of aorta, pulmonary vessels

5.2.6 Dose Prescription

Radiation Therapy in the form of Accelerated Hypofractionated Radiation Therapy (ACRT) (Cohort 1 and Expansion Cohort 3):

ACRT is to be carried out using hypofractionated radiotherapy in 4 Gy per fraction for a total dose of 60 Gy in 15 fractions. Radiation treatment will be administered 5 days per week, 1 fraction per day. It is recommended that radiation treatment begin on a Monday, Tuesday, or Wednesday. Treatment may begin on Thursday though not preferred. There are no field reductions. All fields must be treated daily and the entire PTV must be treated daily.

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 priority table 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.

Radiation Therapy in the form of conventionally fractionated radiation therapy (Cohort 2 and Expansion Cohort 4):

Photon radiation should be carried out using standard fractionated radiation therapy in 2 Gy per fraction for a total dose of 60 Gy in 30 fractions. Radiation treatment will be administered 5 days per week, 1 fraction per day. It is recommended that radiation treatment begin on a Monday, Tuesday, or Wednesday. Treatment may begin on Thursday though not preferred. There are no field reductions. All fields must be treated daily and the entire PTV must be treated daily.

Accelerated Hypofractionated RT (ACRT): 4 Gy x 15 fractions = 60 Gy (Cohort 1 & Expansion Cohort 3)					
Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Frequency**	**Dose specification technique**
PTV_6000	60	4.0	15	Daily 1 fraction per day	Covering up to 95% of PTV but at minimum of 95% of PTV should get at least 45 Gy depending on proximity of adjacent normal structures according to dose avoidance

					rules given in Sec. 5.2.7 below.

Standard RT: 2 Gy x 30 fractions = 60 Gy (Cohort 2 & Expansion Cohort 4)					
Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Frequency**	**Dose specification technique**
PTV_6000	60	2.0	30	Daily 1 fraction per day	Covering 95% of PTV

5.2.7 Compliance Criteria

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

Normalization of Dose: The plan is normalized such that 95% of the PTV_6000 volume receives prescription dose of 60 Gy.

Accelerated Hypofractionated RT (ACRT) Compliance Criteria (Cohort 1 & Expansion Cohort 3)

ACRT Target Volume Constraints and Compliance Criteria (Cohort 1 & Expansion Cohort 3)

Accelerated Hypofractionated RT (ACRT): 4 Gy x 15 Fractions = 60 Gy			
Name of Structure	**Dosimetric Parameter**	**Per Protocol**	**Variation Acceptable**
PTV_6000	D95%[Gy]	60	50 to 61.2
	D99%[Gy]	>= 52.5	>= 45
	D0.03cc[Gy]	<= 66	<= 69

Per Protocol range is excluded from Variation Acceptable range.
Note: 45 Gy in 15 fractions is the minimal PTV dose depending on adjacent normal tissue constraints

ACRT Normal Structure Constraints and Compliance Criteria (Cohort 1 & Expansion Cohort 3)

Accelerated Hypofractionated RT (ACRT): 4 Gy x 15 Fractions = 60 Gy				
Name of Structure	**Dosimetric Parameter**	**Per Protocol**	**Variation Acceptable**	**a/b**
Lungs-GTV	V5 [%]	<=65	<=70	2.5

	V16.5 [%]	<=37	<=40	2.5
	Mean[Gy]	<=16.5	<=18.5	2.5
SpinalCord	D0.03cc[Gy]	<=36.5	<=40.2	2.5
SpinalCord_PRV03	D0.03cc[Gy]	<=40.2	<=43.9	2.5
Esophagus	D0.03cc[Gy]	<=58.9	<=61.3	10
	Mean[Gy]	<=31	<=32	10
BrachialPlexus	D0.03cc[Gy]	<= 49.8	<=52	2.5
Heart	D0.03cc[Gy]	<= 49.8	<=52	2.5
	Mean [Gy]	<=16.5	<= 18.5	2.5
Trachea	D0.03cc[Gy]	<=52	<=53.5	2.5
GreatVes	D0.03cc[Gy]	<=53.5	<=55	2.5

Note: It is recommended that the esophagus not be circumferentially irradiated with >53.1 Gy (i.e., the 53.1 Gy isodose line should not encompass the entire axial cross-section of the esophagus at any level).
Per Protocol range is excluded from Variation Acceptable range.

ACRT Delivery Compliance Criteria (Cohort 1 & Expansion Cohort 3)

	Per Protocol	**Variation Acceptable**
Start Date	Monday, Tuesday, or Wednesday	Thursday
Overall Treatment Time	<26 days	26-33 days
Interruptions (other than holidays)	0-3 days	4-7 days

<u>Standard RT Compliance Criteria (Cohort 2 & Expansion Cohort 4)</u>

Standard RT Target Volume Constraints and Compliance Criteria (Cohort 2 & Expansion Cohort 4)

Name of Structure	**Standard RT: 2 Gy x 30 Fractions = 60 Gy**		
PTV_6000	**Dosimetric Parameter**	**Per Protocol**	**Variation Acceptable**
	D95%[Gy]	60	58.8 to 61.2
	D99%[Gy]	>= 54	>=51
	D0.03cc[Gy]	<= 66	<= 69

Per Protocol range is excluded from Variation Acceptable range.

Normal Structure Constraints and Compliance Criteria (Cohort 2 & Expansion Cohort 4)

Standard RT: 2 Gy x 30 Fractions = 60 Gy				
Name of Structure	**Dosimetric Parameter**	**Per Protocol**	**Variation Acceptable**	**a/b**
Lungs-GTV	V5[%]	**<=65**	<= 70	**2.5**
	V20[%]	**<=**37	<=40	**2.5**
	Mean[Gy]	**<=**20	<=22	**2.5**
SpinalCord	D0.03cc[Gy]	**<=**45	<=50	**2.5**
SpinalCord_PRV03	D0.03cc[Gy]	<=50	<=55	2.5
Esophagus	D0.03cc[Gy]	**<=**67	<=70	**10**
	Mean[Gy]	**<=**34	<=35	**10**
BrachialPlexus	D0.03cc[Gy]	**<=63**	<=66	**2.5**
Heart	D0.03cc[Gy]	**<=63**	<=66	**2.5**
	Mean[Gy]	**<=**20	<=22	**2.5**
Trachea	D0.03cc[Gy]	**<=**66	<=68	**2.5**
GreatVes	D0.03cc[Gy]	**<=**68	<=70	**2.5**

Note: 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).
Per Protocol range is excluded from Variation Acceptable range.

Standard RT Delivery Compliance Criteria (Cohort 2 & Expansion Cohort 4)

	Per Protocol	**Variation Acceptable**
Start Date	Monday, Tuesday, or Wednesday	Thursday
Overall Treatment Time (30 fractions)	<47 days	47-53 days
Interruptions (other than holidays)	0-3 Days	4-7 days

5.2.8 Treatment Planning Priorities and Instructions

Critical Structure and Target priorities must be listed in order of decreasing importance
1. SpinalCord
2. Lungs-GTV
3. Esophagus

4. BrachialPlexus
5. Heart
6. Trachea
7. PTV
8. GreatVes
9. ChestWall
10. Skin

Dose Calculations

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

For Convolution/Superposition type algorithms, dose should be reported as computed inherently by the given algorithm. For Monte Carlo or Grid Based Boltzmann Solver algorithms, conversion of Dm (dose-to-medium) to Dw (dose-to-water) should be avoided. Dm, computed inherently by these algorithms, should be reported. These principles hold for Pencil Beam type algorithms and for homogeneous dose calculations when allowed for a clinical trial (e.g., conical collimators in stereotactic radiosurgery).

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. In the case in which contrast is present during the treatment planning CT, the density of the contrast should be overridden to a representative background electron density.

Dose matrix resolution

Dose grid size should be <= 3 mm in all directions.

5.2.9 Patient specific QA

Any patient-specific QA that needs to be acquired should follow institutional guidelines and AAPM task group report recommendations.

For IMRT/VMAT plans, patient specific QA is highly recommended. The recommended patient specific QA criterion is for 90% of the comparison points to pass a ±3%/3mm Gamma Index analysis.

5.2.10 Daily Treatment Localization/IGRT

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

Daily image guidance that allows for 3D shifts is the minimum requirement for this trial. Most advanced imaging techniques can be utilized, as long as they also allow for 3D shifts. The setup margin in this trial is tied to the use of daily image guidance. When able to localize using soft tissue, the target will be most effective for localization. Other soft tissues in the lung such as the carina can help for mediastinal alignment. Fiducial markers can be used for localization as needed. Bony alignment as a surrogate is also acceptable. Any linear shifts seen that are ≥2 mm should be applied prior to treatment.

-Minimal IGRT requirements

Location	No Fiducials	With Fiducials**
Lung*	Imaging that allows for 3D shifts	Imaging that allows for 3D shifts

*Registration using a soft tissue surrogate for the tumor is recommended. Free-breathing CTs are not to be used as reference images for 4D CBCT IGRT process
**Clearly visible anatomical markers are acceptable as fiducials, e.g. inserted radio opaque markers.

5.2.11 Case Review
Pre-treatment reviews are required for all cases. See Sections 8.3 and 12.1 for specifics on submission process and requirements. RT may not begin until approval is received. Three (3) business days are required for the pre-treatment review once all required data is received in completion.

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.

- Anticonvulsants
- Antiemetics
- Anticoagulants
- Antidiarrheals
- Analgesics
- Hematopoietic Growth Factors
- Nutritional supplementation
- Highly active antiretroviral therapy (HAART)
- Megastrol administered as appetite stimulant is acceptable while the patient is enrolled in the study
- Premedication may be administered at the discretion of the treating physician.
- The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

5.3.2 Therapies Not Permitted:

- Traditional herbal medicines should not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug interactions that may cause, or confound assessment of, toxicity;
- Patients are not allowed to receive immunostimulatory agents, including but not

limited to IFN-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with MEDI4736 (durvalumab), could potentially increase the risk for autoimmune conditions.

- Patients should also not be receiving immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, or thalidomide. These agents could potentially alter the activity and the safety of MEDI4736 (durvalumab). Systemic corticosteroids may be administered at the discretion of the treating physician. If feasible, alternatives should be considered.
- Patients who donate blood while participating in this study, or: 1) for at least 90 days following the last infusion of durvalumab; or 2) 90 days after receipt of the final dose of durvalumab; or 3) until after 4-5X the half-life of durvalumab or until the time specified in the prescribing information of durvalumab, whichever occurs longest.
- Colony stimulating factors, including G-CSF, pegylated G-CSF are not permitted at any time. Erythropoietin analogs are not recommended, but may be used in accordance with ASCO guidelines.
- Immunotherapy, chemotherapy or radiation therapy not specified in this protocol
- Investigational agents other than MEDI4736 (durvalumab).
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than the following two clinical situations:
    - To control radiation-related nausea, if viewed as absolutely necessary for symptom control by the radiation oncologist. Every effort should be made to minimize glucocorticoid administration, e.g. utilization of appropriate alternative medications including 5HT3, NK-1 antagonists, olanzapine etc. (note: no more than 4 mg decadron or 10 mg prednisone daily).
    - To modulate symptoms from an adverse event of suspected immunologic etiology. Note: The use of physiologic doses of corticosteroids (e.g. ≤ 10 mg per day of prednisone or equivalent) may be approved after consultation with the Principal Investigator.
    - Patients who, in the assessment of the treating investigator, require the use of any of the aforementioned treatments for clinical management should be removed from protocol treatment. Patients may receive other medications that the investigator deems to be medically necessary.

5.3.3 Participation in Other Trials

- Patients are not to participate in other therapeutic trials. However, trials that do not add experimental agents are allowed (e.g. imaging trials, quality of life, etc).

5.4 Duration of Therapy

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

applies:

- Completion of all 13 cycles of MEDI4736 (durvalumab),
- Disease progression*
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

*At time of disease progression, patients will be managed per the discretion of the treating physician and will continue to be followed per the follow-up assessments in Section 4 of the protocol.

6. TREATMENT MODIFICATIONS/MANAGEMENT (13-JAN-2021)

6.1 Toxicity Management Guidelines for Radiation-Related, Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions for MEDI4736 (durvalumab)

Radiation-Related Toxicities:

Severe adverse events that may be related to radiation therapy during the course of radiation such as any grade 3-4 cardiopulmonary SAEs (congestive heart failure, pneumonitis, arrhythmias, myocardial infarction), grade 4 esophagitis, or any AEs that lead to hospitalization that could be attributed to radiation therapy to make continued therapy infeasible should lead to the radiation therapy to be held. RT could be resumed if AEs return to grade 2 or less, but if the AEs do not return to grade 2 or less within 14 days, RT will be permanently discontinued.

MEDI4736 (Durvalumab) Related-Toxicities:

For MEDI4736 (durvalumab), there will not be any dose escalation or de-escalation. If the MEDI4736 (durvalumab) dose is held or interrupted it will not be made up. If RT is held or discontinued, MEDI4736 (durvalumab) may be continued as scheduled. If the patient meets retreatment criteria, the full dose of 1500 mg will be administered. If the patient does not meet retreatment criteria before the next scheduled dose, if/when the toxicity resolves to the point where treatment is possible, the doses of MEDI4736 (durvalumab) are applied off schedule every 4 weeks.

Adverse events (both non-serious and serious) associated with MEDI4736 (durvalumab) exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. MEDI4736 (durvalumab) must be withheld for drug-related toxicities and severe or life-threatening AEs as per the table below.

All toxicities are per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Guidelines for the management and dosing modifications for immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for MEDI4736 (durvalumab) monotherapy are provided in the subsections below as follows:

- General guidelines for toxicity management and dosing modifications (Table 5a)
- Toxicity management and dosing modifications guidelines for specific immune-related adverse events (irAEs)/immune-mediated AEs (imAEs) and other irAEs/imAEs not specified (Table 5b)

- Toxicity management and dosing modifications guidelines for Infusion-related reactions (Table 5c)
- Toxicity management and dosing modifications guidelines for non-immune-mediated AEs (Table 5d)

Because immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., NCCN, ESMO) in the management of these events. In case of doubt, the Investigator should consult with the Study Physician.

Table 6a: General Guidelines for Toxicity Management and Dosing Modifications for Durvalumab

General Considerations Regarding Immune-Mediated Reactions

- Early identification and management of immune-mediated adverse events (imAEs) are essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse events. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated.

- Institute medical management promptly, including specialty consultation as appropriate. In general:
  - **Withhold** study drug/study regimen for severe (Grade 3) imAEs.
  - **Permanently discontinue** study drug/study regimen for
    - life-threatening (Grade 4) imAEs,
    - recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or
    - an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

- Based on the severity of the imAE, durvalumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤1, corticosteroid should be tapered over ≥28 days. More potent immunosuppressive agents such as TNF inhibitors (e.g., infliximab) should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines.

- With long-term steroid and other immunosuppressive use, consider need for Pneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.

- Because immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., NCCN, ESMO) in the management of these events. In case of doubt, the Investigator should consult with the Study Physician.

All toxicities will be graded according to NCI CTCAE, Version 5.0.

Table 6b: Durvalumab Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/ Interstitial Lung Disease (ILD)	For Any Grade: – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below.		

Table 6b: Durvalumab Dose Delays and Toxicity Management for <u>imAEs</u>

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
	– Initial workup may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory workup, and high- resolution CT scan. – Consider Pulmonary and Infectious disease consult.		
	Grade 1 (asymptomatic, clinical, or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug(s) as clinically appropriate pending workup for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory workup and then as clinically indicated.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug(s) until resolution to Grade ≤1. • If toxicity worsens, treat as Grade 3/4 • If toxicity improves to Grade ≤1, then the decision to retreat will be based upon treating physician's discretion and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (*e.g.*, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider chest CT with contrast and repeat in 3-4 weeks. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day – If still no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start additional immunosuppressive agent such as TNF inhibitors (*e.g.*, infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [*e.g.*, tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the patient and provide Supportive care (e.g., oxygen) – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (*e.g.*, infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper

Table 6b: Durvalumab Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
			steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Diarrhea/ Colitis	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – When symptoms or evaluation indicate a perforation is suspected, **consult a surgeon experienced in abdominal surgery immediately without any delay.** – **Permanently discontinue study drug for any grade of intestinal perforation.** – Patients should be thoroughly evaluated to rule out any alternative etiology (*e.g.*, disease progression, other medications, or infections), including testing for *Clostridium difficile* toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.		
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (*e.g.*, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day; limiting instrumental ADL) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: invasive intervention not indicated)	Hold study durvalumab until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug(s) can be resumed after completion of steroid taper. **Permanently discontinue study drug for any grade of intestinal perforation.**	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (*e.g.*, American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 2 to 3 days or worsens, obtain GI consult for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation. Promptly start IV methylprednisolone 1 to 2 mg/kg/day. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg IV once (may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider)[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics,

Table 6b: Durvalumab Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
			antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; limiting self-care ADL; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	Grade 3 Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. Grade 4 Permanently discontinue study drug/study regimen. **Permanently discontinue study drug for any grade of intestinal perforation.**	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 2 days of IV methylprednisolone 1 to 2 mg/kg/day or equivalent, promptly start further immunosuppressives (*e.g.*, infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (*e.g.*, viral hepatitis, disease progression, concomitant medications).		
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB > ULN and 1.5×ULN if baseline abnormal)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3.0-5.0×baseline if	• Hold study drug/study regimen dose until resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to	**For Grade 2:** – Regular and frequent checking of LFTs (*e.g.*, every 1 to 2 days) until improvement or resolution. – If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV

Table 6b: Durvalumab Dose Delays and Toxicity Management for <u>imAEs</u>

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
	baseline abnormal; and/or TB > 1.5×ULN and ≤3.0×ULN if baseline normal, >1.5-3.0×baseline if baseline abnormal)	Grade ≤1, resume study drug/study regimen after completion of steroid taper. • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and start prompt treatment with IV methylprednisolone 1 to 2 mg/kg/day. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of IV methylprednisolone, promptly start further immunosuppressives (*i.e.*, mycophenolate mofetil at 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 (AST or ALT >5.0×ULN and ≤20×ULN if baseline normal, >5-20×baseline if baseline abnormal; and/or TB >3.0×ULN and ≤10.0×ULN if baseline normal, >3.0-10.0×baseline if baseline abnormal) **Grade 4** (AST or ALT >20xULN if baseline normal, >20xbaseline if baseline abnormal; and/or TB >10xULN if baseline normal, >10.0×baseline if baseline abnormal)	For transaminases elevations ≤8 × ULN, or total bilirubin elevations ≤5 × ULN: • Hold durvalumab until resolution to Grade ≤1 or baseline • Resume study drug(s) if LFT elevations resolve to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • **Permanently discontinue** study drug(s) if no resolution within 14 days **Permanently discontinue** durvalumab for: • Transaminases elevation >8 × ULN or total bilirubin >5 × ULN. • Grade 4 event • Any case meeting Hy's law criteria (AST or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (*i.e.*, elevated alkaline P04) and in the absence of any alternative cause).[b]	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (*i.e.*, mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Table 6b: Durvalumab Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (*e.g.*, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (*e.g.*, disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.		
	Grade 1 (Serum creatinine > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – If baseline serum creatinine is elevated above normal, and there is a rise to >1 to 1.5 × baseline, consider following recommendations in this row.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold durvalumab until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If improvement to Grade ≤1 or baseline, resume study drug(s) after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO/IV equivalent, consider additional workup. – Once the patient is improving, gradually taper

Table 6b: Durvalumab Dose Delays and Toxicity Management for <u>imAEs</u>

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
			steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO/IV equivalent, consider additional workup and prompt treatment with an immunosuppressive in consultation with a nephrologist. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** General Guidance **For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – **Hold study drug if Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or other severe cutaneous adverse reaction (SCAR) is suspected.** – **Permanently discontinue study drugs if SJS, TEN or SCAR is confirmed.**		
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (*e.g.*, diphenhydramine or hydroxyzine) and topical therapy (*e.g.*, emolient, lotion, or institutional standard).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold durvalumab until resolution to Grade ≤1 or baseline. • If toxicity worsens, treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, resume drug(s) after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (*e.g.*, diphenhydramine or hydroxyzine) and topical therapy. – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 week or recurs
	Grade 3 or 4	**Grade 3:**	**For Grade 3 or 4:**

Table 6b: Durvalumab Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
		Hold durvalumab until resolution to Grade ≤1 or baseline. If no improvement within 30 days, permanently discontinue study drug(s). **Grade 4 (or life-threatening):** Permanently discontinue study drug	– Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (*e.g.*, hyperthyroidism, Type 1 diabetes mellitus hypophysitis, hypothyroidism, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity) General Guidance **For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (*e.g.*, disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (*e.g.*, blood glucose and ketone levels, HgA1c) – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study. – For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (*e.g.*, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.		
	Grade 1	No dose modifications.	**For Grade 1 (including asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in two subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.

Table 6b: Durvalumab Dose Delays and Toxicity Management for <u>imAEs</u>

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold durvalumab until patient is clinically stable. - If toxicity worsens, treat as Grade 3/4. - Study drug(s) can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged steroid replacement can resume study drug(s) on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 2 (including symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine workup, except those with isolated hypothyroidism or Type 1 diabetes mellitus, and as guided by an endocrinologist, consider short-term corticosteroids (*e.g.*, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (*e.g.*, hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. **Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis**. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated initiate hormone replacement as needed for management.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold durvalumab until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged steroid replacement (*e.g.*, adrenal insufficiency) can resume study drug(s) on the following conditions:	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine workup, except those with isolated hypothyroidism or Type 1 diabetes mellitus, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (*e.g.*, hydrocortisone, sex hormones).or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (*e.g.*, hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity.

Table 6b: Durvalumab Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
		1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Amylase/ Lipase Increased	**For Any Grade:** – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis. – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT). – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase. – If evidence of pancreatitis, manage according to pancreatitis recommendations.		
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**For Any Grade:** – Consider gastroenterology referral.		
	Grade 1	No dose modifications.	- IV hydration - Manage as per amylase/lipase increased (asymptomatic)
	Grade 2	Hold durvalumab dose until resolution to Grade ≤1.	- Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. - IV hydration
	Grade 3 or 4	Permanently discontinue durvalumab.	- Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. - IV hydration
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, **excluding**	**Any Grade** General Guidance **For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (*e.g.*, disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (*e.g.*, electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.		

Table 6b: Durvalumab Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
Myasthenia Gravis and Guillain-Barré)	– **FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.**		
	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above. – Treat mild signs/symptoms as Grade 1 (*e.g.* loss of deep tendon reflexes or paresthesia)
	Grade 2	**For acute motor** neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. **For sensory** neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. **Permanently discontinue** durvalumab if Grade 2 imAE does not resolve to Grade ≤1 within 30 days. If toxicity worsens, treat as Grade 3 or 4. Study drug(s) can be resumed after improvement to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (*e.g.*, gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (*e.g.*, IV IG or other immunosuppressant depending on the specific imAE).
	Grade 3 or 4	Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (*e.g.*, IV IG or other immunosuppressant depending on the specific imAE). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barré and myasthenia gravis)	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (*e.g.*, disease progression, infections,		

Table 6b: Durvalumab Dose Delays and Toxicity Management for <u>imAEs</u>

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
	metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, **it is essential to have a low threshold to obtain a neurological consult.** – Neurophysiologic diagnostic testing (*e.g.*, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of **steroids as the primary treatment of Guillain-Barre is not typically considered effective.** Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.		
	Grade 1 (Guillain-Barre [GB]: mild symptoms) (Myasthenia gravis [MG]: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.
	Grade 2 (GB: moderate symptoms; limiting instrumental ADL) (MG: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL)	Hold study drug/study regimen dose until resolution to Grade ≤1. **Permanently discontinue** study drug/study regimen if it does not resolve to Grade ≤1 within 30 days <u>or</u> if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (*e.g.*, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to

Table 6b: Durvalumab Dose Delays and Toxicity Management for <u>imAEs</u>

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
			reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4 (Grade 3 GB: severe symptoms; limiting self-care ADL; Grade 4 GB: life-threatening consequences; urgent intervention indicated; intubation) (Grade 3 MG: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL; Grade 4 MG: life-threatening consequences; urgent intervention indicated)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**General Guidance for Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (*e.g.*, pulmonary embolism, congestive heart failure, malignant pericardial effusion). A cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures.		

Table 6b: Durvalumab Dose Delays and Toxicity Management for <u>imAEs</u>

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
	– Initial workup should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory workup as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (*e.g.*, disease progression, other medications, or infections). – **Discontinue drug permanently if biopsy-proven immune-mediated myocarditis regardless of grade.**		
	Grade 1 (asymptomatic or mild symptoms*; clinical or diagnostic observations only; intervention not indicated) *Treat myocarditis with mild symptoms as Grade 2.	No dose modifications required unless clinical suspicion is high for myocarditis, in which case hold durvalumab during diagnostic workup. - If myocarditis is excluded, resume after complete resolution to Grade 0. - **If myocarditis is diagnosed, permanently discontinue durvalumab**	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory workup as clinically indicated. - Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms*) (Grade 4: Life-threatening consequences; urgent intervention indicated (*e.g.*, continuous IV therapy or mechanical hemodynamic support)	**For Grade 2:** - Hold durvalumab - If toxicity rapidly improves to Grade 0 and <u>no</u> evidence for myocarditis, then the decision to reinitiate study drug/study regimen is based upon treating physician's clinical judgment and after completion of steroid taper. - If toxicity does not rapidly improve, permanently discontinue study drug/study regimen. - If cardiac symptoms/signs are **Grade 3-4,** permanently discontinue durvalumab. **If myocarditis is diagnosed, permanently discontinue durvalumab regardless of grade**	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (*e.g.*, oxygen). – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (*e.g.*, infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. **Infliximab is contraindicated for patients who have heart failure.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Table 6b: Durvalumab Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
	* Consider "new onset of symptoms" as referring to patients with prior episode of myocarditis.		
Myositis/Polymyositis ("Poly/myositis")	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also, difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial workup should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory workup as indicated, including a number of possible rheumatological/antibody tests (*i.e.*, consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (*e.g.*, disease progression, other medications, or infections).		
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider neurology consult. – Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from neurology consultant. – If clinical course is *not* rapidly progressive, start systemic steroids (*e.g.*, prednisone 1 to 2 mg/kg/day

Table 6b: Durvalumab Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
			PO or IV equivalent); if no improvement within 3 to 5 days, continue additional workup and start treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider start of immunosuppressive therapy such as TNF inhibitors (*e.g.*, infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 or 4 (Grade 3: pain associated with severe weakness; limiting self-care ADLs Grade 4: life-threatening consequences; urgent intervention indicated)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. **Permanently discontinue** study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** **Permanently discontinue** study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; hospitalization recommended. – Obtain neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from neurology consultant. – If not improvement within 2 to 3 days after IV methylprednisolone at 2 to 4 mg/kg/day, consider start of immunosuppressive therapy such as TNF inhibitors (*e.g.*, infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Other immune-mediated reactions	General Guidance **For Any Grade:** – Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, hemolytic anemia, uveitis, vasculitis). – The study physician may be contacted for immune-mediated reactions not listed in the "specific		

Table 6b: Durvalumab Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
	immune-mediated reactions" section. – Thorough evaluation to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections).		
	Grade 1	No dose modifications.	- Monitor as clinically indicated.
	Grade 2	- Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. - If toxicity worsens, then treat as Grade 3 or Grade 4. - Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. - Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	- Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO)
	Grade 3	- Hold study drug/study regimen.	- Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO)
	Grade 4	- Permanently discontinue study drug/study regimen	- Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO)

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow, MD.

[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE Immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Table 6c: Durvalumab Dose delay and Toxicity Management for Infusion-Related Reactions		
Grade of the Event (NCI CTCAE version 5.0)	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance **For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (*e.g.*, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (*e.g.*, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).	
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug(s) may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug(s) should be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (*e.g.*, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

Table 6d: Durvalumab Dose Delay and Toxicity Management for Non–Immune-Mediated Reactions		
Severity Grade of the Event (NCI CTCAE version 5.0)	**Dose Modifications**	**Toxicity Management**
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (*i.e.*, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Per institutional standard.
Grade 1	No dose modifications.	Per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agent administered in NRG-LU004, MEDI4736 (durvalumab) (NSC #778709), is being made available under an IND sponsored by CTEP.

Refer to the MEDI4736 (durvalumab) investigator brochure (IB) for detailed pharmacologic and safety information.

For MEDI4736 (durvalumab), determination of whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.4 of the protocol.

7.2 Adverse Events and Serious Adverse Events

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

7.2.2 Definition of an Adverse Event (AE)

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

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

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

7.3 Comprehensive Adverse Events and Potential Risks list (CAEPR)

for

MEDI4736 (durvalumab, NSC 778709) (25-NOV-2019)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are

protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2833 patients.* Below is the CAEPR for MEDI4736 (durvalumab).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, April 17, 2019[1]

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (idiopathic thrombocytopenic purpura)[2]	
		Thrombotic thrombocytopenic purpura[2]	
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes insipidus)	
		Endocrine disorders - Other (diabetes mellitus type 1)[2]	
	Hyperthyroidism[2]		
		Hypopituitarism[2]	
	Hypothyroidism[2]		
EYE DISORDERS			
		Keratitis[2]	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
		Gastrointestinal disorders -Other - (gastrointestinal perforation)[2,3]	
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (autoimmune hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
		Immune system disorders - Other (immune related adverse events)[2]	
		Immune system disorders - Other (sarcoidosis)	
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		***Alanine aminotransferase increased[2] (Gr 2)***
	Aspartate aminotransferase increased[2]		***Aspartate aminotransferase increased[2] (Gr 2)***
	Creatinine increased		***Creatinine increased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthritis[2]		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]	
	Myalgia		***Myalgia (Gr 2)***
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2,5]	
		Myasthenia gravis[2]	
		Nervous system disorders - Other (aseptic meningitis)[2]	
		Peripheral sensory neuropathy	
RENAL AND URINARY DISORDERS			
	Dysuria		***Dysuria (Gr 2)***
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough			***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Pneumonitis[2]		
	Respiratory, thoracic and mediastinal disorders - Other (dysphonia)		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Hyperhidrosis		
	Pruritus		***Pruritus (Gr 2)***
	Rash[2,6]		***Rash[2,6] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (scleroderma)	
		Skin and subcutaneous tissue disorders - Other (severe dermatitis)[2,7]	

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***

NOTE: Cardiomyopathy, and graft versus host disease, while not observed on clinical trials of MEDI4736 (durvalumab) at this time, are known events with this class of agent (PD-L1 antagonist).

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

[2]Immune-mediated adverse reactions (irAEs) have been reported in patients receiving MEDI4736 (durvalumab). irAEs can involve any of the organs or systems in the body. Most irAEs were reversible and managed with interruptions of MEDI4736 (durvalumab), administration of corticosteroids and supportive care, however, these events can be serious and fatal.

[3]Gastrointestinal perforations have been observed only in patients receiving MEDI4736 (durvalumab) in combination with tremelimumab (CP-675,206).

[4]Infections includes infection in the lungs, upper respiratory tract, dental and oral soft tissues and other organs under the INFECTIONS AND INFESTATIONS SOC. Infections generally are mild (Gr 1-2) but severe infections including sepsis, necrotizing fasciitis, and osteomyelitis have been reported.

[5]Guillain-Barre Syndrome has been reported in patients receiving MEDI4736 (durvalumab) in combination with tremelimumab (CP-675,206) but can potentially occur after durvalumab monotherapy.

[6]Rash includes the terms: rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, and eczema.

[7]In rare cases, severe dermatitis has been reported to manifest as Stevens-Johnson syndrome, toxic epidermal necrolysis, or rashes complicated by dermal ulceration or necrotic, bullous, or hemorrhagic manifectations.

Adverse events reported on MEDI4736 (durvalumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MEDI4736 (durvalumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Disseminated intravascular coagulation
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (coronary artery disease); Pericardial effusion; Pericardial tamponade; Restrictive cardiomyopathy; Right ventricular dysfunction; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired
EYE DISORDERS - Eye disorders - Other (choroidal effusion with shut down of ciliary body)
GASTROINTESTINAL DISORDERS - Ascites; Constipation; Dental caries; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Mucositis oral; Proctitis; Small intestinal obstruction; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema trunk; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic hemorrhage
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (drug-induced liver injury); Serum sickness
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Wound complication
INVESTIGATIONS - Blood bilirubin increased; CPK increased; Electrocardiogram T wave abnormal; GGT increased; Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Rhabdomyolysis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (brain metastasis swelling); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lung cyst); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare, tumor inflammation); Treatment related secondary malignancy; Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Dizziness; Edema cerebral; Headache; Nervous system disorders - Other (axonal neuropathy); Nervous system disorders - Other (hemiparesis); Paresthesia; Seizure
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin
VASCULAR DISORDERS - Hypertension

Note: MEDI4736 (durvalumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.4 Expedited Reporting of Adverse Events (25-NOV-2019)

All adverse events (AEs) are submitted for expedited reporting protocol-specific rules evaluation using the Medidata Rave data management system. All AEs will be evaluated by the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) to determine whether expedited reporting is recommended based on a set of programmed expedited reporting rules. AEs identified as meeting the programmed expedited reporting requirements can then be submitted in CTEP-AERS. A deep link in Rave will take the user directly to CTEP-AERS where the expedited report may be completed and submitted via CTEP-AERS.

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

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

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

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP as the IND sponsor for this study by telephone at 301-897-7497 and to the NRG Oncology by phone at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.4.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to CTEP at 301-897-7404 and contact NRG Oncology at 1-215-574-3191 for source document submission assistance.
- In the event of site assessment disagreement with a CTEP-AERS rules assessment of an expedited report "NOT recommended", based upon the protocol-specific reporting requirements and criteria outlined in the AE Reporting Tables, sites may bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.4.2 Expedited Reporting Requirements for Adverse Events

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

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

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements

Not applicable.

7.4.3 Reporting to the Site IRB/REB

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

7.4.4 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS . In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

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

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

Second Malignancy:

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

7.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 3 months after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

8.0 REGISTRATION AND STUDY ENTRY PROCEDURES (03-AUG-2020)

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of

Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr).

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

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

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

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

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

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

8.1 Cancer Trials Support Unit Registration Procedures (13-JAN-2021)

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

8.1.1 IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB.

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

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Site registration forms may be downloaded from the protocol specific page on the NRG website. Acceptable documentation of local IRB/REB approval includes:

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

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC to begin the modality credentialing process.

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

- Holds the appropriate CTEP registration type for the protocol;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- Rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds an active CTEP status.

8.1.2 Downloading Site Registration Documents:

Site registration forms may be downloaded from the protocol-specific page on the NRG website.

CIRB-approved protocol documents are located on the CTSU member's website. Permission to view and download this protocol and its supporting CIRB documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select NRG Oncology and protocol number *NRG-LU004*;
- Click on *Documents*, select *Site Registration*, and download the protocol.

8.1.3 Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

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

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

8.1.4 Checking Site's Registration Status:

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

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

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

8.2 RT-Specific Pre-Registration Requirements (25-NOV-2019)

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

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**	
	Treatment Modality	
	Photon	Key Information
Credentialing Status Inquiry Form	x	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
Facility Questionnaire	x	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link.

Phantom Irradiation	x	A Thorax phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org).
Credentialing Notification Issued to:		
Institution	X	Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and NRG Oncology Headquarters that all desired credentialing requirements have been met.

8.3 Digital RT Data Submission to NRG Using TRIAD (13-JAN-2021)

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

8.3.1 TRIAD Access Requirements:

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

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

8.3.2 TRIAD Installations:

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

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

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

8.4 Patient Enrollment (13-JAN-2021)

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

8.4.1 Oncology Patient Enrollment Network (OPEN)

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

Requirements for OPEN access:

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

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

Prior to accessing OPEN site staff should verify the following:

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

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

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

To receive site reimbursement for specific tests and/or biospecimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

9.0 DRUG INFORMATION

9.1 Investigational Study Agent – MEDI4736 (durvalumab) (NSC #778709, IND # [redacted] (03-NOV-2021)

9.1.1 Supply

This study will be conducted under IND# [redacted] to be held by NCI and will require FDA submission and approval as part of the IND. MEDI4736 (durvalumab) is provided by AstraZeneca and distributed by the DCTD/NCI. MEDI4736 (durvalumab) will be supplied to patients on study free of charge.

Agent Ordering and Agent Accountability

NCI-supplied agent may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability

The current version of the IB will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts
• CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
• NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
• PMB policies and guidelines:
http://ctep.cancer.gov/branches/pmb/agent_management.htm
• PMB Online Agent Order Processing (OAOP) application:
https://ctepcore.nci.nih.gov/OAOP/
• CTEP Identity and Access Management (IAM) account:
https://ctepcore.nci.nih.gov/iam/
• CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
• IB Coordinator: IBCoordinator@mail.nih.gov
• PMB email: PMBAfterHours@mail.nih.gov
• PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9.1.2 Agent-Specific Information

Other Names: IMFINZI™

Classification: Anti-PD-L1 MAb

Molecular Weight: ~ 149 kDa

Mode of Action: Durvalumab (MEDI4736) inhibits binding of programmed cell death ligand 1 (PD-L1) to PD-1 and CD80. In-vitro studies demonstrate that durvalumab (MEDI4736) relieves PD-L1-mediated suppression of human T-cell activation. Durvalumab (MEDI4736) does not trigger antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity in cell-based functional assays.

Description: Durvalumab (MEDI4736) is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody.

How Supplied: Durvalumab (MEDI4736) is supplied by AstraZeneca, and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Durvalumab (MEDI4736) injection is a clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. Each vial contains 500 mg of durvalumab (MEDI4736) in 10 mL of solution. Each 1 mL of solution contains 50 mg of durvalumab (MEDI4736) and is formulated in: L-histidine (2 mg), L-histidine hydrochloride monohydrate (2.7 mg), α,α-trehalose dihydrate (104 mg), polysorbate 80 (0.2 mg), and Water for Injection, USP.

Preparation: Durvalumab (MEDI4736) solution for infusion must be diluted prior to administration. To prepare the infusion solution add the dose volume of durvalumab (MEDI4736) to an infusion bag containing 0.9% Sodium Chloride Injection or Dextrose

5% in Water Injection, USP and mix by gentle inversion to ensure homogeneity of the dose in the bag. The final concentration must be between **1 mg/mL to 15 mg/mL**.

Infusion bags must be latex-free and can be made of polypropylene, polyethylene, polyolefin copolymers, or polyvinyl chloride.

Storage: Store intact vials between 2-8°C (36-46°F). Do not freeze. Protect from light by storing in the original box.

> If a storage temperature excursion is identified, promptly return durvalumab (MEDI4736) to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Refer to the package label for expiration.

Total in-use storage time from needle puncture of durvalumab (MEDI4736) vial to start of administration should not exceed 8 hours at room temperature or 24 hours at 2-8°C (36-46°F). Prior to the start of the infusion, ensure that the bag contents are at room temperature (approximately 25°C) to avoid an infusion reaction due to the administration of the solution at low temperatures.

Route of Administration: IV infusion

Method of Administration: Infuse over approximately 60 minutes using an infusion set containing a 0.22 or 0.2 µm in-line filter. No incompatibilities between durvalumab (MEDI4736) and polyethylene, polypropylene, polyvinylchloride, or polyolefin copolymers have been observed. Flush the IV line with a volume of IV bag diluent equal to the priming volume of the infusion set used at the completion of infusion. Do not co-administer other drugs through the same infusion line.

Patient Care Implications: Refer to the protocol for information on evaluation and management of potential immune-related adverse events.

10. PATHOLOGY/BIOSPECIMENS

10.1 Central Pathology Review

Not applicable

10.2 Biospecimen Selection for Integral Biomarker Testing

Not applicable

10.3 Biospecimen Selection for Integrated Biomarker Testing

Not applicable.

10.4 Biospecimen Selection for Exploratory Biomarker Testing (03-NOV-2021)

Tumor tissue and blood will be used for (1) circulating tumor cell (CTC) analysis at Liquid Biotech USA; and (2) various CIMAC immune assays as described in the tables below. See Mandatory Biospecimen Submission Tables (Section 10.5.1, 10.5.2 and 10.5.3) for information on biospecimen collection time points and shipping information.

Specimen Type	Timepoint	CIMAC Tier 1 Analyte Assay	Non-CIMAC Assay
Tissue			
Tissue FFPE block or slides	Archival	1. 1. PD-L1 22C3 in case(s) without the PD-L1 22C3 assay already performed. 2. Multiplex IHC 3. If sufficient tissue/DNA from tissue remains: TCRseq	PD-L1 testing (22c3) (CLIA)
Blood			
PBMC from Green Top Tube (5x10^6/vial)	Baseline Day 15 of RT Day 30 of RT, 3 mos	1) CyTOF	
Plasma from Green Top Tube (500µl/vial)	Baseline Day 15 of RT Day 30 of RT, 3 mos	1) Olink 2) ELISA/Grand Serology	
Streck tube 10 mL (x 1)	Baseline Day 15 of RT Day 30 of RT, 3 mos	1) ctDNA	
ACD tube 8.5 mL (x 1)	Baseline Day 15 of RT Day 30 of RT, 3 mos 6 mos, 12 mos		1) Whole Blood (CTC) Liquid Biotech Assay
Whole blood from EDTA tubes (2 mL)	Baseline Day 15 of RT Day 30 of RT, 3 mos	1) TCRseq	CIMAC-designated lab
		*Numbers indicate prioritization of testing at the research lab	

10.4.1 Exploratory Biomarker Testing Requirements and Methods

- **Mandatory IHC Staining:** PD-L1 Staining ≥50% positive, performed at participating sites' CLIA-certified labs using Dako 22C3 IHC antibody or the Ventana SP263 testing platforms, then values submitted to NRG Oncology via patient OPEN Eligibility Checklist.

  The PD-L1 protein is expressed on the plasma membrane of a range of hematopoietic and solid tissue cells interacting with the PD-1 receptor present on the surface of T- and B-lymphocytes and some myeloid cells. PD-L1/PD-1 binding triggers signal transduction cascades that results in self-tolerance and immune system suppression normally acting as an immune checkpoint that prevents overstimulation and autoimmunity. Upregulation of PD-1 expression is often present on tumor infiltrating lymphocytes and correspondingly, enhanced PD-L1 expression can be found on many tumor cells. Blockade of PD-L1 stimulation of PD-1 impedes immune inhibition and allows for recognition of tumor as non-self, resulting in tumor cytotoxicity. Several clinical trials have demonstrated that PD-L1 status may be predictive of benefit from treatment with checkpoint inhibitors. Durvalumab is a humanized monoclonal antibody targeting PD-1 with increased PD-L1 expression. Tumors with high expression of PD-L1 show increased objective response rate and improved progression free and overall survival compared to low expressors. PD-L1 IHC 22C3 is a qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, Clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue and gastric or gastroesophageal junction adenocarcinoma using EnVision FLEX visualization and performed on Autostainer Link 48. PD-L1 IHC 22C3 is indicated as an aid in identifying NSCLC patients for treatment with pembrolizumab. PD-L1 protein expression in NSCLC is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. The specimen is considered to have PD-L1 expression if TPS ≥ 1% and high PD-L1 expression if TPS ≥ 50%.

- **Mandatory Circulating Tumor Cell (CTC) at Liquid Biotech:** Blood will be shipped directly to Liquid Biotech USA for testing. See Appendix V for details.

- **Mandatory Time of Flight Mass Cytometry (CyTOF):** CIMAC; assessed at baseline (pre-treatment), days 15 and 30, and 3 months

- **Mandatory T Cell Receptor (TCR) Sequencing:** ImmunoSeq at CIMAC-designated lab; assessed at baseline (pre-treatment), days 15 and 30, and 3 months

- **Mandatory Cytokine Analysis:** Multiplex Immunoassay using OLink Technology; assessed at baseline (pre-treatment), days 15 and 30, and 3 months

- **Mandatory ELISA/Grand Serology:** CIMAC

- **Mandatory Circulating Tumor DNA (ctDNA):** DNA Profiling by Deep Sequencing: CIMAC-designated laboratory

- **Optional SP263 Assay (PD-L1)** – In tumors where only the Dako 22C3 testing was done, a qualitative immunohistochemical assay can be performed using rabbit monoclonal anti-PD-L1 clone SP263 intended for use in the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE): CIMAC or other CIMAC-designated laboratory
    - (NOTE: This will be done as an exploratory special study on the unstained sections (if available).

See Mandatory Biospecimen Submission Tables (Section 10.5) and CIMAC Biomarker Testing Appendix (Appendix VIII) for further details.

10.5 Mandatory Biospecimen Submissions (25-NOV-2019)

The patient must give permission to participate in this mandatory study component. Participating sites are required to submit the patient's biospecimens as outlined below.

10.5.1 Mandatory Biospecimen Submission Table for CTC Analysis

See table below and Appendix V for further details.

Mandatory Specimen Collection #1: Blood for CTC analysis
Why specimen is being collected: Integrated marker for predicting response to treatment.
Follow blood collection instructions in Appendix V.

Kits and Shipping costs: All necessary materials for shipping (including blood collection tubes and prepaid FedEx labels) may be obtained from Liquid Biotech USA. Please contact Liquid Biotech USA at support@liquidbiotechusa.com (tel: 267-225-7361) to arrange for delivery of materials.

Ship samples (per instructions in Appendix V below) to:

Liquid Biotech USA
@ Princeton Innovation Center BioLabs
303A College Rd. E.
Princeton, NJ 08540

Questions: contact Liquid Biotech at the email above.

Specimen Type	Collection Time Points	Collection Information and Requirements/ Instructions for Site	Shipping

8.5 mL of blood drawn into vacutainers with ACD-A	Pre-treatment between the time of enrollment and durvalumab initiation (prior to receipt of durvalumab). During treatment on Day 15 (+/- 3 days) from start of radiation and Day 30 (+/- 3 days) from start of radiation for both radiation cohorts. Post treatment at: • 3 months (+/- 14 days) from the start of durvalumab initiation (cycle 4 of durvalumab) • 6 months (+/- 30 days) from the start of durvalumab initiation (cycle 7 of durvalumab); and • 12 months (+/- 30 days) from start of durvalumab initiation (cycle 13 of durvalumab)	Collect blood, mix, label with identifier and time of collection, and place in insulated tube box inside biohazard specimen transport bag. Store at ambient temperature until ready to ship. Samples must be shipped on day of collection.	Shipped ambient the same day of collection, FedEx, priority overnight. **NOTE:** See Appendix V for detailed instructions.

10.5.2 Mandatory Blood Biospecimen Submission Table for CIMAC Assays

Biospecimens should not be submitted until after patient registration and Bank ID assignment. A detailed description of biospecimen procedures can be found in Appendix VIII.

BLOOD		
Pre-Treatment (Prior to receipt of durvalumab)		
Pre-Treatment T Cell Whole Blood (WB01) 30mL drawn into green top sodium heparin (NaHep) tube(s)	Pre-treatment between the time of enrollment and durvalumab initiation (prior to receipt of durvalumab)	NRG BB-Columbus the day the specimen is collected[1]
Pre-Treatment TCR Whole Blood (WB02) 2mL drawn into purple top (EDTA) tube		
Pre-Treatment cfDNA Whole Blood (WB03) 10mL drawn into a Streck (cell-free DNA) tube		
Day 15		
Day 15 T Cell Whole Blood (WB04) 30mL drawn into green top sodium heparin (NaHep) tube(s)	Day 15 (+/- 3 days) from start of radiation	NRG BB-Columbus the day the specimen is collected[1]
Day 15 TCR Whole Blood (WB05) 2mL drawn into purple top (EDTA) tube		
Day 15 cfDNA Whole Blood (WB06) 10mL drawn into a Streck (cell-free DNA) tube		
Day 30		

Day 30 T Cell Whole Blood (WB07) 30mL drawn into green top sodium heparin (NaHep) tube(s)	Day 30 (+/- 3 days) from start of radiation	NRG BB-Columbus the day the specimen is collected[1]
Day 30 RT TCR Whole Blood (WB08) 2mL drawn into purple top (EDTA) tube		
Day 30 RT cfDNA Whole Blood (WB09) 10mL drawn into a Streck (cell-free DNA) tube		
3 Months Post-Treatment		
3 Month T Cell Whole Blood (WB10) 30mL drawn into green top sodium heparin (NaHep) tube(s)	Post treatment at 3 months (+/- 14 days) from start of durvalumab initiation (cycle 4 of durvalumab)	NRG BB-Columbus the day the specimen is collected[1]
3 Month TCR Whole Blood (WB11) 2mL drawn into purple top (EDTA) tube		
3 Month cfDNA Whole Blood (WB12) 10mL drawn into a Streck (cell-free DNA) tube		

1 NRG Oncology BB-Columbus / Protocol NRG-LU004, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org.

10.6 Optional Specimen Submission (03-AUG-2020)

Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. If tissue is insufficient and this submission cannot be made, sites are urged to submit 2 fresh-cut unstained slides if possible. See footnote #2 below and Appendix VI, section 5 for details.

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

Specimen Type	Collection Time Point	Ship Biospecimens To
H&E slide(s) of Archival FFPE Primary Tumor (HNE01)[1] – H&E slide can be a duplicate cut slide, does not have to be the diagnostic slide, but must match the block if a block is being submitted.	Prior to all treatment; collected from diagnostic biopsy (core needle preferred; FNA slides will not be accepted unless an FNA FFPE cell block is submitted)	NRG BB-San Francisco within 8 weeks of registration[3]
FFPE Archival Primary Tumor (FP01)[1] Block if available [2]		

[1] A specimen transmittal form and copy of the corresponding pathology report must be shipped with all tissue biospecimens sent to the NRG BB-San Francisco. The pathology report must have specimen obtained date and pathology accession number visible on the report; all other PHI must be redacted.

[2] The NRGBB-SF can embed the punches for sites without the facilities to embed punches into blocks. If a block or punch absolutely cannot be submitted, sites may submit fresh-cut, air dry and ship two 5 micron unstained sections on supercharged/positive charged (Plus) glass microscope slides (Leica Bond Plus slides if available). The tissue sections should be centered on the slide (12mm (left label), 3mm (top-bottom), and 7mm (right). Unstained slides must be labeled with Study, Case#, accession number, block number and date the slide was cut. Sections must be shipped within 48 hours of sectioning.

[3] NRG Oncology BB-San Francisco / Protocol NRG-LU004, University of California San Francisco, 2340 Sutter Street, Room S341, San Francisco, CA 94115, Phone: (415) 476-7864; FAX: (415) 476-5271, Email: NRGBB@ucsf.edu.

11. SPECIAL STUDIES (NON-TISSUE)

Not applicable to this study.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews (03-AUG-2020)

The Radiation Oncology Study Chair, Dr. Lin, or one of the radiation oncologist co-chairs, will perform a pre-treatment RT Quality Assurance Review for each case enrolled after NRG Headquarters has received complete data.

12.2 Medical Oncology Modality Quality Assurance Reviews

The Medical Oncology Study Chair, Dr. Tsao, will perform a systemic therapy Assurance Review of all patients. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of treatment data as specified in Section 12.2. The scoring mechanism is: 1) Per Protocol, 2) Acceptable Variation, 3) Unacceptable Deviation, and 4) Not Evaluable.

Dr. Tsao will perform a Quality Assurance Review after NRG Headquarters has received complete data for the first 6 cases enrolled. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as NRG Headquarters has received complete data for all cases enrolled, whichever occurs first.

13. DATA AND RECORDS

13.1 Data Management/Collection (03-AUG-2020)

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

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.
- Rave role requirements:
    - Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
    - Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
    - Rave Read Only role must hold an Associates (A) registration type.

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

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and will be listed in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

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

13.2 Rave-CTEP-AERS Integration (03-AUG-2020)

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and

end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence, that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents> Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

13.3 Data Quality Portal (03-AUG-2020)

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

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

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

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

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

13.4 Summary of Data Submission (25-NOV-2019)

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7.4 for information about expedited and routine reporting.

Summary of All Data Submission: Refer to the protocol specific page on the NRG website (www.nrgoncology.org).

See Section 8.3 for TRIAD account access and installation instructions. See data submission table for TRIAD below.

<table>
<tr><td rowspan="4">DICOM Items</td><td>Planning CT PET (if used for contour delineation)</td><td rowspan="5">Must be submitted and approval received prior to start of RT

RT Digital Plan</td></tr>
<tr><td>RT Structure</td></tr>
<tr><td>RT Dose</td></tr>
<tr><td>RT Plan</td></tr>
<tr><td colspan="2">All required structures must be labeled per the tables in Sections 5.2.4
5.2.5</td></tr>
<tr><td colspan="2">Upon submission of the digital data via TRIAD, complete an online
Digital Data Submission Information Form (DDSI):
https://www.irocqa.org/Resources/TRIAD</td><td></td></tr>
</table>

NOTE: ALL SIMULATION AND PORTAL IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

This is a phase I trial to assess the safety and feasibility of MEDI4736 (durvalumab) and RT that is split into 2 parts. In the initial safety part, 6 patients will enroll to the ACRT + MEDI4736 (durvalumab) arm, with a mandatory toxicity evaluation period of 90 days from the start of radiation therapy. After the first 6 patients are enrolled onto the ACRT, 6 patients will be enrolled to the standard radiation + MEDI4736 (durvalumab) arm with a mandatory toxicity evaluation of 8 weeks from the start of radiation therapy. Once all patients have been assessed for toxicity, the expansion part of this study will enroll 6 patients each to the arm(s) that is/are deemed safe. If both arms are deemed safe, then a total of 12 patients will be randomized to receive ACRT + MEDI4736 (durvalumab) or standard radiation + MEDI4736 (durvalumab). If only one of the two arms is deemed safe, then only that arm will enroll 6 additional patients. If neither arm is deemed safe, then the study will not continue onto the expansion part.

14.2 Study Endpoints

14.2.1 Primary endpoint: Safety of MEDI4736 (durvalumab) in combination with RT

14.2.2 Secondary endpoints

- Feasibility of MEDI4736 (durvalumab) in combination with RT
- Adverse events, as measured by CTCAE v 5.0
- Progression free survival, according to RECIST guidelines

14.2.3 Exploratory endpoints

- Progression free survival, according to irRC guidelines
- CTC and immune parameter changes during treatment

14.3 Primary Objectives Study Design (03-AUG-2020)

14.3.1 Primary Hypothesis and Endpoints

The primary hypothesis is that MEDI4736 (durvalumab) in combination with two schedules of radiation therapies (60 Gy in 30 fractions or 60 Gy in 15 fractions) is safe.

14.3.2 How Primary Endpoints Will Be Analyzed

The tolerability of this regimen is defined as having one or no safety events defined as:
1) grade 4-5 non-hematologic serious adverse events (SAEs) as defined in Section 7.4.2 possibly, probably or definitely related to protocol treatment by 90 days from the start of concurrent therapy (start of RT) for the ACRT + MEDI4736 (durvalumab) arm and 8 weeks from the start of concurrent therapy (start of RT) for the standard radiation + MEDI4736 (durvalumab) arm;
2) any adverse events possibly, probably or definitely related to protocol treatment that lead to prolonged dose delays (defined as skipping at least 2 doses of MEDI4736 (durvalumab) during the same monitoring period for each arm);
3) permanent discontinuation of MEDI4736 (durvalumab) due to toxicity possibly, probably or definitely related to protocol treatment within the first 30 days of starting MEDI4736 (durvalumab); or

4) SAEs possibly, probably or definitely related to RT (including grade 3-4 congestive heart failure, pneumonitis, arrhythmias, and myocardial infarction, grade 4 esophagitis, and any AEs that lead to hospitalization) that causes either an interruption or early termination of RT as specified in Section 6.1.

The proportion of patients who have tolerated the treatment will be provided. All adverse events will be graded according to CTCAE v 5.0. All DLTs will be adjudicated by the study PI and either the disease site chair or a study chair in terms of attribution to protocol treatment and whether the event meets the definition of a DLT. If the adjudicators are not in agreement, a third adjudicator will be brought in to review the DLT.

14.3.3 Sample Size and Power Calculations

Evaluable patients must be eligible at the time of study registration and have started protocol treatment. If a patient dies or withdraws consent from the study within the safety monitoring period without experiencing a safety event that patient will be replaced. Each arm will enroll a maximum of 12 evaluable patients for assessment of tolerability. In the first part of the study for either arm, if 0-1 of 6 evaluable patients develop any of the safety events after completing RT, then the regimen will be deemed safe and that arm will continue to the second part of the study and enroll 6 additional evaluable patients. However, if 2 or more of 6 evaluable patients develop any safety events, that arm is considered not safe and will not be pursued in the second part. With a cohort of 6 patients, the probability of the treatment being judged to be too toxic when the true toxicity rate is 40% or higher is at least 77%. If the true toxicity rate is 18% or lower, the probability that the treatment will be deemed to be safe is at least 70%.

If 4 or more of the 12 evaluable patients on an arm experience a safety event, the treatment will be considered not tolerable. If 4 patients experience a safety event prior to reaching the target sample size of 12 patients, accrual to that cohort will be closed. If 3 patients experience a safety event once 9 patients have been enrolled but prior to reaching 12 patients, accrual will be suspended to monitor the remaining patients still in the safety assessment window for whom a safety event has not been reported. Accrual to that cohort will only be reopened if no additional patients have experienced a safety event.

The other cohort will remain open to accrual, if applicable, during this time. If fewer than 4 of the 12 evaluable patients on an arm experience a safety event, then the treatment will be considered tolerable. With a cohort of 12 patients, the probability of the treatment being judged to be too toxic when the true toxicity rate is 40% or higher is at least 78%. If the true toxicity rate is 18% or lower, the probability that the treatment will be deemed to be safe is 85%. In order to proceed to a phase II trial, the treatment(s) must be considered both safe (as defined above) and feasible (as defined in Section 14.6.2).

14.4 Study Monitoring of Primary Objectives

Interim Analysis to Monitor Study Progress

Interim reports will be prepared twice each year until the final analysis has been accepted for presentation or publication. In general, these reports will contain information about

the accrual rate with projected completion date for the accrual phase, exclusion rates, pretreatment characteristics of patients accrued, and the frequency and severity of AEs.

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

After the start of the accrual, the study team, including the study chairs, study statisticians, data managers and protocol administrator, and a representative from each participating site will hold at least monthly conference calls to review the overall conduct of the study lead by the study statistician. Data on treatment dose delivery, adverse events reported, patient demographics and eligibility will be assembled and reviewed. At each meeting, consideration is also given to the rate of accrual. Brief minutes of each meeting will be written by the study chairs to document the review of information and any decision made. The meeting minutes will be submitted to the NRG early phase protocol monitoring oversight committee for review.

If one or both arms are to move forward to the expansion cohort based on the criteria stated in Section 14.3.3, a review of the data with the study team and CTEP will take place.

14.5 Accrual/Study Duration Considerations

Accrual is expected to be 4 patients/month after a 3 month initial ramp-up period. Initial Safety Schedules (enrollment of 6 patients/arm) is expected to close after 6 months. Expansion Cohorts will open, assuming ACRT + MEDI4736 (durvalumab) is shown to be safe and feasible, approximately 4-6 months after closing Initial Safety Schedules (to allow for 8-16 weeks of follow-up to assess prolonged dose delays as well as time for data collection and analysis). It is projected to take 4 months to accrue to Randomization stage (1 month ramp-up period and 3 months accruing 4 patients/month). This stage will similarly require 8-16 weeks of follow-up to assess prolonged dose delays. The primary analysis is projected to occur approximately 20 months from study activation.

14.6 Secondary Endpoints

14.6.1 Secondary Hypotheses and Endpoints:

- MEDI4736 (durvalumab) in combination with RT is feasible
- Adverse events, as measured by CTCAE v 5.0
- Progression free survival

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Feasibility

Feasibility is based on an evaluation of the percentage of patients who received at least 80% of the planned dose of MEDI4736 (durvalumab) therapy during the first 8 weeks following initial dose of MEDI4736 (durvalumab). Feasibility will only be assessed for

the treatment cohort(s) that moves to the expansion phase. The observation of at least 80% (10/12 per arm) of patients who received at least 80% of the planned dose is considered to be evidence that this regimen is feasible in this setting.

Adverse events
Adverse events (AE) will be evaluated using the CTCAE v 5.0. Counts of all AEs by grade will be provided by treatment arm. Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm and within the subset of AEs related to treatment. Severe AEs will be any grade 4 or greater non-hematologic toxicities and will be summarized by frequency tables by treatment arm. No formal statistical testing will be performed on these summary data.

Progression Free Survival
Tumor response will be assessed by the RECIST guidelines (as reported by the sites) as defined in Section 4. Progression free survival (PFS), defined as the time from registration to progressive disease or death, whichever occurs first, will be estimated using the Kaplan Meier method. Plots and descriptive statistics will be provided for both treatment arms but no formal testing performed due to lack of statistical power.

14.6.3 Exploratory Hypotheses and Endpoints

Progression Free Survival
Tumor measurements will be collected at baseline, the end of treatment and throughout follow-up in order to determine response using the irRC guidelines. Progression free survival (PFS), defined as the time from registration to progressive disease or death, whichever occurs first, will be estimated using the Kaplan Meier method. Plots and descriptive statistics will be provided for both treatment arms but no formal testing performed due to lack of statistical power.

Biomarker Analysis
Biomarker analyses will be conducted for feasibility purposes. There is not sufficient power to detect differences between arms or any prognostic ability of the biomarkers described. Therefore all biomarker analyses, including the immune parameters described in Section 10.4.1, will focus on descriptive statistics and change from baseline to subsequent collection times. Circulating tumor cells will be collected and analyzed at the time of progression. It is hypothesized that progressed patients will have a value of green fluorescent proton-expressing cells per ML > 1.3 (Frick 2018, Dorsey 2015). Therefore, at 2 years, an analysis will be conducted to determine if every progressed patient has a value > 1.3.

14.6.4 Gender/Ethnicity/Race Distribution

There will not be sufficient sample sizes to conduct any subgroup analyses based on race, ethnicity, and/or gender.

Racial Categories	**DOMESTIC PLANNED ENROLLMENT REPORT**		
	Ethnic Categories		
	Not Hispanic or	Hispanic or Latino	

	Latino				Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	1	0	0	1
Asian	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	1	1	0	0	2
White	8	9	1	1	19
More Than One Race	0	0	0	0	0
Total	10	12	1	1	24

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APPENDIX I: RECIST CRITERIA

	RECIST 1.1	irRECIST
Target and non-target lesions	Sum of the longest diameters of target lesions (uni-dimensional) Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions) Maximum of five lesions (two per organ)	Same
New lesion	Represents PD	**Does not correspond to a formal progression** **The longest diameter will be added to the total measured tumor burden of all target lesions at baseline**
CR	Disappearance of all target and non-target lesions Nodal short axis diameter < 10 mm No new lesions	Same
PR	Decrease of 30% in tumour burden relative to baseline Non-unequivocal progression of non-target lesions No new lesions	Same
SD	Neither PR or PD	Same
PD	Increase ≥20% of the sum of LD compared with nadir (minimum 5 mm) or progression of non-target lesions or new lesion	**irPD Increase ≥20% (minimum 5 mm) in TMTB compared with nadir or progression of non-target lesions or new lesion** **Confirmation of progression recommended minimum 4 weeks after the first irPD assessment**
Confirmed PD	Not required	**New unequivocal progression or worsened progression from initial PD visit** **Appearance of another new lesion**

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; TMTB, total measured tumour burden.

APPENDIX II: AJCC STAGING SYSTEM

Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT, The Eighth Edition Lung Cancer Stage Classification, Chest January 2017: 193-203

LUNG

Table 1

T (Primary Tumor)		**Label**
T0	No primary tumor.	
Tis	Carcinoma in situ (Squamous or Adenocarcinoma)	Tis
T1	Tumor ≤3 cm,	
T1a(mi)	Minimally Invasive Adenocarcinoma	$T1a_{(mi)}$
T1a	Superficial spreading tumor in central airways[a]	$T1a_{ss}$
T1a	Tumor ≤1 cm	$T1a_{\leq 1}$
T1b	Tumor >1 but ≤2 cm	$T1b_{>1-2}$
T1c	Tumor >2 but ≤3 cm	$T1c_{>2-3}$
T2	Tumor >3 but ≤5 cm or tumor involving:	
	visceral pleura[b],	$T2_{Visc\ Pl}$
	main bronchus (not carina), atelectasis to hilum[b]	$T2_{Centr}$
T2a	Tumor >3 but ≤4 cm	$T2a_{>3-4}$
T2b	Tumor >4 but ≤5 cm	$T2b_{>4-5}$
T3	Tumor >5 but ≤7 cm	$T3_{>5-7}$
	or invading chest wall, pericardium, phrenic nerve	$T3_{Inv}$
	or separate tumor nodule(s) in the same lobe	$T3_{Satell}$
T4	Tumor >7 cm	$T4_{>7}$
	or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine;	$T4_{Inv}$
	or tumor nodule(s) in a different ipsilateral lobe	$T4_{Ipsi\ Nod}$
N (Regional Lymph Nodes)		
N0	No regional node metastasis	
N1	Metastasis in ipsilateral pulmonary or hilar nodes	
N2	Metastasis in ipsilateral mediastinal/subcarinal nodes	
N3	Metastasis in contralateral mediastinal/hilar, or supraclavicular nodes	
M (Distant Metastasis)		
M0	No distant metastasis	$M1a_{Pl\ Dissem}$
M1a	Malignant pleural/pericardial effusion[c] or pleural/pericardial nodules	
	or separate tumor nodule(s) in a contralateral lobe;	$M1a_{Contr\ Nod}$
M1b	Single extrathoracic metastasis	$M1b_{Single}$
M1c	Multiple extrathoracic metastasies (1 or >1 organ)	$M1c_{Multi}$
TS, NX: T or N status not able to be assessed		
[a]	Superficial spreading tumor of any size but confined to the tracheal or bronchial wall	
	Such tumors are classified as T2s if >3≤4 cm, T2b if >4≤5 cm	
[b]	Pleural effusions are excluded that are cytologically negative, non-bloody, transudative,	
[c]	and clinically judged not to be due to cancer	

Table 2

STAGE GROUPING					
T/M	**Label**	**N0**	**N1**	**N2**	**N3**
T1	T1a ≤1	IA1	IIB	IIIA	IIIB
	T1b >1-2	IA2	IIB	IIIA	IIIB
	T1c >2-3	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Yisc Pl*	IB	IIB	IIIA	IIIB
	T2a *>3-4*	IB	IIB	IIIA	IIIB
	T2b *>4-5*	IIA	IIB	IIIA	IIIB
T3	T3 *>5-7*	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 *>7*	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a*Contr Nod*	IVA	IVA	IVA	IVA
	M1a*Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

See Table 1 text and legend for expansion of abbreviations.

APPENDIX III: CTEP COLLABORATIVE AGREEMENTS LANGUAGE

Protocols that involve agent(s) covered by a collaborative agreement with a biotech/pharma company(ies) must incorporate the NCI/ DCTD Collaborative Agreement Language shown below.

> The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:
>
> 1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
>
> 2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
>
>   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
>
>   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
>
>   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

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

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

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

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

   Email : ncicteppubs@mail.nih.gov

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

APPENDIX IV: FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE (25-NOV-2019)

1. Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	**Serum Creatinine (SCr), *µmol/L (mg/dL)***	**Equation**
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al.*, 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)

Output is in mL/min/1.73 m^2 and needs no further conversions.

3. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg\ /\ dL)} \{\times 0.85\ for\ female\ patients\}$$

References

1. Levey, AS, Stevens LA, Schmid CH, et al (2009). A new equation to estimate glomerular filtration rate. Ann Inter Med. 150:604-612.
2. Levey, AS, Coresh J, Greene T, et al (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 145:247-254.
3. Cockcroft, DW and Gault MH (1976). Prediction of creatinine clearance from serum creatinine. Nephron. 16:31-41.

APPENDIX V: CLINICAL BLOOD SAMPLE SHIPMENT PREPARATION AND TRANSPORTATION FOR TELOMESCAN (25-NOV-2019)

I. RATIONALE

The purpose of this document is to describe the procedure for handling, packaging, and shipping blood samples from study participants, by ensuring safe and timely delivery to Liquid Biotech USA.

1. Circulating Tumor Cell (CTC)

A. Overview

Currently, there is little known about the numbers, time course, and effect of therapy on Circulating Tumor Cells (CTCs) in NSCLC patients. The biospecimens collected in this study will allow for an assessment of (1) CTC changes during treatment with durvalumab and radiotherapy and after completion of treatment, and (2) the relationship between CTC changes during and following treatment with radiographic tumor response and disease recurrence. CTCs will be enriched from whole blood and treated with TelomeScan (OBP-401). TelomeScan is a genetically engineered adenovirus that replicates and produces GFP (Green Fluorescent Protein) specifically in live, cancerous cells with high TERT expression. GFP expressing cells will be imaged and enumerated. The disappearance of CTCs / mL is an indication of disease clearance, and the reappearance of CTCs / mL is an indication of progressive disease or recurrence.

B. Laboratory Testing Procedures

Blood specimens are required for this analysis. The procedure of blood collection for each patient will be as follows: Blood will be drawn into a waste tube (to avoid collecting skin material and potential contaminating skin stem cells). The waste tube will either be discarded or used to investigate other laboratory methods involving CTC virus transduction. Subsequently, blood will be collected in ACD-A tubes at ambient temperature and placed in an insulated tube box inside a biohazard plastic bag and transported to the laboratory for processing.

II. MATERIALS

No.	Product	Quantity
1	TelomeScan corrugated shipping box	1
2	Biohazard Specimen Transport Bag	1
3	Absorbent pad	1
4	Gel pack (Phase 22™ Cryopak)	2
5	List of contents card	1
6	Barcoded BD Vacutainer™ Blood Collection Tube with ACD-A (8.5mL)	3
7	Insulated tube holder box	1
8	Commercial Grade Packaging tape	1 (supplied as needed per site)

III. PROCEDURE

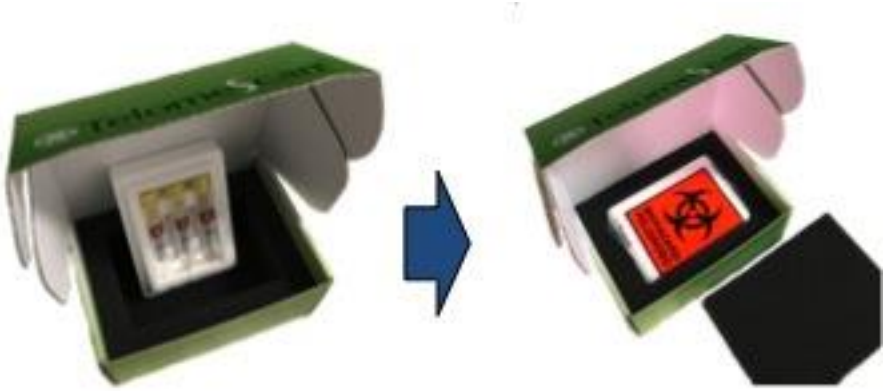
SHIPMENT PREPARATION INSTRUCTIONS

1. All necessary materials for shipping (including blood collection tubes and 2 gel packs for internal temperature control) may be obtained from Liquid Biotech USA. Please contact Liquid Biotech USA at support@liquidbiotechusa.com (tel: 267-225-7361) to arrange for delivery of materials. Prior to blood collection, it is recommended for patient visit dates to be logged by going to www.liquidbiotechusa.com and clicking the "Schedule" button on the main page.

2. Using the barcoded blood collection tubes with Acid-Citrate-Dextrose Solution A (ACD-A), completely collect whole blood. It is critical that tubes are inverted 8-10 times immediately following collection of each tube. The first 5 mL of the blood draw should be drawn in a discard tube to avoid skin cell contamination. Extra ACD-A tubes are supplied which may be used for the initial 5mL discard. Only 1 completely filled tube is required for testing. Each tube should be filled with 8.5mL of blood to completely fill the tube. It is necessary to ship samples on the same day as the blood draw. Samples should be stored at **ambient temperature** until shipped.
   NOTE: Liquid Biotech USA is NOT able to accept deliveries on a weekend or major US holiday. Please do NOT draw blood on a Friday or the 2 days prior to a major US holiday, as the sample will not be received in a timely manner. If the patient can only be seen on one of these days, please coordinate special transportation needs with Liquid Biotech USA.

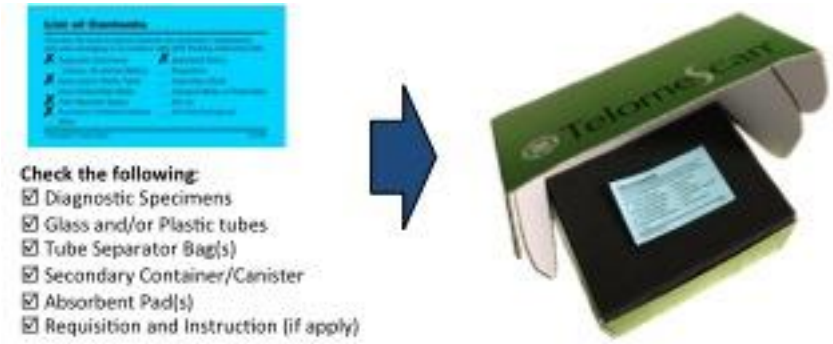
3. Barcoded tubes should be clearly labeled to include date and time of blood draw. **NOTE:** Sites may include a unique identifier number documentation purposes.

4. Place filled tube(s) in the insulated tube holder and place inside a Biohazard Specimen Transport Bag with absorbent material.



5. Place the tube holder in bag between the 2 gel packs that are supplied with the kit. These gel packs change phase between solid and liquid at 72°F. When shipping during the colder seasons (external low temperature <32°F), it is recommended to ship packs in the liquid state. When shipping during the warmer seasons (external high temperature >86°F) it is recommended to ship packs in the solid state.

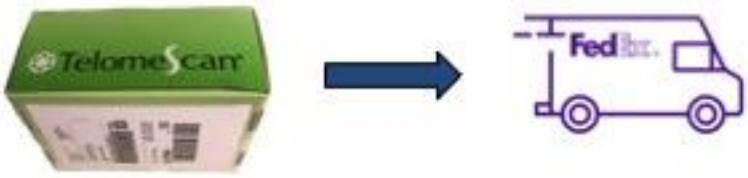
6. Fill out the itemized list of contents card and place on top of the Styrofoam box. The card should have checked Diagnostic Specimens, Glass and/or Plastic tubes, Tube Separator Bag(s), Secondary Container/Canister, and Absorbent Pad(s). Optionally, the "Requisition" and "Instruction Sheet" should be checked if included.



7. Seal the corrugated box with packaging tape across the front flap.

8. Samples should be shipped at **ambient temperature the same day they are collected**.

9. Kits are pre-labeled with FedEx shipping information. Ship the package at ambient temperature by contacting FedEx for pick-up at 1-800-463-3339.



NOTE: It is critical that samples are shipped the same day as blood collection (using FedEx overnight), so that they may be processed within approximately 24 hours of the blood draw. Samples that are not received by Liquid Biotech USA on the day following blood collection will not be processed.

IV. HEALTH AND SAFETY

1. Standard safety precautions are to be followed. Always wear gloves when handling blood samples.
2. Refer to the risk assessment, hazard data sheets, and Departmental policy at your location for additional safety information.

V. PERSONNEL

Appropriate staff for sample packaging preparation and shipment may include all trusted and responsible institution lab personnel qualified to handle blood samples.

VI. Packaging and shipment checklist of clinical specimens

Check or Initial	Item/Activity
	All primary receptacles (i.e., specimen collection containers) have positive closures, such as conventional caps.
	Each primary receptacle is labeled with the date/time the sample was collected, and optionally a unique identifier.
	For liquid specimens, the primary receptacle is leak-proof and contains a maximum of 10 ml.
	When shipped by air, the primary or secondary containers are able to withstand, without leakage, an internal pressure producing a pressure differential of not less than 95kPa (14 psi) in the range of -40°C to 55°C (-40°F to 130°F).
	The primary receptacles are individually wrapped or separated and placed inside a

	leak-proof secondary container.
	The secondary container is certified by the manufacturer prior to use.
	Absorbent material has been placed between the primary receptacle and the secondary container (enough absorbent material to absorb the entire contents of all the primary receptacles).
	The secondary container is not over packed (a pencil will fit between the primary receptacles after the absorbent material has been added).
	An itemized list of the contents is included with each shipment. The list includes the telephone number, fax number, and/or an e-mail address where problems may be reported by the receiving lab.
	A sturdy outer package is used to ship the primary receptacle(s) and secondary container(s). The outer packaging consists of corrugated fiberboard, wood, metal, or rigid plastic and is appropriately sized for the contents.
	For liquid, the outer packaging does not contain more than a total of 4 L. Each individual primary receptacle contains a maximum of 10 ml.
	If a courier such as DHL, FedEx, or UPS is used, then the waybill number has been written on the outside of each secondary container.
	Each completed package is capable of withstanding a 4 foot (1.2 meter) drop test as outlined by IATA and DOT.
	The outermost packaging includes an approved UN3373 label, "Biological Substance Category B" and all other labels and markings required by DOT and IATA.

VII. RECORDS

Number	Sample ID	Collection Date	Collection Time	# of tubes collected	Shipment Date	Shipment Time	Initials
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
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APPENDIX VI: NRG BIOSPECIMEN BANK – SAN FRANCISCO
BIOSPECIMEN PROCEDURES (25-NOV-2019)

A. Shipping instructions for Banking Samples
B. FFPE Specimen Plug Kit Collection

A. Shipping Instructions for Banking FFPE:

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:
NRG Oncology Biospecimen Bank – San Francisco **UCSF – Box 1800** **2340 Sutter St., Room S341** **San Francisco, CA 94143**	**NRG Oncology Biospecimen Bank – San Francisco** **University of California San Francisco** **2340 Sutter St., Room S341** **San Francisco, CA 94115** **415-476-7864**

1. Include all required specimen paperwork in pocket of biohazard bag.

2. Check that the Specimen Transmittal (ST) Form has been completely filled out. Use NRG labels for the top box (Study & Case).

3. Only send samples that have a case # assigned. If the patient does not have a case number it means they are not registered yet. Contact NRG Oncology data managers with questions regarding registration.

4. Check that all samples are labeled with the NRG Study, case number, and date of procedure.

5. **FFPE Specimens for Banking:**
   - H&E Slide of primary tumor (can be duplicate cut slide, does not have to be diagnostic slide).
   - FFPE Tissue Block of primary tumor (must be same block as H&E slide being submitted). If an FNA was done we cannot accept FNA slides unless there is an FFPE cell block with tumor cells available. Sites are to submit one FNA H&E and matching FNA FFPE cell block if sufficient tumor cells are available. If there are insufficient cells then note this on the ST form with the H&E being submitted.
   - For sites unable to submit the complete tumor tissue block then then the following alternative is acceptable: Either:
     - Two unstained slides with date cut on the slides.
     - OR Two 2mm (or 3mm) punches (tumor size dependent) embedded in paraffin with a corresponding H&E. (Punch kits available from NRGBB-SF upon request). If sites are unable to embed the punches they may send the punches to the biobank to be embedded.

- If sites are unable to provide punches due to limited amounts of tissue, then TWO freshly cut 5 micron unstained slides are an acceptable alternative in such cases. Sites must label the unstained slides with Study, Case#, accession number, block number and date the slides were cut. Slides must be shipped to NRGBB-SF within 2 business days from when they were cut.

Please make sure all FFPE specimens are labeled with Study#, Case#, Specimen accession number and block ID. Redact or cover up the patient name if present. Do not add paper sticky labels over this information. It is the Biospecimen Banks SOP to remove all sticky labels on slides before adding an NRGBB label.

All FFPE submission must include the H&E slide that matches the samples. We cannot accept FFPE submissions without the H&E slide. If submitting embedded punches, an H&E from the punch block must be included along with the original block H&E with the area punched marked on the original H&E.

If patients consent to banking DO NOT ship us 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). We can punch and return blocks if noted in the protocol. You may indicate that you want us to punch and return the block on the ST form and you can include a return request form and return airbill with the submission. Punch kits can be requested from us by email (NRGBB@ucsf.edu) if sites wish to punch the block themselves.

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 it is likely that they will break during shipping.

DO NOT ship slides in cardboard slide flats or single unit plastic slide holders.

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 highly 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. Do not ship in a flat or padded envelope without a protective box/container inside, they can be crushed, even if in a plastic slide holder.

Urgent overnight shipments (central review) should always be sent by Courier. Do not send by First overnight or Saturday delivery as our building is not open before 8am or on weekends.

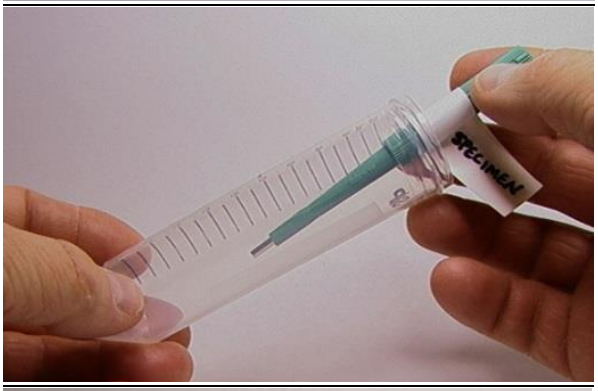
- ✓ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank- San Francisco by e-mail: NRGBB@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

- ✓ **For forms and additional information please visit our website: http://NRGBB.UCSF.EDU**

B. NRG FFPE SPECIMEN PLUG KIT INSTRUCTIONS:

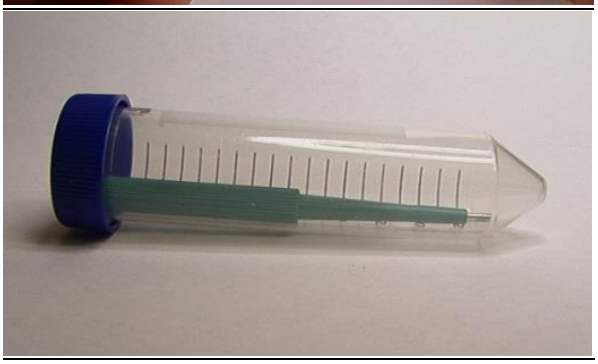
This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank- San Francisco. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.



Step 2
Label the punch tool with the proper specimen ID and Block ID. DON'T remove specimen from the punch if punch is not being embedded by the site.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.
Site that have the capacity to embed the blocks may do so. They should submit a fresh H&E from the punch block.



Step 3 (for non-embedded samples)
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

The bank will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE: If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank- San Francisco and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the ST form the request to perform the plug procedure and return of the block. Include a return request form with a return airbill.**

Ship specimen plug kit, specimen in punch tool, or block and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the

NRG Oncology Biospecimen Bank- San Francisco by e-mail: NRGBB@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

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:**
NRG Oncology Biospecimen Bank- San Francisco **UCSF- Box 1800** **2340 Sutter St, room S341** **San Francisco, CA 94143**	**NRG Oncology Biospecimen Bank- San Francisco** **University of California San Francisco** **2340 Sutter St, room S341** **San Francisco, CA 94115** **415-476-7864**

APPENDIX VII: NRG BIOSPECIMEN BANK-COLUMBUS
BIOSPECIMEN PROCEDURES (25-NOV-2019)

1. Obtaining a Bank ID for Biospecimens

One Bank ID (N # # # # # # # # #) is assigned per patient per study. All biospecimens and accompanying paperwork must be labeled with this coded patient number.

A Bank ID is automatically assigned once a subject has been enrolled and appears in Rave. The Bank ID will appear in the header at the top of the subject's main page in Rave.

Please contact User Support if you need assistance (support@nrgoncology.org).

2. Requesting Biospecimen Kits

Upon request, a biospecimen kit including a Streck tube and ambient shipper will be provided for the collection and shipment of cfDNA whole blood biospecimens. A separate kit is needed for each cfDNA whole blood biospecimen.

Sites can order online via the Kit Management link (https://ricapps.nationwidechildrens.org/KitManagement). If you are new to Kit Management, you must register for an account prior to ordering NRG-LU004 kits. Each site may order two NRG-LU004 kits per day.
Supplies will <u>not</u> be provided for the collection or shipment of whole blood collected in sodium heparin (NaHep) or EDTA tubes.

Please contact the NRG BB-Columbus if you need assistance (Email: BPCBank@nationwidechildrens.org; Phone: 866-464-2262).

Be sure to plan ahead and allow time for kits to be shipped by ground transportation. Kits should arrive within 3-5 business days.

3. Whole Blood Biospecimens Shipped to the NRG BB-Columbus

Labeling Whole Blood
A waterproof permanent marker or printed label should be used to label each blood biospecimen with:

Bank ID (N # # # # # # # # #)*
Patient ID (e.g., AB # # # - LU004 - # # # # #)
specimen code (see protocol section 10.5.3)
collection date (mm/dd/yyyy)

***** *Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N000000010 may be written as N10.*

Required Documentation

All blood biospecimens should be submitted with the following documentation:

- Blood Biospecimen Submission Form

All blood biospecimens will be processed as per the current CIMAC Umbrella.

3.1 T Cell Whole Blood

3.1.1 Collection Time Points

T cell whole blood should be collected as per section 10.5.2.

3.1.2 Collecting T Cell Whole Blood

1. Label the green top sodium heparin (NaHep) collection tube(s) as described above. Multiple tubes may be used to collect the required amount. **Do <u>not</u> use glass blood collection tubes.**
2. Draw 30mL of blood into the labeled green top tube(s).
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and sodium heparin.
4. Whole blood specimens should be kept at room temperature until the specimens can be shipped. Whole blood must be shipped to the NRG BB-Columbus **the day the specimen is collected**. If the specimen cannot be shipped the day it is collected, it should be discarded.

3.2 T Cell Repertoire (TCR) Whole Blood

3.2.1 Collection Time Points

T cell repertoire (TCR) whole blood should be collected as per section 10.5.2.

3.2.2 Collecting T Cell Repertoire (TCR) Whole Blood

1. Label the lavender/purple top (EDTA) collection tube as described above. **Do <u>not</u> use glass blood collection tubes.**
2. Draw 2mL of blood into the labeled lavender/purple top tube.
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.
4. Whole blood specimens should be kept at room temperature until the specimens can be shipped. Whole blood must be shipped to the NRG BB-Columbus **the day the specimen is collected**. If the specimen cannot be shipped the day it is collected, it should be discarded.

3.3 Cell-Free DNA (cfDNA) Whole Blood

3.3.1 Collection Time Points

Cell-free DNA (cfDNA) whole blood should be collected as per section 10.5.2.

3.3.2 Special Notes Regarding the Collection of Blood in Streck (cf DNA) Tubes

- Heparin should be avoided in pre-collection flush procedures.
- All other blood biospecimens should be drawn <u>*before*</u> the Streck (cell-free DNA) tube when multiple blood biospecimens are collected on the same day.
- Over or under filling a Streck (cell-free DNA) tube will result in an incorrect blood-to-additive ratio.
- No other tube may be substituted for a Streck (cell-free DNA) tube.

3.3.3 Collecting Streck (Cell-Free DNA) Whole Blood

1. Label the **Streck** (cell-free DNA) collection tube as described below.
2. Draw **10mL** of blood into the labeled tube.
3. Immediately after collection, gently invert the tube 5-10 times.
4. Ship whole blood to the NRG BB-Columbus the day the biospecimen is collected. If the whole blood **absolutely** cannot be shipped the day it is collected, the tube must remain at **room temperature** until shipment.

4. Shipping Whole Blood Biospecimens to the NRG BB-Columbus

- Biospecimens should not be shipped until after patient registration.
- The required documentation must be included for each biospecimen.
- All biospecimens should be shipped to:
  NRG BB-Columbus / Protocol NRG LU004
  Nationwide Children's Hospital
  700 Children's Dr, WA1340
  Columbus, OH 43205
  Phone: 614-722-2865
  FAX: 614-722-2897
  Email: BPCBank@nationwidechildrens.org

- Whole blood biospecimens can be shipped to the NRG BB-Columbus **Monday through Friday for Tuesday through Saturday delivery**. Do not ship whole blood the day before a holiday. Ship biospecimens via FedEx priority overnight.
- When shipping whole blood biospecimens, **your site must comply with IATA standards** (www.iata.org). If you have questions regarding your shipment, contact the NRG BB-Columbus at BPCBank@nationwidechildrens.org or by phoning 866-464-2262.

4.1 Whole Blood Collected in Sodium Heparin (NaHep) and EDTA Tubes

To ship whole blood collected in Sodium Heparin (NaHep) and EDTA tubes you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen sticker, and (5) a pre-paid FedEx air bill.
**If you will be shipping both whole blood collected in sodium heparin (NaHep) and EDTA, please put each biospecimen in a separate plastic zip-lock bag before placing the biospecimens in the shipping bag.*

If you do not have these materials available at your site, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484; Website: www.saftpak.com).

4.1.1 Shipping Whole Blood in Sodium Heparin (NaHep) and EDTA Tubes

Note: Sodium heparin (NaHep) whole blood must be processed immediately upon receipt at the NRG BB-Columbus. To ensure this processing, please note the special instructions in #7 below.

1. Ship whole blood collected in sodium heparin (NaHep) or EDTA tubes using your own shipping container and supplies.
2. Place the whole blood biospecimens in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.
3. Wrap the biohazard envelope in bubble wrap or another padded material.
4. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.
5. Place the Tyvek envelope in a sturdy shipping container (e.g., cardboard FedEx box).
6. Insert a copy of the Blood Biospecimen Submission Form for each biospecimen.
7. Attach an Exempt Human Specimen sticker to the outside of the shipping container. A neon- or brightly-colored sticker that states "CIMAC Blood," as well as the blood collection date and time (e.g., 1/2/2019, 12:32pm), must also be attached to the shipping container.
8. Print a pre-paid FedEx air bill using the Kit Management link (https://ricapps.nationwidechildrens.org/KitManagement/) and attach to the top of the shipping container.
9. Make arrangements for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

4.2 Whole Blood Collected in Streck Tubes

To ship whole blood collected in Streck tubes you will a Streck Cell-Free DNA Ambient Shipper. Refer to Section 2 for details.

4.2.1 Shipping Whole Blood Using a Streck Cell-Free DNA Ambient Shipper

1. Before packaging cfDNA whole blood biospecimens, verify that each biospecimen is labeled according to the instructions above.
2. Prepare the SAF-T-TEMP Gel Pak for shipment. *Note: If contents of the Pak are crunchy, place Pak in a warm water bath until gel is smooth.* ***Do not refrigerate, freeze, or microwave.***
3. Place the SAF-T-TEMP Pak in bottom of insulated chest. *Note: The insulated chest must be shipped inside the provided cardboard box.*
4. Place the blood collection tube in zip-lock bags.
5. Next, place zip-lock bag into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
6. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
7. Place packaged Streck blood collection tube and a completed copy of the Blood Biospecimen Submission Form on top of SAF-T-TEMP Gel Pak.
8. Place the lid on the insulated chest.
9. Close the outer flaps of the shipping box and tape shut.
10. Print a pre-paid FedEx air bill using the Kit Management link (https://ricapps.nationwidechildrens.org/KitManagement/) and attach to the top of the shipping container.

11. Attach an Exempt Human Specimen sticker to the side of the box.
12. Make arrangements for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

APPENDIX VIII: CANCER IMMUNE MONITORING AND ANALYSIS CENTER (CIMAC) BIOMARKER TESTING (03-NOV-2021)

1. CyTOF

A. Overview

Assessment of changes in immune cell diversity over time is required to quantify the immune cell subsets in circulation, with each subset given in percentages rather than absolute amount or levels. The dynamic changes in immune cell subsets throughout therapy may tell us whether specific subsets of T cells are being expanded, such as memory T cells or activated T cells. We hypothesize that expansion of specific subsets of cells will correlate most strongly with the disease outcomes of patients. The immune cell subsets that change with the different radiation schedules with immunotherapy could also relate to enhanced toxicities, which will be monitored very closely as the primary endpoint of this phase I study.

B. Laboratory Testing Procedures

Assessing multiple cell types simultaneously in a high dimensional manner requires multiparametric technology that could simultaneously assess all of the parameters on a single cell. Using Time of Flight Mass Cytometry (CyTOF), antibodies conjugated with rare transition element isotopes that differ by one atomic number could be quantified and distinguished using a TOF mass cytometer. The theoretical maximum of parameters is 100, but the most common uses have only interrogated up to 34 surface or intracellular proteins. This already greatly exceeds the capability of standard fluorescence-based flow cytometry. Using MatLab analysis, one can resolve cell identify (e.g., CD8, CD4, Treg, MDSC, NK, B cells) and expression levels of various activating, inhibitory, or signaling molecules on these cells.

2. TCR Sequencing

A. Overview

Lymphocyte maturation is a process marked by immunophenotypic changes, as well as discrete and regulated molecular events. The first event in the process of antitumor cytotoxic T-cell response is antigen capture by antigen-presenting cells (APCs). The antigens are processed and subsequently presented on HLA class I molecules to CD8+ T cells to activate the T-cell response against these specific antigens. Following activation, effector CD8+ T cells infiltrate into tumor tissues, releasing cytotoxic agent upon recognition of cancer cells through the interaction between TCR and its cognate antigen bound to HLA class I.

The diversity of T cells is determined by their TCR. The complimentary determining region 3 (CDR3) of the TCR chain is the most variable portion of the TCR and is critical for MHC–peptide complex recognition. The range of individual TCR-bearing T-cell clones that comprises the repertoire specific for a particular antigenic MHC–peptide complex varies substantially in terms of TCR frequency and diversity. A consequence of this specificity is that the TCR CDR3 sequence can be used as a "molecular tag" to identify each T-cell clone. Recently presented data have indicated that that large clonal T-cell expansions were associated with inferior PFS and OS in B-cell lymphoma.

B. Laboratory Testing Procedures

CIMAC will designate a laboratory to perform TCR sequencing.*
*Note: at CIMAC discretion, if sufficient material is available.

3. Cytokine Analysis

A. Overview

This exploratory analysis will identify the quantity and types of cytokines released in the blood during and after therapy. Cytokines and chemokines mediate the cross talk between cells of the immune system, both locally and systemically. Certain inflammatory mediators such as interferons act as surrogates of the activation of the immune system, and also signal the effectiveness of cancer therapy. Certain markers are also immunosuppressive (e.g., TGFbeta), so the effectiveness of the immune system response is a balance of immunostimulating and immunosuppressive cytokines. Radiation therapy could also illicit profound cytokine release and the amount could have relationship to both the radiation dose and fractionation schemes, and the synergistic interaction with immunotherapy. We hypothesize that proinflammatory cytokines could be release differentially depending on the radiation schedule, which could further be accentuated by immunotherapy. Inflammatory mediators could also contribute to immune related adverse events that may be exacerbated by radiation therapy. Therefore, we may also see early surrogates of toxicity by monitoring dynamic alterations of cytokine levels.

B. Laboratory Testing Procedures

Multiplex Immunoassay using the OLink Technology. Plasma (prepared from blood collected in green-top sodium-heparin tubes) will be collected and sent to the NRGBB-Columbus for processing, then sent to the CIMAC laboratory at the Icahn School of Medicine at Mount Sinai in New York to conduct the OLink assay. Samples will be collected at baseline, Day 15 and 30 post treatment, and at 3 months from the start of durvalumab (i.e. cycle 4). Olink assay has large dynamic range and each assay has internal controls that will ensure the robustness of the test.

4. ELISA/Grand Serology

A. Overview

B. One approach to test whether tumors become more immunogenic as a result of immunotherapy is to measure naturally occurring antibodies in patient serum or plasma. Autologous serotyping has resulted in a growing list of immunogenic human cancer antigens1, including mutational, overexpressed, oncogenic viral, differentiation, and cancer-testis antigens. These antigens, though usually intracellular, reflect the immune system's capacity to detect abnormalities associated with neoplasia. The presence of antibodies to tumor antigens can be used as a marker of tumor presence or progression, but may also help generate T cell responses via immune complexes with cognate antigen. In some cases, such as the cancer/testis antigen NY-ESO-1, serum antibodies are associated with spontaneous T cell responses in peripheral blood. We propose to test the hypotheses that immunotherapy leads to induction or increase in immunity to locally expressed antigens by assessing serological changes pre-post treatment, and that the serological repertoire in patients may be useful as a prognostic or predictive tool.

Laboratory Testing Procedures

Using serological markers as a surrogate for presence of antitumor immunity is proposed as a quick and affordable way to assess tumor immunocompetence and response. A series of known tumor antigens will be assessed in a hypothesis-driven manner for their capacity to elicit autoantibodies in treated patients. Using ELISA, we will test a set of 25 tumor antigens, including mutational, stem-cell, and cancer-testis antigens such as TP53, NY-ESO-1, SOX2, PRAME, WT1, MAGE-A3, SSX2, etc., most of which already have demonstrated immunogenicity in various solid and hematologic tumors. Grand Serology is also ideally suited to test for potential for antigen spreading, i.e., development of seroreactivity to antigens unrelated to immunogenes, which is a useful measurement to assess in immunotherapy.

5. Circulating Tumor DNA (ctDNA)

A. Overview

The detectability of any strand of DNA bearing cancer specific mutations can be quantified as well as the number of molecules per mL of blood. Any molecule of cancer specific DNA (or ctDNA) can be determined as minimal residual disease, and the disappearance of the ctDNA in the blood is an indication of disease clearance. The level may also indicate disease burden as well.

B. Laboratory Testing Procedures

Ultradeep allelic sequencing of ctDNA – to be performed by the appropriate CIMAC laboratory.

6. PD-L1 (SP263) Immunohistochemistry (IHC)

a. Overview

PD-L1 is an informative immunotherapy biomarker: Aberrant expression of PD-L1 on tumor and immune cells in the tumor microenvironment impedes anti-tumor immunity, allowing tumors to grow and metastasize. SP263 tumor cell staining quickly calculates PD-L1 positivity for user-defined regions of interest.

b. Laboratory Testing Procedures

PD-L1 (SP263) IHC will be done using optional tissue biospecimens for cases that were stained using the Dako 22C3 (the Dako 22C3 will be used in case(s) without the PD-L1 22C3 assay already performed, Multiplex IHC, and if sufficient tissue/DNA from tissue remains – TCRseq).