Title: **The Selective Personalized Radio-Immunotherapy for Locally Advanced NSCLC (SPRINT)**

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TITLE: The Selective Personalized Radio-Immunotherapy for locally advanced NSCLC Trial (SPRINT)

IND Number: IND Exempt

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1.0 TRIAL SUMMARY

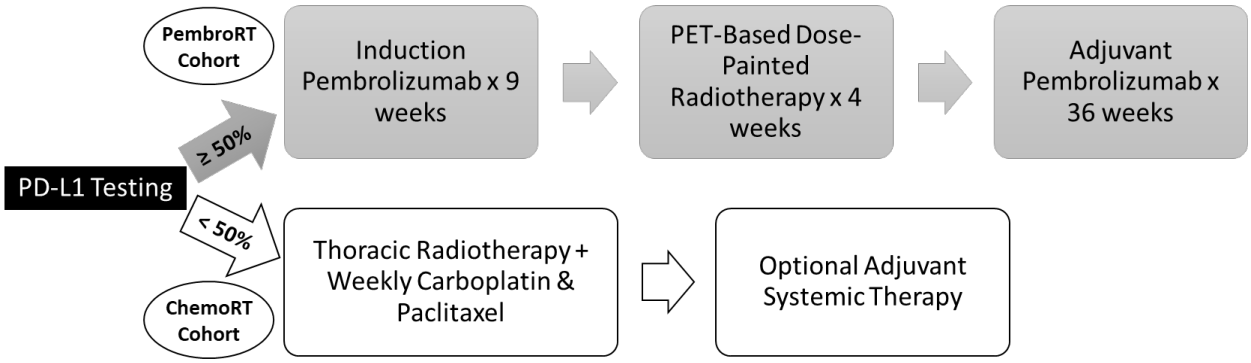
Abbreviated Title	Radioimmunotherapy for LA-NSCLC
Trial Phase	*II*
Clinical Indication	Locally advanced non-small cell lung cancer
Trial Type	Single Arm, Open Label, with 2 cohorts
Type of control	None
Route of administration	Intravenous
Trial Blinding	None
Treatment Groups	PembroRT Cohort – Subjects with PD-L1 expression ≥ 50% ChemoRT Cohort - Subjects with PD-L1 expression < 50%
Number of trial participants	PembroRT Cohort – 25 ChemoRT Cohort – Approximately 38
Estimated enrollment period	3/1/2018 to 9/1/2019
Estimated duration of trial	18 months
Duration of Participation	28 months
Estimated average length of treatment per patient	PembroRT Cohort - One year

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase II trial evaluating the efficacy and safety of sequential pembrolizumab (200 mg every three weeks) and accelerated, dose-painted radiotherapy for patients with locally advanced NSCLC with PD-L1 expression ≥ 50%. Patients with PD-L1 expression < 50% will also be enrolled and treated with standard concurrent chemoradiotherapy to serve as a non-randomized comparison group.

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis

(1) **Objective:** To characterize progression-free survival rates following treatment with sequential pembrolizumab and radiotherapy for locally advanced NSCLC with PD-L1 expression ≥ 50%.

Hypothesis: We hypothesize that sequential pembrolizumab and radiotherapy for locally advanced NSCLC with PD-L1 expression ≥ 50% prolongs progression-free survival compared to historical outcomes.

3.2 Secondary Objective(s) & Hypotheses

(1) **Objective**: To characterize freedom from distant metastasis rates following treatment with sequential pembrolizumab and radiotherapy for locally advanced NSCLC with PD-L1 expression ≥ 50%.

Hypothesis: We hypothesize that sequential pembrolizumab and radiotherapy for locally advanced NSCLC with PD-L1 expression ≥ 50% prolongs freedom from distant metastasis compared to historical outcomes.

(2) **Objective**: To characterize freedom from intrathoracic disease progression rates following treatment with sequential pembrolizumab and radiotherapy for locally advanced NSCLC with PD-L1 expression ≥ 50%.

Hypothesis: We hypothesize that sequential pembrolizumab and radiotherapy for locally advanced NSCLC with PD-L1 expression ≥ 50% prolongs freedom from intrathoracic disease progression compared to historical outcomes.

(3) **Objective**: To characterize overall survival rates following treatment with sequential pembrolizumab and radiotherapy for locally advanced NSCLC with PD-L1 expression ≥ 50%.

Hypothesis: We hypothesize that sequential pembrolizumab and radiotherapy for locally advanced NSCLC with PD-L1 expression ≥ 50% prolongs overall survival compared to historical outcomes.

(4) **Objective**: To estimate the rate of disease progression during 3 cycles of induction pembrolizumab prior to radiotherapy for locally advanced NSCLC with PD-L1 expression ≥ 50%.

Hypothesis: We hypothesize that the rate of disease progression during 3 cycles of induction pembrolizumab prior to radiotherapy for locally advanced NSCLC with PD-L1 expression ≥ 50% is less than 10%.

(5) **Objective**: To demonstrate, within the limitations of a nonrandomized study, that sequential pembrolizumab and radiotherapy for locally advanced NSCLC reduces severe adverse event rates compared to standard concurrent chemoradiotherapy.

Hypothesis: We hypothesize that sequential pembrolizumab and radiotherapy for locally advanced NSCLC reduces severe adverse event rates compared to standard concurrent chemoradiotherapy.

(6) **Objective**: To demonstrate, within the limitations of a nonrandomized study, that sequential pembrolizumab and radiotherapy for locally advanced NSCLC does not significantly increase rates of pneumonitis compared to standard concurrent chemoradiotherapy.

Hypothesis: We hypothesize that that sequential pembrolizumab and radiotherapy for locally advanced NSCLC not significantly increase rates of pneumonitis compared to standard concurrent chemoradiotherapy.

(7) **Objective**: To demonstrate, within the limitations of a nonrandomized study, that sequential pembrolizumab and radiotherapy for locally advanced NSCLC reduces patient-reported treatment-related toxicities compared to standard concurrent chemoradiotherapy.

Hypothesis: We hypothesize that sequential pembrolizumab and radiotherapy for locally advanced NSCLC reduces patient-reported treatment-related toxicities compared to standard concurrent chemoradiotherapy.

(8) **Objective**: To demonstrate, within the limitations of a nonrandomized study, that sequential pembrolizumab and radiotherapy for locally advanced NSCLC preserves physical function compared to standard concurrent chemoradiotherapy.

Hypothesis: We hypothesize that sequential pembrolizumab and radiotherapy for locally advanced NSCLC preserves physical function, as measured by daily step counts, compared to standard concurrent chemoradiotherapy.

(9) **Objective**: To demonstrate, within the limitations of a nonrandomized study, that sequential pembrolizumab and radiotherapy for locally advanced NSCLC reduces hospitalization rates compared to standard concurrent chemoradiotherapy.

Hypothesis: We hypothesize that sequential pembrolizumab and radiotherapy for locally advanced NSCLC reduces hospitalization rates compared to standard concurrent chemoradiotherapy.

3.3 Translational Objectives

(1) **Objective:** To demonstrate, within the limitations of a nonrandomized study, that sequential pembrolizumab and radiotherapy for locally advanced NSCLC with PD-L1

expression ≥ 50% increases the rate of circulating tumor DNA clearance compared to standard concurrent chemoradiotherapy.

(2) **Objective:** To correlate PD-L1 TPS score and expression of alternative immune checkpoint molecules (e.g.: HHLA2, B7x, and B7-H3) with clinical outcomes.

(3) **Objective:** To correlate baseline tumor mutational burden with clinical outcomes.

(4) **Objective:** To correlate markers of immune activation and expansion of immune cell subsets with clinical outcomes.

4.0 BACKGROUND & RATIONALE

4.1 Locally Advanced Non-small Cell Lung Cancer

Lung cancer is the leading cause of cancer-related death worldwide, with more than 1.5 million deaths per year [1, 2]. More than 220,000 new cases of lung cancer are diagnosed each year in the United States. Non–small-cell lung cancer represents more than 80% of lung cancers, and about 35% of NSCLC patients present with stage III disease [3]. Standard treatment for patients with locally advanced NSCLC, which may be defined as stage III disease or unresectable stage II disease, typically consists of conventionally-fractionated (1.8-2.0 Gy/day) radiotherapy to a total dose of approximately 60 Gy with concurrent chemotherapy. This treatment approach yields median survival times of only 16-30 months and can cause significant acute and late toxicities [4-9]. The five-year survival rate following concurrent chemoradiotherapy for stage III NSCLC is approximately 20%. Outcomes for patients who are deemed unfit for concurrent chemoradiotherapy are even poorer.

In the recently published PACIFIC study [10], the anti-programmed death ligand 1 (PD-L1) antibody durvalumab was compared to placebo as consolidation therapy lasting up to 12 months in patients with stage III NSCLC without disease progression after concurrent chemoradiotherapy. Adjuvant durvalumab significantly prolonged progression-free survival. Overall survival data from that trial are not yet available.

4.2 Pembrolizumab

The introduction of immune checkpoint inhibitors has revolutionized the management of advanced NSCLC. Most lung cancers, in particular those associated with smoking, harbor many missense mutations and are some of the most immunogenic tumors through the presentation of neo-antigens. In many lung tumors, a T-cell response is established but is negatively regulated via the tumoral expression of checkpoint molecules. In the majority of cases of advanced NSCLC, the molecular makeup of the tumor measured by tumor mutation burden, the inflamed status of the tumor measured by markers of immune activation such as expansion of T4/T8 subsets, regulatory T-cell numbers and myeloid derived suppressor cells, and tumoral “defense” response, assessed by PD-L1 expression, provide promising biomarkers to assess candidacy for checkpoint inhibitor therapy [11].

In the pivotal Keynote-010 study, pembrolizumab was proven to prolong progression-free and overall survival compared to docetaxel in patients with PD-L1 positive (defined as PD-L1

expression on at least 1% of tumor cells) NSCLC that was previously treated with at least one line of , with a striking improvement in the subset of patients with PD-L1 expression of at least 50% [12]. This study led to FDA approval of pembrolizumab in the second line setting for PD-L1 positive (expression>1%) tumors and provided impetus for biomarker selected first-line studies such as the Keynote-024 study. In Keynote-024, single-agent pembrolizumab was compared to standard doublet chemotherapy for patients with treatment-naïve advanced NSCLC with PD-L1 tumor proportion score (TPS) of 50% or higher. Treatment with pembrolizumab rather than chemotherapy led to a significant overall survival benefit and fewer adverse event, leading to the approval of pembrolizumab as first-line treatment for advanced PD-L1 positive (≥ 50%) NSCLC [13].

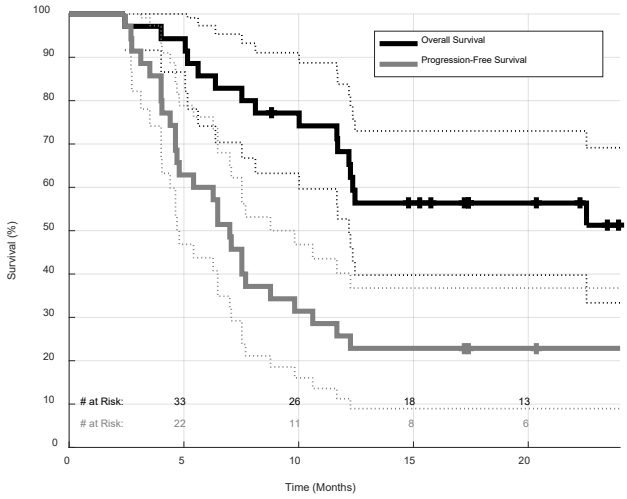
4.3 Radiotherapy

Locally-advanced NSCLC is typically treated with thoracic radiotherapy, often in combination with concurrent chemotherapy. Despite advances in the evaluation, treatment techniques, and supportive care measures provided to locally advanced NSCLC patients, local disease progression and distant metastases frequently develop following definitive therapy. Randomized trials have tested changes or additions to systemic therapy[14-18], radiotherapy dose escalation, and the addition of surgical resection[19] but have failed to improve overall survival for this patient population. A recent landmark randomized trial demonstrated that radiotherapy dose escalation, applied to the primary tumor and all involved regional lymph nodes, may reduce survival rates, highlighting gaps in our understanding of the effects of thoracic radiotherapy for LA-NSCLC.

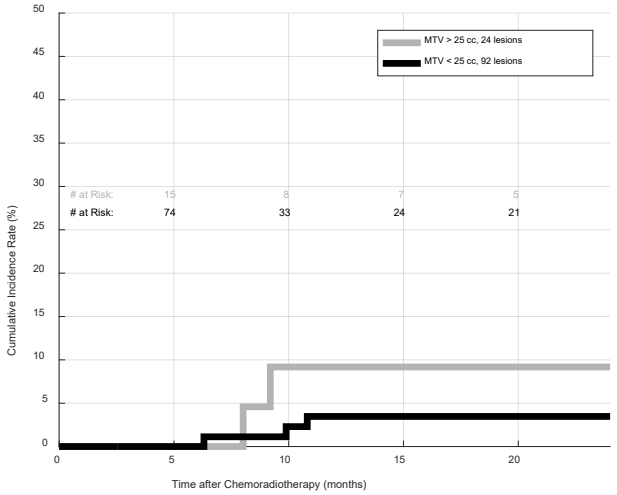
A growing body of literature indicates that minimizing cardiac irradiation should be a goal in planning thoracic radiotherapy. Recent publications have demonstrated a strong association between cardiac irradiation and both cardiac events [20-23] and all-cause mortality[17]. The risks of cardiac irradiation may be highest in subjects with comorbid conditions such as existing heart disease[20, 21] or a smoking history [23], which are common in NSCLC patients. Somewhat surprisingly, these effects have been seen within a few years of radiotherapy delivery [17, 20-22] and in populations with high risk of cancer-specific mortality [17, 20, 21]. In retrospect, this is consistent with previous analyses demonstrating that excessive [24] or unnecessary [25] mediastinal irradiation for lung cancer can meaningfully reduce survival rates. Thoracic irradiation may directly lead to coronary artery stenosis[26] and may also impair patients' immune systems [27].

Based on accumulating evidence demonstrating the prognostic and predictive value of FDG-PET metrics [28-32], we recently performed a single-institution phase II study testing dose-painted intensity-modulated radiotherapy (IMRT) as a strategy to improve the efficacy and safety of chemoradiotherapy for locally advanced NSCLC[33]. In that trial, tumors and lymph nodes deemed to be at low risk for local progression following chemoradiotherapy were treated with a relatively low radiotherapy dose of 52.5 Gy. Our results indicate that this novel strategy yields high rates of metabolic response, local disease control, and overall survival. The aforementioned high-profile studies highlighting the importance of minimizing cardiac irradiation in NSCLC

patients will draw additional attention to our dose-painting approach for locally advanced NSCLC.



Kaplan-Meier curves for overall survival and progression-free survival from the Montefiore/Einstein phase II study of dose-painted IMRT for LA-NSCLC.



Cumulative incidence curves for disease progression in individual tumors or lymph nodes from the Montefiore/Einstein phase II study of dose-painted IMRT for LA-NSCLC. Progression at other sites or death from any cause were treated as competing risks. Of note, lesions with metabolic tumor volumes (MTV) below 25 cc were treated with relatively low radiotherapy doses of 57 Gy (n=20) or 52.5 Gy (n=72).

4.4 Activity Monitoring

In addition to pioneering a novel way to deliver thoracic radiotherapy, we at the Montefiore/Einstein Cancer Center have established a novel program to monitor patients for acute complications during radiotherapy. We performed a pilot trial in which patients undergoing concurrent chemoradiotherapy for a variety of malignancies were equipped with commercial fitness trackers, and activity levels were monitored throughout the treatment course[34]. We found that daily step counts can serve as powerful and dynamic predictors of unplanned hospitalization during chemoradiotherapy. Specifically, we found a 38% reduction in the risk of hospitalization for every 1,000 steps taken each day. In a follow-up study, we are utilizing activity data to provide customized supportive care for patients based on changes in activity levels, with the aim of reducing the rate of hospitalization during treatment. A third trial at our institution is testing a simple pedometer-based walking program as an intervention to reduce systemic inflammation and reduce treatment interruptions during chemoradiotherapy. A fourth study will explore activity data as a predictor of adverse events for patients with advanced malignancies receiving systemic therapy. Activity data is now collected automatically by wireless access clients every time a patient enters our cancer center.

4.5 Patient-Reported Outcomes

Patient-reported outcomes are becoming a standard tool for evaluating health-related quality of life, treatment preferences, and treatment quality in cancer care[35]. They may be particularly important in studies involving radiotherapy for NSCLC. This is exemplified by the results of RTOG 0617, which was a multi-institutional randomized trial testing uniform radiotherapy dose escalation (including all tumors and regional lymph nodes) with concurrent chemotherapy for LA-NSCLC. Dose escalation from 60 Gy to 74 Gy was unexpectedly found to increase the risk of mortality, with median overall survival durations of 29 months with the standard dose of 60 Gy and only 20 months for subjects treated with 74 Gy[17]. Investigators found no statistically significant differences in serious (grade ≥ 3) adverse events between radiotherapy dose groups, demonstrating the disconnect between physician-scored toxicity and important clinical outcomes. Impairments in patient-reported quality of life, on the other hand, occurred more frequently in the high dose radiotherapy arm[36]. Additionally, baseline quality of life score was found to be a powerful predictor of overall survival.

The National Cancer Institute recently developed the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)[37]. The PRO-CTCAE item library is comprised of 78 symptomatic adverse events, each of which is elicited using between one and three questions (representing frequency, severity, and/or interference), for a total of 124 individual questions. For any given clinical trial, relevant PRO-CTCAE items can be selected from the online library to create a concise patient questionnaire that has been validated in several languages. This promising tool has not yet been utilized extensively in chemoradiotherapy trials for NSCLC. One recent study demonstrated the extent to which CTCAE and PRO-CTCAE findings may differ in this setting[38]. As an example, clinicians using CTCAE reported that high-level anxiety occurred in 0/130 subjects. PRO-CTCAE demonstrated that 28/120 subjects

had high-level anxiety. Large differences between CTCAE and PRO-CTCAE were observed for several other adverse events, including anorexia, cough, dysphagia, fatigue, and pain.

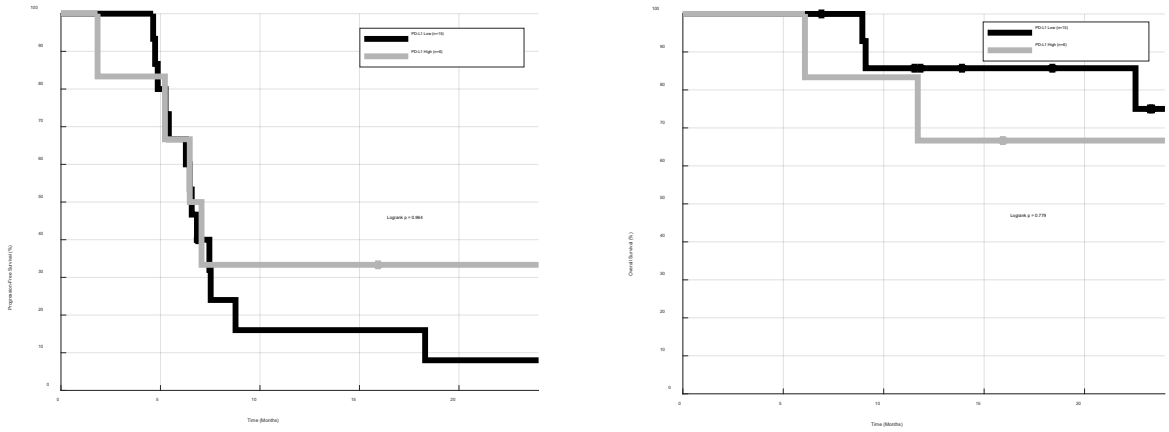
We have developed a concise PRO-CTCAE tool that includes the elements that are likely most relevant to LA-NSCLC patients who are treated with thoracic radiotherapy (Appendix). We expect that patient-reported outcomes for these elements will be improved with the use of radiotherapy and pembrolizumab compared to standard chemoradiotherapy in this setting.

4.6 Study Rationale

We hypothesize that a combination of pembrolizumab and dose-painted radiotherapy will yield improved efficacy and tolerability compared to standard chemoradiotherapy for locally advanced NSCLC patients with high (≥ 50%) PD-L1 expression. We will explore this hypothesis in the "pembroRT" arm of this prospective non-randomized trial. Subjects with PD-L1 expression below 50% will also be enrolled to a "chemoRT arm" and treated with standard concurrent chemoradiotherapy, to allow exploratory comparisons of toxicities and clinical outcomes following pembrolizumab and radiotherapy versus chemotherapy and radiotherapy. Subjects on both arms will use wearable fitness trackers, which will allow us to monitor closely for adverse events and demonstrate that our novel treatment approach preserves functional status compared to standard chemoradiotherapy. We will also follow patient-reported outcomes for subjects in both cohorts.

While study subjects allocated to the "chemoRT" arm of this trial based on low PD-L1 expression, will not be receiving novel therapy, we believe that the inclusion of the "chemoRT" arm in this trial is critical for several reasons:

- *To characterize outcomes following chemoradiotherapy and modern adjuvant therapy.* Since RTOG 0617 was conducted (2007-2011)[17], and even after our in-house PAINT trial (2013-2016)[33], early results from the PACIFIC trial have changed the standard of care for many patients with locally advanced NSCLC[10]. Clinicians caring for this patient population are currently in an unusual situation, where we consider treatment with one year of adjuvant durvalumab following chemoradiotherapy without published data demonstrating how this treatment affects overall survival. It is therefore important that we characterize survival rates in a contemporary patient cohort receiving chemoradiotherapy for locally advanced NSCLC. Of note, the PACIFIC trial demonstrated that the prolongation of PFS and distant metastasis-free survival with durvalumab was not influenced by PD-L1 expression. Additionally, we have not found that PD-L1 expression is a prognostic factor for patients treated with chemoradiotherapy at our institution (see figures below). While comparisons of outcomes in our two study cohorts will be limited by the non-randomized treatment allocation, outcomes in the "chemoRT" cohort will provide some frame of reference for outcomes seen in the "pembroRT" group.



Kaplan-Meier curves depicting progression-free survival and overall survival in patients who have been treated with concurrent chemoradiotherapy for locally advanced NSCLC at our institution and underwent tumor PD-L1 testing.

- *To allow comparison of the safety profiles of "pembroRT" and "chemoRT".* We expect that, compared to standard chemoradiotherapy, sequential pembrolizumab and dose-painted accelerated radiotherapy will reduce clinician and patient-reported serious adverse event rates, reduce hospitalization rates, and preserve physical function. Of note, we have not found that PD-L1 expression is associated with hospitalization rates or step counts in patients we have treated with chemoradiotherapy for locally advanced NSCLC (see figures below). While comparisons of outcomes in our two study cohorts will be limited by the non-randomized treatment allocation, adverse event rates in the "chemoRT" cohort will provide some frame of reference for those seen in the "pembroRT" group.

4.6.1 Justification for Pembrolizumab Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). These studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.6.2 Rationale for Endpoints

4.6.2.1 Efficacy Endpoints

- Progression-free survival duration following study enrollment (primary endpoint).
    - Progression-free survival is a standard assessment of clinical benefit of treatments for locally advanced NSCLC.
- Duration of freedom from distant metastasis following study enrollment.
    - Freedom from distant metastasis is a standard assessment for patients with locally advanced NSCLC, who are at high risk of developing metastatic disease.
- Duration of freedom from intrathoracic disease progression following study enrollment.

- Freedom from intrathoracic disease progression is a standard assessment for patients with locally advanced NSCLC, who are at high risk of developing local/regional disease progression.

- Survival duration following study enrollment.
  - Overall survival is a standard assessment of clinical benefit of treatments for NSCLC.

- Disease progression during induction pembrolizumab for patients with PD-L1 expression ≥ 50%.
  - As induction pembrolizumab prior to radiotherapy for locally advanced NSCLC is a novel treatment approach, it will be important to characterize the rate of disease progression during induction therapy.

4.6.2.2 Safety Endpoints

- Severe (grade ≥ 3) adverse events, scored using CTCAE v 4.03.
  - It will be important to characterize the toxicity profile of sequential pembrolizumab and radiotherapy for locally advanced NSCLC, as this is a novel treatment approach.

- Pneumonitis (grade ≥ 2).
  - It will be important to characterize the rate of pneumonitis, which may occur because of radiotherapy or immunotherapy, for study subjects.

- Patient-reported treatment-related toxicity, scored using PRO-CTCAE.
  - See Section 4.5

- Unplanned hospitalization.
  - Many patients treated with radiotherapy or chemoradiotherapy for locally advanced NSCLC are hospitalized due to treatment toxicity. It will be important to characterize the hospitalization rate for patients treated with pembrolizumab and radiotherapy for locally advanced NSCLC.

- Daily step counts, measured using wearable fitness trackers.
  - See Section 4.4

4.6.2.3 Translational Endpoints

- Clearance of circulating tumor DNA following radiotherapy.

- Subjects in the PembroRT and ChemoRT cohorts will undergo circulating tumor DNA testing at study entry and several weeks after the completion of thoracic radiotherapy. Circulating tumor DNA clearance may be a powerful predictor of disease control following conventional treatment for locally advanced NSCLC[39]. We will test the prognostic utility of circulating tumor DNA testing for patients treated with pembrolizumab and radiotherapy and compare rates of circulating tumor DNA clearance in the two study cohorts.

- PD-L1 TPS score and expression of alternate immune checkpoint molecules.

  - Tumor PD-L1 expression as determined by immunohistochemistry (IHC) has been implicated as a predictive biomarker for benefit from treatment with PD-1/PD-L1 inhibitors[40, 41]. We will assess baseline PD-L1 expression for each study subject using our in-house and FDA-approved immunohistochemical assay on archival FFPE tumor tissue. Sections cut from FFPE blocks will be deparaffinized and subjected to heat-induced epitope retrieval. Slides will be incubated with the primary antibody (monoclonal mouse anti-PD-L1, clone 22C3) and visualized using the EnVision FLEX system on the Dako Autostainer Link 48. Protein expression will be quantified as tumor proportion score (TPS), which is the percentage of tumor cells demonstrating PD-L1 membrane staining. Subjects will be assigned to the PembroRT or ChemoRT cohort based on PD-L1 expression, using a cutoff of 50%. Within each cohort, we will explore if PD-L1 expression level is associated with clinical outcomes, including progression-free survival and overall survival.

  - We will also quantify baseline tumor expression of alternate immune checkpoint molecules in peripheral blood as well as from fresh tumor material (if available). From blood samples, peripheral blood mononuclear cells will be isolated using Ficoll Paque density gradient centrifugation, followed by antibody labeling and analysis. From biopsy specimens, tumor will be dissociated without enzymatic digestion, followed by antibody labeling for multi-color flow cytometric analysis that will focus on expression of HHLA2, PD-L1, PD-L2, B7-H3, and B7x (B7-H4/B7S1) in CD8-positive T cells and regulatory cells. We will explore if expression of immune checkpoint molecules is associated with clinical outcomes.

- Tumor mutational burden.

  - Tumor mutational burden has been identified as a predictive factor for response to immune checkpoint blockade in several settings[42-44]. We will utilize a validated commercial platform to explore tumor mutational burden as a prognostic factor for study subjects.

- Markers of immune activation.

  - The PD-1 receptor and its ligands define a novel regulatory pathway with potential inhibitory effects on T, B, and monocyte responses[41, 45]. We will characterize how study therapy affects several markers of immune activation

throughout the treatment course. Blood collected from study subjects will be centrifuged to isolate peripheral blood mononuclear cells, and flow cytometry will be performed for immunophenotyping of mononuclear cells using several panels to quantify populations of B cells, CD4 and CD8 cells, natural killer cells, monocytes, and myeloid and plasmacytoid dendritic cells. CD4, CD8, and regulatory T cell populations will be tested for markers of activation, including expression of PD-1, ICOS, and CTLA-4. We may identify predictors of long-term clinical outcomes. Additionally, we may identify bottlenecks where treatment resistance may be overcome by the addition of additional immunomodulatory agents in the future.

5.0 METHODOLOGY

5.1 Study Population

5.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of non-small cell lung cancer will be enrolled in this study.
2. Previously untreated, pathologically proven NSCLC with measurable disease (at least 1 unidimensional, radiographically measurable lesion based on RECIST v1.1) and one of the following stages: (prior resection for early stage disease is allowed)
    a. AJCC version 8 Stage II disease, medically or technically unresectable
    b. AJCC version 8 Stage III disease
3. Whole body PET/CT within 42 days prior to study entry demonstrating hypermetabolic pulmonary lesion(s) and/or thoracic lymph node(s). If PET/CT was obtained more than 42 days prior to study entry and is not repeated, CT within 28 days prior to study entry demonstrating no evidence of metastatic disease is required.
4. MRI of the brain or head CT with contrast within 42 days prior to study entry.
5. PFTs within 42 days of study entry
6. ECOG performance status 0-1
7. Adequate end-organ function, based on routine clinical and laboratory workup:
    a. ANC >1,500 cells/µl, Platelets ≥ 100,000 cells/µl, Hemoglobin ≥ 9.0 g/dl
    b. Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 50 ml/min
    c. Total bilirubin ≤ 1.5 x ULN (or direct bilirubin below the ULN), AST and ALT ≤ 2.5 x ULN
    d. International normalized ratio (INR) (or prothrombin time (PT)) and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN unless participant is receiving anticoagulant therapy, as long as values are within the intended therapeutic range

e. Thyroid stimulating hormone (TSH) within normal limits. If TSH is not within normal limits, the participant may be eligible if T3 and free T4 are within normal limits.

8. A female participant is eligible to participate if she is not pregnant (see Exclusion Criteria), not breastfeeding, and at least one of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP) as defined in the Appendix
    b. A WOCBP who agrees to follow the contraceptive guidance in the Appendix during the treatment period and for at least 120 days after the last dose of study treatment with pembrolizumab (pembroRT cohort) or at least 180 days after the last dose of chemotherapy (chemoRT cohort).
9. A male participant must agree to use contraception during the treatment period and for at least 28 days after the last dose of study treatment and refrain from donating sperm during this period.
10. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

5.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Malignant pleural or pericardial effusion, based on clinical, imaging, or pathologic evaluation.
2. Systemic therapy for lung cancer within the past year.
3. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).
4. Contraindication to protocol-specified radiotherapy, such as prior thoracic radiotherapy or active serious collagen vascular disease (e.g. scleroderma).
5. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.
6. Active malignancy other than lung cancer that requires active treatment other than hormonal therapy or is deemed by the treating physicians to be likely to affect the subject's survival duration.
7. A history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
8. Active infection requiring antimicrobial therapy.

9. Has a known history of active TB (Bacillus Tuberculosis).

10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

12. Pregnancy, assessed in WOCBP (defined in Appendix) with urine pregnancy test within 72 hours prior to study treatment allocation. If urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test is required. If more than 72 hours elapse between screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative.

13. For patients receiving pembrolizumab/radiotherapy

    a. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
    b. Active autoimmune disease other than vitiligo, thyroid disorders, Sjogren's disease, and well-controlled rheumatoid arthritis not requiring disease-modifying therapy.
    c. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
    d. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

5.1.3 Lifestyle Restrictions

5.1.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.1.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix for approved methods of contraception.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.2.2.

5.1.5 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrollment.

5.2 Study Treatments and Activity Monitoring

5.2.1 Pembrolizumab (PembroRT Cohort Only)

5.2.1.1 Pembrolizumab Timing

The timing of pembrolizumab infusions is summarized in the Study Flow Chart. Trial treatment may be administered up to 3 days before or after the scheduled treatment due to administrative reasons. Trial treatments should be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. Given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2.1.2 Pembrolizumab Dose Modification and Management of Immune-Related Adverse Events

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

Table 3 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4. Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.2 Chemotherapy (ChemoRT Cohort Only)

Chemotherapy will be administered weekly during radiotherapy. This concurrent chemotherapy will consist of carboplatin (AUC 2, IV) and paclitaxel (50 mg/m2, IV). Standard institutional procedures will be used for chemotherapy formulation, calculation of AUC, and chemotherapy administration. Treating physicians may implement dose reductions or withhold chemotherapy in the event of adverse events or laboratory abnormalities, per usual care.

Adjuvant systemic therapy may be administered for patients on the ChemoRT cohort, at the discretion of the treating physicians. In some cases, this may consist of adjuvant systemic doses of chemotherapy (e.g.: carboplatin AUC 6 and paclitaxel 200 mg/m^2). Based on emerging data[10], patients on the ChemoRT cohort may be treated with adjuvant immunotherapy.

5.2.3 Radiotherapy

The timing of radiotherapy with respect to systemic therapy in the two study cohorts is summarized in the Study Flow Chart.

Immobilization, Simulation, and Localization

Patients will be immobilized in a stable position capable of allowing accurate daily reproducibility of the target position. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients' external contours) with reference to the stereotactic coordinate system. Patient immobilization must be reliable enough to ensure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV) with any significant probability (i.e., < 5%).

Special considerations will be made to account for the effect of internal organ motion (e.g., breathing) on target positioning and reproducibility. Acceptable maneuvers include reliable abdominal compression, accelerator beam gating with the respiratory cycle, active breath-holding techniques, and use of 4D simulation CT to generate internal target volumes (ITVs).

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

Computed tomography will be the primary image platform for targeting and treatment planning. Axial acquisitions with gantry 0 degrees and spacing ≤ 3.0 mm between scans in the region of the tumor are required. Images will be transferred to the treatment planning system for radiotherapy planning.

Isocenter or reference point port localization images (anterior/posterior and lateral) should be obtained immediately before each treatment to ensure proper alignment of the geometric center (isocenter) of the simulated fields. Verification CT scans and portal films following each treatment may be taken at the discretion of the treating physician but are not required.

Target Volumes and Treatment Planning

Target lesions will be drawn on simulation CT imaging, using lung or mediastinal window levels as appropriate. PET imaging should be registered to simulation CT scans to aid with localization of hypermetabolic lesions. If 4D CT simulation is used, gross tumor volumes (GTVs) should be generated on each CT phase that will be used for treatment (typically 4/10 phases if respiratory gating is employed or 10/10 phases if the patient will be treated while breathing freely). GTVs will be combined to form internal target volumes (ITVs).

For patients treated with pembrolizumab and radiotherapy, the low-risk GTV (GTV_4800) shall include the pulmonary tumor(s) as well as any suspicious lymph nodes (based on appearance, PET findings, size ≥ 1cm in short axis, or pathologic data). A high-risk gross tumor volume (GTV_5500), will also be defined and will include only lesions with MTV > 20 cc on PET obtained after induction pembrolizumab and before radiotherapy. MTV calculations will be performed on PET imaging using a semiautomatic gradient-based contouring algorithm ("PET Edge", MIMvista Corp, Cleveland, OH) or using a thresholding tool to encompass all voxels with SUV > 40% of the maximum SUV[46]. GTV_5500 will be contained within GTV_4800. Each GTV (or ITV) will be expanded by 7-10 mm to form a CTV (CTV_4800 and CTV_5500). CTVs may be trimmed to exclude anatomic boundaries to microscopic tumor spread. CTV_5500 will contained within CTV_4800. Each CTV will be expanded to form a PTV. PTV expansions will be 5 mm in all directions if respiratory motion has been accounted for (e.g.: with beam gating, breath hold, or use of 4D-CT to form internal target volumes). Otherwise, PTV expansions will be 5 mm radially and approximately 10 mm in the superior and inferior directions. PTV_5500 will be contained within PTV_4800. Adaptive radiotherapy (adjustment of target volumes during the course of radiotherapy) is not allowed in this protocol, unless difficulties with daily patient setup require repeating the CT simulation procedure.

Subjects receiving standard concurrent chemoradiotherapy may be treated with a standard treatment planning approach, where the entire target volume is treated with a uniform prescription dose, or with a dose-painting technique. The prescription dose must be between 48 Gy and 66.6 Gy, delivered over a course of 20-37 fractions.

Megavoltage equipment is required with effective photon energies of 6-18 MV. Use of IMRT or volumetric modulated arc therapy (VMAT) should be used for dose-painting in this protocol. If these treatment techniques are not available for some reason (e.g.: a subject's insurance company refuses to authorize IMRT), treatment may be delivered using a sequential boost technique (2.75 Gy x 17 to the low-risk PTV followed by 2.75 Gy x 3 to the high-risk PTV). All treatment planning will be performed using tissue heterogeneity corrections.

Target Coverage

The goal is to deliver conformal treatment that minimizes normal tissue irradiation. As a guideline, a conformity index (ratio of the volume of the highest prescription isodose surface to the corresponding PTV) of < 1.5 is desirable. The prescription isodose surface should encompass at least 95% of each PTV. The minimum PTV dose (to 0.3 cm^3) must not fall below 90% of the prescription dose. The maximum dose must not exceed a value that is 115% of the highest prescribed dose, and the hot spot must be located within the PTV.

Critical Structures

Lung, spinal cord, esophagus, brachial plexus, and heart/pericardium should be contoured based on atlases published on the RTOG web site. Dosimetric constraints for organs at risk are listed below. These have been adapted from recent cooperative group chemoradiotherapy protocols.

Structure	Metric	No Deviation	Deviation Acceptable	Deviation Unacceptable
Lungs-CTV	Max Dose Mean Dose Volume>20 Gy Volume>5 Gy	≤110% Rx Dose ≤20 Gy ≤35% ≤50%	≤113% Rx Dose ≤21 Gy ≤36% ≤55%	>113% Rx Dose >21 Gy >36% >55%
Heart & Pericardium	Max Dose Mean Dose Volume>40 Gy Volume>60 Gy	≤65 Gy ≤30 Gy ≤80% ≤30%	≤67 Gy ≤31 Gy ≤85% ≤33%	>67 Gy >31 Gy >85% >33%
Esophagus	Mean Dose	≤34 Gy	≤35 Gy	>35 Gy
Spinal Cord	Max Dose (>25 fractions) Max Dose (20-25 fractions)	≤50 Gy ≤44 Gy	≤52 Gy ≤46 Gy	>52 Gy >46 Gy
Brachial Plexus	Max Dose (>25 fractions) Max Dose (20-25 fractions)	≤63 Gy ≤55 Gy	≤65 Gy ≤58 Gy	>65 Gy >58 Gy

Radiotherapy Adverse Events

Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy. Radiation induced myocarditis or transverse myelitis rarely when the pericardium and spinal cord receive doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung may occur,

typically within lung volumes receiving≥ 20 Gy and within the first six months after treatment. It is important to spare as much normal lung as possible to avoid symptomatic lung injury. Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or systemic therapy, provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous Xylocaine, Carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required. It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. Esophagitis should be graded using CTCAE v.4.0. If high grade esophagitis occurs, and a treatment interruption is being considered, every effort should be made to minimize the treatment break duration. Acute esophageal toxicity, which typically manifests as dysphagia, odynophagia, and reflux symptoms, should be pharmacologically managed with the following approach:

1) Ketoconazole 200 mg PO q day **OR**
2) Fluconazole 100 mg PO q day until the completion of radiation
3) Mixture of: 2% viscous lidocaine: 60 cc Mylanta: 30 cc sucralfate (1 gm/cc): 10 cc Take 15-30 cc PO q3-4 hrs prn. (*Contraindications: pts on Dilantin, Cipro, Digoxin*)
4) Ranitidine 150 mg PO BID (or other H2 blocker or a proton pump inhibitor such as omeprazole) until the completion of radiation
5) Grade 4 esophagitis: hold RT + chemotherapy until grade 2 or less. We expect a significant portion of patients will experience grade 3 esophagitis.

5.2.4 Physical Activity Monitoring

Some study sites may elect not to offer activity monitoring to study subjects. Additionally, some subjects may choose not to participate in the optional activity monitoring component of the protocol. The remainder of this section applies to subjects who consent to participate in physical activity monitoring.

A commercially-available fitness tracker (e.g., Garmin Vivofit) will be placed on the patient's wrist at the time of study registration. The device will be activated and synced with a computer or mobile device, and the device will be set to show the time. Patients will be shown how to remove the device (similar to removing a wristwatch) in case they wish to remove it temporarily or permanently. However, patients will be asked to keep the device on continuously throughout the first six months of the study. Patients may continue to wear the device for an additional six months if they wish to do so. The device is waterproof, so patients will not need to remove it when bathing. The device has a battery life of over one year, so patients will not need to charge it. Data will be synced every time the patient enters one of the Medical Oncology or Radiation Oncology clinics using a wireless access client or by a member of the study team.

5.3 Treatment Allocation

Subjects will be stratified based on baseline PD-L1 TPS score. Subjects whose score is less than 50% will be treated with chemotherapy and radiotherapy (ChemoRT Cohort). Subjects whose score is 50% or higher will be treated with pembrolizumab and radiotherapy (PembroRT Cohort).

5.4 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician.

5.4.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.4.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab

- (PembroRT Cohort only) Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the agreement of the investigator, the Sponsor and the participant.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.4.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, [Table 3]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to [Table 3] in Section 5.2.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.5 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative

and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 7.1.2.6
- Unacceptable adverse experiences as described in Section 5.2.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Recurrent Grade 2 pneumonitis
- The participant is lost to follow-up
- Completion of 15 treatments (approximately 1 year) with pembrolizumab

  Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 15 doses may be eligible for retreatment if they progress after stopping study treatment. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

- Administrative reasons

5.6 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

5.7 Study Registration and Data Management

Most study subjects will be enrolled by the study sponsors at Montefiore Medical Center. This study will also be activated at three additional subsites (Rogel Cancer Center-University of Michigan, New York University Langone Health and Henry Ford Cancer Institution). The following procedures will be performed for registration of each study subject:

- (subsites only) Notify sponsor when a patient is in screening. If an ICF is signed, a copy of the ICF will be sent to the sponsor.
- (all sites) Complete screening procedures and generate a signed eligibility checklist
- (subsites only) Send a copy of the signed eligibility checklist to the sponsor.
- (sponsor only) Enroll study subject with CPDMU and in Velos. All subjects will be registered through the Clinical Trials Office at Montefiore Medical Center (Telephone: 718-379-6861, Monday through Friday 9:00am – 5:00pm Eastern Standard Time). The "On Study Form" and the completed Informed Consent Form will be emailed to the clinical trials office at Montefiore Medical Center, (cpdmuregistration@montefiore.org) at the time of registration and prior to patient treatment initiation. At the time of registration, all eligibility criteria must be checked. A signed eligibility checklist will be stored for each subject.
- (all sites) Complete local study subject registration processes.

Study data will be warehoused by the lead investigators at Montefiore Medical Center and the Albert Einstein College of Medicine. Data for study subjects who are treated at other institutions will be recorded on electronic case report forms (CRF) in a deidentified manner and transmitted to the Montefiore/Einstein investigators. Data for subjects from institutions other than Montefiore will be recorded in Velos in a de-identified manner following our institutional standard operating procedure, where subjects are given a de-identified medical record number (eg: "NYU-01-001") and an approximate date of birth is entered. Local investigators will be responsible for maintaining a log linking study subject identification numbers to patient identities. Local investigators must complete local subject registration processes and maintain accurate documentation (source data) that supports the information entered in the CRF.

For the purpose of data collection, all untoward events that occur after informed consent through 90 days after the last dose of study drug must be recorded on the subject's CRF by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits. The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are recorded on appropriate CRFs and reported in accordance with protocol instructions. The study period during which all AEs must be

reported begins after informed consent is obtained and study treatment is initiated and ends 90 days after last administration of study treatment, or at the time of initiation of another anti-cancer therapy, whichever occurs first. AEs and SAEs that are observed or reported prior to initiation of study treatment should be recorded on appropriate CRFs if they are associated with protocol-mandated interventions (e.g., invasive procedures such as biopsies).

6.0 TRIAL FLOW CHART

PD-L1 ≥ 50%: PembroRT	Eval	Induction Pembrolizumab									Radiotherapy								Maintenance Pembrolizumab											
	Week:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	21	24	27	30	33	36	39	42	45	48	51
History, Physical, Toxicity Assessment	X	X			X			X			X	X	X	X		X		X+	X	X	X	X	X	X	X	X	X	X	X
PRO-CTCAE Assessment	X	X			X			X				X		X		X		X+			X			X			X			X
PET/CT	X								X+																					
CT C/A																		X^+				X^+				X^+				X^+
Biopsy, Tumor PD-L1 Testing	X																													
Serum Correlative Studies	X																	X												
Pembrolizumab		X			X			X											X	X	X	X	X	X	X	X	X	X	X	X
Dose-Painted Radiotherapy											XXXXX	XXXXX	XXXXX	XXXXX																

PD-L1 < 50%: ChemoRT	Eval	Chemoradiotherapy									Optional Adjuvant Therapy, Observation																			
	Week:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	21	24	27	30	33	36	39	42	45	48	51
History, Physical, Toxicity Assessment	X	X	X	X	X	X	X	X			X+				X+			X+				X+				X+				X+
PRO-CTCAE Assessment	X	X		X		X		X			X+				X+			X+				X+				X+				X+
PET/CT	X																													
CT C/A											X^+							X^+				X^+				X^+				X^+
Biopsy, Tumor PD-L1 Testing	X																													
Serum Correlative Studies	X										X+																			
Carboplatin/Paclitaxel		X	X	X	X	(X)	(X)	(X)				(X*+)			(X*+)			(X*+)												
Radiotherapy		XXXXX	XXXXX	XXXXX	XXXXX	(XXXXX)	(XXXXX)	(XXXXX)																						

() - Optional

^ - May be replaced by PET/CT

* - Every 3 weeks, starting 4-6 weeks after completion of radiotherapy

+ - May be performed one week before or after the protocol-specified timepoint

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart summarizes selected trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial.

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix) at each clinic visit, as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Except where PET/CT is indicated based on the Study Flow Chart, computed tomography (CT) is the preferred tumor imaging. For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Brain imaging is required for all participants at screening. MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Participant eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be used to determine progression.

When the Investigator identifies radiographic progression per RECIST 1.1, efforts should be made to verify radiologic PD. Treatment should continue until PD has been verified. Regardless of whether PD is verified, if the Investigator considers the participant has progressed, but elects to implement iRECIST, the Investigator will assess for confirmation of progression by iRECIST at subsequent time points.

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 42 days prior to the date of allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

The screening images must be submitted to the central imaging vendor for retrospective review.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 42 days prior to the date of allocation and can be assessed by the central imaging vendor.

Brain imaging is required to rule out radiographically detectable untreated brain metastases. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated or CT is mandated by local practice.

7.1.2.6.1 Tumor Imaging During the Study

On-study imaging assessments should be performed at the timepoints (±7 days) detailed in the Trial Flow Chart for each study cohort. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator. Once disease progression is confirmed, imaging should be performed as needed for routine clinical care and does not need to adhere to the Trial Flow Chart.

Per iRECIST (Section 9.2.1.6), disease progression should be confirmed by the site 4 to 8 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the Investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 9.2.1.6. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who

have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 9.2.1.6.

7.1.2.6.2 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4-week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression and the Investigator elects not to implement iRECIST, this is the final required tumor imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment.

7.1.2.6.3 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

7.1.2.6.4 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

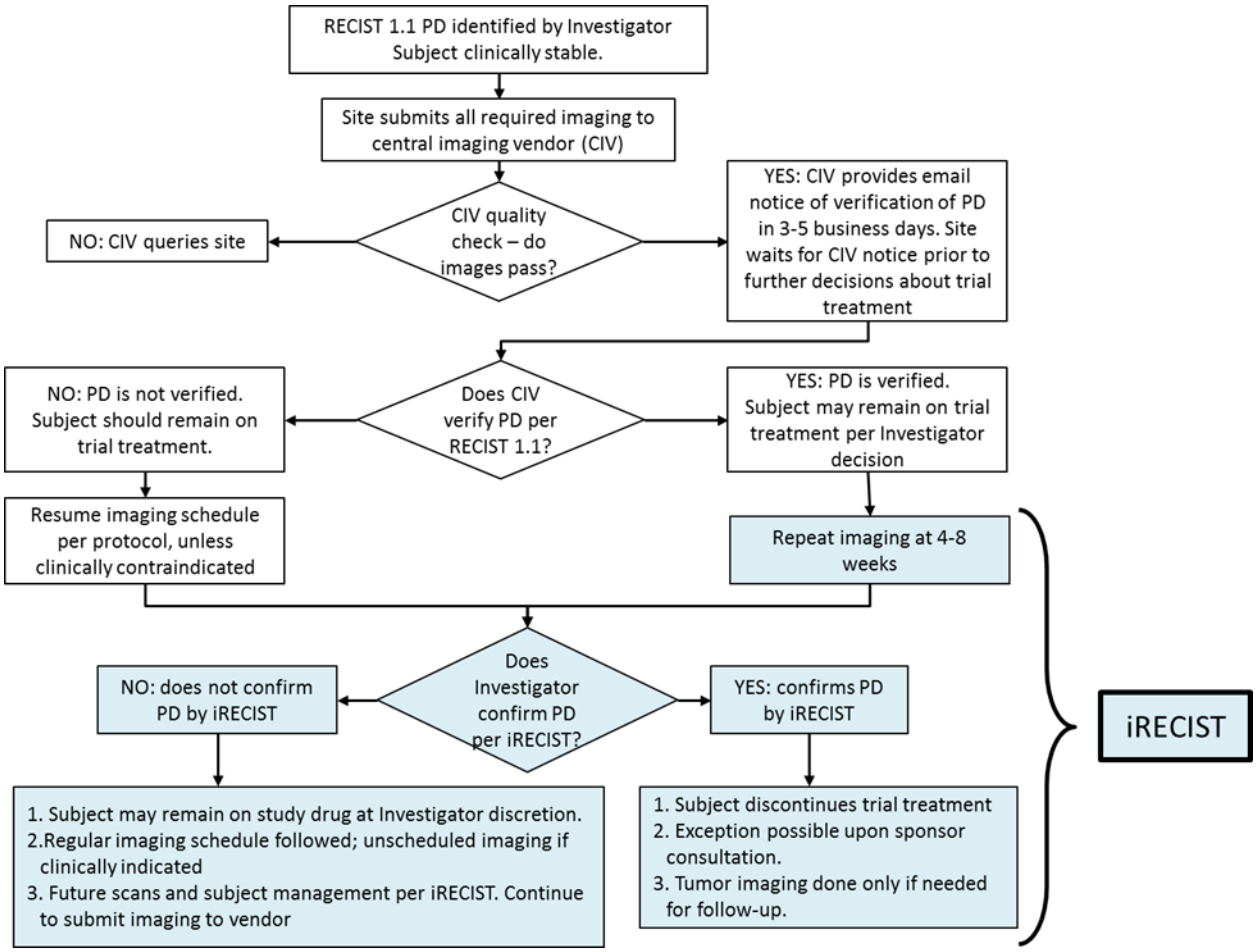
A description of the adaptations and iRECIST process is provided in the Appendix, with additional detail in the iRECIST publication[47]. iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions.

Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



7.1.3 Other Procedures

7.1.3.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4 Visit Requirements

Visit requirements are outlined in the Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5 Post-treatment Visits

7.1.5.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.5.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (84 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

7.1.5.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

● All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.

● All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

● All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days (pembroRT cohort) or 180 days (chemoRT cohort) following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

● Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a

non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and infant exposure during breast feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of pembrolizumab (pembroRT cohort) or 180 days following cessation of chemotherapy (chemoRT cohort) or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the

same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to Merck Global Safety.

All participants with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

SAE reports and any other relevant safety information are to be forwarded to Principal Investigator (Nitin Ohri, M.D., nohri@montefiore.org) as well as the study sponsor's Data Safety Monitoring Committee (rupatel@montefiore.org).

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

> *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 7 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis); or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes	

	listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan – Primary Endpoint and Sample Size Calculation

The **primary endpoint** is progression-free survival (PFS) in the PembroRT cohort one year following study enrollment. PFS duration will be defined as the time from study registration to the date of disease progression or death from any cause. In cases where a scan is concerning for progressive disease based on RECIST 1.1 criteria, and progression is confirmed on a subsequent scan 4-8 weeks later (satisfying iRECIST criteria for progression), the date of disease progression would be the date of the first scan demonstrating progression. PFS rates will be estimated using the Kaplan-Meier Survival method, from which the probability of PFS at various time points and corresponding 95% confidence intervals will be estimated. If a patient is lost to follow-up without having disease progression, progression-free survival will be censored at the date of the patient's last clinic visit. Based on published multi-institutional trials and data from our institution, we expect the one-year progression-free survival rate (H0) to be to 40% with standard chemoradiotherapy. We hypothesize that this rate will be at least 65% (H1) for subjects in the PembroRT cohort. A one sample two-sided log-rank test will be used to compare the one-year PFS rate in the PembroRT cohort against the expected rate with ChemoRT. We plan to accrue **25 subjects to the PembroRT cohort**. Assuming that the accrual period will last 18 months and that event rates will follow an exponential distribution, this sample size will provide 81% power to detect an improvement in PFS at 1 year at a 5% level of significance using a one sample two-sided log-rank test [48, 49].

The ChemoRT cohort will be open to accrual while accrual to the PembroRT cohort is ongoing. We expect that approximately 40% of patients with locally advanced NSCLC have PD-L1 expression of at least 50%. We therefore expect that approximately 38 subjects will be enrolled and treated with standard concurrent chemoradiotherapy as part of this trial, which will yield a **total sample size of approximately 63 subjects**.

8.2 Statistical Analysis Plan – Secondary Endpoints

Time-to-event outcomes (overall survival, freedom from distant metastasis, freedom from intrathoracic progression, freedom from hospitalization) will be analyzed using the Kaplan-Meier method, from which rates at various time points and corresponding 95% confidence intervals will be estimated. Exploratory comparisons for time-to-event outcomes between the PembroRT and ChemoRT cohorts will be performed using log-rank tests. Univariate and

multivariable Cox regression models will be used to evaluate associations between time-to-event outcomes and clinical covariates, including study cohort.

Rates of radiographic responses and disease progression during induction pembrolizumab for subjects in the PembroRT cohort will be described using counts and percentages. Logistic regression models will be used to evaluate potential predictors of response or progression (e.g.: PD-L1 TPS).

Hospitalization rates and adverse event rates, scored using CTCAE as well as PRO-CTCAE, will be presented as counts and percentages. Exploratory comparisons between the PembroRT cohort and the ChemoRT cohort will be performed using chi-square or Fisher Exact testing, as appropriate.

Daily step counts throughout the study period will be presented using descriptive statistics and will be analyzed using a generalized linear mixed-model for repeated measures.

Rates of circulating tumor DNA clearance will be presented as counts and percentages, and predictors of circulating tumor DNA clearance will be explored using chi-square or Fisher exact testing, as appropriate. Exploratory analyses will be performed to evaluate PD-L1 expression, expression of alternative immune checkpoint molecules (e.g., HHLA2, B7x, and B7-H3), baseline tumor mutational burden, and markers of immune activation (e.g., expansion of T4/T8 subsets, myeloid derived suppressor cell levels, expansion of T-cell repertoire) as predictors of PFS and overall survival.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Pembrolizumab will be provided by Merck as summarized in Table 8.

Table 8 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

11.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10 while receiving study therapy.

Table 10 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b]

○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b] ● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected

Appendix 4: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 5 and Figures 1 and 3). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. I

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
    - Please note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The

assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in the Trial Flow Chart.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold ($\geq$ 20% and $\geq$ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.

  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication[47].

Appendix 5: PRO-CTCAE Assessment Tool

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
3.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
5.	In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

6.	In the last 7 days, what was the SEVERITY of your WHEEZING (WHISTLING NOISE IN THE CHEST WITH BREATHING) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

7.	In the last 7 days, what was the SEVERITY of your SKIN BURNS FROM RADIATION at their WORST?					
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe	○ Not applicable

8.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

9.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

10.	In the last 7 days, how OFTEN did you feel ANXIETY?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

11.	In the last 7 days, how OFTEN did you FEEL THAT NOTHING COULD CHEER YOU UP?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your FEELINGS THAT NOTHING COULD CHEER YOU UP at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FEELING THAT NOTHING COULD CHEER YOU UP INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

12.	In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

REFERENCES

1. Torre, L.A., et al., *Global cancer statistics, 2012.* CA Cancer J Clin, 2015. **65**(2): p. 87-108.
2. Ferlay, J., et al., *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012.* Int J Cancer, 2015. **136**(5): p. E359-86.
3. Aupérin, A., et al., *Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non–small-cell lung cancer.* Journal of Clinical Oncology, 2010. **28**(13): p. 2181-2190.
4. Belani, C.P., et al., *Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol.* J Clin Oncol, 2005. **23**(25): p. 5883-91.
5. Fournel, P., et al., *Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non–small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique–Groupe Francais de Pneumo-Cancérologie NPC 95-01 study.* Journal of clinical oncology, 2005. **23**(25): p. 5910.
6. Furuse, K., et al., *Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non–small-cell lung cancer.* Journal of clinical oncology, 1999. **17**(9): p. 2692.
7. Zatloukal, P., et al., *Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study.* Lung Cancer, 2004. **46**(1): p. 87-98.
8. Curran, W.J., Jr., et al., *Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410.* J Natl Cancer Inst, 2011. **103**(19): p. 1452-60.
9. Eberhardt, W.E., et al., *2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer.* Ann Oncol, 2015. **26**(8): p. 1573-88.
10. Antonia, S.J., et al., *Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer.* N Engl J Med, 2017.
11. Blank, C., T.F. Gajewski, and A. Mackensen, *Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy.* Cancer Immunology, Immunotherapy, 2005. **54**(4): p. 307-314.
12. Herbst, R.S., et al., *Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial.* The Lancet, 2016. **387**(10027): p. 1540-1550.
13. Reck, M., et al., *Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer.* N Engl J Med, 2016. **375**(19): p. 1823-1833.
14. Vokes, E.E., et al., *Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non–small-cell lung cancer: Cancer and Leukemia Group B.* Journal of clinical oncology, 2007. **25**(13): p. 1698.
15. Hanna, N., et al., *Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III*

non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol, 2008. **26**(35): p. 5755-60.

16. Kelly, K., et al., *Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023.* J Clin Oncol, 2008. **26**(15): p. 2450-6.
17. Bradley, J.D., et al., *Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study.* The Lancet Oncology, 2015. **16**(2): p. 187-199.
18. Senan, S., et al., *PROCLAIM: Randomized phase III Trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non–small-cell lung cancer.* Journal of Clinical Oncology, 2016. **34**(9): p. 953-962.
19. Albain, K.S., et al., *Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial.* Lancet, 2009. **374**(9687): p. 379-86.
20. Wang, K., et al., *Cardiac Toxicity After Radiotherapy for Stage III Non–Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy.* Journal of Clinical Oncology, 2017: p. JCO. 2016.70. 0229.
21. Dess, R.T., et al., *Cardiac Events After Radiation Therapy: Combined Analysis of Prospective Multicenter Trials for Locally Advanced Non–Small-Cell Lung Cancer.* Journal of Clinical Oncology, 2017: p. JCO. 2016.71. 6142.
22. Darby, S.C., et al., *Risk of ischemic heart disease in women after radiotherapy for breast cancer.* New England Journal of Medicine, 2013. **368**(11): p. 987-998.
23. Taylor, C., et al., *Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials.* Journal of Clinical Oncology, 2017. **35**(15): p. 1641-1649.
24. Machtay, M., et al., *Risk of death from intercurrent disease is not excessively increased by modern postoperative radiotherapy for high-risk resected non–small-cell lung carcinoma.* Journal of clinical oncology, 2001. **19**(19): p. 3912-3917.
25. Group, P.M.-a.T., *Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials.* The Lancet, 1998. **352**(9124): p. 257-263.
26. Nilsson, G., et al., *Distribution of coronary artery stenosis after radiation for breast cancer.* Journal of Clinical Oncology, 2011. **30**(4): p. 380-386.
27. Tang, C., et al., *Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes.* International Journal of Radiation Oncology* Biology* Physics, 2014. **89**(5): p. 1084-1091.
28. Machtay, M., et al., *Prediction of Survival by [18F]Fluorodeoxyglucose Positron Emission Tomography in Patients With Locally Advanced Non-Small-Cell Lung Cancer Undergoing Definitive Chemoradiation Therapy: Results of the ACRIN 6668/RTOG 0235 Trial.* J Clin Oncol, 2013. **31**(30): p. 3823-30.
29. Ohri, N., et al., *Pretreatment FDG-PET Metrics in Stage III Non–Small Cell Lung Cancer: ACRIN 6668/RTOG 0235.* Journal of the National Cancer Institute, 2015. **107**(4): p. djv004.

30. Ohri, N., et al., *Pre-treatment FDG-PET predicts the site of in-field progression following concurrent chemoradiotherapy for stage III non-small cell lung cancer.* Lung Cancer, 2015. **87**(1): p. 23-27.
31. Ohri, N., et al., *Pretreatment 18F-FDG PET Textural Features in Locally Advanced Non–Small Cell Lung Cancer: Secondary Analysis of ACRIN 6668/RTOG 0235.* Journal of Nuclear Medicine, 2016. **57**(6): p. 842-848.
32. Ohri, N., et al., *18 F-Fluorodeoxyglucose/Positron Emission Tomography Predicts Patterns of Failure After Definitive Chemoradiation Therapy for Locally Advanced Non-Small Cell Lung Cancer.* International Journal of Radiation Oncology* Biology* Physics, 2017. **97**(2): p. 372-380.
33. Ohri, N., et al., *Positron Emission Tomography–Adjusted Intensity Modulated Radiation Therapy for Locally Advanced Non-Small Cell Lung Cancer.* International Journal of Radiation Oncology* Biology* Physics, 2017.
34. Ohri, N., et al., *Continuous Activity Monitoring during Concurrent Chemoradiotherapy.* International Journal of Radiation Oncology* Biology* Physics, 2016.
35. Gotay, C.C., et al., *The Prognostic Significance of Patient-Reported Outcomes in Cancer Clinical Trials.* J Clin Oncol, 2008. **26**: p. 1355-1363.
36. Movsas, B., et al., *Quality of life (QOL) analysis of the randomized radiation (RT) dose-escalation NSCLC trial (RTOG 0617): the rest of the story.* Int J Radiat Oncol Biol Phys, 2013. **87**(2 Supplement): p. S1-S2.
37. Basch, E., et al., *Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE).* Journal of the National Cancer Institute, 2014. **106**(9): p. dju244.
38. Fogh, S., et al., *A Randomized Phase II Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis During the Treatment of Lung Cancer: Results of Trial.* International Journal of Radiation Oncology* Biology* Physics, 2016.
39. Newman, A.M., et al., *An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage.* Nature medicine, 2014. **20**(5): p. 548-554.
40. Sacher, A.G. and L. Gandhi, *Biomarkers for the Clinical Use of PD-1/PD-L1 Inhibitors in Non–Small-Cell Lung Cancer: A Review.* JAMA oncology, 2016. **2**(9): p. 1217-1222.
41. Woo, S.-R., L. Corrales, and T.F. Gajewski, *Innate immune recognition of cancer.* Annual review of immunology, 2015. **33**: p. 445-474.
42. Snyder, A., et al., *Genetic basis for clinical response to CTLA-4 blockade in melanoma.* New England Journal of Medicine, 2014. **371**(23): p. 2189-2199.
43. Rizvi, N.A., et al., *Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer.* Science, 2015. **348**(6230): p. 124-128.
44. Le, D.T., et al., *PD-1 blockade in tumors with mismatch-repair deficiency.* New England Journal of Medicine, 2015. **372**(26): p. 2509-2520.
45. Bennett, F., et al., *Program death-1 engagement upon TCR activation has distinct effects on costimulation and cytokine-driven proliferation: attenuation of ICOS, IL-4, and IL-21, but not CD28, IL-7, and IL-15 responses.* The Journal of Immunology, 2003. **170**(2): p. 711-718.

46. Werner-Wasik, M., et al., *What is the best way to contour lung tumors on PET scans? Multiobserver validation of a gradient-based method using a NSCLC digital PET phantom.* International Journal of Radiation Oncology* Biology* Physics, 2012. **82**(3): p. 1164-1171.
47. Seymour, L., et al., *iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics.* The Lancet Oncology, 2017. **18**(3): p. e143-e152.
48. Wu, J., *A new one-sample log-rank test.* Journal of Biometrics & Biostatistics, 2014. **5**(4): p. 1.
49. Finkelstein, D.M., A. Muzikansky, and D.A. Schoenfeld, *Comparing survival of a sample to that of a standard population.* Journal of the National Cancer Institute, 2003. **95**(19): p. 1434-1439.