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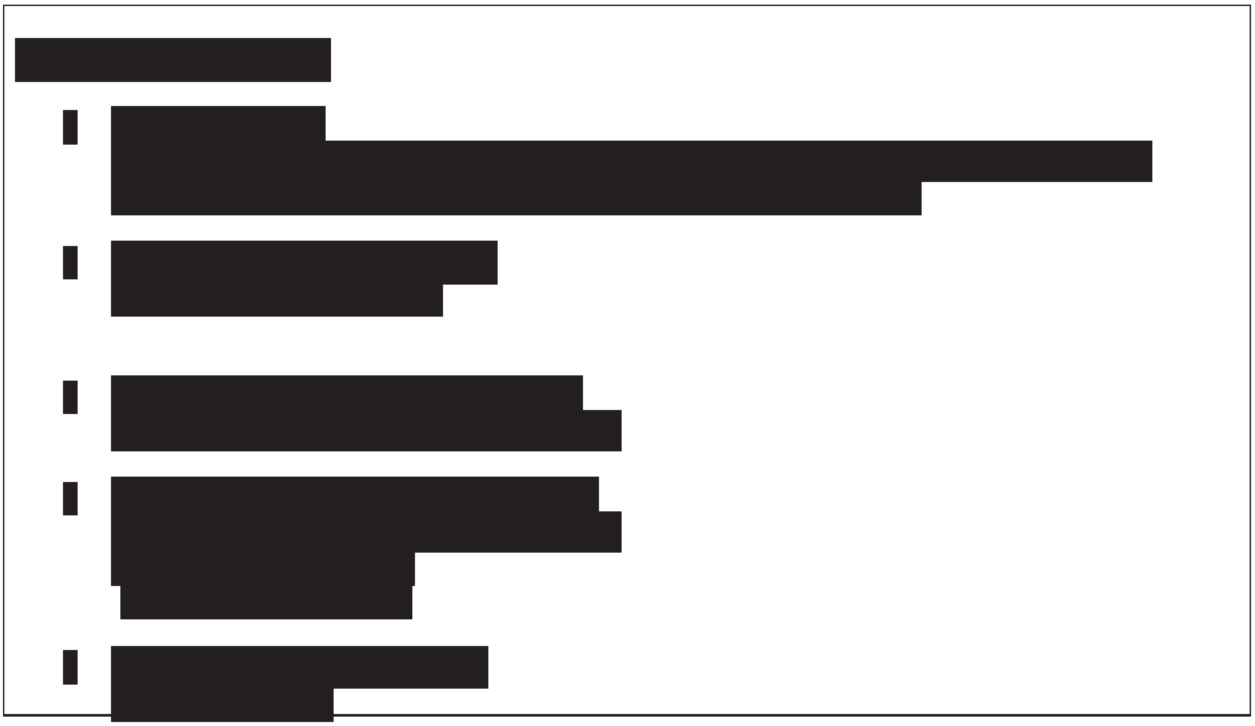

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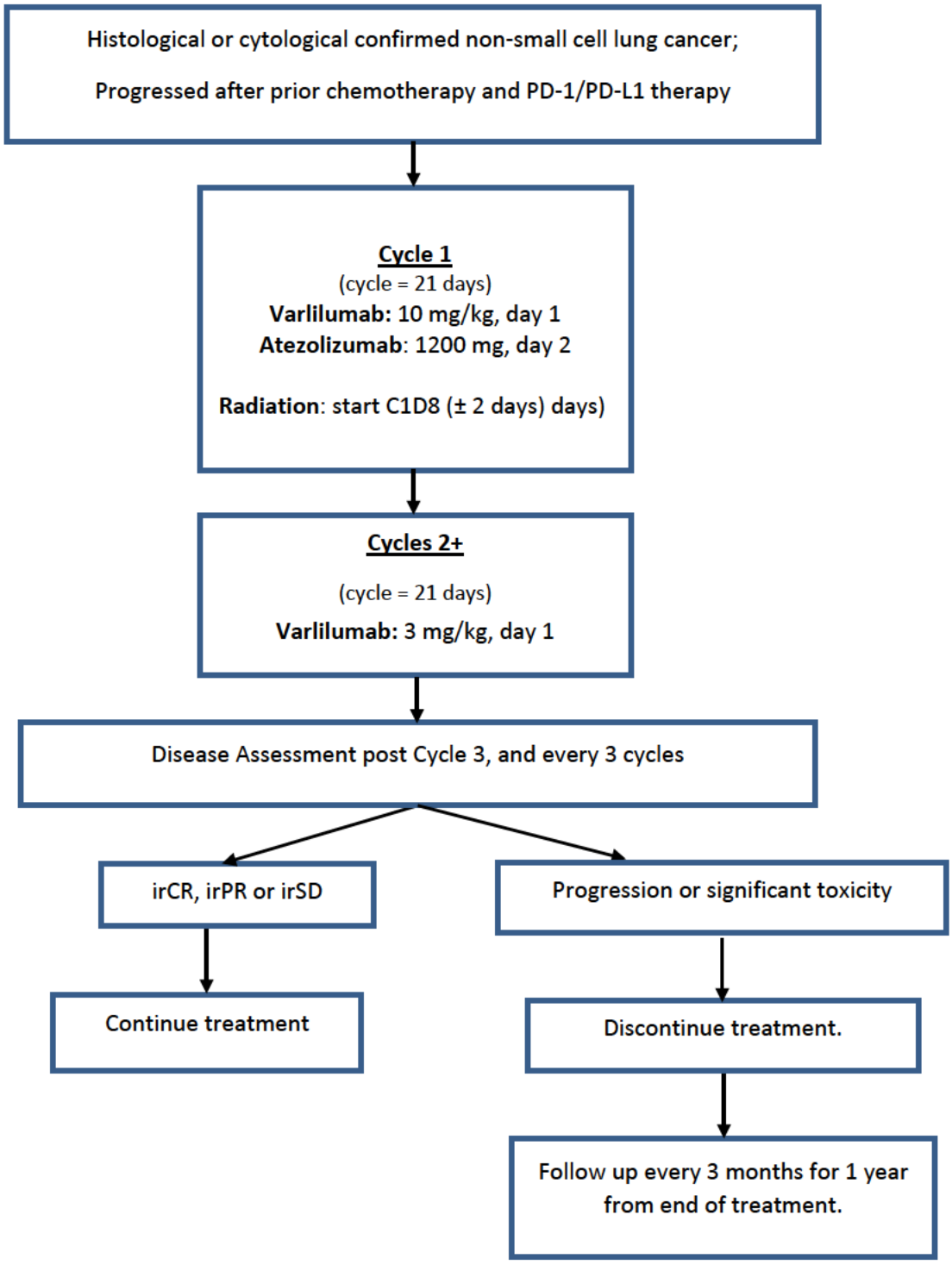
PHASE I SCHEMA



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LIST OF ABBREVIATIONS

AE	Adverse Event
ANC	Absolute neutrophil count
BUN	Blood urea nitrogen
CBC	Complete blood count
CBR	Clinical Benefit Rate
CINJ	Cancer Institute of New Jersey
CNS	Central Nervous System
CT	computer tomography
CR	Complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein 4
DLT	Dose Limiting Toxicity
DSMP	Data Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
HHS	Department of Health and Human Services
IHC	Immunohistochemistry
IRB	Institutional Review Board
ir	Immune-related
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
kg	kilograms
mL	milliliters
mcg/μg	Micrograms
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerable Dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer
OHRS	Office of Human Research Services
OHRP	Office of Human Research Protection
ORR	Objective Response Rate
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PET	Positron Emission Tomography
PHI	Protected health information
PI	Principal Investigator
PR	Partial response
RECIST	Response Evaluation Criteria In Solid Tumors
RT	Radiation Therapy
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal

1.0 Research Design

1.1 Purpose/Specific Aims

A. Objectives

Primary Objective(s)

- The primary objective is to assess the safety and tolerability of combined therapy with atezolizumab and varlilumab in combination with radiation in adult patients with metastatic NSCLC who have progressed on prior PD-1/PD-L1 therapy.

Secondary Objective(s)

- To determine objective response rate (excluding the irradiated lesion) of therapy with atezolizumab and varlilumab in combination with radiation
- To estimate clinical benefit rate of the combination
- To estimate median progression-free survival of the combination
- To compare the frequency of immune-related adverse events (irAEs). irAE's are defined as any treatment-related AE that is inflammatory in nature, consistent with the mechanism of action of immunotherapy and generally medically manageable with topical and/or systemic immunosuppressants.

B. Hypotheses / Research Question(s)

Primary Hypothesis/hypotheses

We hypothesize that therapy with atezolizumab and varlilumab in combination with radiation will be safe and well tolerated by patients with metastatic NSCLC.

Secondary Hypothesis/Hypotheses

We hypothesize based on existing preclinical and clinical data that combining two immunotherapy agents targeting non-overlapping immune regulatory molecules (PD-1 and CD-27) with targeted radiation may be synergistic. Targeted radiation may improve antigen presentation and immune infiltration and this combination may help overcoming resistance to PD-1/PD-L1 antibody for treatment of NSCLC.

1.2 Research Significance

1.2.1 Metastatic non-small cell lung cancer

Lung cancer remains the leading cause of cancer mortality worldwide and NSCLC accounts for more than 85% of all lung cancers [1, 2]. From 2005 to 2011, 57% of the lung cancers diagnosed in the USA presented with metastases at the time of diagnosis. The prognosis for these patients with metastatic or stage IV NSCLC is extremely poor with five-year survival rates reported at less than 5% [3]. Platinum-based doublet chemotherapy is the standard first-line treatment for metastatic NSCLC when genomic testing reveals no activating EGFR mutations, ALK or ROS1 translocation/re-arrangements (found in 10-20% of NSCLC tumors) [4]. Platinum-based regimens produce response rates ranging only between 15-30% [5, 6]. For patients whose disease progresses on first-line chemotherapy, second-line therapy historically consisted of taxane-based salvage chemotherapy with a low response rate and median survival of only approximately 6 months [7, 8]. NSCLC is a remarkably heterogeneous disease that presents a large mutational load encoding a large number of potential neoantigens [9]. Yet, this disease often evades the actions of the immune system.

The opportunity to explore immune therapies greatly expanded with the identification of the checkpoint inhibitor agents targeting PD-1 or PD-L1. For the first time, these agents demonstrated responses in advanced NSCLC, with some patients exhibiting durable responses after discontinuing therapy. In 2015, two immune checkpoint inhibitors targeting PD-1, nivolumab and pembrolizumab were approved for second-line therapy of NSCLC. In 2016, another checkpoint inhibitor targeting PD-L1, atezolizumab was approved for the same indication. Moreover, pembrolizumab also received approval in 2016 for first-line NSCLC treatment in patients with high PD-L1 expressing tumors as well as for first-line NSCLC treatment in combination with chemotherapy in 2017. These recent approvals position immunotherapeutic agents as the preferred first-line as well as second-line therapy for NSCLC and also have led to an increased interest in approaches to increase response rates to these agents.

1.2.2 Atezolizumab for NSCLC treatment

Immune checkpoint inhibitors such as atezolizumab inhibit the brakes on the immune system resulting in antigen-specific T cell responses. Atezolizumab is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells (Investigator's Brochure v10, July 2017). Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells. Atezolizumab targets human programmed death-ligand 1 (PD-L1) and inhibits the interaction with its PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studies as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy. Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial carcinoma and as well as metastatic non-small cell lung carcinoma. As of May 10, 2016, atezolizumab has been administered (alone or in combination with other agents) to approximately 6053 patients with solid tumors and hematologic malignancies. The first-in-human monotherapy study PCD4989g (in patients with locally advanced or metastatic solid tumors or hematologic malignancies) provides the majority of monotherapy safety data, with 629 safety-evaluable patients as of the data extraction date. Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of AEs have been determined. Fatigue, decreased appetite, nausea, diarrhea, constipation, and cough were commonly reported AEs in single and combination therapy. AE profiles are similar across tumor types studied, including non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), triple-negative breast cancer (TNBC), and urothelial carcinoma (UC), and are consistent with the mechanism of action of atezolizumab. The overall immune-mediated AEs reported were considered moderate in severity, and the majority of patients were able to continue on atezolizumab therapy. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the atezolizumab clinical program. To date, immune-related adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, and meningoencephalitis.

[redacted]

Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial carcinoma and as well as metastatic non-small cell lung carcinoma. In a randomized, open-label, phase 3 trial (OAK) in 194 academic or community oncology centers in 31 countries, 1255 patients with pretreated stage IIIB or IV squamous or non-squamous non-small-cell lung cancer were enrolled [10]. Patients were randomly assigned (1:1) to intravenously receive either atezolizumab 1200 mg or docetaxel 75 mg/m^2 every 3 weeks. Overall survival was significantly longer with atezolizumab compared with docetaxel (median overall survival was 13·8 months vs 9·6 months; hazard ratio 0·73 [95% CI 0·62-0·87], p=0·0003). Patients in the PD-L1 low or undetectable subgroup also had improved survival with atezolizumab (median overall survival 12·6 months vs 8·9 months; HR 0·75 [95% CI 0·59-0·96]). Fewer patients had treatment-related grade 3 or 4 adverse events with atezolizumab (90 [15%] of 609 patients) versus docetaxel (247 [43%] of 578 patients). One treatment-related death from a respiratory tract infection was reported in the docetaxel group. Despite the encouraging results with atezolizumab and other checkpoint inhibitors for NSCLC, responses in immunotherapy remain limited to specific subgroups of patients. There is a need for novel immunotherapy combinations that can provide durable responses for higher number of patients with tolerable safety profile.

1.2.3 CD27

Antibodies that recognize immune cell surface molecules can be used to enhance or target immune responses against tumors. These include antibodies that activate antigen presenting cells (e.g. anti-CD40), antibodies that block immune checkpoints (e.g., anti-CTLA-4, anti-PD-1), and T cell co-stimulatory antibodies (e.g., anti-4-1BB). The costimulatory molecule CD27 is a member of the tumor necrosis factor (TNF) receptor superfamily, and is constitutively expressed on the majority of mature T cells, memory B cells, and a portion of natural killer cells. The interaction of CD27 with its ligand CD70 plays key roles in the following processes:

- Costimulation through CD27 on T cells causes activation, proliferation, survival, and maturation of effector capacity and memory
- Costimulation through CD27 on human B cells activates and promotes the generation of plasma cells, proliferation, and the production of immunoglobulin
- Costimulation through CD27 on natural killer cells induces cytolytic activity.

Antibodies targeting CD27 can potentially be either agonists or antagonists of these CD27-CD70 pathway activities. In addition to the immune enhancing properties of agonist anti-CD27 mAbs, CD27-targeting antibodies may also provide direct therapeutic effects against tumors with CD27 expression. The expression of CD27 on various types of lymphomas and leukemias such as Chronic Lymphocytic Leukemia, Mantle Cell Lymphoma, Primary Central Nervous System Lymphoma, Burkitt's Lymphoma, and Marginal Zone B cell Lymphoma has been well documented [11-16]. CD27 expression is present on most B cell malignancies at varying levels, and is also expressed by adult T-cell leukemia/lymphoma [14, 16, 17].

Varlilumab (CDX-1127) is an agonist fully human IgG1 agonist anti-CD27 monoclonal antibody that is expected to activate CD27 expressing T cells in the context of T cell receptor stimulation. Varlilumab was selected on the basis of its agonistic properties and direct therapeutic effect against CD27 expressing tumors.

1.2.4 Varlilumab

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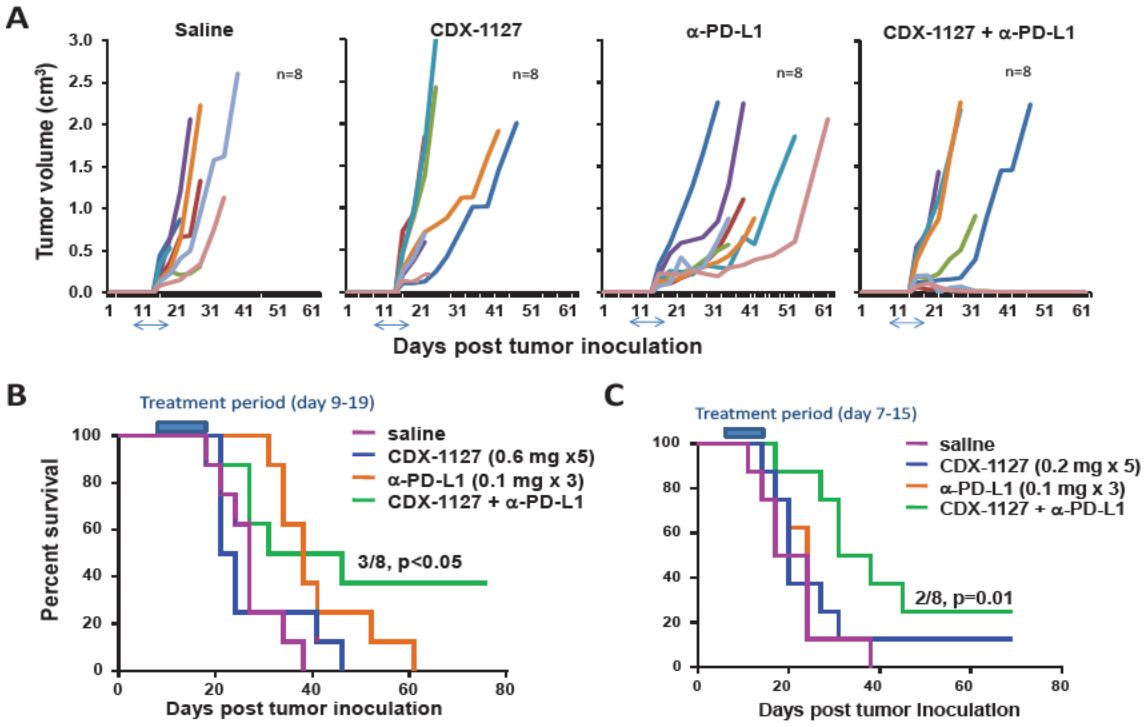
CD27 has distinct properties, including a restricted distribution of expression, requirement for concomitant T cell receptor activation, comparable expression patterns in human and non-human primates in which toxicity studies have been conducted, and lack of observed toxicity in preclinical studies, that suggest agonist anti-CD27 monoclonal antibodies may have less acute toxicity than other agonist monoclonal antibodies targeting costimulatory molecules that have been studied in the clinic to date. Varlilumab acts as an agonist of CD27 and reacts with the ligand binding site of CD27 as demonstrated by inhibition of CD70 binding to CD27. Varlilumab does not bind other tumor necrosis factor receptor (TNFR) family members. As shown in both lymphocyte proliferation and cytokine induction studies, varlilumab does not lead to direct activation of lymphocytes in the absence of signaling through the T cell receptor (TCR). BCL_1 B-lymphoma and CT26 (colon cancer) tumor challenge models using human CD27-transgenic (Tg) showed treatment of mice with varlilumab resulted in substantial improved survival at the higher dose levels (>150 µg x 5) while a biologically effective response was observed for ≥0.5 mg/kg x 5 repeated dose in this model. Varlilumab also showed significant antitumor effects against a variety of human tumor cell lines including Raji, Daudi, Namalwa and CCRF-CEM cell challenge in SCID mice. It was further hypothesized that immune modifiers, such as checkpoint inhibitors that block CTLA-4 or PD-1 signaling, would offer an additional synergistic combination by allowing CD27-driven T cell response to overcome self-regulation and potentially broaden the immune response. Varlilumab and anti-PD-L1 mAb were evaluated in a CT26 colon cancer model and the E.G7 thymoma model, and the combination treatment resulted in improved anti-tumor activity and survival, as compared to monotherapy (**Figure** 1).

Figure 1. Enhanced Antitumor Activity with Varlilumab Plus Anti-PD-L1 mAb



A & B) Mice were inoculated with 1.5 x 10^4 CT26 tumor cells and treated as indicated on days 9-19. C) Mice were inoculated with 10^6 E.G7 tumor cells and treated as indicated on days 7-15.

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Pharmacokinetics

The pharmacokinetic data has been examined in the CDX1127-01 study for all dose-escalation patients with solid tumors and all patients with hematologic malignancies. The pharmacokinetic profile is dose proportional and dose accumulation is observed with weekly dosing. Pharmacokinetics were similar for patients with solid tumors and hematologic malignancies with T1/2 ranging from 3 days at 0.3 mg/kg to 11 days at 3 mg/kgfrom dose 1, increasing to 17 days after dose 5 at 10 mg/kg. The volume of distribution ranged from 26-79 mL/kg (1820-5530 mL for a 70 kg patient) approximating serum volume of 3000 mL. Exposure was linear across dose groups from 0.1-10 mg/kg with correlation coefficients of dose vs mean exposure from 0.9946 (C_{max}, Day 1), 0.9956 (AUC_{last}, Day 1) and 0.9991 (AUC_{inf}, Day 1; data not shown).

Clinical Summary

As of August 1 2018, 343 patients have been enrolled into the Celldex sponsored varlilumab clinical development program and 28 patients have been enrolled in non-sponsored studies. Ninety patients were treated with varlilumab monotherapy in the initial clinical study (Protocol CDX1127-01), while the remaining patients have received varlilumab in combination with other anticancer agents.

Protocol CDX1127-01 was a Phase 1, open-label, dose-escalation safety and pharmacokinetic study of varlilumab in patients with selected refractory or relapsed hematologic malignancies or solid tumors. A total of 90 patients were enrolled. Fifty-five patients (25 with solid tumors and 30 with B- or T-cell hematologic malignancies) were enrolled in the dose-escalation portion, which called for patients to receive varlilumab dose levels escalating from 0.1 to 10 mg/kg, as a single dose with 28-day observation followed by up to 20 weekly doses. In the expansion phase, 16 patients with melanoma and 15 patients with renal cell cancer (RCC) received varlilumab 3 mg/kg weekly for up to 20 doses. In dose escalation in 25 patients with solid tumors, one patient with metastatic RCC experienced a partial response (78% shrinkage, progression-free survival > 3.6 years). Eight patients experienced stable disease > 3 months, including a patient with metastatic RCC with progression-free survival of > 4.6 years. Treatment-related adverse events were generally grade 1 or 2 in severity. One Dose-Limiting Toxicity (DLT) was reported in a patient with Stage III ovarian cancer who experienced asymptomatic Grade 3 hyponatremia (129 mmol/L), with onset 13 days after receipt of a single dose of varlilumab at 1 mg/kg. The event resolved after three weeks without treatment. Treatment-related events that were reported in ≥5% of the patients were fatigue (28%), rash (including maculo-papular rash; 14%), nausea (12%), decreased appetite (12%), diarrhea (10%), headache (8%), vomiting (8%), pruritus (including pruritus generalized; 8%) and pyrexia (6%). Three Grade 3 treatment-related events have occurred in the solid tumor dose-escalation cohort: hyponatremia (the DLT described above), increased alkaline phosphate and decreased lymphocyte count and one Grade 3 treatment-related event of hypertension occurred in the solid tumor expansion cohort. There was one grade 4 treatment-related event of asthma in the solid tumor RCC expansion cohort. Thus, evidence of single agent clinical activity was seen in this heavily pre-treated population of patients with progressive, metastatic disease.

Combination of PD-1/PD-L1 inhibition and varlilumab

Preclinical studies demonstrate synergistic antitumor activity of PD-1 blockade and CD27 agonist antibody, varlilumab. Two studies have investigated the combination of varlilumab with nivolumab and atezolizumab respectively as discussed below and show that the combination were well tolerated with demonstrated clinical activity.

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CDX1127-02 is a Phase I/II open label study of varlilumab and nivolumab combination therapy. The Phase I part of the study consisted of a dose escalation assessment of the safety and tolerability of varlilumab (0.1 mg/kg, 1.0 mg/kg and 10 mg/kg) administered with nivolumab (3 mg/kg) every 2 weeks. Varlilumab treatment continued for up to 4 treatment cycles (each consisting of four varlilumab doses over eight weeks), while there was no pre-defined maximum duration of nivolumab dosing. The phase I portion of the study has completed enrollment and 36 patients received the combination (21 with colorectal cancer, 8 with ovarian carcinoma, 4 with melanoma, and 3 with head and neck squamous cell carcinoma). Patients received the combination of varlilumab (0.1, 1.0 or 10 mg/kg every two weeks) with nivolumab (3 mg/kg every two weeks), the majority had PD-L1 negative tumors at baseline and 80% of patients had CRC or ovarian cancer, representing patient populations expected to have minimal response to checkpoint blockade. However, notable cases of clinical activity have been observed. A patient with PD-L1 negative. high mutational burden CRC had 95% shrinkage of target tumors and continues to receive nivolumab monotherapy treatment at 3.4+ years. A second patient with SCCHN and low PD-L1 expression had 59% shrinkage of target tumors and experienced a PFS of 6.7 months. A patient with PD-L1 negative ovarian cancer experienced an unconfirmed PR (49% shrinkage) at 1.6 months, but discontinued treatment due to a DLT of hepatitis and subsequently died due to disease progression. One hundred and thirty-nine patients were enrolled in the Phase 2 portion of the study (58 ovarian, 24 head and neck, 22 GBM, 21 CRC and 14 RCC). Clinical response was observed in patients in the Phase 2 portion of the study, though overall the response rates did not exceed that expected with nivolumab monotherapy. There was evidence of biological activity and interesting changes in the tumor microenvironment, particularly in patients with ovarian cancer. In the ovarian cancer cohort, increased PD-L1 and CD8 TIL were observed in ~60% of patients with paired biopsy samples and was associated with improved PFS and OS. For patients with GBM durable therapeutic benefit was achieved in a subset of patients with unmethylated MGMT promoter (OS12 = 50%). In SCCHN, results in the subgroup (n=9) with PD-L1 negative tumors that are reported to have minimal benefit from PD-1 monotherapy, had 1 response (13%) and median OS of 11 months. The alternative varlilumab dosing regimens tested did not demonstrate evidence of enhanced clinical or immune activity compared to every 2 week dosing, and the data suggests that continuous CD27 signaling may have enhanced clinical activity. The 3 mg/kg dosing of varlilumab every 2 weeks may have more clinical activity than the other doses studied. . All dose levels were well tolerated without identification of a maximally tolerated dose. Three DLTs were reported in dose-escalation (grade 3 interstitial nephritis, grade 5 pneumonitis, grade 4 thrombocytopenia). There have been 15 patients (4 in Phase 1 and 11 in Phase 2), who have discontinued treatment due to adverse event(s). Treatment-related events that were reported in ≥20% of the patients in the dose escalation portion were fatigue (28%), infusion reaction (25%), pruritus (22%) and lymphopenia (22%) (Table 14). There was 1 grade 5 treatment related event of pneumonitis. There were 3 patients that had grade 4 treatment related AEs of hepatitis (DLT), lipase increased and blood bilirubin increased. The following treatment related grade 3 AEs were reported; lymphopenia (6 patients), lipase increased (2 patients), ALT increased (2 patients), and in 1 patient each for the following; blood bilirubin increased, AST increased, alkaline phosphatase increased, acute kidney injury, vomiting, worsening rash, pruritic, and serum amylase increased. Treatment-related events that were reported in ≥10% of patients in Phase 2 study were rash maculo-papular (17%), fatigue (16%), pruritus and rash each at 14%. There were 28 total patients that had grade 3 or higher treatment related adverse events in Phase 2 of the study. There was 1 grade 5 treatment related cardiovascular event

all other events were either grade 3 or 4. The most frequent grade 3 or 4 treatment-related events were lymphocyte count decreased in 7 patients (5%), lipase increased in 6 patients (4%), and amylase increased and lymphopenia in 4 patients each (3%).

CDX1127-06 is a Phase I/II open-label study of varlilumab, in combination with atezolizumab. This study included a Dose-Escalation Phase including patients with unresectable stage III or IV melanoma, RCC, triple negative breast cancer, bladder cancer, head and neck cancer or non-small cell lung cancer (NSCLC). In the Dose-Escalation Phase, up to 3 dose levels of varlilumab (0.3 mg/kg, 1.0 mg/kg and 3.0 mg/kg, given every three weeks) were sequentially evaluated in combination with a fixed dose of atezolizumab (1200 mg). Eighteen patients with either bladder cancer or RCC were enrolled in the Phase I portion of the study. After completion of the dose-escalation portion, the study was closed to focus resources on the CDX1127-02 study, which was exploring varlilumab with checkpoint inhibition in renal cell carcinoma, as well as alternative varlilumab dosing regimens that may more optimally signal CD27 expressing T cells in a broader Phase 2 platform. A total of 18 subjects were enrolled; 6 subjects each in Dose-Escalation Cohorts 1 (0.3 mg/kg varlilumab q3w), 2 (1.0 mg/kg varlilumab q3w), and 3 (3.0 mg/kg varlilumab q3w). Of the 18 subjects enrolled, 8 subjects had bladder cancer and 10 subjects had RCC. One subject with bladder cancer in the varlilumab 0.3 mg/kg + atezolizumab 1200 mg cohort experienced a durable partial response with a shrinkage to a maximum of 86% at 11.2 months. A best response of stable disease (SD) was noted for 7 (38.9%) patients (3 with bladder cancer and 4 with RCC). There were no dose-limiting toxicities. Two patients discontinued treatment due to adverse events. There were 14 patients who reported AEs related to treatment. The most frequent related treatment AEs grades 1-3 were fatigue (39%), pruritus (28%), anemia (17%), diarrhea (17%) and nausea (17%). There was one grade 4 treatment-related AE of increased lipase and there were no fatal treatment-related AEs (grade 5).
Four patients had serious adverse events (one with increased creatinine, two with colitis and one with infusion-related reaction).

1.2.5 Synergistic effect of radiation (RT) and immunotherapy used in combination
Combining RT and immunotherapy has a synergistic effect on immune-mediated tumor regression even in sites outside of radiation fields. Tumor-antigen release achieved through RT promotes specific tumor targeting by the adaptive immune system that is further augmented by systemic immunotherapy [18]. Dewan et al. demonstrated that fractionated RT was able to cause shrinkage of tumors outside of the radiation field when combined with CTLA blockade compared to either of these therapies used alone [19]. This *abscopal response* has been reported specifically in NSCLC also [20] and may contribute to a durable response. Moreover, PD-L1 has been shown to be upregulated in tumor microenvironment after RT in mouse models. And administration of systemic immunotherapy together reduces local accumulation of tumor-infiltration myeloid-derived suppressor cells which suppress T-cells [21]. Clinical efficacy of using RT in combination with immunotherapy was demonstrated by the START trial, a randomized phase III trial comparing MUC1 antigen-specific vaccine tecemotide for stage III unresectable NSCLC to placebo. Although there was no significant difference in survival between the two groups, there was a significant survival benefit in subgroup of patients who initially received concurrent chemoradiotherapy (median survival 30.8 months vs. 20.6 months, p=0.016) [22], suggesting a clear synergy with RT and immunotherapy and supporting the rationale of our proposed study.

Similarly, Stereotactic Body Radiation Therapy (SBRT) also induces endogenous antigen-specific immune responses when combined with PD-1 inhibitors. In animal models, SBRT

delivered to melanoma or breast tumors resulted in the development of antigen-specific T cell- and B cell-mediated immune responses. These immune-stimulating effects of SBRT were significantly increased when combined with anti-PD-1 therapy or regulatory T cell (Treg) depletion, resulting in improved local tumor control [23]. The combination of PD-1 blockade and localized RT has resulted in long-term survival in mice with orthotopic brain tumors also. Median survival improved to 53 days in the combination arm (compared to 25 days in the control arm and 28 days in the radiation arm). Moreover, long-term survival was seen only in the combined treatment arm, with 15%-40% of animals alive at day 180+ after treatment. Immunologic data on day 21 after implantation showed increased tumor infiltration by cytotoxic T cells (CD8+/interferon-γ+/tumor necrosis factor-α+) and decreased regulatory T cells (CD4+/FOXP3) in the combined treatment group compared with the single modality arms [24]. In a recently reported trial by Luke et al., 79 patients with metastatic solid tumors received SBRT to two to four metastatic sites followed by pembrolizumab. The treatment was overall well tolerated with six patients experiencing dose-limiting toxicities with no radiation dose reductions. In the 68 patients with imaging follow-up, the ORR was 13.2%. Median overall survival was 9.6 months (95% CI, 6.5 months to undetermined) and median progression-free survival was 3.1 months (95% CI, 2.9 to 3.4 months) [25].

Recently, two trials reported significant improvement in response rate with the combination of SBRT and immunotherapy at the annual ASCO meeting in June 2018._McArthur et al. (Abstract 1017) reported a response rate of 33% in 9 evaluable patients with metastatic breast cancer who received 3000 cGy of radiation in combination with pembrolizumab compared to historically reported rates of only 5-7% in this population, Theelen et al. (Abstract 9023; PEMBRO-RT study) reported a response rate of 41% (n=32) with the combination of SBRT and pembrolizumab compared to only 19% (n=32) with pembrolizumab alone in patients with metastatic NSCLC.

1.2.6 Study Rationale

In spite of responses seen with PD-1 or PD-L1 inhibitors across multiple tumor types, there is still a need to improve response rates further and increase the potential for long-term clinical benefit. In lung cancer, preliminary data indicate that there will be an increasing population of patients who have failed to respond to PD-1/PD-L1 directed therapies. Although response rates may be increased with combined checkpoint blockade, the majority of patients will likely not respond. Based on the available supporting data, we propose a phase I trial of the PD-L1 inhibitor Atezolizumab and anti-CD27 antibody, Varlilumab in combination with palliative radiation in patients with pretreated stage IV NSCLC who have progressed on prior PD-1 or PD-L1 therapy. We hypothesize based on existing preclinical and clinical data that combining a T-cell agonist with checkpoint blockade inhibitor may be synergistic and this synergy may be potentiated further by using targeted radiation. Targeted radiation improves antigen presentation and immune infiltration and this combination may help overcoming resistance to PD-1/PD-L1 antibody for treatment of NSCLC. Also, we plan to administer atezolizumab and varlilumab sequentially (varlilumab on day 1 and atezolizumab in day 2). A study by Messenheimer et al. in mouse models has demonstrated that sequential combination of T cell agonist followed with anti-PD-1 results in significant increase in therapeutic efficacy as sequential administration does not result in T-cell exhaustion [26].

The combination of radiation and concurrent immune checkpoint blockade is relatively novel; therefore, we will also carefully monitor safety and toxicity on this protocol. The potential overlapping toxicity should be limited to the local effects of radiation including pneumonitis,

skin inflammation and swelling, lymphopenia and general symptoms such as fatigue. The primary objective of this trial is to characterize the safety and tolerability of atezolizumab and varlilumab in combination with radiation in subjects with advanced or metastatic NSCLC. The primary safety analysis will be based on subjects who experience toxicities based on CTCAE criteria. The attribution to drug, time-of-onset, duration of the event, its resolution and any concomitant medications administered will be recorded. A secondary objective is to evaluate objective response rate and progression-free survival. Overall response rate based on irRECIST will be assessed by the investigators. Subjects must have measurable disease.

1.2.7 Rationale for Dosing

Radiation

SBRT is being used in our trial based on potential immune effects, tolerability and favorable side effect profile. In the trial combining SBRT and pembrolizumab reported by Luke et al described above, SBRT doses varied from 45 Gy in three fractions for peripheral lung, liver, and abdominal/pelvic; 50 Gy in five fractions for central lung and mediastinal/cervical; 30 Gy in three fractions for osseous and spinal/paraspinal lesions [25]. There were no radiation-dose reductions. All planning constraints (including < 15% normal lung volume receiving 20 Gy) were met. Using response defined by 30% reduction in any single, nonirradiated target metastasis, the nonirradiated RR was 26.9%. To assess whether SBRT might result in favorable immunologic changes in the tumor microenvironment, expression of four preselected IFN-γ–associated genes were analyzed in post irradiation biopsy specimens. Increased gene expression was significantly correlated with responses in nonirradiated tumors (P = .023). The feasibility of delivering 8 Gy fractions for palliation at sites throughout the body has also been confirmed by a study in patients with oligometastatic disease [27]. The NRG Oncology Group also used 50 Gy (in 5 fractions) for central lung lesions and mediastinal lymph nodes or 45 Gy (in 3 fractions) for peripheral lung lesions in a phase 1 trial of SBRT for treatment of multiple metastases [28]. Based on these prior studies, we will be using SBRT at a dose of 40 to 50 Gy (in 4 or 5 fractions) in our proposed trial.

Varlilumab

CDX1127-01 phase I trial investigated safety of varlilumab monotherapy across doses ranging from 0.1 to 10 mg/kg. All doses were well tolerated and only one dose-limiting toxicity (DLT) was reported at the 1 mg/kg dose. Six patients received the dose of 10 mg/kg and tolerated therapy well with no DLT at this dose. CDX1127-02 investigated the combination of varlilumab (dose range, 0.1 mg/kg to 10 mg/kg) with nivolumab. Of the five DLTs reported on this study, only one (grade 4 hepatitis) was at the 10 mg/kg varlilumab dose while 3 DLTs were at 3 mg/kg and one at 1 mg/kg. Fifteen patients received the 10 mg/kg dose. Similarly, of the 4 patients who discontinued therapy due to adverse events in dose escalation, only 1 patient had received 10 mg /kg dose. Therefore, no significant difference has been detected in the safety profile of the varlilumab doses ranging from 0.1 to 10 mg/kg.

However, one factor that may impact efficacy of T-cell agonists (such as varlilumab) when used in combination with immunotherpay is T-cell exhaustion through mechanisms such as chronic CD27 signaling. Therefore, to optimize the efficacy of varlilumab, we propose the following dosing regimen in our study:

- cycle 1 varlilumab to be administered at 10 mg/kg for increased CD27 engagement with the goal of maximizing T-cell activity
- reduce varlilumab to 3 mg/kg with cycle 2 to prevent chronic CD27 signaling and T cell exhaustion

[redacted]

- Sequential administration of varlilumab on day 1 followed by atezolizumab on day 2 (shown in preclinical data by Messenheimer *et al* to prevent T cell exhaustion).

1.2.8 Rationale for Correlative Endpoints

We plan a series of correlative studies to help identify the mechanism of action of combined checkpoint blockade in combination with radiation, identify biomarkers of response, and explain the mechanisms governing treatment response or failure. Subjects will be required to have newly obtained tumor biopsies (pre-treatment and during cycle 2) to support the ability to investigate the effect of the combination being investigated on immune biomarkers by immunohistochemistry. Subjects will be enrolled on this trial regardless of PD-L1 expression. Thus, tissue availability but not high biomarker expression is required for trial entry. This data will be of importance given the novelty of the combination of varlilumab, atezolizumab and radiation.

Data from ongoing studies with agents targeting the PD-1/PD-L1 pathway suggest, as shown in a number of tumor types (e.g., NSCLC, renal cell carcinoma, and melanoma), that monotherapy may be more efficacious for tumors with PD-L1-expression. Similar patterns were seen in a data set presented by Merck & Co at the World Conference on Lung Cancer and in a prospective trial evaluating PD-L1 expression in patients treated with pembrolizumab [9]. Therefore, it appears that the selection of patients based on PD-L1 expression levels within the tumor microenvironment may improve the probability and/or quality of responses to PD-1 pathway-targeting agents and may have merit as a patient enrichment tool. Pre-clinical data suggest that radiotherapy may upregulate intratumoral PD-L1 expression [29] but little is known about the dose response of these effects. Additionally little is known about how the pattern of expression (i.e., tumor cells vs. infiltrating immune cells) affects response. According to a recent publication [30] roughly 50% of NSCLCs express PD-L1 in tumor cells and 50% in tumor infiltrating immune cells.

In addition to PD-L1 expression, increased numbers of tumor infiltrating lymphocytes have also been associated with benefit following treatment with PD-1 pathway blockade. CD8+ T-cells present at the invasive front margin between tumor and stroma was associated with favorable response in patients with metastatic melanoma treated with the PD-1 inhibitor pembrolizumab [31]. Similarly, in patients with mismatch repair deficient tumors, CD8+ T-cells, particularly at the invasive front margins, were associated with a trend towards response or stable disease [32]. Radiation has also been demonstrated to impact levels of tumor infiltrating T-cells in animal models and clinical series [33, 34]. Interestingly, this effect may extend outside of the radiation treatment field in patients treated with checkpoint blockade [20]. Therefore, we will also evaluate CD3+ CD8+ T cell infiltration in the tumor microenvironment as a predictor of outcome and also determine changes in this parameter induced by radiation.

1.3 Research Design and Methods

A. Research Procedures

This is an open-label, Phase I trial to determine the safety and clinical benefit of the PD-L1 inhibitor Atezolizumab and anti-CD27 antibody, Varlilumab in combination with palliative radiation in patients with stage IV NSCLC. No PK evaluation is planned in this study as the combination of atezolizumab and varlilumab has already been evaluated in a phase 1 trial.

Dosing Regimen:

[redacted]

On Day 1 in a 21-day cycle, all patients will receive varlilumab (10 mg/kg in cycle 1, 3 mg/kg cycle 2 onwards, IV).

On Day 2 in a 21-day cycle, all patients will receive atezolizumab (1200 mg, IV).
Radiation will be administered between cycles 1 and 2.

Dosing	Atezolizumab (Day 2 of each cycle)	Varlilumab (Day 1 of each cycle)	Radiation dose*
	1200 mg IV every 3 weeks	10 mg/kg cycle 1; 3 mg/kg every 3 weeks cycle 2 onwards	10 Gy x 5 or 10 Gy x 4
1 cycle= 21 days.			

** Radiation to be administered starting C1D8 (between the two doses of varlilumab on C1D1 and C2D1)*

Radiation will be administered only once. However, if there is evidence of clinical benefit as determined by treating physician or patient requires palliative radiation for a symptomatic lesion, a second round of radiation to a different lesion is allowed.

i. Treatment Plan

Treatment Administration

- On Day 1 of cycle 1, all patients will receive varlilumab (10 mg/kg) via IV infusion over 90 minutes (±5 minutes). On day 1 of treatment cycles starting cycle 2, all patients will receive varlilumab (3 mg/kg) via IV infusion over 90 minutes (±5 minutes). Each treatment cycle will be 21 days. On cycle 1 dose 1, patients should be observed for at least 2 hours after the study drug administration to monitor for infusion reaction/cytokine release syndrome/hypersensitivity reaction. For all subsequent doses, patients should be monitored for at least 1 hour following the last administration of study drug.
- On Day 2 in a 21-day cycle, all patients will receive atezolizumab (1200 mg) via IV infusion over 60 minutes (±5 minutes). On cycle 1 dose 1, patients should be observed for at least 1 hour after the study drug administration to monitor for infusion reaction or hypersensitivity reaction. For all subsequent doses, patients should be monitored for at least 30 minutes following the last administration of study drug.
- Treatment will continue for up to 1 year (18 cycles). Atezolizumab can be continued after completion of one year of therapy at the treating physician's discretion if there is evidence of clinical benefit.

ii. Radiation

Prior to radiation simulation, initial staging scans will be analyzed by the radiation oncologist in detail. Lesions must be safe to radiate at the doses prescribed by the protocol as determined by the radiation oncologist. Lesions selected for potential radiation must be in the lung and prioritized based on the following criteria: (1) Lesions progressing on prior PD-1/PD-L1 targeted therapy, (2) the largest feasible lesion that may provide palliative benefit.

Radiation Therapy Administration

The use of image guided radiation therapy (IGRT) is mandatory. Radiation must begin on cycle 1, day 8 (± 2 days).

[redacted]

Radiation Dose Specifications
The total dose will be 50Gy in 5 fractions of 10 Gy or 40 Gy in 4 fractions of 10 Gy via stereotactic body radiotherapy (SBRT). If there is an extenuating situation that warrants reducing the dose per fraction to less than 10 Gy, the dose may be reduced only after discussion with the principal investigator(s). All fields must be treated during each fraction and the entire PTV must be treated during each fraction. Patients will receive 5 fractions of radiation, on an every 2-day basis i.e., 2-3 treatments per week, so that the SBRT schedule is completed within 1.5-2 weeks.

Technical Factors/Treatment Planning
Photon beam energies > 10 MV but not > 15 MV will be allowed only for a limited number (≤ 50% of all beams or all beam angles) beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the isocenter. Lower photon beam energies are preferred (i.e 6 MV).

Beam Energy: 6 - 15 MV will be used. Multi-leaf collimation (MLC) or individually-shaped divergent custom blocks will be used to spare normal tissues outside of the target volume. 3D Conformal Radiation Therapy (3D-CRT) is preferred but Intensity-Modulated Radiation Therapy (IMRT) is allowed. The PTV is to be treated with any combination of coplanar or noncoplanar fields optimized to deliver the specified dose while restricting the dose to the normal tissues. Each field is to be treated with each fraction throughout the course of treatment. All radiation doses will be calculated with heterogeneity corrections that take into account the density differences within the irradiated volume.

Localization, Simulation, and Immobilization
Immobilization to assure reproducibility of the setup is necessary. Each patient will be positioned in an immobilization device in the treatment position on a flat table. 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 (see Section 6.1). 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 must 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, tumor tracking, and active breath-holding techniques.

Isocenter or reference point port localization images (anterior/posterior and lateral) should be obtained at each treatment on the treatment unit (or patients should undergo a tomographic imaging study using the linear accelerator couch, if available) immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. Verification CT scans and portal films may be taken at the discretion of the participating institution but are not required for protocol participation.

Computed tomography will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting and must be done with IV contrast unless the patient has allergic problems with contrast or has renal insufficiency

[redacted]

Helical and four-dimensional CT (4DCT) is permitted for the study. Using either approach, the target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume (GTV). The target will generally be drawn using CT pulmonary windows; however, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. This target will not be enlarged whatsoever for prophylactic treatment (including no "margin" for presumed microscopic extension); rather, include only abnormal CT signal consistent with gross tumor (i.e., the GTV and the clinical target volume [CTV] are identical).

An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane (craniocaudal) will be added to the GTV to constitute the PTV for centers acquiring image datasets using helical scanning. If 4DCT is performed, PTV margins may be 0.3-0.5 cm.

As an alternative, sites equipped with 4-D CT scanning equipment may generate an Internal Target Volume (ITV) using the inspiration and expiration reconstructions or maximum intensity projections (MIP) as appropriate. Sites should be aware that the MIP reconstruction may erroneously define an ITV in cases of significant irregular breathing or when tumors abut soft tissue structures (e.g., the diaphragm). The 4-D scan acquired for planning, however, should be obtained after initial assessment of tumor motion confirming that the tumor motion will be no greater than 0.5 cm in the axial plane and 1.0 cm in the craniocaudal plane. In general, an ITV should NOT be defined by the merger of a deep inspiration CT scan and a deep expiration CT scan as such would typically overestimate tumor motion. The ITV, then, is generated using a CT dataset where motion control maneuvers are already successfully employed. This ITV can be expanded by the institution's geometric set-up uncertainty (e.g., 3-5 mm) to generate the PTV.

There are many valid approaches to defining target volumes and margins using multiple datasets representing different phases of the breathing cycle. These include but not limited to: a. the ITV (Internal Target Volume) concept from ICRU 62 with an appropriate margin accounting for geometric uncertainties (uniform 5 mm recommended) to define the PTV;
b. the mean target position with an appropriate margin to account for target motion and geometric uncertainties to define the PTV;
c. two helical scans, one scan with the patient at inhale breath-hold and the second scan with patient at exhale breath-hold.

Dosimetry
3D Conformal Planning: Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, ≥ 10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of seven non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For this protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3.5 cm when treating small lesions (see above). As such, prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100%); however, higher isodoses (hotspots)

[redacted]

must be manipulated to occur within the target and not in adjacent normal tissue. The isocenter in stereotactic coordinates will be determined from system fiducials (or directly from the tumor in the case of volumetric imaging) and translated to the treatment record.

The treatment dose plan will be made up of multiple static beams or arcs as described above. The plan should be normalized to a defined point corresponding closely to the center of mass of the PTV (COMPTV). Typically, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. Regardless, the point identified as COMPTV must have defined stereotactic coordinates and received 100% of the normalized dose. Because the beam apertures coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning (typically around 80% but ranging from 60-90%). The prescription dose will be delivered to the margin of the PTV and fulfill the requirements below. As such, a "hotspot" will exist within the PTV centrally at the COMPTV with a magnitude of prescribed dose times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

Intensity Modulated Radiation Therapy (IMRT): IMRT is allowed in this study. The use of IMRT in this study is at the discretion of the participating institution. However, IMRT should be considered only when target coverage, OAR dose limits, or dose spillage are not achievable with 3D conformal planning. In addition, IMRT plans should follow the same planning principles as discussed above for 3D conformal planning. The number of segments (control points) and the area of each segment should be optimized to ensure deliverability and avoid complex beam fluences. Ideally, the number of segments should be minimized (2-3 segments per beam should be adequate), and the area of each segment should be maximized (the aperture of one segment from each beam should correspond to the projection of the PTV along a beam's eye view).

For purposes of dose planning and calculation of monitor units for actual treatment, approved corrections for tissue heterogeneity must be used. Examples of appropriate tissue density heterogeneity correction algorithms include properly commissioned superposition/convolution (collapsed cone), AAA, and Monte Carlo. Simple pencil beam and Clarkson algorithms that account for attenuation but not scatter will not be allowed.

Dose Calculations

For purposes of dose planning and calculation of monitor units for actual treatment, this protocol will require tissue density heterogeneity correction. Successful treatment planning will require accomplishment of all of the following criteria:

1. Normalization: The treatment plan should be normalized such that 100% corresponds to the center of mass of the PTV (COMPTV). This point will typically also correspond (but is not required to correspond) to the isocenter of the treatment beams.
2. Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose.
3. Target Dose Heterogeneity: The prescription isodose surface selected in number 2 (above) must be ≥ 60% of the dose at the center of mass of the PTV (COMPTV) and ≤ 90% of the dose at the center of mass of the PTV (COMPTV). The COMPTV corresponds to the normalization point (100%) of the plan as noted in number 1 above.

[redacted]

4. High Dose Spillage: a. Location: Any dose > 105% of the prescription dose should occur primarily within the PTV itself and not within the normal tissues outside the PTV. Therefore, the cumulative volume of all tissue outside the PTV receiving a dose > 105% of prescription dose should be no more than 15% of the PTV volume. b. Volume: Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1 through 4 to the volume of the PTV is ideally < 1.2 (see table below). These criteria will not be required to be met in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3.5 cm (see Section 6.2) results in the inability to meet a conformality ratio of 1.2. 5. Low Dose Spillage: The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria: a. Location: The maximum total dose over all fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction must be no greater than D2cm where D2cm is given by the table below. b. Volume: The ratio of the volume of 50% of the prescription dose isodose to the volume of the PTV must be no greater than R50% where R50% is given. See Table 1 below. 6. Respect all critical organ dose-volume limits listed in section below.

Table 1: Conformality of Prescribed Dose for Calculations Based on Deposition of Photon Beam Energy in Heterogeneous Tissue

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV Volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, $R_{50\%}$		Maximum Dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D_{2cm} (Gy)		Percent of Lung Receiving 20 Gy Total or More, V_{20} (%)	
	Deviation		Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor	None	Minor
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15
3.8	<1.2	.<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	>91.0	<10	<15
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	>94.0	<10	<15

For values of PTV volume not specified, linear interpolation between table entries is required.

Critical Organ Dose-Volume Limits: Table 2 lists maximum dose limits to a point or volume within several critical organs. These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation. The dose is listed as total over 5 fractions and per fraction. The esophagus, trachea, bronchi and heart may be situated adjacent to the treated GTV/PTV. As such, there is no specified limit as tumors that are immediately adjacent to that organ will not be able to be treated to any of the prescription

[redacted]

doses without irradiating a small volume of that organ to the prescribed dose. In such a case, the planning needs to be done so that there is no hot spot within that organ, even if that organ is part of the PTV, i.e., that no part of any OAR receives more than 105% of the prescribed dose (see Figure 2 below). In addition, the volume of the OAR in question needs to be minimized, both in length and in the width (i.e., circumference), with efforts made to reduce the dose to the contralateral wall of the organ. In Table 3, suggested volume limits are listed for these organs to be used for treatment planning purposes. Since the tumor and normal tissue may not allow strict avoidance, the volume limits (columns 2 and 3) will not be scored as protocol violations if exceeded. However, the maximum point dose limits (column 4) must be respected.

For tumors that are not immediately adjacent to any OAR, centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures; we expect that the OAR doses will be as low as achievable (ideally, < 6 Gy/fraction).

Table 2

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Avoidance Endpoint
Spinal Cord	<0.25 cc <0.5 cc	22.5 Gy (4.5 Gy/fx) 13.5 Gy (2.7 Gy/fx)	30 Gy (6 Gy/fx)	myelitis
Ipsilateral Brachial Plexus	<3 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	neuropathy
Skin	<10 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	ulceration
Parallel Tissue	**Critical Volume**	**Critical Volume Dose Max (Gy)**		**Avoidance Endpoint**
Lung (Right & Left)	1500 cc	12.5 Gy (2.5 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	13.5 Gy (2.7 Gy/fx)		Pneumonitis

Table 3

Serial Tissue*	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Avoidance Endpoint
Esophagus, non-adjacent wall	<5 cc	27.5 Gy (5.5 Gy/fx)	105% of PTV prescription	stenosis/fistula
Heart/Pericardium	<15 cc	32 Gy (6.4 Gy/fx)	105% of PTV prescription	pericarditis
Great vessels, non-adjacent wall	<10 cc	47 Gy (9.4 Gy/fx)	105% of PTV prescription	aneurysm
Trachea and ipsilateral bronchus, non-adjacent wall	<4 cc	18 Gy (3.6 Gy/fx)	105% of PTV prescription	stenosis/fistula

*The volume maximum column shows suggested limits for these structures for planning purposes. Exceeded these limits is not a protocol violation. However, exceeding the Maximum Point Dose column is a violation per Section 6.7.2.

Critical Structures

[redacted]

Normal tissue constraints shall be prioritized in the following order for treatment planning: 1=spinal cord, 2=lungs, 3=esophagus, 4=brachial plexus, and 5=heart.

Spinal Cord: The spinal cord should be contoured based on the bony limits of the spinal canal from the top of C1 to the bottom of L2. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.
Lungs: The total lung volume is defined as the sum of the volume of both lungs minus the GTV. The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with the cord dose constraints. The proportion of total lung volume that receives more than 20 Gy (V20) should not exceed 31%. Additionally, the mean lung dose should not exceed 20 Gy. If either of these constraints is exceeded, for the 3D-CRT cases, one might increase the weighting of any AP/PA fields and reduce any oblique fields. This can be done as long as the cord dose (above), which takes precedence, is not exceeded. For 3D-CRT or IMRT cases, one can reduce the CTV to the minimum range suggested above especially near the spinal cord. Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.
Esophagus: The esophagus contour should include the mucosal, submucosa, and all muscular layers out to the fatty adventitia, from the bottom of the cricoid cartilage to the gastroesophageal junction. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV and ideally from the post-cricoid space to the GE junction.
Brachial Plexus: The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib.
Heart: The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.
Great Vessels: The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV. For right sided tumors, the vena cava will be contoured, and for left sided tumors, the aorta will be contoured.

Dose Specifications
Patients will receive 10Gy x 5 treatments or 10Gy x 4 treatments based on the treating physician's discretion. Only photons treatments are allowed, and volumetric treatment planning is mandated.

Image Guided Treatment
- Image-guided radiation therapy (IGRT), consisting of images and appropriate image alignment software tool, is required on this protocol.

- Patients will be treated only on units with image guidance capabilities. Such units include ones with on-board imaging, CT-on-rails, or other dedicated imaging system for patient positioning. At a minimum, these units must include orthogonal x-ray imaging systems for patient positioning and employ software tools for image registration.
- To achieve compliance with the PTV expansions stated in the protocol, daily imaging is required.

iii. Laboratory and other assessments

1. **Hematology:** Hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, and platelet count will be obtained for all treatment cycles. WBC (including differential) outside of normal range can be retested to determine eligibility. Complete blood count (CBC) will be monitored on a more frequent basis, in accordance with institutional guidelines, should a patient have grade 4 hematological AEs. Results of all baseline tests must be reviewed for eligibility by the treating Investigator or their designee prior to registration. In addition, results of hemoglobin, absolute neutrophil count, and platelet count must be reviewed prior to each infusion.
2. **Blood chemistry/electrolytes:** Sodium, potassium, chloride, bicarbonate, calcium, magnesium, glucose, BUN, serum creatinine, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, lipase, amylase, and total bilirubin (plus direct bilirubin if total bilirubin is elevated). Results of all baseline tests must be reviewed for eligibility by the treating Investigator or their designee prior to registration. Results of AST, ALT, AP, bilirubin, and creatinine must be reviewed prior to each infusion.
3. **Pregnancy test:** Urine dipstick pregnancy tests are to be performed for females of childbearing potential at screening visit. Positive urine tests are to be confirmed with serum pregnancy testing.
4. **Urinalysis**: Glucose, blood, protein and pH. If blood or protein in urine is present, a microscopic examination is required. Results of all baseline tests must be reviewed for eligibility by the treating investigator or their designee prior to registration.
5. **Endocrine tests**: Including thyroid stimulating hormone (TSH), and T3 and/or T4 (free or total will be performed as per local standards).

iv. Screening and on-treatment evaluations

<u>Screening Visit and Baseline</u> (within 28 days prior to registration)

At the screening visit, information will be collected and patients will have clinical evaluations as follows:

- Informed consent
- Medical history (including events up until treatment); demographics; smoking history; trial awareness question
- Diagnosis and staging
- Tumor assessments and measurement
- Concomitant medications (starting from the time the patient signs the informed consent)
- Complete physical examination, including height (screen only) and weight
- Vital sign measurements
- ECOG Performance status;
- Hematology, serum chemistry and urinalysis, endocrine labs, coagulation tests

[redacted]

- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing)
- Pre-treatment tumor biopsy (mandatory)

On Treatment Evaluations

Day 1 of Each Cycle
- Concomitant medications
- Physical examination
- Vital sign measurements
- ECOG Performance status
- Hematology, serum chemistry
- Endocrine labs
- Varlilumab infusion
- Radiation (only with cycle 1 to be administered starting day 8 ± 2 days)
- AEs. Patients should specifically be asked about signs of constipation and treatment provided when indicated.
- Post-treatment tumor biopsy (only with cycle 2)
- Collection of whole blood for PBMC banking (only with cycle 1 and cycle 3)

Day 2 of Each Cycle
- Vital sign measurements
- Atezolizumab infusion

Post Cycle 3 and Thereafter
- Disease assessment will be done every 3 cycles (post C3, C6, etc.).

v. Dose Modifications or Interruptions

The NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

In the event of multiple toxicities, dose delays and modifications should occur in accordance with the highest grade of AEs observed. All patients with evidence of radiographically confirmed progressive disease or clinical evidence of disease progression or global deterioration of health unrelated to progressive disease, as defined by irRECIST, will be discontinued from study treatment.

If there is a concern for pseudoprogression, radiologic imaging may be repeated approximately 4-6 weeks later in order to confirm continued PD (as compared to the initial scan showing progression). Treatment may continue at the discretion of the treating physician while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction or stabilization in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar.

[redacted]

In the absence of disease progression, laboratory tests are required prior to Day 1 of each cycle as per the schedule of assessments. The follow criteria must be met:

- AST ≤ 3 ULN, ALT ≤ 3 ULN (≤ 1.5 x ULN if alkaline phosphatase is > 2.5 x ULN)
- Serum bilirubin ≤ 1.5 x ULN (unless patient has Gilbert's disease, then bilirubin ≤ 3.0 x ULN)
- Creatinine ≤ 1.5 x ULN or eGFR ≥40 mL/min/1.73m^2
- Hemoglobin ≥ 9 g/dL
- Absolute neutrophil count ≥ 1.0 x 10^9/L
- Platelets ≥ 100 x 10^9/L

Atezolizumab and varlilumab dose reductions are not allowed.

At the discretion of the Investigator, the dose may be delayed for up to 6 weeks for any toxicity possibly or probably related to treatment. Dosage interruptions to assess or treat intercurrent illnesses are allowed and should be clearly described in the study eCRF. A delay greater than 6 weeks will require the patient to be removed from the study (except in case of potential patient benefit, which must be approved by the Sponsor Investigator).

Treatment will be held for:

- Drug-related grade 4 hematological toxicities (except for lymphopenia)
- ≥Grade 3 non-hematological toxicity (except for fatigue, alopecia and vitiligo OR isolated laboratory abnormalities with no clinical correlate)
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator (in consultation with the study monitor), warrants delaying the dose of study medication
- In the event of isolated CNS progression during study treatment, study drug(s) may be withheld while palliative treatment is administered, e.g. a standard course of whole brain radiotherapy in accordance with institutional practice, and restarted within 1 week after completion of radiotherapy. During this time the patient should be fully evaluated for other sites of disease progression. If treatment is delayed >6 weeks, the patient must be permanently discontinued from all study therapy, except as specified in Dose Discontinuation Criteria.
- If guidelines for an irAE are not specified in Table below, atezolizumab and varlilumab should be held for any ≥grade 3 irAE (except for alopecia, fatigue, vitiligo or lymphopenia), and can be resumed if the irAE recovers to grade 0-1. Systemic corticosteroids (1-2 mg/kg/day) are indicated for all grade 3 or 4 irAEs if not otherwise specified. Steroids should be tapered once symptoms improve to grade 1 or less and tapered over at least 1 month.

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Atezolizumab and varlilumab are considered immuno-oncology agents in this protocol. Because of the potential for clinically meaningful I-O agent related AEs requiring early recognition and prompt intervention, Treatment guidelines have been developed for suspected toxicities; pulmonary, GI, hepatotoxicity, endocrine, dermatologic, pancreatic, eye, pericardial effusions, and infusion related reactive. The treatment guidelines recommended for utilization in this clinical trial are contained in the atezolizumab investigator brochure.

[redacted]

Investigators should be familiar with the guidelines and promptly consult them for guidance in managing suspected drug related toxicity. If an irAE is suspected, a thorough evaluation should be conducted in an effort to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to diagnosing an irAE. Serological, immunological and histological (biopsy) data should be considered to support the diagnosis of an immune-related toxicity. All irAEs are graded according to CTCAE, version 5.

Treatment should be permanently discontinued for:

- Life-threatening or grade 4 AE (except for lymphopenia)
- Any severe or grade 3 treatment-related AE that recurs (except for fatigue, alopecia, vitiligo or lymphopenia)
- Inability to reduce corticosteroid dose to ≤10 mg of prednisolone or equivalent/day within 6 weeks
- Persistent grade 2 or 3 treatment-related adverse reactions that do not recover to grade 1 or resolve within 6 weeks after last dose.

vi. Dose Modifications Guidelines

Adverse Reaction	Withhold for:	Permanently Discontinue for:
Pneumonitis	Grade 2 • Promptly initiate empiric steroids (prednisone 1-2 mg/kg/day or equivalent) • If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. If still no improvement within 3-5 days, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab). • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment	Grade 3 or 4 • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Hospitalize the patient, obtain pulmonary consult, supportive care (oxygen etc.) • If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab) • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment
Hepatitis	≥ Grade 2 if patient has baseline AST, ALT or total bilirubin that is within normal limits • Regular checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day or IV equivalent. • If still no improvement within 3-5 days, consider additional workup and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • If still no improvement within 3-5 days despite 2-4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil). Infliximab should NOT be used.	AST or ALT > 8 x ULN OR total bilirubin >5 x ULN OR concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN Any grade 4 • Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent • If still no improvement within 3-5 days, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Infliximab should NOT be used. • Hepatology consult, abdominal workup, and imaging as appropriate. • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment

[redacted]

Adverse Reaction	Withhold for:	Permanently Discontinue for:
	• Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	
Diarrhea/Colitis	Grade 2 or 3 • Symptomatic treatment including hydration, electrolyte replacement, dietary changes, and loperamide and/or budesonide. Consider hospitalization if grade 3. • Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent • If event is not responsive within 3-5 days or worsens, GI consult should be obtained for further workup such as imaging and/or colonoscopy, and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • If still no improvement within 3-5 days despite 2-4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab. Caution: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	Grade 4 • Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent • Hospitalize patient, urgent GI consult and imaging and/or colonoscopy as appropriate • If still no improvement within 3-5 days, promptly start further immunosuppressives (e.g. infliximab). Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment
Nephritis and renal dysfunction	Grade 2 • Carefully monitor serum creatinine every 2-3 days and as clinically warranted • Consult Nephrologist and consider renal biopsy if clinically indicated • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day or IV equivalent	Grade 3 or 4 • Carefully monitor serum creatinine every 1-2 days • Consult Nephrologist and consider renal biopsy if clinically indicated • Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent

[redacted]

Adverse Reaction	Withhold for:	Permanently Discontinue for:
	• If event is not responsive within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started. • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	• If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment
Rash (excluding Bullous skin formations) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED AND STUDY DRUG DISCONTINUED**	Grade 2 or 3 • Obtain dermatology consult • Symptomatic topical treatment • Consider moderate-strength topical steroid • If no improvement of rash/skin lesions within 3-5 days or is worsening, promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • Consider skin biopsy if persistent for >1-2 weeks or recurs • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	Grade 4 • Hospitalize patient and consult dermatology • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Consider skin biopsy • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment
Type I diabetes mellitus [TIDM] (if new onset) or Hyperglycemia	Grade 2 or 3 • Obtain endocrinology consult • Consider short term corticosteroids or hormone replacement therapy as indicated • If no improvement within 3-5 days or is worsening, promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • Consider hospitalization if grade 3	Grade 4 • Hospitalize patient and consult endocrinology • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Administer hormone replacement therapy as indicated

Ad		Permanently Discontinue for:
	• Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	• Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment
Hypophysitis	Grade 2 or 3 • Obtain endocrinology consult • Consider short term corticosteroids or hormone replacement therapy as indicated • If no improvement within 3-5 days or is worsening, promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • Consider hospitalization if grade 3 • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	Grade 4 • Hospitalize patient and consult endocrinology • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Administer hormone replacement therapy as indicated • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment
Adrenal insufficiency	Grade 2 or 3 • Obtain endocrinology consult • Consider short term corticosteroids or hormone replacement therapy as indicated • If no improvement within 3-5 days or is worsening, promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • Consider hospitalization if grade 3 • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	Grade 4 • Hospitalize patient and consult endocrinology • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Administer hormone replacement therapy as indicated • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment
Immune mediated Neurotoxicity	Grade 2 • Discuss with the study physician	Grade 3 or 4 • Discuss with study physician

[redacted]

Adverse Reaction	Withhold for:	Permanently Discontinue for:
	• Obtain Neurology Consult • Pain medications as indicated • Promptly start systemic steroids prednisone 1-2mg/kg/day or IV equivalent • If no improvement within 3-5 days despite 1-2 mg/kg/day prednisone or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)	• Hospitalize and obtain Neurology Consult • Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent • If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) • Once stable, gradually taper steroids over ≥4 weeks
Uveitis	≥ Grade 2 • - Obtain ophthalmology consult • - Promptly initiate topical steroids • - If no improvement within 3-5 days or is worsening, promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • - Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	≥ Grade 2 (if not improving to grade 1 within 2 weeks while receiving topical treatment OR requiring systemic treatment)

There are no dose recommendations for hypothyroidism or hyperthyroidism. Isolated grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to <grade 4 within 1 week of onset do not require treatment modifications. If the decision is made to resume dosing, the patient should restart treatment on the next regularly scheduled dosing visit. Skipped doses are not to be replaced. Patients should receive appropriate supportive care measures as deemed necessary by the Investigator.

Management of Infusion Reactions: Preliminary data shows that there may be an increase in low-grade infusion reactions when varlilumab is combined with checkpoint blockade treatment. If necessary, appropriate pre-medication with diphenhydramine and acetaminophen has prevented further infusion reactions.Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to

[redacted]

both AEs. The table below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of the treatment.

Management of Infusion Related Reaction (IRR), Allergic Reaction,

Description	Action
CTCAE Grade 1 IRR, allergic reaction or bronchospasm[1]	Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional drug administrations.
CTCAE Grade 2 IRR, allergic reaction or bronchospasm	Stop the infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further drug will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional drug administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.
CTCAE Grade 3 or 4 IRR, allergic reaction, bronchospasm or hypersensitivity reaction[1]	Immediately discontinue infusion of drug. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. ***Drug will be permanently discontinued***. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg,

[redacted]

	appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).
[1]Hypersensitivity reactions included in CTCAEv5 include anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis; in the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).	

[redacted]

[redacted]

vii. Toxicity Monitoring and Adverse Event Reporting

All patients who receive one dose of protocol therapy will be evaluable for assessment of toxicity. Prior to each cycle the treating physician will fully assess the patient's condition with respect to possible treatment related toxicities. All adverse events, whether observed by the physician or reported by the patient, occurring during the active portion of therapy, or up to 30 days after the last dose of treatment will be graded by a numerical score according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (http://ctep.cancer.gov/reporting/ctc.html) and recorded in the patient's medical record. For the purposes of reporting laboratory abnormalities, only Grade 3-4 adverse events will be recorded on the adverse event CRF pages. Grade 1-2 laboratory abnormalities will not be recorded on the adverse event CRF pages. Information entered on the adverse event CRF pages will include:

- Specific type and duration of reaction (i.e., start and stop dates, resolution).
- Severity/grade.
- Relationship to study drug (causality, attribution).
- Management of the event, if treated with medication and other actions taken to alleviate the clinical event.
- Whether or not it was considered a SAE.

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

a) Definition of Serious Adverse Events (SAEs)

A serious adverse event (experience) is one occurring at any dose level that results in any of the following outcomes:

- Death
- Life-threatening immediate risk of death from the reaction. threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. NOTE: Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Requires intervention to prevent one of the outcomes listed in this definition.

The definition of serious adverse event (experience) also includes *important medical events*. Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events will usually be considered serious. Examples of such events are intensive treatment in

[redacted]

an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

b) Adverse Event Reporting Requirements
An adverse experience is defined as any unintended or abnormal clinical observation that is not of benefit to the patient. Either the condition was not present prior to exposure to the study therapy, or it has worsened in intensity or frequency following exposure to the study therapy. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

irAE's are defined as any treatment-related AE that is inflammatory in nature, is consistent with the mechanism of action of immunotherapy and generally medically manageable with topical and/or systemic immunosuppressants

All "unexpected" (defined below) and/or "serious" (defined below) adverse events occurring during the active portion of therapy, or up to 30 days after the last dose of treatment, will be reported to the Office of Human Research Services at (732) 235-7577 or (732) 235-8675. Events will be promptly reported, in writing, to the local IRB in accordance with IRB policy. If a death occurs the IRB will be notified within 24-hours of initial receipt of information. All other SAEs must be reported to the IRB within three to ten days of initial receipt of information. Written follow-up reports are required when additional information is needed to fully characterize the event. Copies of each report sent to the IRB will be kept in the study regulatory file.

Reporting SAEs using commercially available drugs:
In addition, any unexpected (*not listed in the package insert or IB*) serious adverse events that are **associated** (definitely, probably or possibly related) with the use of atezolizumab must be reported to the FDA within 10 business days using a FDA Form MedWatch 3500 form http://www.fda.gov/medwatch/safety/3500.pdf (fax # 1-800-FDA-0178).

Reporting SAEs for IND studies:
The PI shall notify the FDA of any adverse experience associated with the use of the drugs that is both serious and unexpected, as soon as possible and in no event later than 15 calendar days after the PI's discovery of the event. Each written notification may be submitted on FDA Form MedWatch 3500A http://www.fda.gov/medwatch/safety/3500a.pdf (fax # 1-800-FDA-0178).

The PI shall also notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experiences associated with the use of the drugs, as soon as possible but no later than 7 calendar days from the PI's discovery of the event information.

[redacted]

Reporting to Celldex:
Expedited reporting by investigator to Celldex. Reporting to Celldex is required in addition to reporting to the FDA and does not replace the requirement to notify the FDA if required.

- The PI will inform Celldex in writing using an SAE form or MEDWATCH 3500A form of any SAE or irAE within 24 hours of being aware of the event (see section 8.2 for the definition of SAE). The written report must be completed and supplied to Celldex by facsimile or email within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report.

[redacted]

- In addition, the following Events of Interest must be reported to [redacted], or designee, within 24 hours of becoming aware of the event:
  - Any DLT, regardless of whether or not the event is considered an SAE
  - All Grade ≥ 3 adverse events attributed to study treatment, except for asymptomatic laboratory results (e.g. decreased lymphocyte count or increased lipase)
  - Any overdose (defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important).

Adverse Events and Immune Related Adverse Events

- AEs and irAEs will be recorded from time of signed informed consent until 100 days after discontinuation of study drug(s).
- AEs will be recorded whether or not they are considered related to the study drug(s).
- All AEs/ irAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- Asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.
- All patients experiencing SAE/AEs or serious irAEs/ irAEs resulting in permanent discontinuation from the study regardless of seriousness or relationship to study drug or experiencing treatment-related toxicities of grade ≥2 at the End of Treatment visit should be followed-up monthly until all the toxicities are resolved to grade ≤1, or stabilized, or patient receives other anti-cancer therapy, whichever occurs first.

Reporting of pregnancy related events
A female patient of childbearing potential must be instructed to immediately inform the Investigator if she becomes pregnant during the study. Pregnancies occurring up to 12

[redacted]

weeks (in a patient or partner of a patient) after the completion of treatment must also be reported to the Investigator. The Investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects on the fetus (congenital anomalies). Monitoring of the patient will continue until conclusion of the pregnancy. Patients who become pregnant while on study will be discontinued from the study treatment and all safety follow up procedures will be performed.

Pregnancy is not an SAE. However, the outcome of a pregnancy must be reported to detect a potential SAE (congenital anomaly, premature birth, or birth defect). All pregnancies must be initially reported and follow-up information must be provided. If the outcome of the pregnancy meets any SAE criterion (including stillbirth, neonatal death, spontaneous abortion, or congenital anomaly – including that in an aborted fetus), the Investigator must follow the procedures for reporting SAEs. Any neonatal death occurring ≤30 days after birth will be reported as an SAE. If a pregnancy occurs in the female partner of a male patient, the Investigator will then (and only then) also be required to obtain her consent to hold her data on file. If the female partner is unwilling to sign the consent, her data may not be held in the safety database. However, this will not affect the ability of the male patient to continue in the study.

Rapid Notification of Adverse Events of Interest

In addition to serious adverse events, the following adverse events will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events, even if the nature of the adverse event is not deemed serious:

- All Grade ≥3 adverse events attributed to study treatment
- ≥ Grade 2 diarrhea/colitis
- Any ≥ grade 2 eye pain or reduction of visual acuity that does not improve to ≤ grade 1 severity within 2 weeks of the initiation of topical therapy or requires systemic treatment
- Any overdose (defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important).

c) Definition of Related

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	The Adverse Event is ***not related*** to the drug(s)
Unlikely	The Adverse Event is ***doubtfully related*** to the drug(s)
Possible	The Adverse Event ***may be related*** to the drug(s)
Probable	The Adverse Event is ***likely related*** to the drug(s)
Definite	The Adverse Event is ***clearly related*** to the drug(s)

d) Definition of Unexpected

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from

[redacted]

the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. For varlilumab, expectedness assessments are made against the approved reference safety information (RSI). The RSI for varlilumab is specified within the varlilumab Investigator Brochure, Section 6.3.3 (Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions).

viii. **Study discontinuation and follow-up**

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Documented disease progression
- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
- If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant
- If treatment is interrupted for ≥ 6 weeks.
- Intercurrent illness that prevents further administration of treatment
- non-compliance with treatment plan

All patients who have received at least 1 dose of study drug and have discontinued treatment for any reason will have a 30-day Safety assessment performed.

The Safety Follow up assessments should include the following:

- Concomitant medications
- Complete physical examination, including weight
- Vital signs measurements
- ECOG Performance Status
- Hematology, serum chemistry, endocrine labs
- AEs
- Disease assessment should be done at the discretion of the treating physician.

An additional assessment of AEs will be performed 100 days (±7 days) after last dose of study drugs.

<u>Adverse Event Assessments</u>

Information regarding the occurrence of SAEs will be collected from the time the patient signs the informed consent form. AEs will be collected after randomization. SAEs and AEs will be collected throughout their participation in the study, including a period of 100 days after the patient's last active dose of study drug, unless a new treatment has been started. SAEs that occurs more than 100 days after the last dose of study drug need not be reported unless the Investigator considers them related to study drug.

<u>Safety Follow-up Evaluations</u>

[redacted]

For the purpose of this study, all AEs irrespective of causality will be collected from Cycle 1 Day 1. A safety follow-up visit should occur when subjects permanently stop study treatment for whatever reason (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) after the last dose of treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

Long Term Follow-up Evaluations

Patients will be followed at least every 3 months (±7 days) for survival for up to one year following their Safety Follow up visit, unless the trial is completed or terminated or informed consent is withdrawn. Follow up will continue even if the patient receives another anticancer therapy. Patients can consent to participate in follow-up assessments even if consent for study participation has been withdrawn.

Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

ix. Concomitant Medications

The Investigators should be experienced in the use of atezolizumab and familiar with the prescribing information provided by the manufacturer.

Any other medication which is considered necessary for the patient's welfare, including bisphosphonates, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator.

Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial 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-investigator. Pre-medication as prophylaxis for infusion reaction should only be initiated if clinically indicated.

All medications will be recorded in an appropriate section of the CRF.

No other cancer therapies or investigational agents are permitted during the entire duration of the study treatment (from 14 days before the first administration until the 30-day safety evaluation).

Thoracocentesis or paracentesis may be administered, if needed for comfort. If surgical intervention or localized radiation become indicated (either for palliation or down-staging of previously non-resectable tumor), these interventions are permitted, but should be avoided if clinically feasible until after the second response assessment. A tumor response assessment should be conducted prior to any intervention, in order to document progression and/or confirm an objective response. Patients who undergo surgical resection or radiation in the absence of progression may continue to receive study treatment until remaining lesions meet criteria for progression of disease.

[redacted]

Supportive Care Guidelines

Acetaminophen may be used to manage drug-related adverse events such as fever, myalgias or arthralgias and anti-histamines may be used to manage drug-related adverse events such pruritus. Appropriate anti-emetic prophylaxis (excluding steroids) should be given per institutional policy if nausea or vomiting occurs. Suggested regimen includes a 5HT3 antagonist such as ondansetron. The use of anti-emetics must be recorded on the eCRF.

If diarrhea occurs, it must be treated. Anti-diarrheals such as loperamide (or diphenoxylate/atropine) must be prescribed for diarrhea. Suggested loperamide use is 4 mg orally after first loose stool, then 2 mg after each stool not to exceed 16 mg in 24 hours. Anti-diarrheal medications must be recorded on the eCRF.

Prophylaxis with bowel motility agents should follow institutional practice, including the use of agents such as stool softeners, bulking agents, stimulating agents and/or dopamine antagonists. The use of opiates should be limited to when clearly indicated and prophylaxis for opiate induced constipation with agents such as methylnaltrexone should be administered.

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Atezolizumab and Varlilumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity.

Patients who are started on steroids for management of an immune-related event should not resume immunotherapy until steroids have been tapered to ≤ prednisone 10mg daily or an equivalent dose of an alternative corticosteroid.

B. Data Points/Treatment Evaluation

For the purposes of this study, all tumor assessments must be completed following the same methodology as used for the screening assessment. Methodology and disease response will be assessed as specified in irRECIST . During study treatment, disease status will be assessed every 3 cycles. Perform CT scan of the abdomen/pelvis, CT of the chest, or additional staging as required for each patient. A bone scan will only be performed in patients with known bone metastasis at study entry to monitor the status of metastatic disease in bone. If radiologic imaging shows progressive disease (PD), tumor assessment may be repeated approximately 4-6 weeks later in order to confirm continued PD (as compared to the initial scan). Treatment may continue at the discretion of the treating physician while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction or stabilization in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar.

Response and progression will be evaluated in this study using the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) [35]. irRECIST differs from RECIST (Version

[redacted]

1.1) in that the sum of the longest diameters of all target lesions AND new lesions if any are used to determine response. The presence of new lesions per se does not determine progression; the total tumor burden is considered. For the irRECIST, only index and measurable new lesions are taken into account. At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (up to 5 new lesions per organ; 10 visceral lesions) are added together to provide the total tumor burden: Tumor Burden = SPD_{index} lesions + SPD_{new}, measurable lesions.

i. Measurable Disease
Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

ii. Non-Measurable Disease
All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

iii. Guidelines for Evaluation of Measurable Disease
All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique will be used whenever possible to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion.

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

Conventional CT and MRI- These techniques will be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT will be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

[redacted]

Ultrasound (US)- Because one of the endpoints of the study is objective response evaluation, US will not be used to measure tumor lesions. US might be used, at the discretion of the investigator, to confirm the complete disappearance of superficial lesions assessed by clinical examination.

Tumor markers- Tumor markers alone will not be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, histology- These techniques may be used to differentiate between partial responses (PR) and complete responses (CR) if necessary and determined by the investigator. Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

iv. Response Criteria

Evaluation of Index Lesions

irComplete Response (irCR):	Complete disappearance of all index lesions.
irPartial Response (irPR):	Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all index and all new measurable lesions (ie., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by ≥25% when compared to SPD at nadir.
irProgressive Disease (irPD):	At least 25% increase Percentage Change in Tumor Burden (i.e., taking sum of the products of all index lesions and any new lesions) when compared to SPD at nadir.
irStable Disease (irSD):	Does not meet criteria for irCR or irPR, in the absence of progressive disease.

Evaluation of Non-Index Lesions

irComplete Response (irCR):	Complete disappearance of all non-index lesions.
irPartial Response (irPR)/ irStable Disease (irSD):	non-index lesion(s) are not considered in the definition of PR, these terms do not apply.
irProgressive Disease (irPD):	Increases in number or size of non-index lesion(s)

[redacted]

	does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount).
Impact of New Lesions on irRC New lesions in and by themselves do not qualify as progressive disease. However their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.	

Evaluation of Immune-related Best Overall Response (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered. irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

Index and new, measurable lesions (tumor burden)*,%	Non-index lesions	New, non-measurable lesions	Overall response
↓100	Absent	Absent	irCR
↓100	Stable	Any	irPR
↓100	Unequivocal progression	Any	irPR
↓≥50	Absent/stable	Any	irPR
↓≥50	Unequivocal progression	Any	irPR
↓<50 to <25↑	Absent/stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25	Any	Any	irPD

*Decreases assessed relative to baseline, including measurable lesions only (>5 × 5 mm).

v. Confirmatory Measurement/Duration of Response

Confirmation

To be assigned a status of irPR or irCR, changes in tumor measurements must be confirmed by repeat assessments that will be performed no less than 4 weeks after the criteria for response are first met. In the case of irSD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 6 weeks.

[redacted]

Patients with apparent immune related pseudo-progression will be allowed to continue therapy until a subsequent tumor response assessment 4-6 weeks later, to confirm whether true progression has occurred.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are met for irCR or irPR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall irCR is measured from the time measurement criteria are first met for urCR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

C. Study Duration

Treatment will continue for up to 1 year (18 cycles) or until disease progression, development of unacceptable toxicity or one of the protocol-defined reasons for treatment discontinuation occurs. Patients can continue on monotherapy with atezolizumab at the end of one year of combination therapy if evidence of clinical benefit. The enrollment will be done over a period of approximately one year.

D. Endpoints

Primary Endpoint(s)
- Grade 3 and 4 toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Secondary Endpoints
- The objective response rate (ORR) is the proportion of all subjects with confirmed irPR or irCR according to irRECIST from the start of treatment until disease progression/recurrence.
- Clinical Benefit Rate (CBR) is defined as the percentage of patients who achieve irCR, irPR and irstable disease.
- PFS is defined as the time from cycle 1, day 1 of treatment until the criteria for disease progression is met as defined by irRECIST or death as a result of any cause.
- Grade 3 and 4 irAE's

Correlative/Exploratory Endpoints

Pre-treatment and post-treatment mandatory tumor biopsies (of the same non-irradiated lesion) will be performed to measure the following endpoints:
- pre- and post-treatment tumor PD-L1 expression
- pre- and post-treatment tumor levels of infiltrating CD3+, CD8+ T-cells

[redacted]

1.4 Preliminary Data

Please see section 1.2.

1.5 Sample Size Justification

A total of 15 patients will be enrolled in the study. After treating the 6th patient with at least one dose of study drug, there will be a lead-in time of minimum 30 days to evaluate for "unacceptable toxicities" defined as a) any definitive therapy-related death; or b) any unexpected and previously unreported grade 4 toxicities definitely related to study treatment. Accrual will be halted for this period of 30 days. If such events are observed in one subject, the Data Safety Monitoring Committee will discuss and provide recommendations to the sponsor-investigator whether to modify or terminate the trial. Patients who withdraw from the study before the first day of Cycle 1 will be replaced.

The study will recruit a maximum of 15 patients and continuously monitor the SAEs. The study will be stopped if there is 85% probability that the SAE is greater than 50%. We formulate the following statistical strategy:

Denote the probability of SAE by p. When there are n patients, the possible number of events is k = 0, 1, …, n, which follows a Binomial distribution with parameters (n, p). Assume the conjugate prior of Beta distribution Beta(α=1.375, β=3.625) for p, which has the mean of 27.5% (the mean from historical similar studies and equivalent of 5 patients for the prior). The posterior distribution of p, given k, is the Beta distribution $h(p|k)$ with the parameters (k+α, n-k+β). Hence the posterior probability of {p>50%} after observing k events out of n patients is the integration of $h(p|k)$ from 0.50 to 1. Denote this probability by H(n, k). The following table display H(n, k) for n = 1, .., 15 patients and k = 0, …, n events. In the table for H(n, k), we shade the area where the posterior probability of {p>50%} is greater than 85%. If any of these cases of (n,k) occurs, the stopping rule applies and we stop the trial and conclude that with 85% certainty that the SAE is greater than 50%. From the table, we notice that we need only to begin to monitor when we have 6 patients.

H(n,k): Posterior probability that SAE rate p > 50% given (*n*, *k*) (shaded prob>85%)
k: Number of SAE

	k															
n	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	0.070	0.291														
2	0.037	0.180	0.460													
3	0.019	0.109	0.320	0.610												
4	0.010	0.064	0.214	0.465	0.730											
5	0.005	0.037	0.139	0.340	0.598	0.820										
6	0.003	0.021	0.088	0.240	0.469	0.709	0.883									
7	0.001	0.012	0.055	0.164	0.354	0.589	0.796	0.925								
8	0.001	0.007	0.033	0.109	0.259	0.471	0.692	0.861	0.954							
9	0.000	0.004	0.020	0.071	0.184	0.365	0.582	0.776	0.907	0.972						
10	0.000	0.002	0.012	0.046	0.128	0.275	0.474	0.679	0.842	0.939	0.983					
11	0.000	0.001	0.007	0.029	0.087	0.201	0.374	0.576	0.760	0.891	0.961	0.990				

[redacted]

12	0.000	0.001	0.004	0.018	0.058	0.144	0.288	0.475	0.668	0.825	0.926	0.975	0.994			
13	0.000	0.000	0.002	0.011	0.038	0.101	0.216	0.381	0.572	0.747	0.876	0.951	0.985	0.996		
14	0.000	0.000	0.001	0.007	0.024	0.069	0.158	0.299	0.477	0.659	0.811	0.913	0.968	0.991	0.998	
15	0.000	0.000	0.001	0.004	0.015	0.047	0.114	0.228	0.388	0.568	0.735	0.862	0.940	0.979	0.994	0.999

Safety Population: all patients who receive at least 1 cycle and have at least 1 post-dose safety assessment.

Efficacy Evaluable Population: Patients who receive 2 cycles of therapy and the radiation to lung lesion

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

Independent variables measured are:

- demographics
- comorbidities
- performance status
- prior cancer treatment
- cancer-related information such as tumor histology

B. Dependent Variables or Outcome Measures

The primary outcome is the incidence of grade 3 and 4 toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5

The secondary outcomes are:

- ORR: proportion of patients with a best overall response of CR or PR, divided by the number of assigned patients CBR: complete response, partial response, or stable disease.
- Median PFS: PFS is time from randomization to the first documented tumor progression, or death due to any cause whichever occurred first.

1.7 Drugs/Devices/Biologics

i. Investigational Agent (Varlilumab)

Product description: Detailed technical information regarding varlilumab can be found in the Investigator's Brochure. Varlilumab is a recombinant, fully human mAb of the IgG1κ isotype that specifically binds human CD27. Varlilumab Drug Product is formulated as a clear, colorless, sterile solution intended for single-use parenteral administration. Varlilumab is provided in vials containing a nominal volume of 10.0 ml of a buffered solution composed of 5.0 mg/mL varlilumab protein, Sodium Phosphate, Potassium Phosphate, Potassium Chloride, Sodium Chloride, and Polysorbate 80 with a pH of 7.0. Varlilumab will be labeled according to the requirements of local law and legislation. A copy of label text will be made available to study sites upon request.

Preparation: The individual dose is calculated using the actual body weight of the patient at enrollment (using weight obtained at either screen or Day X), and the dose may remain

[redacted]

constant throughout the study unless a greater than 10% change in weight is observed.The following formula should be used to calculate the volume of CDX-1127 required for each administration:

$$\frac{BodyWeight(kg) \times DesiredDose(mg/kg)}{5mg/mL} = \text{Volume of CDX-1127 (mL)}$$

Preparation of the Dilution

The varlilumab dose to be administered will be diluted to a final volume of 90 ml for infusion, according to the instructions provided by Celldex in the pharmacy manual. No dilution is necessary in cases where the drug volume is greater than 90 ml. Recommended safety measures for preparation and handling of varlilumab include laboratory coats and gloves. Varlilumab cannot be mixed with any other drug in the infusion bag or the administration set.

Administration: Varlilumab will be given once every 3 weeks for a total of 18 doses. Varlilumab will be administered as an intravenous infusion over 90 minutes. Varlilumab must be administered using an infusion pump with an approved 0.2 micron in-line filter connected to the infusion set. Varlilumab should not be administered as a bolus injection.

Storage requirements: Varlilumab drug product is shipped in insulated shippers and must be stored at 2 - 8°C (36 - 46°F) until use. A temperature log must be kept to document the refrigerator temperature. If the temperature is not maintained, Celldex should be contacted.

Stability: Varlilumab should be protected from light. However, sufficient light protection is provided by the secondary container (carton); no specific light protection is needed during preparation of the dosing solution and infusion. Varlilumab is not formulated with a preservative. Therefore, once the sterile vials are entered (i.e., once varlilumab is drawn into a syringe), the vial should be used as soon as possible (typically within 3 hours if kept at room temperature or within 6 hours if refrigerated; or in accordance with any applicable institutional guidance).

Route of administration: Intravenous

Drug Interactions: The effect of varlilumab on the absorption, metabolism, or excretion of other drugs has not been studied. As varlilumab is a human monoclonal antibody, inhibition or induction of cytochrome P450 (CYP) enzymes or other typical drug metabolizing enzymes is unexpected, and thus, interaction with other medications metabolized through these pathways is unlikely. To date, there have been no unexpected interactions observed between varlilumab and other drugs.

Drug Accountability: Varlilumab will be supplied by Celldex Therapeutics, Inc. as open-label stock. The investigational product is to be used only for this protocol and not for any other purpose, and must be kept in an appropriate, secure area (e.g., locked refrigerator/cabinet) and stored in accordance with the conditions specified in this protocol/and on the labels. The Investigator will assume responsibility for administration and dispensation of study medication. An accurate record of all study treatments received, dispensed, returned, and destroyed must be maintained. Drug supplies will be inventoried and accounted for throughout the study, and accountability records must be available for

[redacted]

inspection at any time and provided to Celldex Therapeutics, Inc. upon the completion of the study. Upon receipt of any investigational product, an inventory must be conducted to confirm the quantity and condition of material received, and verification of receipt must be completed and faxed to the appropriate drug delivery personnel. Resupply of study medication may be requested in accordance with instructions provided by Celldex Therapeutics, Inc.

Drug Destruction/Disposal: Empty and partially empty containers of study drug will be disposed of in accordance with institutional policies and procedures. Unused containers of study drug will be returned to the study sponsor following completion of the study.

ii. Commercial Agent (Atezolizumab)

Product description: Atezolizumab is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids). Atezolizumab targets human PD-L1 and inhibits its interaction with its receptor PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells. Atezolizumab is provided by Genentech/F.Hoffmann-La Roche LTD and distributed by the Pharmaceutical Management Branch, CTEP, NCI. The agent is supplied in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. Atezolizumab is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, at a pH of 5.8. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume.

Preparation: The prescribed dose of atezolizumab should be diluted in 250 mL 0.9% NaCl and infused through a 0.2 micrometer in-line filter. The IV bag may be constructed of PVC or PO; the IV infusion line may be constructed of PVC or PE; and the 0.2 micrometer in-line filter may be constructed of PES. The prepared solution may be stored at room temperature for no more than 6 hours from the time of preparation including time for administration of the infusion, or at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from time of preparation..

Administration: Atezolizumab is administered as an intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer atezolizumab as an intravenous push or bolus. No premedication is indicated for administration of Cycle 1 of atezolizumab. Patients who experience an infusion related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions.

Storage Requirements: 2°C–8°C (36°F–46°F). Vial contents should not be frozen or shaken and should be protected from direct sunlight. If a storage temperature excursion is identified, promptly return atezolizumab to 2°C-8°C (36°F-46°F) and quarantine the supplies.

[redacted]

Stability: No preservative is used in atezolizumab; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in the vial.

Route of administration: intravenous

Drug Interactions: Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

1.8 Specimen Collection

Correlative sciences will include mandatory pre-treatment and post-treatment (after cycle 2) biopsies in all patients to measure PD-L1 expression as well as infiltration of CD3+, CD4+, CD8+ T-cells by immunohistochemistry (IHC). The goal is to measure changes in these biomarkers as a predictor of response to combined checkpoint blockade in combination with radiation as well as to evaluate the abscopal effect of the radiation treatment. The biopsies should be taken from the lesion that will not be irradiated. Tumor core biopsies will be fixed in 10% neutral buffered formalin and paraffin embedded according to standard protocols.

(a) PD-L1 expression: PD-L1 expression has demonstrated variable utility as a predictive marker in the setting of immune checkpoint blockade and may be impacted by local radiotherapy. We hypothesize that there will be a correlation between PD-L1 expression levels and response and that radiation may alter the PD-L1 expression. Formalin fixed-paraffin embedded (FFPE) tumor slides will be prepared and H&E stained. PD-L1 staining will be performed on tumor and stromal cells using IHC. Following chromogenic IHC for PD-L1 we will score the percentage of cells staining positively for PD-L1 incrementally, as 0%, 1%, 5%, 10% and thereafter in 10% increments (20-100%) by visual estimation. Scoring will be performed for the percentage of malignant tumor cells and for the percentage of non-malignant inflammatory cell compartment that express PD-L1, separately.

(b) CD3+/CD4+ T-cell infiltration: We predict that increased T-cell infiltration into the tumor microenvironment will predict for response to therapy. We additionally hypothesize that radiation will increase the infiltration of CD3+/CD8+ and CD3+/CD4+ T-cells into the tumor microenvironment. IHC staining will also be performed on FFPE tumor slices for CD3, CD4+, and CD8 to identify tumor infiltrating lymphocytes at the tumor stroma interface.

(c) PBMC banking: Peripheral blood mononuclear cell (PBMCs) isolated from peripheral whole blood will be banked in the CINJ biorepository for future research (Cycle 1 day 1 and cycle 3 day 1).

Collection and Handling Procedures

a) Collection of tumor tissue

- Fresh tumor tissue will be collected by biopsy and fixed by 10% neutral buffered formalin overnight, dehydrated and paraffin embedded. Four-micrometer-thick sections will be cut. The paraffin blocks and unstained slides will be stored at room temperature.

[redacted]

- [redacted]

b) Collection of peripheral blood

- Peripheral blood will be collected by venipuncture and processed to separate PBMC. The PBMC sample will be cryopreserved and banked at the RCINJ biorepository.

Please refer to the Correlative lab manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

1.9 Data Collection

A. Primary Data Collection

i. Case Report Forms

[redacted]

ii. Data Submission Timeline and Forms

Completion of eCRFs will occur in accordance with NCI guidelines. Baseline (pre-study) eCRFs (e.g., enrollment, medical history, concomitant medications, disease assessment, etc.) will be completed no later than 14 days after the start of treatment. Treatment eCRFs (e.g., drug administration, adverse events, chemistries, etc.) will be completed no later than 14 days following each cycle of treatment. Off-treatment information (e.g., follow-up, best response, etc.) will be completed no later than 14 days after the end of protocol treatment.

iii. Research Charts

A research chart (i.e., shadow chart) is maintained at OHRS for each patient enrolled. Copies of significant study source documents will be maintained in the research chart. Examples of source document copies that will be maintained in the research chart include: signed informed consent form, documents that verify eligibility and treatment and documents that verify Grade 3-4 adverse events and response. This information will be [redacted]

iv. Reports

Publications and annual reports for submission to the IRB and FDA will be written by the [redacted].

[redacted]

B. Secondary Data Collection
N/A

[redacted]

1.10 Timetable/Schedule of Events

	Screen	Cycle = 21 days[2]						Cycle = 21 days[2]		Safety follow up	Long-term Follow up
		Cycle 1			Cycles 2			Cycle 3+			
	-28 days[1]	D1	D2	D8	D1	D2	D8	D1	D2	30 days post Tx	Q 3 months (±14 days)
REQUIRED ASSESSMENTS											
Informed Consent	X										
Medical history, smoking history, trial awareness	X										
Diagnosis and Staging[3]	X										
AEs (esp. constipation) & Concomitant Medications[4]	X	X			X			X		+30	
PE, VS, ECOG PS, weight, height (screen only)[5]	X	X			X			X		X	
LABORATORY ASSESSMENTS											
Complete Blood Count, Chemistry[6]	X	X			X			X		X	
LDH, Lipase, Amylase[6]	X	X			X			X		X	
PT, PTT, INR	X										
TSH, T3/T4[7]	X	X			X			X		X	
Urinalysis	X										
Pregnancy test WOCBP[8]	-14 d	X			X			X			
DISEASE ASSESSMENT											
Disease Imaging[9]	X							Q3 cycles			
TREATMENT EXPOSURE											
Varlilumab		X			X			X			
Atezolizumab			X			X			X		
Radiation				X ± 2 d							
CORRELATIVE STUDIES (SPECIMEN COLLECTION)											
Pre-treatment tumor biopsy[10]	-14d										
Post-treatment tumor biopsy[10]							X				
Blood for PBMC		X						X			
FOLLOW-UP											
Survival status, subsequent therapy											X

Key to Footnotes

1. Screening (baseline) labs performed within 7 days of C1D1 treatment do not need to be repeated.

[redacted]

2. A window of ±3 days will be applied to all treatment visits; a window of ±7 days will apply for all safety follow-up visits and tumor imaging.
3. Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging
4. AEs and Con meds: Patients should specifically be asked about signs of constipation and treatment provided when indicated. A safety follow-up visit will occur 30 days (±7 days) after the last dose of treatment. Patients with drug related AEs of ≥grade 2 observed at the 30-day safety assessment, should be followed-up monthly during clinical visits until the AE has resolved to grade 1, the event is believed to be chronic, or patient receives other anti-cancer therapy, whichever occurs first. Concomitant medications are to be recorded up to the 30-day Safety Visit. Concomitant medications should only be recorded after the safety visit if it relates to an unresolved AE.
5. Physical Exam (PE), Vital Signs (VS), ECOG Performance Status (PS), weight, and height (screening only). Vital signs include: temperature, blood pressure, heart rate, and respiratory rate. Thereafter, vital signs are collected immediately before and after each infusion.
6. **CBC to include**: hemoglobin, hematocrit, red blood cell and white blood cell (with differential) counts with differential and platelets. CBC may be monitored on a more frequent basis, in accordance with institutional guidelines, should a patient have grade 4 hematologic AEs. **Chemistry to include**: sodium, potassium, bicarbonate, chloride, bicarbonate, calcium, magnesium, glucose, urea Nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total protein, albumin, lipase, amylase, and total bilirubin (plus direct bilirubin if total bilirubin is elevated).
7. Thyroid stimulating hormone (TSH), and triiodothyronine (T3) and/or thyroxine (T4); free or total T3/T4 will be performed as per local standards.
8. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test within 14 days of treatment. Positive urine tests should be confirmed with a serum test.
9. Perform CT scan of the abdomen/pelvis, CT of the chest, or additional staging as required for each patient. A bone scan will only be performed in patients with known bone metastasis at study entry to monitor the status of metastatic disease in bone. Target and non-target lesion response and overall disease response are to be assessed (irRECIST) every 3 cycles (post C3, C6, etc.). End of treatment tumor assessment will be done at the discretion of the treating physician.
10. Mandatory submission of tumor biopsy for correlative endpoints. Biopsy to be done post-treatment should be performed between C2D8 and C2D15.

[redacted]

2.0 Project Management

2.1 Research Staff and Qualifications

All study personnel involved in the project have been properly trained and have experience in conducting clinical trials as well as handling confidential data.

2.2 Research Staff Training

All study personnel will attend the site initiation visit for training about study-specific protocol.

2.3 Resources Available

[redacted] office will help to coordinate IRB submission at Rutgers, the State University of New Jersey.

2.4 Research Sites

[redacted]

3.0 Multi-Center Research

N/A

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

A. Method to Identify Potential Subjects

Potential subjects will be identified by the study investigators at the lung cancer clinic at [redacted].

B. Recruitment Details

All recruitment will be done through the lung cancer clinic at Rutgers Cancer Institute.

C. Subject Screening

Inclusion Criteria

The patients must satisfy all of the following inclusion/exclusion criteria in order to be eligible for the study:

1. Must have signed and dated written informed consent form in accordance with regulatory and institutional guidelines.

2. Males and females aged >18 years at time of consent.

3. Histological or cytological evidence of advanced, unresectable NSCLC.

4. Patients must be PD-1/PD-L1 experienced with disease progression documented either on therapy with anti-PD-1/PD-L1 or within 12 weeks of the last dose. Treatment should be initiated at least 4 weeks since last dose of PD-1/PD-L1 targeted therapy.

[redacted]

5. Patients must have progressed on at least one line of prior platinum-based chemotherapy in the metastatic setting. Subjects with unresectable stage III NSCLC who received platinum-based chemotherapy as part of chemoradiation or consolidation chemotherapy after chemoradiation are eligible if they progress within 6 months of last dose of chemotherapy. Treatment should be initiated at least 4 weeks since last dose of systemic therapy.

6. Subjects with an actionable molecular alteration (such as EGFR mutation, ALK or ROS-1 rearrangement, BRAF V600E mutation) are eligible only after failing standard-of-care targeted therapy with TKI. Patients with a EGFR T790M resistant mutation must have failed a 3rd generation TKI such as osimertinib.

7. Must not have received any prior therapy with immune regulatory molecule (such as targeting OX-40, IDO-1, LAG-3) or anti-CD27 monoclonal antibody (including varlilumab)

8. Must have at least one lesion that has not previously been irradiated (and is not within a previously radiated field) and for which palliative radiation is potentially indicated. The lesion to be irradiated must be in the lung. Patient must have at least one additional measurable lesion (other than the lesion being radiated) as per irRECIST criteria. Patient must agree to undergo a mandatory biopsy of the non-irradiated lesion pre-treatment and post-treatment (after cycle 2). Pre-treatment tissue obtained by biopsy or resection performed according to standard of care may be utilized, provided tissue was obtained within 8 weeks of study entry, and subsequent to the last systemic anticancer therapy received.

9. Patients should have fewer than 10 metastatic sites and expected survival of more than 3 months

10. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

11. Treatment to be initiated at least 2 weeks since last dose of prior systemic anticancer therapy (chemotherapy, radiation, and/or surgery).

12. Recovery to grade 1 of any clinically significant toxicity (excluding alopecia, grade 2 fatigue, vitiligo, endocrinopathies on stable replacement therapy, grade 2 neuropathy from chemotherapy and grade 2 hearing loss from platinum chemotherapy) prior to initiation of study drugs.

13. Female patients of childbearing potential have a negative pregnancy test at baseline. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression.

   i. Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within 14 days of treatment inititation
   ii. Sexually active women of childbearing potential enrolled in the study must agree to use 2 forms of accepted methods of contraception during the course of the

[redacted]

study and for 12 weeks after their last dose of study drug. Effective birth control includes (a) intrauterine device plus 1 barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner.

iii. For male patients who are sexually active and who are partners of premenopausal women: agreement to use 2 forms of contraception as in criterion 10(ii) above during the treatment period and for 12 weeks after the last dose of study drug.

14. Adequate laboratory values.
    i. Absolute neutrophil count ≥1,500/μL
    ii. Platelet count ≥100,000/μL
    iii. Hemoglobin ≥9.0 g/dL
    iv. Total bilirubin ≤2 x upper limit of normal (ULN) or ≤3 x ULN for subjects with Gilbert's disease or liver metastases
    v. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN (≤5 x ULN if evidence of hepatic involvement by malignant disease)
    vi. Creatinine ≤ 1.5 x ULN or estimated glomerular filtration rate (eGFR) ≥40 mL/min/1.73m^2

15. Measurable disease according to irRECIST (Section 8) obtained by imaging within 28 days prior to treatment initiation

Exclusion Criteria

1. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 23 weeks (female) or 31 weeks (male) after the last dose of study drug.

2. Treatment with any investigational agent within 28 days prior to registration for protocol therapy.

3. History of psychiatric illness or social situations that would limit compliance with study requirements. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

4. Known active, untreated central nervous system (CNS) metastases and/or carcinomatous meningitis except for patients with ≤3 small (< 0.6 cm) asymptomatic brain lesions where treatment is not indicated. Patients with neurological symptoms must undergo a head computed tomography (CT) scan or brain magnetic resonance imaging (MRI) to exclude brain metastasis. Patients whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images obtained after treatment to the brain metastases at least 4 weeks apart and show no evidence of intracranial progression)

5. Known history of human immunodeficiency virus (HIV) or active hepatitis B (by surface antigen expression or polymerase chain reaction [PCR]) or active hepatitis C (by PCR) infection.

6. Diagnosis of immunodeficiency or is receiving systemic steroid therapy (>10 mg daily prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to study registration.

7. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs) or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Vitiligo, alopecia, hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment, celiac disease controlled by diet alone or conditions not expected to recur in the absence of an external trigger are permitted.

8. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III–IV within 6 months prior to their first dose of study drugs.

9. Prior malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) unless a complete remission was achieved at least 1 year prior to study entry.

10. Any active grade 3 or higher viral, bacterial, or fungal infection within 2 weeks of the first dose of the study drugs. Routine antimicrobial prophylaxis is permitted.

11. Active diverticulitis

12. History of idiopathic pulmonary fibrosis, pneumonitis (including drug-induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

4.2 Secondary Subjects

N/A

4.3 Number of Subjects

A. Total Number of Subjects

We plan to enroll 15 patients on the study. Approximately 25-30 patients will be screened for enrollment.

B. Total Number of Subjects If Multicenter Study

N/A

C. Feasibility

The patients will be enrolled over a period of one year. More than 50 patients meeting the eligibility criteria are treated at the Rutgers Cancer Institute every year.

[redacted]

4.4 Consent Procedures

A. Consent Process

- **Location of Consent Process**
  [redacted]
- **Ongoing Consent**
  N/A
- **Individual Roles for Researchers Involved in Consent**
  Consent will be obtained by the study personnel (the treating physician and the research nurse)
- **Consent Discussion Duration**
  30-60 minutes
- **Coercion or Undue Influence**
  Both the treating physician and research nurse will explain to the subject that participation in study is completely voluntary and subject can withdraw consent at any time. The informed consent document may not include any exculpatory language through which the subject or representative is made to waive any of the subject's legal rights or releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.
- **Subject Understanding**
  Subject will be provided a copy of the signed consent and encouraged to ask questions about the consent. The information given to the patient, or the representative, shall be in a language understandable to the subject or representative.

B. Waiver or Alteration of Consent Process

N/A

C. Documentation of Consent

- **Documenting Consent**
  The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

- **Waiver of Documentation Of Consent (i.e., will not obtain subject's signature)**
  N/A

4.5 Special Consent/Populations

A. Minors-Subjects Who Are Not Yet Adults

N/A

B. Wards of the State

N/A

C. Non-English-Speaking Subjects

- **Process for Non-English-Speaking Subjects**

[redacted]

If subjects who do not speak English will be enrolled, a phone translator will be used to discuss the study as well as the consent in detail. A translator will also be used at each study visit during the physical examination and adverse event assessment.

- **Short Form Consent for Non-English Speakers**
  A consent short form for non-English speakers will be used.

D. Adults Unable to Consent / Cognitively Impaired Adults (for interventional studies)
N/A

4.6 Economic Burden and/or Compensation for Subjects

A. Expenses
Costs for all research related testing such as required biopsy on the study will be covered by the study.

B. Compensation/Incentives
No compensation for participating in the study will be provided to the study subjects.

C. Compensation Documentation
N/A

4.7 Risks of Harm/Potential for Benefits to Subjects

A. Description of Risks of Harm to Subjects

- **Reasonably Foreseeable Risks of Harm**
  The study drug may have side effects that may be expected or unexpected. The expected side effects are discussed in the consent. All adverse events will be reported timely according to institutional guidelines.
- **Risk of Harm from an Intervention on a Subject with an Existing Condition**
  N/A
- **Other Foreseeable Risks of Harm**
  There is a slight risk of loss of confidentiality of subject information.
- **Observation and Sensitive Information**
  N/A

B. Procedures which Risk Harm to Embryo, Fetus, and/or Pregnant Subjects
N/A

C. Risks of Harm to Non-Subjects
N/A

D. Assessment of Social Behavior Considerations
N/A

E. Minimizing Risks of Harm

- **Certificate of Confidentiality**
  N/A
- **Provisions to Protect the Privacy Interests of Subjects**
  All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected

[redacted]

electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel. Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, Celldex, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. If the results of the study are published, the subjects' identity will remain confidential.

F. Potential Benefits to Subjects

Subjects may or may not derive clinical benefit from the study therapy depending on the response of their tumor to the study treatment.

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)

Personal identifiers will not be used for reporting results or shared with anyone other than the study personnel.

5.2 Family Educational Rights and Privacy Act (FERPA)

N/A

5.3 NJ Access to Medical Research Act (Surrogate Consent)

N/A

5.4 General Data Protection Regulation (GDPR)

N/A

5.5 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

N/A

6.0 Data Management Plan

6.1 Data Analysis

Objective Response Rate (ORR): ORR to protocol treatment will be evaluated by irRECIST, and the best overall response will be classified as complete response (CR), partial response (PR), stable disease, progressive disease (PD), and not evaluable (NE). ORR is defined as the proportion of patients with a best overall response of CR or PR, divided by the number of assigned patients. CT scans at baseline and during the study will be reviewed by study investigators to determine objective response, date of response and progression.

Progression-free Survival (PFS)

PFS is time from randomization to the first documented tumor progression, or death due to any cause whichever occurred first. PFS time of any living patient with no documented progression, or any patient starting other cytotoxic and/or cytostatic therapies, will be

[redacted]

censored at the date of last evaluable disease assessment on-study. PFS time of patients with no evaluable disease assessment on-study will be censored at randomization. The log-rank test will be used to analyze PFS for comparison of treatment effects, i.e., the only covariate that will be used is the treatment arm. Distributions of PFS times will be estimated using the Kaplan- Meier product-limit method. The median PFS times with two-sided 95% CIs will be estimated for each treatment group. For the definition of disease progression, refer to irRECIST version.

6.2 Data Security

All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel. Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, Celldex, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

A research chart (i.e., shadow chart) is maintained at OHRS for each patient enrolled. Copies of significant study source documents will be maintained in the research chart. Examples of source document copies that will be maintained in the research chart include: signed informed consent form, documents that verify eligibility and treatment and documents that verify Grade 3-4 adverse events and response. This information will be updated on a prospective basis and will be confidentially maintained at the Cancer Institute of New Jersey, OHRS on the 5th floor in a locked cabinet. Only the key personnel delegated on the delegation of authority log are permitted to access these charts. All users of this system will complete user training, as required or appropriate per regulations.

6.3 Data and Safety Monitoring

A. Data/Safety Monitoring Plan

Monitoring of this study will occur in accordance with the Cancer Institute of New Jersey's NCI approved Data and Safety Monitoring Plan (DSMP). The DSMP is enacted in part by the Human Research Oversight Committee (HROC). HROC is an established group within the Office of Human Research Services, and it is responsible for oversight of all therapeutic and non-therapeutic clinical trials conducted by RCINJ and it meets regularly to review deviations. HROC will serve as the Data Safety Monitoring Board (DSMB) for this clinical trial. All unexpected and serious adverse events will be reported to the DSMB (as well as each institutional IRB and study sponsor) according to the reporting requirements and per the Rutgers University DSMP. An "initiation audit" will be conducted at the [redacted] Subsequent audits will occur on an annual basis prior to annual IRB continuing review, if the findings from the initiation audit were satisfactory. More frequent audits of patient data and study conduct will occur if necessary. Prior audit findings and/or situations that may arise during the course of the study will determine the need for more frequent auditing. All audit findings will be

[redacted]

discussed with the principal investigator and reported to the [redacted] Review Board.

B. Data/Safety Monitoring Board Details
HROC will serve as the Data Safety Monitoring Board (DSMB) for this clinical trial.

6.4 Reporting Results

A. Individual Subjects' Results
Study results from research tests will not be shared with the study subjects.

B. Aggregate Results
Aggregate research results will not be shared with study subjects.

C. Professional Reporting
The policies and procedures of [redacted] legal department (see: Investigator's Handbook) will govern publication of the trial. It is expected that the results of this trial will be submitted for publication in a timely manner following the conclusion. [redacted] any abstract or manuscript.

D. Clinical Trials Registration, Results Reporting and Consent Posting
The trial will be registered on www.clinicaltrials.gov. A copy of the IRB-approved informed consent document and written justification for any changes made to the informed consent for this protocol must be on file at the [redacted] patients are enrolled.

6.5 Secondary Use of the Data
Samples will be stored by the biorepository and data from these samples may be used for future research.

7.0 Research Repositories – Specimens and/or Data
All Samples for future research will be banked at the [redacted] Biospecimen Repository. The biorepository supports transdisciplinary and translational research through cost-effective, quality controlled biospecimen procurement and processing and cancer focused clinical trial support. The Biorepository follows best practices as dictated by the College of American Pathologists (CAP) guidelines.

8.0 Approvals/Authorizations

Approval will be obtained from Scientific Review Board (SRB) at [redacted] and [redacted]

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Appendix A
Performance Status Criteria

ECOG Performance Status Scale	
Grade	Descriptions

[redacted]

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.