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FLT3 Ligand Immunotherapy and Stereotactic Radiotherapy for Advanced Non-small Cell Lung Cancer

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FLT3 Ligand Immunotherapy and Stereotactic Radiotherapy for Advanced Solid Tumors

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Abbreviations

AE	Adverse Event
AJCC	American Joint Committee on Cancer
BED	Biologically effective dose
CRT	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DLT	Dose-limiting toxicity
DSMB	Data safety and monitoring board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FLT3	Fms-like tyrosine kinase 3
HIPAA	Health Insurance Portability and Accountability Act
irRC	Immune-related response criteria
ICOS	Inducible costimulator
IRB	Institutional review board
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
PET	Positron emission tomography
PFS	Progression-free survival
PHI	Protected health information
PI	Principal investigator
PTV	Planning target volume
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SBRT	Stereotactic body radiotherapy
WHO	World Health Organization

Contents

1.0 OBJECTIVES

1.1 Primary Objective

- To explore the efficacy of combining stereotactic body radiotherapy (SBRT) with FLT3 ligand immunotherapy for advanced non-small cell lung cancer (NSCLC) and for other advanced solid tumors after treatment with immune checkpoint inhibitors targeting the PD-1/PD-L1 axis.

1.2 Secondary Objectives

- To establish the feasibility and safety of combining SBRT with FLT3 ligand immunotherapy for advanced NSCLC and for other advanced solid tumors after treatment with immune checkpoint inhibitors targeting the PD-1/PD-L1 axis.
- To quantify and evaluate potential surrogate outcomes for clinical efficacy of this treatment approach, including radiographic responses, immunologic responses, and circulating tumor cell levels.

2.0 BACKGROUND

2.1 Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality in the United States and worldwide, causing nearly one million deaths each year.[1] For the approximately 40% of NSCLC patients who present with stage IV disease and other patients who progress after presenting with localized disease, standard first-line therapy typically consists of combination chemotherapy, usually with a platinum doublet. Median progression-free survival (PFS) for such patients is on the order of 6 months.[2, 3] Second-line systemic therapy, when it can be delivered, yields even poorer outcomes, with median PFS durations of approximately 3 months.[4, 5] While targeted therapy clearly improves outcomes for the minority of patients with identifiable driver mutations, novel strategies to improve outcomes for the remainder of advanced NSCLC patients are sorely needed.

Cancer immunotherapy, which refers to treatment strategies that induce the patient's own immune system to attack tumor cells, is an emerging tool in the oncologist's armamentarium. Sipuleucel-T, a therapeutic vaccine for prostate cancer, gained FDA approved for the treatment of metastatic, hormone refractory prostate cancer in 2010. Ipilimumab, a monoclonal antibody to CTLA-4 that promotes cancer cell killing by cytotoxic T lymphocytes, was approved for the treatment of advanced melanoma in 2011. Pembrolizumab and nivolumab, which both blocks the protein programmed cell death 1 (PD-1) from binding its ligands PD-L1 and PD-L2 to permit cytotoxic T cell activation, were both approved by the FDA for the treatment of advanced melanoma in 2014. Although several groups are exploring methods to utilize the immune system to fight lung cancer, the use of immunotherapy for NSCLC remains largely investigational at this point.[6-8] Of note, nivolumab gained approval for the second-line treatment of advanced squamous NSCLC in March 2015 after demonstrating an overall survival benefit (median 9 months versus 6 months) when compared to docetaxel in a randomized multicenter trial.

Our group and others have demonstrated that ionizing radiotherapy (RT) has the potential to enhance the effectiveness of cancer immunotherapy. RT may serve to amplify the tumor-specific peptide repertoire and upregulate cell surface expression of MHC determinants and costimulatory molecules. [9, 10] RT may also evoke changes in the tumor microenvironment that facilitate the host immune response.[11, 12] We believe that RT is a key to unlocking the potential of immunotherapy as an effective approach in the treatment of NSCLC.

2.2 FLT3 Ligand

Fms-like tyrosine kinase 3 (FLT3) ligand is a potent hematopoietic growth factor that mobilizes stem cells and greatly increases the number of circulating dendritic cells (DCs) in blood and organs.[13] FLT3 ligand has been shown to evoke immune responses and cause tumor regression in animal models of fibrosarcoma, breast cancer, prostate cancer, and lung adenocarcinoma.[14-17]

Amgen's recombinant human FLT3L, AMG949, has been studied in numerous industry and investigator-initiated clinical trials. Collectively, approximately 150 healthy volunteers and 380 cancer patients were enrolled on those trials. Adverse events requiring cessation of treatment were rare (<5%). However, FLT3L did not demonstrate definitive anti-tumor activity in patients with ovarian cancer, breast cancer, or non-Hodgkin's lymphoma. This may have been related to the immobilization of immature DCs by FLT3 or limited DC access to tumor antigens.

Celldex Pharmaceuticals has developed a new FLT3L (CDX-301). CDX-301 is produced using a serum-free manufacturing process, and it is identical in amino acid sequence to AMG949. A phase I study using 30 healthy volunteers has been completed, and no major toxicities were observed. (See Section 7.2 for further details) DC expansion has been shown to peaks approximately two weeks after initiation of FLT3 ligand therapy (Figure 1). Based on promising data from our laboratory demonstrating synergy between ablative local RT and FLT3 ligand immunotherapy in murine NSCLC models (summarized below), our first clinical trials in this arena will test the combination of CDX-301 and SBRT for advanced NSCLC.

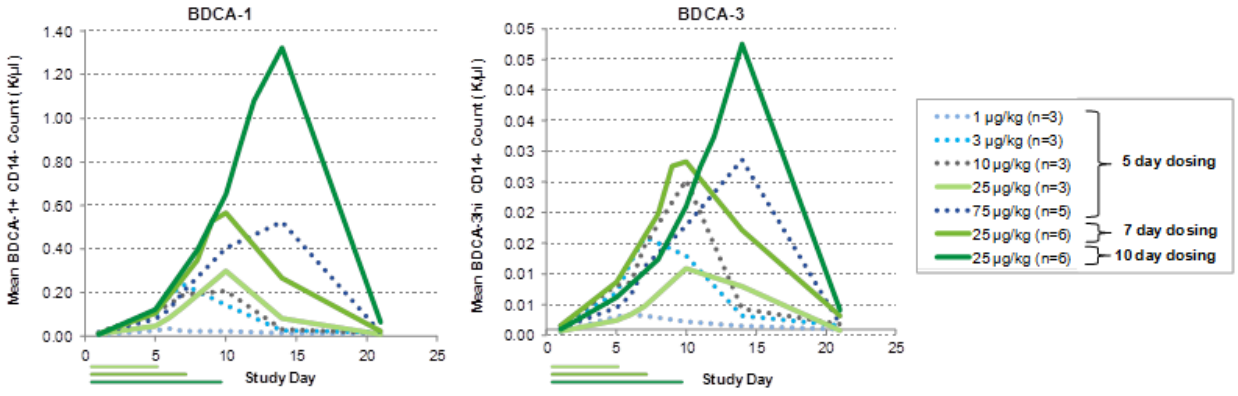

Figure 1 – Expansion of two dendritic cell populations in healthy volunteers treated with CDX-301 peaks at 10-14 days after treatment initiation. (source: Celldex Therapeutics)

2.3 Stereotactic Body Radiotherapy

In recent years, hypofractionated stereotactic body radiotherapy (SBRT) has emerged as an effective treatment option for numerous malignancies. SBRT uses the principles of intracranial stereotactic radiosurgery (large daily doses delivered precisely to a small target volume over a short treatment course) to treat extracranial disease sites. For stage I NSCLC, SBRT has demonstrated excellent local control rates. [18-20] Increased utilization of SBRT has been linked to improvements in overall survival. [21] Serious adverse events following SBRT for NSCLC are very rare[22], except when aggressive SBRT regimens are used to treat central lesions. [23] Importantly, the highly-conformal manner in which SBRT is delivered allows safe treatment of lung tumors in patients with poor pulmonary function.[24] SBRT has also been shown to be safe in extrathoracic disease sites such as the liver and spine.[25, 26]

A wide variety of dosing and fractionation schedules has been used to deliver lung SBRT for NSCLC.[19, 20] Although there is evidence of a dose-response relationship when relatively low-dose regimens (BED < 100 Gy) are used,[19, 20] more intense regimens have yielded consistently excellent results and are considered to be ablative. These include 10-12.5 Gy x 4-5 fractions, 18-20 Gy x 3 fractions, and 25-34 Gy in a single fraction. A randomized RTOG study demonstrated that 34 Gy x 1 fraction is a safe and effective regimen for peripheral tumors.[27] This single fraction dose will be the new standard for the treatment of peripheral lesions in upcoming RTOG SBRT trials. For central lesions, less aggressive regimens such as 10-12 Gy x 5 are recommended. The National Comprehensive Cancer Network (NCCN) now provides guidelines for the selection of an SBRT schedule as well as dosimetric constraints that should be met for each organ at risk and course length:

Table 2. Commonly Used Doses for SABR

Total Dose	# Fractions	Example Indications
25-34 Gy	1	Peripheral, small (<2 cm) tumors, esp. >1 cm from chest wall
45-60 Gy	3	Peripheral tumors and >1 cm from chest wall
48-50 Gy	4	Central or peripheral tumors <4-5 cm, especially <1 cm from chest wall
50-55 Gy	5	Central or peripheral tumors, especially <1 cm from chest wall
60-70 Gy	8-10	Central tumors

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal Cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Brachial Plexus	17.5 Gy	21 Gy (7 Gy/fx)	27.2 Gy (6.8 Gy/fx)	30 Gy (6 Gy/fx)
Heart/ Pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	35 Gy (7 Gy/fx)
Great Vessels	37 Gy	39 Gy (13 Gy/fx)	49 Gy (12.25 Gy/fx)	55 Gy (11 Gy/fx)
Trachea & Proximal Bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Rib	30 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Skin	26 Gy	30 Gy (10 Gy/fx)	36 Gy (9 Gy/fx)	40 Gy (8 Gy/fx)
Stomach	12.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	35 Gy (7 Gy/fx)

*Based on constraints used in recent and ongoing RTOG SABR trials (RTOG 0618, 0813, & 0915).

SBRT is now often used to treat primary tumors and metastases in sites outside the lung, both for NSCLC and for other malignancies. Techniques to safely deliver

SBRT to the skeleton, abdomen, pelvis, and extremities have been established[28]. SBRT for patients with limited metastatic disease may become a standard approach based on recently completed[29, 30] and ongoing randomized trials.

2.4 FLT3 Ligand and Radiotherapy

Published laboratory results from our department demonstrate that pretreatment of a single lesion with high-dose RT increases the systemic efficacy of FLT3 ligand in a murine model of lung adenocarcinoma. [14] Mice with established, 3-week-old Lewis lung tumors were given a single dose of localized primary footpad tumor RT (60 Gy), with or without FLT3 ligand (administered daily for 10 days after RT). The combination of RT and FLT3 ligand significantly increased survival compared to either treatment alone and compared to controls (Figure 2). Examination of animal lung tissue revealed that the lungs of mice treated with RT and FLT3 ligand showed no carcinoma cells but had infiltrates of neutrophils, lymphocytes, and mononuclear leukocytes. Lungs from other cohorts demonstrated massive tumor cell infiltration. (Figure 3)

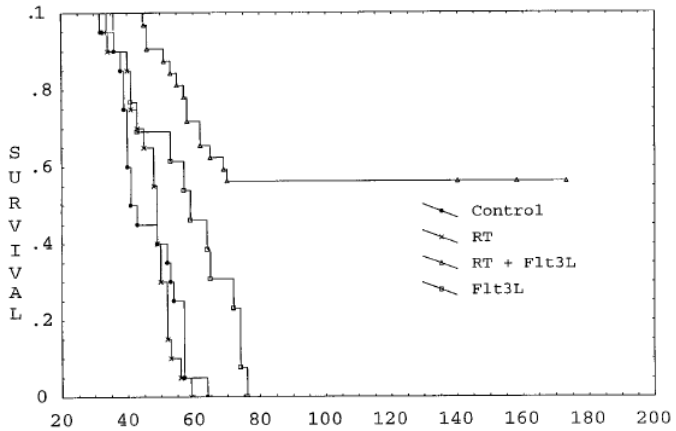

Figure 2 – Local RT acts synergistically with FLT3 ligand in a murine NSCLC model to improve overall survival.

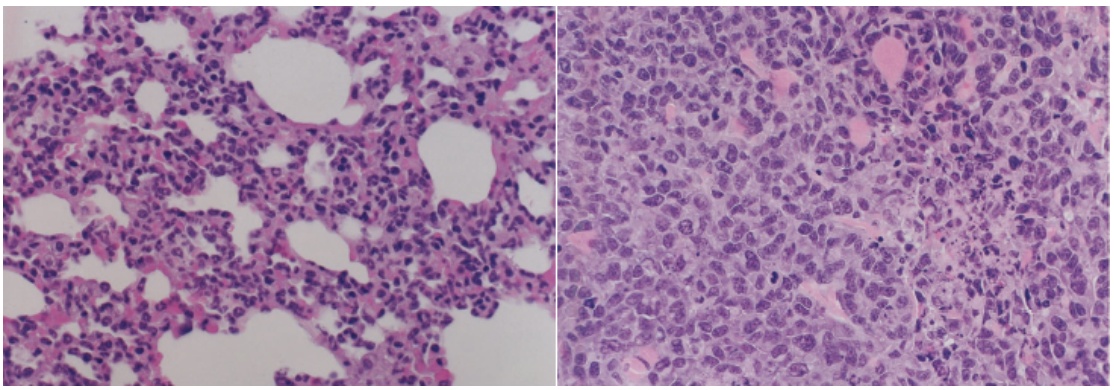

Figure 3 – Murine lungs following treatment with RT plus FLT3 ligand demonstrate leukocytic infiltrates without tumor cells (left), compared to tumor-laden lungs of mice from other cohorts (right).

We recently obtained similar results in a newer, unpublished experiment using the Celldex FLT3 ligand CDX-301. (Figures 4 and 5) Again, in a murine adenocarcinoma model, combination therapy with RT and FLT3 ligand improved overall survival compared to either treatment alone. In this case, the dose of 60 Gy was divided into three fractions to mimic an SBRT schedule commonly employed in NSCLC patients. Poorer outcomes were seen in the combination therapy arm compared to that in the prior study, likely because surviving mice were re-challenged with tumor cells eight weeks after completion of immunotherapy. We hypothesize that additional cycles of FLT3 ligand, possibly in combination with repeat irradiation of viable lesions, might prolong treatment efficacy.

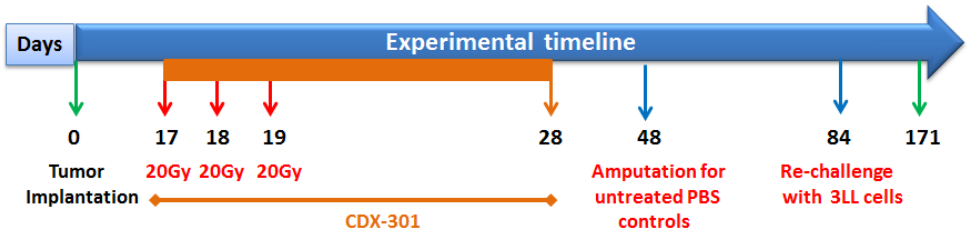

Figure 4 – Design for murine study of FLT3 ligand (CDX-301) and hypofractionated RT.

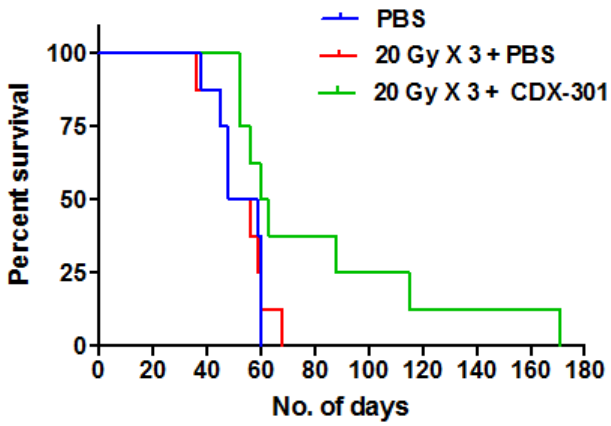

Figure 5 – Murine survival curves. Log-rank testing of the combination therapy arm against each monotherapy arm yields p-values of 0.04.

The data summarized above indicate that the combination of SBRT to a pulmonary or metastatic NSCLC lesion and CDX-301 is likely to be well-tolerated and may have significant clinical activity in advanced NSCLC patients. The study described herein will be the first clinical trial to test this approach.

2.5 FLT3 Ligand and Stereotactic Radiotherapy – Early Clinical Experience

From October 2016 to October 2017, we enrolled 10 subjects with advanced NSCLC on this clinical trial, which was initially only available to patients with advanced NSCLC. One subject suffered clinical deterioration and passed away before initiating study therapy. The remaining nine subjects were treated with stereotactic radiotherapy

directed at a thoracic lesion as well as FLT3 ligand. One of these subjects had been treated with one prior line of therapy for advanced NSCLC, four received two prior lines of therapy, and four received three prior lines of therapy. Seven out of nine subjects were previously treated with an immune checkpoint inhibitor targeting the PD-1/PD-L1 axis (atezolizumab, durvalumab, nivolumab, or pembrolizumab).

No dose-limiting toxicities have been observed. One subject developed pneumonitis involving the lung that was not treated with radiotherapy outside the dose-limiting toxicity window. After multidisciplinary discussion, it was deemed that this was likely a delayed side effect of atezolizumab, which the patient received prior to study enrollment. The patient was treated with a corticosteroid taper over several weeks and supplemental oxygen as needed. His respiratory status returned to baseline after approximately one month. No other serious adverse events have been observed.

Early efficacy results have been encouraging, particularly in subjects who were previously treated with immune checkpoint inhibitors. Among all subjects, the actuarial rate of progression-free survival at 4 months (based on CT, primary endpoint) is 56%, which is consistent with the hypothesized rate of 40.5% or higher. Among subjects who were previously treated with immune checkpoint therapy, this rate is 71%. Several patients have demonstrated an impressive response to therapy, even when SBRT target lesions are excluded from response assessment. Using PERCIST criteria, a partial response (reduction in total glycolytic activity of at least 40%) has been observed in 5 out of 9 subjects. All 5 responders were previously treated with immune checkpoint therapy. With a median follow-up duration of 10 months for surviving patients, the median overall survival time has not been reached (Figure 7).

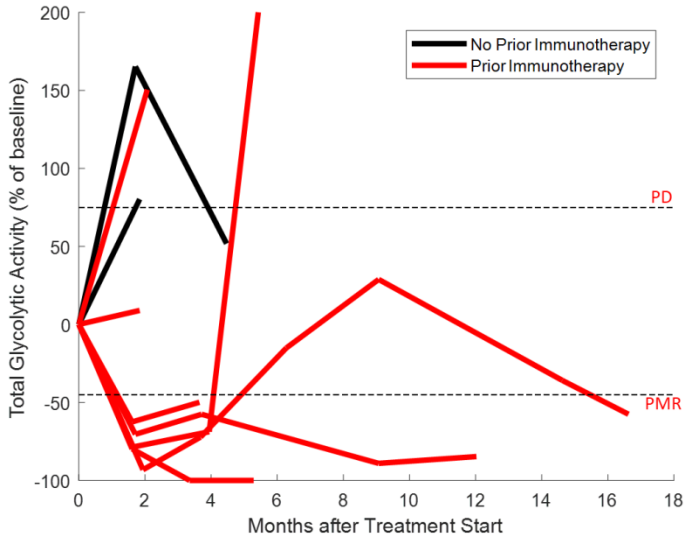

Figure 6 – Spider plots depicting response to study therapy on PET for the first 9 study subjects. TGA values do not include SBRT target lesions.

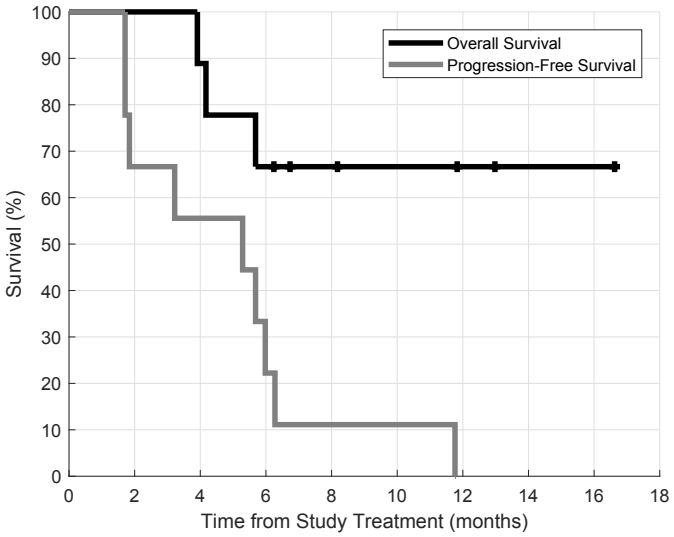

Figure 7 – Kaplan-Meier curves for overall survival
and progression-free survival for the first 9 study subjects

Based on these exciting results, which were presented at the Clinical Trials Plenary Session at the 2018 AACR Annual Meeting, we are adding a second study cohort to this protocol. This group will include patients with advanced solid tumors other than NSCLC who have previously been treated with immune checkpoint therapy targeting the PD-1/PD-L1 axis.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

- Cohort 1: AJCC stage 3 or 4 histologically proven NSCLC not amenable to curative therapy
  Cohort 2: Advanced solid (excluding lymphomas and leukemias) malignancy other than NSCLC not amenable to curative therapy and previously treated with immune checkpoint therapy targeting the PD-1/PD-L1 axis with an agent approved by the FDA for that setting.
- Age ≥ 18 years
- Prior treatment with at least one standard chemotherapy regimen or targeted agent prior to enrollment
- Radiological assessment within 21 days prior to study entry demonstrating measurable disease that includes at least one pulmonary or extrapulmonary lesion ≥ 1 cm in greatest dimension that would be amenable to SBRT and at least one measurable lesion that would be outside of the SBRT treatment fields
- History/physical examination within 30 days prior to registration
- ECOG performance status 0-2
- Signed, written informed consent

3.2 Exclusion Criteria

- Less than 21 days between registration and the last receipt of chemotherapy, biotherapy, immunotherapy, radiotherapy (excluding palliative radiotherapy), or major surgery. Prior receipt of immunomodulatory therapy (e.g.: nivolumab) is permitted, as long as there has been a 21-day washout period following the most recent treatment.
- Untreated central nervous system metastases. Patients with a history of brain metastases must have had no CNS-directed therapy within the past 60 days and radiological assessment within 30 days of study entry demonstrating a lack of progressive CNS disease
- Ongoing or recent (within 21 days prior to study entry) use of high dose oral corticosteroids (≥ 2 mg of dexamethasone daily or equivalent). Intranasal and/or inhaled corticosteroid use is permitted.
- Any unresolved CTCAE grade > 2 toxicity from previous anti-cancer therapy. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by study therapy (e.g., hearing loss) may be enrolled after discussion with the principal investigators.
- History of allogeneic organ transplant or autoimmune disease
- Other active malignancy for which systemic therapy is indicated. History of adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy asides from hormonal therapy, adequately treated stage 1or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 5 years is permitted.
- Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by the treating physicians
- The following laboratory results, within 10 days of first study drug administration:
    - Hemoglobin ≤ 9.0 g/dL, Absolute neutrophil count ≤ 1.5 x 10^9/L, Platelet count ≤ 100 x 10^9/L
    - Serum creatinine ≥ 1.5 x ULN and creatinine clearance (by Cockcroft-Gault formula) < 60 mL/min
- Women of child bearing potential: positive pregnancy test (serum)

4.0 STUDY DESIGN

4.1 General Design

This is a single-arm, phase II study with two cohorts. A total of 29 patients will be enrolled in Cohort 1, and 20 patients will be enrolled in Cohort 2. All patients will be treated with SBRT to a single pulmonary or extrapulmonary lesion as well as FLT3 ligand immunotherapy. Patients will be followed closely for the development of any

treatment-related toxicities. Whole-body PET/CT imaging will be performed prior to study entry and every 8 weeks thereafter.

4.2 Study Calendar

	Pre-rx	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Weeks 16, 24, 32
Stereotactic Radiotherapy (SBRT)		X X X								
FLT3 Ligand Therapy		XXXXX								
History and Physical Examination	X	X	X	X	X		X		X	X
Blood Tests: CBC, CMP	X	X	X	X	X		X		X	X
PET/CT	X								X	X
Immune Correlates	X		X		X				X	X

Additional cycles of SBRT and FLT3 ligand may be administered after 8 weeks or more in cases where treatment is well-tolerated and seems to provide clinical benefit, at the discretion of the treating physicians. In addition to the time points specified above, blood samples for immune correlates will also be drawn at the first clinic visit following disease progression. Immune correlates will include anti-drug antibody testing for CDX-301, which will be performed by sending study samples to Celldex. For diseases where PET/CT is not commonly used (e.g., hepatocellular carcinoma), PET/CT may be replaced by CT and/or MRI.

4.3 Primary Endpoint

- The primary endpoint is progression-free survival rate at four months (PFS4), defined as the rate estimate of the percentage of patients who are alive and progression-free at 16 weeks (~4 months) after initiation of study therapy.

4.4 Secondary Endpoints

- Dose limiting toxicities (DLTs): For the purposes of this study, a DLT will be defined as any treatment-emergent grade 3-5 toxicity, scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, and occurring within 30 days after treatment with SBRT in combination with FLT3 ligand therapy. Asymptomatic laboratory abnormalities (e.g.: leukocytosis) that do not require intervention will not be counted as DLTs. For subjects who receive more than one “cycle” of SBRT and FLT3 ligand, only adverse events that occur after the first cycle will be scored as potential DLTs.
- Clinical/radiographic endpoints: These will include radiographic response rates, disease progression, and death. Radiographic endpoints will be scored using according to immune-related response criteria (irRC).[31] To allow comparison of our data with historical experiences, we will also score radiographic findings using RECIST 1.1 criteria.[32] Pre- and post-treatment assessments will include PET/CT imaging, so that we can assess responses using PERCIST criteria[33] and with volumetric PET measures, which have been shown to be prognostic in metastatic NSCLC patients [34, 35] and predictive of clinical outcomes in advanced NSCLC patients treated with targeted therapy.[36] SBRT target lesions will not be considered in the radiographic evaluation of treatment responses, as rates of treatment response and disease control in lesions treated

with SBRT have been shown to be excellent and may not be indicative of the effectiveness of combined modality therapy.

- Potential surrogate outcomes for clinical endpoints: We will collect plasma samples at regular intervals to facilitate monitoring immune responses such as DC expansion. We will also follow T-cell inducible costimulator (ICOS) expression. ICOS is a member of the immunoglobulin superfamily. Responses to immunotherapy have been associated with increased ICOS expression on CD8+ T-cells, particularly following CTLA-4 blockade.[37-40] We will follow serum levels of high-mobility group box 1 (HMGB1), whose release has been linked to antitumor immune responses.[41, 42] Flow cytometry will be performed to track measures of DC maturation such as CD83 and CD86 expression.[43] Other correlative studies will be performed in collaboration with Dr. Guha's laboratory and the study sponsor.

5.0 STUDY THERAPY

5.1 Stereotactic Body Radiotherapy

- SBRT will be administered during the first week of study therapy.
- A single pulmonary or extrapulmonary lesion that measures at least 1 cm in greatest dimension will be treated.
- The target lesion for SBRT will be chosen by the treating radiation oncologist with the following considerations:
    - Confidence that the target lesion is cancerous (based on prior biopsy, growth on serial imaging, and/or hypermetabolic uptake on FDG-PET)
    - Safety of SBRT to the target lesion and ability to meet the dosimetric constraints listed below
- Based on lesion size and location, one of three SBRT schedules will be selected for each patient receiving SBRT to a pulmonary lesion. At least 95% of the planning target volume (PTV) will receive the full prescription dose. Based on the criteria described below, we expect that approximately equal numbers of subjects will receive each of these SBRT schedules:

Schedule	Criteria	Interval between treatments	Course duration
34 Gy x 1	Peripheral tumor measuring ≤ 2 cm in greatest dimension and > 1 cm from the chest wall	-	-
18 Gy x 3	Peripheral tumor measuring ≤ 5 cm and not eligible for 34 Gy x 1 fraction	42-54 hours	5 days
10 Gy x 5	Central or peripheral tumor not eligible for 34 Gy x 1 fraction or 18 Gy x 3 fractions	18-30 hours	5 days

- Based on lesion location, the following SBRT schedules will be employed for each patient receiving SBRT to an extrapulmonary lesion. At least 95% of the planning target volume (PTV) will receive the full prescription dose. If this cannot be achieved while respecting normal tissue constraints, the prescription dose may be lowered by up to 20%. These treatment schedules are adopted from an ongoing cooperative group clinic trial (NRG-BR001):

Schedule	Target Lesion Location	Interval between treatments	Course duration
10 Gy x 3	Spinal or Paraspinal	42-54 hours	5 days
10 Gy x 3	Osseous	42-54 hours	5 days
10 Gy x 5	Mediastinal or Cervical Lymph Node	18-30 hours	5 days
15 Gy x 3	Liver	42-54 hours	5 days
15 Gy x 3	Abdominal or Pelvic (lymph node or adrenal gland)	42-54 hours	5 days

- The following normal tissue constraints will be used for SBRT planning:

	1 Fraction	3 Fractions	5 Fractions
Brachial plexus	max dose < 17.5 Gy	max dose < 21 Gy	max dose < 30 Gy
Esophagus	max dose < 15.4 Gy	max dose < 30 Gy	max dose < 32.5 Gy
Great vessels	max dose < 37 Gy	max dose < 39 Gy	max dose < 55 Gy
Heart/pericardium	max dose < 22 Gy	max dose < 30 Gy	max dose < 35 Gy
Lungs	At least 1500 cc receiving < 12.5 Gy	At least 1500 cc receiving < 12.5 Gy	At least 1500 cc receiving < 12.5 Gy
Ribs	max dose < 30 Gy	max dose < 30 Gy	max dose < 50 Gy
Skin	max dose < 26 Gy	max dose < 30 Gy	max dose < 40 Gy
Spinal cord	max dose < 14 Gy	max dose < 18 Gy	max dose < 30 Gy
Stomach	max dose < 12.4 Gy	max dose < 27` Gy	max dose < 35 Gy

5.2 FLT3 Ligand Therapy (CDX-301)

- Daily subcutaneous injections of CDX-301 (75 μg/kg) will be administered for 5 days, beginning on the first day of SBRT.
- Additional “cycles” of SBRT (to distinct lesions) and CDX-301 may be administered every 2-4 months to subjects who demonstrate evidence of clinical benefit (lack of treatment-related toxicity and no disease progression).
- Study therapy will be discontinued in cases of treatment-related toxicity or disease progression.

5.3 Treatment Modifications

If SBRT is interrupted due to a non-dose-limiting adverse event or any reason other than toxicity, such as a holiday, bad weather, or a transportation problem, the SBRT treatment course will be extended accordingly. In the case of in-field RT toxicities requiring treatment interruption, the SBRT course will be terminated.

CDX-301 therapy will be terminated in the case of any DLT (defined in Section 4.4). CDX-301 will be held if marked leukocytosis (WBCs > 50,000 cells/mm^3) is observed.

5.4 Toxicity Management

Excessive Hematopoietic Stimulation

Leukocytosis, especially monocytosis, is expected during administration of CDX-301. Hematological parameters, including WBC and differential, will be monitored as detailed in Section 4.2. CDX-301 will not be administered if marked leukocytosis (WBCs > 50,000 cells/mm^3) is observed.

Injection Site Reactions / Dermatological Toxicities

Injection site reactions, generally mild to moderate but occasionally severe, were frequently reported in association with FLT3L administration. Pre-medication with diphenhydramine may be effective in the prevention of pruritic and erythemic reactions and will be considered for subjects who experience local reactions after treatment with CDX-301. Injection site reactions may also be treated with analgesics.

Patients will be monitored by our nursing staff for at least 15 minutes following each CDX-301 injection. Patients may then receive SBRT (based on the selected fractionation schedule, but always on day 1), followed by a physician evaluation that will take place approximately one hour after CDX-301 injection.

5.5 Investigational Drug Description

CDX-301

CDX-301 is a recombinant human Flt3 ligand (Flt3L) that is a hematopoietic growth factor which is structurally related to stem cell factor (SCF) and macrophage colony-stimulating factor (M-CSF). It is naturally expressed as a membrane bound or secreted protein and binds to fms-like tyrosine kinase 3 (Flt3; or FLK-2, STK-1; CD135), a receptor tyrosine kinase in the same family as c-kit, c-fms, and PDGFR A and B.

Each 2 mL clear borosilicate glass vial contains 2.5 mg/mL CDX-301 glycoprotein in a 1.0 mL (with an overfill to 1.2 mL) volume of buffered solution composed of 10 mM sodium phosphate, 140 mM NaCl, pH 7.0. CDX-301 Drug Product is formulated as a sterile solution intended for single-use subcutaneous administration.

Investigational Drug Supply

An initial study drug shipment will be provided following receipt of all required documents. Additional supplies should be ordered with at least one week advance notice using a form supplied by Celldex.

Storage

All study supplies must be stored in a secured area with limited, approved

access. CDX-301 temperature must be maintained between 2° to 8°C (36 to 46°F) and monitored daily. Deviations in storage conditions must be reported to IIR@celldex.com within 24 hours of awareness.

CDX-301 Dose Calculation

The individual dose is calculated using the actual baseline body weight of the subject according to the calculations below. All subjects will receive 75 µg/kg of CDX-301 at each administration.

Body Weight (kg) x Dose Level (75µg/kg) = Desired Dose (µg)

Desired Dose (µg) ÷ 2500 µg/mL = Volume of CDX-301 (mL)

For example, for an 80 kg subject, the total dose required to deliver the 75 µg/kg dose would be 6000 µg. The calculated volume required from the 2500 µg/ml CDX-301 stock solution to obtain 6000 µg of CDX-301 would be 2.4 ml. See example formula below:

(80 kg x 75 µg/kg) ÷ 2500 µg/mL = 2.4 mL (Three vials will be needed to administer this dose)

CDX-301 Preparation

CDX-301 liquid should be withdrawn from the vial gently, avoiding foaming and excess shearing. As the maximum volume of any individual injection will be 2.0 ml, the dose may be split into up to 3 separate syringes/subcutaneous injections as needed to administer the required volume.

CDX-301 Administration

CDX-301 will be administered as a daily subcutaneous injection. The injection site may be rotated between the extremities. CDX-301 injections should not be given to areas of skin with conditions such as scarring, tattoos or persistent injection site reactions that will not allow easy access for study drug administration or evaluation of localized adverse events. CDX-301 administration will be performed within the clinical setting by trained staff personnel.

6.0 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint – Progression-Free Survival

Cohort 1:

We will present the progression free survival rate at 4 months as a percentage along with its 95% confidence interval. In addition, Progression-free survival will be examined using the Kaplan-Meier method.

A total of 29 patients will be enrolled in Cohort 1 to test the null hypothesis (H0) that PFS4 is 20% or less versus the alternative hypothesis (H1) that PFS4 is 40.5% or greater. If at least 10 of 29 patients are alive without progression at 4 months, this study regimen will be considered for further development in this setting. Using this criterion, the probability of pursuing this regimen for further study if the true PFS4 is ≥ 40.5% is at least 80%. The chance that this regimen will be considered for further development if the true PFS4 is 20% or lower is at most 5%.

Cohort 2:

A total of 20 patients will be enrolled in Cohort 2. We will estimate the PFS4 probability along with its 95% confidence interval using the Kaplan Meier survival procedure. We will also present median progression-free survival duration.

We assume a type-II censoring mechanism in this study, where the study will continue until 16 events occur in this cohort. We also hypothesize that progression-free survival durations will follow an exponential distribution with a mean of 5.8 months. Under these assumptions, a sample size of 20 subjects would produce a two-sided 95% confidence interval width of 4.4 months for the median progression-free survival duration (95% CI: 2.6 months to 7.0 months).

6.2 Secondary Endpoints - Safety and Tolerability

An early stopping rule for safety will be implemented for Cohort 1 as follows. After the first 6 patients have been enrolled, accrual will be temporarily suspended while these patients are monitored for occurrence of DLTs. The trial will be terminated early if more than 1 patient experiences a DLT. If 1 or fewer grade 3 toxicities and 0 grade 5 toxicities are observed after the sixth patient has been observed for 30 days following completion of treatment, the trial will continue until a total of 29 patients have been evaluated. At the end of the trial, the treatment will be considered safe and worthy of further study if no more than 4 patients experience a DLT. For the first six patients enrolled, we will not initiate treatment for more than one patient on the same day.

The target Grade 3 toxicity rate is no more than 10% and a toxicity rate greater than 30% is considered clinically unacceptable. The design specified above has the following operating characteristics: The probability of accepting the treatment for further study if the toxicity rate is unacceptably high (>30%) is at most 4%. In contrast, there is at least am 84% probability of accepting the treatment for further study if the toxicity rate is less than 10%.

The proportion of patients who develop a DLT will be computed. 95% confidence intervals for the DLT rate will be calculated using Clopper-Pearson exact confidence method.

6.3 Other Secondary Endpoints

irRC, RECIST, and PERCIST response rates, based on first post-treatment imaging, will be reported using descriptive statistics. Rates of disease-free and overall survival will be reported using actuarial methods. Exploratory analyses will be

performed to evaluate surrogate endpoints, including radiographic responses and immune correlates, as predictors of clinical outcomes. We will also perform statistical tests to explore if response rates, time-to-event outcomes, and immune responses correlate with SBRT fraction size.

7.0 REGULATORY CONSIDERATIONS

7.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

7.2 Potential Risks

Subjects participating in this Phase II study are at risk for the development of treatment-related toxicities. Risks from lung SBRT include damage to the lungs, heart, and esophagus that may cause transient symptoms or permanent dysfunction. Risks from SBRT to other sites include damage to nearby organs, depending on the target location. The risk profile of SBRT to the lung or other sites has been characterized clearly over the past decade, and SBRT planning and dosing for patients enrolled on this study will be optimized to keep the expected risk of severe complications related to SBRT below 5%.

CDX-301 and AMG949 were generally well-tolerated in prior clinical trials. In the Celldex-sponsored phase 1 study in 30 healthy volunteers, treatment-related toxicity was infrequent and reported only at the 25 and 75 μg/kg/day dose levels. One Grade 3 event, community acquired pneumonia, was considered to be treatment-related. No additional infections, DLT, SAE, or Grade 3 toxicities were reported. All other treatment-related adverse events were Grade 1; these included lymphadenopathy in six subjects and single cases of diarrhea, injection site erythema, folliculitis, and dry mouth.

In studies of AMG949 administered as single agent to healthy volunteers (n=36), there were no deaths, SAEs, Grade 3/4 adverse events, or premature withdrawals from treatment. Grade 2 events were limited to injection site reactions and/or pain. Laboratory results were generally unremarkable and showed no suggestion of a dose response. The expected pharmacologic effects of rhuFlt3L (increased WBC and monocytes) were observed in both studies.

Across all previous trials of AMG949, the most common treatment-related adverse events were injection site reactions. These events were generally mild to moderate, consisting of erythema, induration, urticaria, pain, and bruising. Rarely, more severe reactions with blistering have also been reported. In Immunex-sponsored

studies, additional adverse events occurring for subjects receiving AMG949 with or without GM-CSF, regardless of causality, included headache, pain, asthenia, myalgia, nausea, diarrhea, arthralgia, fever, rash, paresthesia, pruritus and vomiting. The majority of adverse events were mild to moderate in severity. Serious adverse events deemed to be related to AMG949 occurred in 6 of the 294 subjects treated in Immunex-sponsored trials. These events were three cases of hypercoagulability (IV line clotting), single cases of left arm thrombosis and deep vein thrombosis in the leg, and a case of fever, chills, and hypotension.

This will be the first study combining SBRT and FLT3L therapy, so the full range of potential toxicities remains unknown.

7.3 Additional Warnings and Precautions

Drug-drug Interactions

Interactions between CDX-301 and other drugs have not been fully evaluated.

Allergic Reaction

CDX-301 is a fully human protein and it is unlikely that it will induce a hypersensitivity reaction. No such reactions have been observed in the AMG949 or CDX-301 programs to date. If such reactions were to be observed, possible manifestations could include fever, chills, rash, rigors, pruritus, or other symptoms.

Immunogenicity

None of the 30 healthy volunteers treated with CDX-301 (5 to 10-day regimen) have developed anti-rhuFlt3L antibody. Approximately 16% of subjects treated with AMG949 in Immunex sponsored studies and tested for immune response were noted to develop anti-rhuFlt3L antibody. Anti-rhuFlt3L antibodies appeared to develop more frequently in studies with greater exposure to AMG949. However, none of the anti-rhuFlt3L antibodies were neutralizing.

Coagulation

No thrombotic events have been reported as potentially related to CDX-301 in the prior healthy volunteer study. However, thrombotic events (hypercoagulability, IV line thrombosis, and venous thrombosis) were observed rarely in oncology patients (n=6) receiving AMG949 and was more common when combined with GM-CSF or G-CSF. Low grade thrombocytopenia has also been observed following AMG949 administration.

Evaluation of coagulation parameters and clotting factors in several of these patients did not reveal any abnormalities.

Autoimmune Disease

Subjects with a known history of autoimmune disorders should not be given CDX-301 until further studies have determined the safety profile of CDX-301 in this patient population. Pre-clinical studies have demonstrated that rhuFlt3L may have a complicated role in regulating autoimmune diseases and can either exacerbate or ameliorate autoimmune disease manifestations. Therefore, CDX-301 may have the potential to exacerbate autoimmune disorders by its immunomodulatory effects. Subjects administered CDX-301 will be monitored for the development of potential autoimmune phenomena, which may include asymptomatic autoantibody seroconversion or hyper- or hypothyroidism.

Development of Immune Tolerance

CDX-301-mediated increases in immature dendritic cells and/or Treg cells could potentially be tolerogenic. Therefore, CDX-301 could potentially have deleterious effects in an infectious disease setting or other pre-existing or developing disease. AMG949 worsened the outcome in a mouse Streptococcus pneumoniae pneumonia challenge model[44], indicating that rhuFlt3L treatment could pose a risk for increased lung injury associated with S pneumoniae pneumonia. Study subjects will be monitored closely for the development of infections signs and symptoms. As described in Section **Error! Reference source not found.**, any SAE will be reported to the medical monitor within 24 hours.

rhuFlt3L may also be associated with a differential response to vaccines. In another murine model, intramuscular injection of rhuFlt3L in combination with a hepatitis B vaccine suppressed the antibody response to the vaccine in a dose-dependent manner, although in situ delivery by plasmid increased the antibody response [45]. In a clinical study in which healthy volunteers were administered hepatitis B vaccine and either placebo or AMG949, there was no inter-group difference in hepatitis B antibody responses, demonstrating that AMG949 neither augmented nor tolerized humoral responses to the vaccine. Patients on this study should not receive any vaccinations until at least 28 days after the last dose of CDX-301.

Leukemia

There are data showing that prophylactic treatment with rhuFlt3L can prevent or abrogate leukemic activity[46]. There also are data showing the expression of Flt3 and the Flt3L receptor on some leukemias and extensive data that support an association between an increase in proliferation or suppression of apoptosis in clinical leukemias that

bear constitutively activated Flt3 mutations. These mutations do not appear to be causal for AML[47-50]. It is not known whether the addition of rhuFlt3L to patients with leukemia expressing Flt3 will promote leukemic proliferation or whether the ligand can promote the development of leukemia in people without pre-existing leukemia. Since the effect of administered rhuFlt3L is transient, it would seem unlikely to have any persistent effects, and no cases of leukemia were reported after rhuFlt3L administration in previous studies.

Pregnancy, Carcinogenesis, and Teratogenicity

The effects of CDX-301 on fertility, pregnancy, or the unborn fetus have not been determined. It is not known if CDX-301 is excreted in milk or can cross the placenta. For this reason, pregnant and nursing women will not be enrolled into this study. Women of childbearing potential enrolled into the clinical study must take adequate contraceptive measures.

7.4 Potential Benefits to Human Subjects and Others

The benefits to an individual patient are unknown. This treatment regimen may delay the progression of metastatic disease in the lungs and elsewhere. Delaying disease progression may theoretically prolong survival.

7.5 Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in this approved protocol. All revisions to the protocol must be provided to the PI. The PI should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

The investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the PI.

7.6 Inclusion of Women and Minorities

Recruitment will be open to all women and minorities that qualify under the study's eligibility criteria. There will be no effort to exclude women or minority patients from the trial if inclusion criteria are met. Based on our hospital's patient population, we expect the following demographic breakdown for subjects enrolled on this study:

	Gender

Ethnic Category	Females	Males	Total
Hispanic or Latino	8	8	16
Not Hispanic or Latino	16	17	33
Ethnic Category: Total of All Subjects	24	25	49
Racial Category	**Females**	**Males**	**Total**
American Indian/Alaska Native	0	0	0
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black of African American	6	6	12
White	16	17	33
Racial Category: Total of All Subjects	24	25	49

Projected distribution of gender and minorities across both study cohorts.

7.7 Patients Under the Age of 18 Years

Children will be excluded from this study. Since the incidence of NSCLC in children is extremely low, it is unlikely that any patients under the age of 18 will meet our eligibility criteria.

8.0 DATA HANDLING AND RECORD KEEPING

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.
- In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

8.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

8.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done, or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.0 DATA SAFETY AND MONITORING BOARDS

All trials initiated by the Montefiore Medical Center are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB reviews trial performance information such as accrual information.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).

- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial. The study leadership will provide information on cumulative toxicities and relevant recommendations to the local PI to be shared with their IRB's.

10.0 ADVERSE EVENTS

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject and does not necessarily have to have a causal relationship with study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of treatment. During clinical trials, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

AEs will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial intervention or medication. All AEs considered related to trial intervention or medication will be followed until resolution, even if this occurs post-trial.

10.1 Adverse Event Definitions

Adverse Event (AE): any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

Serious Adverse Event (SAE): An AE occurring at any dose that results in any of the following outcomes (CFR 312.32)

- Death
- Life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization excluding those for study therapy administration, transfusional support, disease staging/re-staging procedures, thoracentesis / paracentesis, or placement of an indwelling catheter, unless associated with other serious events
- Persistent or significant disability or incapacity
- Congenital anomaly / birth defect.

The definition of SAE also includes important medical event. Medical and scientific judgment should 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 should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.
The definition of “related” is that there is a reasonable possibility that the drug or the study intervention caused the adverse experience.

Unexpected Adverse Event: An AE that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening: Any adverse experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

AEs will use the descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix A). A list of AEs that have occurred or might occur can be found in sections above.

10.2 Adverse Event Reporting

Study site personnel must notify the PI and the sponsor (Montefiore/Einstein) within 24 hours of any SAE experienced by a patient. In general, SAEs assessed as clearly being due to disease progression, and not due to study drug(s), should be excluded from AE reporting. Study-specific clinical outcomes of death because of disease progression are exempt from SAE reporting, unless the investigator deems them related to use of the study drug. Hospitalization for study drug administration is not an SAE.

The following steps will be taken to report promptly and document accurately any SAE, even if it may not appear to be related to the study treatment:

- Report the SAE to the PI and the treating physician by email, telephone or fax within 24 hours of becoming aware that a patient has experienced an SAE.
- Record the SAE accurately on the AE page of the patient's CRF.
- Using the standard IRB-SAE report form, submit all known patient information within 24 hours of SAE occurrence to the clinical trial office to submit to IRB and DSMB. Date and sign each report before submission. Include the following information (or as much as possible to obtain and still report the event within 24 hours):
    - Study protocol number and indication
    - Study site and investigator's identification
    - Patient's ID (patient number and initials), age or date of birth, and sex
    - Date of enrollment
    - Description of SAE, including date of onset and duration, severity, and outcome
    - Date of first and most recent (last) dose administered
    - Action taken regarding study treatment
    - Relationship of SAE to study treatment
    - Concomitant medications, including regimen and indication
    - Intervention, including concomitant medications used to treat SAE
    - Pertinent laboratory data/diagnostic tests conducted and date
    - Pertinent medical history of patient
    - Date of hospital admission/discharge

- Date of death (if applicable)

  Fatal or life-threatening, unexpected adverse events will be reported to the FDA by telephone, facsimile, or in writing as soon as possible, but no later than 7 calendar days after first knowledge by the sponsor followed by as complete a report as possible within 8 additional calendar days. Serious, unexpected adverse events that are not fatal or life-threatening will be reported to the FDA by telephone, facsimile, or in writing as soon as possible, but no later than 15 calendar days after first knowledge by the sponsor. The Reference Safety Information for the assessment of expectedness of serious adverse reactions for CDX-301 is contained within the Investigators Brochure.

Within 10 days of initial IRB notification, the PI is required to submit a completed Adverse Event Report to the IRB. The treating physicians should perform appropriate diagnostic tests and therapeutic measures and submit all follow-up substantiating data, such as diagnostic test reports and autopsy report to the PI, IRB, and DSMB.

<u>Expedited Reporting of SAEs to Celldex</u>

Note that reporting to Celldex is required in addition to reporting to the FDA, as necessary, and does not replace the requirement to notify the FDA, if required.

- The investigator will inform Celldex in writing using an SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event (see Section 10.1 for the definition of SAE). The written report must be completed and supplied to Celldex by email or facsimile 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.

- Completed SAE reports are to be submitted to:

Celldex Therapeutics, Inc.
Pharmacovigilance
Facsimile: 781-644-6434
Email: SAE@celldex.com
For questions regarding SAE reporting: 908-323-2233 (SAE Hotline)

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12.0 APPENDICES

12.1 Appendix A – Common Toxicity Criteria

NCI CTCAE Version 4.0

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from the CTEP homepage: (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTC Version 4.0

12.2 Appendix B – ECOG/WHO/Zubrod Performance Status

Performance Status	Definition
0	No symptoms; normal activity level
1	Symptomatic, but able to carry out normal daily activities
2	Symptomatic; in bed less than half of the day; needs some assistance with daily activities
3	Symptomatic; in bed more than half of the day
4	Bedridden