Testing the immunologic effects of CDX-301 and CDX-1140 in resectable pancreatic cancer patients

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Protocol Revision History

Initial Approval	**19 November 2020**
Amendment #1	**03 February 2021**
Amendment #2	**30 September 2021**
Amendment #2.1	**08 December 2021**
Amendment #3	**06 October 2022**
Amendment #4	**13 December 2022**
Amendment #4.1	**30 November 2023**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

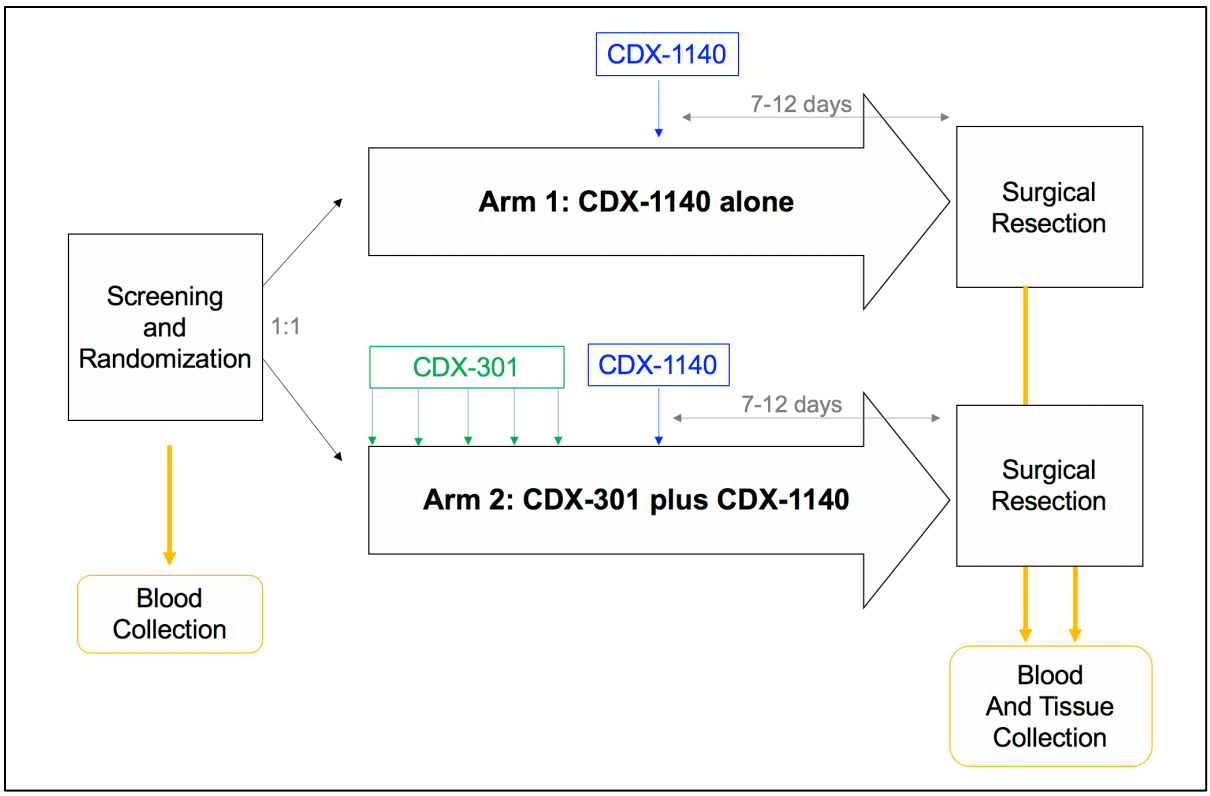
PROTOCOL SUMMARY

Synopsis

Title:	Testing the immunologic effects of CDX-301 and CDX-1140 in resectable pancreatic cancer patients
Study Description:	Our central hypothesis is that the addition of CDX-301 to CDX-1140 radically improves anti-tumor immunity in patients with pancreatic ductal adenocarcinoma.
Objectives:	Primary Objective: To determine the amount of intratumoral conventional dendritic cells in patients with resectable pancreatic cancer treated with neoadjuvant CDX-1140 vs. CDX-301 plus CDX-1140. Exploratory Objectives: 1. To determine the changes in global immune profile of in patients with resectable pancreatic cancer treated with neoadjuvant CDX-1140 vs. CDX-301 plus CDX-1140. 2. To assess local control rate in patients with resectable pancreatic cancer treated with neoadjuvant CDX-1140 vs. CDX-301 plus CDX-1140. 3. To assess distant metastasis-free survival of surgically resectable pancreatic cancer patients treated with neoadjuvant CDX-1140 vs. CDX-301 plus CDX-1140. 4. To assess overall survival of surgically resectable pancreatic cancer patients treated with neoadjuvant CDX-1140 vs. CDX-301 plus CDX-1140. 5. To assess extent of surgical margin negative resection in patients treated with neoadjuvant CDX-1140 vs. CDX-301 plus CDX-1140. 6. To assess the safety and tolerability profile of CDX-1140 vs. CDX-301 plus CDX-1140 in surgically resectable pancreatic cancer patients.
Endpoints:	Primary Endpoint: Intratumoral conventional dendritic cells (cDCs) at surgery. Exploratory Endpoints: Global immune profiling by CyTOF, single cell RNASeq analysis, and histologic assessments, local control rate, distant metastasis-free survival, overall survival, margin negative resection rate, and adverse events.
Study Population:	The study will enroll adults with surgically resectable pancreatic ductal adenocarcinoma. Enrollment will continue until 12 patients evaluable for the primary objective have been enrolled in each arm.
Phase:	II
Description of Sites / Facilities Enrolling:	Siteman Cancer Center at Washington University School of Medicine.

Description of Study Intervention:	Consenting and eligible patients will be randomized on a 1:1 basis CDX-1140 followed by surgery or CDX-301 plus CDX-1140 followed by surgery until 12 patients evaluable for the primary objective have been enrolled in each arm. Patients randomized to the CDX-1140 monotherapy arm will receive a single IV infusion at a dose of 1.5 mg/kg, with surgery to follow 7-12 days after administration of CDX-1140. Patients randomized to the CDX-301 + CDX-1140 arm will receive CDX-301 at 75 mcg/kg/day as a subcutaneous injection every day for 5 days (Days 1-5) with CDX-1140 IV at 1.5 mg/kg on Day 8 +/- 1 day. Surgery will be 7-12 days after administration of CDX-1140. For both arms, patients will undergo blood collection at the start of treatment and at the time of surgery, and all surgically resected tissues will be subjected to biomarker analysis.
Study Duration:	36 months (recruitment) + 3 weeks (intervention) + 24 months (follow-up) + 24 months (analysis)
Participant Duration:	30 days

SCHEMA


CDX-1140
7-12 days
Arm 1: CDX-1140 alone
Surgical Resection
Screening and Randomization
1:1
CDX-301
CDX-1140
7-12 days
Arm 2: CDX-301 plus CDX-1140
Surgical Resection
Blood Collection
Blood And Tissue Collection

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SCHEDULE OF ACTIVITIES

Arm 1 Calendar

	Screening[3]	7-12 days prior to surgery	Surgery	Follow-up[4]
Informed consent	X			
ECOG PS	X		X[7]	
CBC w/diff	X			
CMP	X			
INR, aPTT	X			
Pregnancy test[1]	X			
Randomization	X[2]			
CDX-1140		X		
Research blood	X	X[5]	X	
Research tissue			X	
AE assessment[6]		X	X[7,8]	X
Progression and survival				X

1. For female patients of childbearing potential only.
2. After confirmation of eligibility.
3. Screening should occur no more than 6 weeks prior to surgery, CBC within 3 weeks prior to start of CDX-1140.
4. Follow-up will occur at standard of care office visits (approx. Q6M) for 24 months after surgery.
5. Prior to CDX1140 administration.
6. AEs will be collected from time of administration of CDX-1140 until surgery, or until 60 days after end of treatment if surgery doesn't take place. A phone call or medical record check may take place at the 60 day time point (+/- 2 weeks) for AE collection if surgery doesn't take place.
7. Follow-up in person visit or call with physician's office will occur 24-48 hours after administration of CDX-1140 to evaluate any acute changes.
8. Assessment of AEs may be done at an outpatient visit 7 +/- 2 days after administration of CDX-1140 or after admission for surgery.

Arm 2 Calendar

	Screening[5]	**D1**	**D2**	**D3**	**D4**	**D5**	**D8[10]**	**Surgery[3]**	**Follow-up[6]**
Informed consent	X								
ECOG PS	X							X[8]	
CBC w/diff	X								
CMP	X								
INR, aPTT	X								
Pregnancy test[1]	X								
Randomization	X[2]								
CDX-1140							X		
CDX-301		X	X	X	X	X			
Research blood	X[4]						X[4]	X[4]	
Research tissue								X	
AE assessment			X ----------					X[7,8,9]	X[7]
Progression and survival									X

1. For female patients of childbearing potential only.
2. After confirmation of eligibility.
3. 7-12 days after administration of CDX-1140.
4. First research blood draw will take place at screening or at any point prior to the first dose of CDX-301, second on day 8 prior to CDX1140 administration, and third at time of surgery.
5. Screening should occur no more than 6 weeks prior to surgery, CBC within 3 weeks prior to start of CDX-1140.
6. Follow-up will occur at standard of care office visits (approx. Q6M) for 24 months after surgery.
7. AEs will be collected from time of administration of CDX-301 until surgery, or until 60 days after end of treatment if surgery doesn't take place. A phone call or medical record check may take place at the 60 day time point (+/- 2 weeks) for AE collection if surgery doesn't take place.
8. Follow-up in person visit or call with physician's office will occur 24-48 hours after administration of CDX-1140 to evaluate any acute changes.
9. Assessment of AEs may be done at an outpatient visit 7 +/- 2 days after administration of CDX-1140 or after admission for surgery.
10. Administration of CDX-1140 is on day 8 +/- 1 day.

1.0 INTRODUCTION

1.1 Study Rationale

The prognosis for pancreatic ductal adenocarcinoma (PDAC) patients is dismal. Therefore, the development of new and effective clinical approaches represents a significant unmet medical need. Unfortunately, attempts at immunotherapy in PDAC to date have not achieved significant clinical benefit as single agents[1]. This is likely due to the presence of a uniquely suppressive tumor microenvironment (TME). Two major drivers of this tumor protective microenvironment include a dense fibrotic tumor stroma and robust infiltration by tumor-supportive myeloid cells[2, 3]. High stromal density provides a barrier to the delivery of cytotoxic agents and limits T cell infiltration and function[4, 5]. Additionally, data from our group has shown that significant infiltration of PDAC tumors by immune-suppressive macrophages decreases the efficacy of immunotherapy by inducing dysfunction in T cells[6-9]. While much focus has been on immune suppression within the PDAC TME, our recent data described below suggest immune priming by conventional dendritic cells (cDCs) may ultimately be the larger barrier to overcome.

Conventional dendritic cells (cDCs) are central for generating tumor antigen specific responses in T cells [10]. Thus, in animal models and human correlative studies, cDCs have been shown to be critical for responsiveness to both checkpoint immunotherapy and the induction of tumor immunity by radiation therapy[10]. Our striking new data has found that cDCs are severely dysfunctional in human PDAC patients. This dysfunction is driven by two mechanisms: 1) As we recently published (*Meyer et al. Nature Comms. 2018 [11]*) PDAC patients have impaired development of cDCs in their bone marrow, leading to functional depletion of circulating pre-DCs, impaired cross presentation to cytotoxic T lymphocytes (CTLs), and poor responsiveness to checkpoint inhibitors[11]; 2) In recent data (*Hedge et al Cancer Cell 2020 [12]*), we have shown that even when cDC development is not impaired, cDC1s are physically/biochemically excluded from the PDAC TME. We have found that treatment with systemic FLT3L and CD40 agonists overcomes cDC exclusion to drive tumor immunity that in turn slows tumor progression.

1.2 Background

1.2.1 Study disease

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease whose incidence is increasing [13, 14]. Currently, pancreatic cancer is the third most common cause of cancer death in the United States. Only 24% of pancreatic cancer patients survive >1 year from diagnosis, and only 9% live for 5 years [13, 15]. Current therapies are woefully inadequate and costly[14, 16]. Efforts focusing on early detection are still in their infancy[17]. Proximate solutions to modifiable risk factors, such as smoking and obesity, are lacking[18, 19]. Many standard therapies that are effective for other cancers, including immune checkpoint blockade and radiation therapy, have little to no effect on survival in pancreatic cancer. In the last decade, multi-agent

cytotoxic chemotherapy has modestly improved the median survival at the cost of significant toxicity[20, 21]. Unfortunately, this increase in median survival has not translated into an overall survival benefit. New agents and novel approaches are desperately needed for pancreatic cancer. Any progress towards an effective treatment strategy for pancreatic cancer would be a highly significant healthcare advance.

1.2.2 Summary of Nonclinical Findings for CDX-301

Hundreds of non-clinical studies have documented the biological activities of Flt3L *in vivo* and *in vitro*. Notably, CDX-301 is human Flt3L. Administration of recombinant human Flt3L into mice and other laboratory species results in a broad expansion of HSC. These effects are transient, and hematopoietic values return to normal upon stopping recombinant Flt3L treatment. The most distinguishable *in vivo* CDX-301 effects have been observed within the dendritic cell (DC) compartment. Large numbers of DCs are generated in murine spleen, bone marrow, and the peripheral circulation, and these effects of recombinant Flt3L are far more potent than those following treatment with other DC growth promoting cytokines such as GM-SCF.

1.2.3 CDX-1140 Physical, Chemical, and Pharmaceutical Properties

CDX-1140 is a human IgG2κ mAb with a calculated polypeptide molecular weight of 144,766 Da and a potential N-linked glycosylation site on the heavy chain. Based on the amino acid sequence, glycoform analysis, peptide mapping, and mass spectrometry, the overall structure of CDX-1140 is as expected for a human IgG2κ mAb with pairs of heavy and light chains stabilized through intra- and inter-chain disulfide bonds[22]. CDX-1140 is generated by *in vitro* Chinese hamster ovary (CHO) cell culture and using standard mAb purification methods. The CDX-1140 formulated drug substance and drug product are identical in terms of formulation and concentration.

1.2.4 Rationale for CD40 agonism with CDX-1140

Similar to other TNFR/TNFL family members, CD40 signaling through the receptor appears optimal when the CD40L is constrained in a trimeric arrangement, thereby enforcing a co-localization or clustering of the CD40 itself, and the subsequent recruitment and interaction with TNF receptor associated factors (TRAFs). Thus, the requirement for FcR-mediated cross-linking of the agonist CD40 mAbs to effect a similar co-localization is reflected in the isotype-dependence and FcR specificities of the resulting agonist activities.

Two research groups concluded that FcγRIIb engagement was required for anti-CD40 agonist activity [23, 24]; however, it was cross-linking and not the intracellular signaling that was required, and cellular distribution as much as affinity was important for *in vivo* activity. Subsequently, it was shown that human IgG2 isotypes

of anti-CD40 mAb had greater agonist activities, such as B cell proliferation and CD70 up-regulation on DCs, than corresponding IgG1 isotypes and that this was a consequence of the IgG2 hinge region and was independent of FcγR binding [25]. In general, the capacity of a particular mAb to promote colocalization or clustering of CD40, whether through FcγR interactions or independent of such interactions, favors downstream signaling and agonistic activities. Among several agonist anti-CD40 mAb currently in oncology clinical trials is the highly agonistic CP-870,893 mAb [26, 27]. While clinical experience with CP-870,893 has provided encouraging evidence of activity, this was associated with significant dose-limiting toxicity and a maximally tolerated dose (MTD) of 0.2 mg/kg. Such a low dose (≤ 0.2 mg/kg) may not be ideal for systemic use, because saturation of CD40 on tissue resident DCs or macrophages may not be achieved at these dose levels due to the wide-spread expression of CD40 on non-immune cells and some tumors[28, 29]. As these authors suggest, perhaps an alternative anti-CD40 mAb better suited for systemic use would have somewhat less potent agonist activity than CP-870,893 and thus could be used at higher doses, improving the likelihood of fully engaging macrophages and DCs in these tissues. As such we anticipate CDX-1140 overcome these issues.

1.2.5 Selected preclinical studies of CDX-301 and CDX-1140

Flt3L Mobilizes Dendritic Cells

- In mice, Flt3L increases the number of DC in the spleen, lymph nodes and peripheral blood. These DC are equivalent to splenic DC from untreated mice in presenting alloantigens and/or soluble antigens to T cells *in vitro*, and in priming an antigen-specific T cell response in naïve mice *in vivo* [30].
- Flt3L administered subcutaneously at 100 μg/kg/day for 5-7 days was as effective as 14 days of such dosing in expanding the numbers of circulating DC in rhesus macaques. Numbers of DC peaked at approximately 4 days post 7 days of treatment and decreased thereafter. The DC were predominantly of immature phenotype but were capable of being activated and expressing IL-12 upon subsequent *in vitro* culture and stimulation with CD40L [31].
- Flt3L treatment of humanized mice generated large numbers of human CD141+ (BDCA-3) and CD1c+ (BDCA-1) DC, and to a lesser extent plasmacytoid DCs, in the blood, spleen, and bone marrow. The CD141+ DC could be efficiently activated with poly-ICLC and crosspresentantigen to CD8 T cells [32].

Flt3L Enhances Immune Responses

- In mice immunized with ovalbumin, administration of Flt3L influences the class of antibody produced and enables productive immune responses to otherwise tolerogenic protocols [33].
- Flt3L-treated mice developed lower cellular and humoral immune responses to transcutaneous administered hen egg lysozyme (HEL) than did PBS-treated control mice. In the presence of cholera toxin, however, Flt3L-treated mice developed significantly higher cellular and humoral immune responses to HEL when compared to PBS-treated mice [34].

Flt3L Enhances Anti-Tumor Responses and Retards Tumor Growth

- Flt3L completely prevented B10.2 fibrosarcomas in >70% of mice when administered on the day of tumor cell inoculation (partial regression was observed in most other Flt3L-treated animals). Delaying treatment with a higher dose of Flt3L to 1 week after tumor inoculation still resulted in complete rejection of established tumors in 72% of mice. Spleen cells from Flt3L-treated mice transferred anti-tumor activity, which was abrogated by antibody

1.2.6 Pancreas Cancer-Specific Studies with CDX-301 and CDX-1140

Mobilizing cDCs into early pancreatic lesions can reverse fibro-inflammatory responses

We tested if increasing cDCs in early stages of PDAC could reassert T_H1 and CTL-mediated disease control. To accomplish this, we stimulated hematopoietic mobilization of cDC precursors using Fms-related tyrosine kinase 3 ligand (Flt3L) treatment [35-37]. Flt3L administration at early stages of tumorigenesis resulted in robust infiltration of cDCs in the pancreas, including a 10-fold increase in cDC1s and revert disease acceleration and fibro-inflammatory pathology of PDAC in mice. Flt3L treatment also resulted in reduced number of pathogenic ROR-γt^+ IL-17A-expressing T_H cells and increases in IFN-γ-producing T_H1 cells. Flt3L treatment increased $CD8^+$ T cell, proximity to lesions, effector function as measured by IFN-γ^+ and TNF-α^+ production, and proliferation. Together these data imply that restoring cDC numbers in early stages of PDAC results in a switch from pathogenic tumor-promoting T_H17 to tumor-restraining T_H1 and $CD8^+$ CTL responses to neoantigens.

Enhancing cDC infiltration and activation in advanced PDAC leads to disease stabilization

Our observations raised the possibility that Flt3L-based cDC mobilization in established pancreatic tumors could benefit anti-tumor immunity. Additionally, our previous work has shown that established PDAC in human patients and mouse PDAC models can impair cDC1 development in the bone marrow [36] and therapeutic strategies might require boosting cDC mobilization to overcome this disruption. Thus, we treated PDAC bearing mice bearing advanced tumors with Flt3L. Notably, increases in cDC infiltration upon Flt3L treatment were more modest in established PDAC compared to premalignant pancreas and in this advanced setting FLT3L alone did not change intratumoral CTL infiltration.

To overcome this barrier, we administered CD40-agonist IgGs to improve licensing and enhance APC function and survival [38, 39]. We found the combination of Flt3L with CD40 agonists worked synergistically to drive massive influx of cDC1s and cDC2s, with CD40 agonist showing clear superiority and a >64-fold increase in cDC1s. Additionally, the combination with Flt3L triggered markedly enhanced intratumoral $CD8^+$ CTL and $CD4^+$ T_H cell infiltration without T_{REG} induction. Notably, the CD40 agonist plus Flt3L treatment elicited integrated anti-tumor

responses involving marked increases in infiltrating NK cells, NKT cells and γδT cells.

Combining Flt3L administration with CD40 agonism resulted in improved disease control beginning a week into treatment in multiple PDAC mouse models. Together these data suggest synergistic activities of FLT3L (CDX-301) plus CD40 agonists (CDX-1140) can directly improve tumor immunity and retard disease progression in mouse models of PDAC.

1.3 Study Design

1.3.1 Overall Design

Hypothesis: The combination of CDX-301 and CDX-1140 will work synergistically to improve anti-tumor immunity, both within tumor tissue and systemically. Specifically, we believe these two agents will combine to increase cDCs and T cells within tumor tissues.

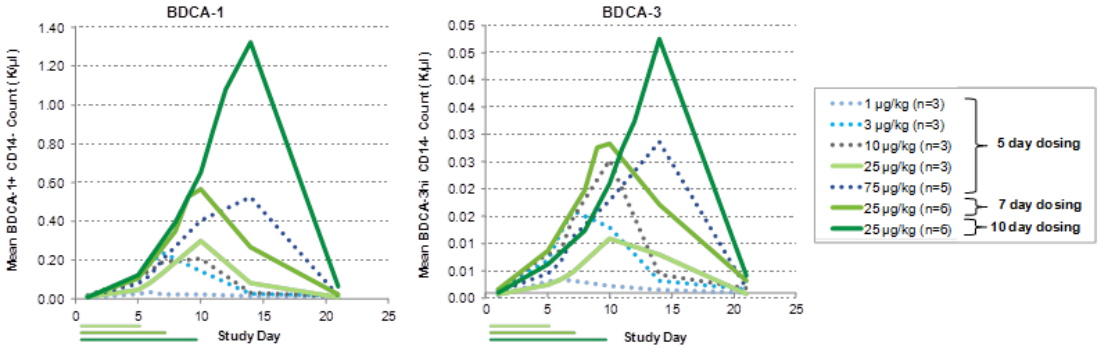
Clinical trial design: The trial is a phase II, single institution, open-label, randomized trial treating patients with surgically resectable pancreas cancer. Patients will be accrued upon designation of surgical resectability by our tumor board. Patients will be randomized to receive either CDX-1140 alone or CDX-310 plus CDX-1140 prior to surgery. Patients will receive a single 7-day cycle of treatment followed by surgery 7-12 days after cycle completion. Surgical resection tissue will be accessed for endpoint and compared historical controls.

1.3.2 Justification for Dose

Recombinant human FLT3 ligand, AMG949 originally developed by Immunex and subsequently acquired by Amgen, 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, FLT3 ligand 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 mobilization of immature DCs by FLT3 ligand and the absence of appropriate DC maturation signals and/or limited DC access to tumor antigens.

More recently, recombinant human FLT3 ligand (CDX-301) developed by Celldex, which is identical in amino acid sequence to AMG949 but produced utilizing a serum-free manufacturing process, has been demonstrated to expand and mobilizes DCs into the peripheral blood and tissues, including into the tumor microenvironment. As of May 28, 2020, healthy volunteers (n=30), allogenic hematopoietic stem cell donors (n=4) or cancer patients (n=116), for a total of 150 subjects, have been treated with CDX-301 as monotherapy or in combination with other agents.

CDX-301 has been shown to expand CD141^{+}(BDCA3^{+}) conventional DCs (cDCs) in healthy volunteers. In these same subjects, CDX-301 was also shown to expand precursor cDCs (pre-cDCs) that produce the two major cDC subsets, the CD141^{+}(BDCA3^{+}) and the CD1c^{+} DCs. DC expansion peaks approximately two weeks after initiation of FLT3 ligand therapy (see figure below). The intratumoral injection of CDX-301 also increases the number of CD141^{+} DCs in blood and in the injected tumor[40]. CDX-301 also expanded CD141+ DCs and augmented the kinetics, magnitude, and frequency of cellular and immune responses to a NY-ESO-1 vaccine (CDX-1401) in patients with resected melanoma.



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

CDX-301 has been evaluated in two Celldex-sponsored clinical studies as monotherapy in healthy volunteers and donor/recipients (CDX301-02 and CDX301-03), in one study in combination with the antibody-drug conjugate glembatumumab vedotin in advanced melanoma (CDX011-05), and in one study in combination with CDX-1140 in advanced malignancies (CDX1140-01). CDX-301 has also been investigated in four investigator-initiated studies: in combination with radiotherapy for non-small cell lung cancer (CDX301-53), in combination with poly-ICLC and radiotherapy in lymphoma (CDX301-51), in combination with poly-ICLC, radiotherapy and pembrolizumab in non-Hodgkin's lymphoma, metastatic breast cancer and head and neck squamous cell carcinoma (CDX301-58), and in combination with poly-ICLC and the cancer vaccine CDX-1401 in malignant melanoma (CDX1401-54). CDX-301 has been well tolerated. One SAE of grade 3 community-acquired pneumonia in the healthy volunteer study CDX301-02 was attributed to CDX-301. Across all trials, no additional SAEs, and no deaths, have been assessed as related to CDX-301. In general treatment-related AE following CDX-301 administration are infrequent and mild to moderate in severity. Across all trials through August 2019, the most common treatment-related AE has been lymphadenopathy in 6 subjects (13%). Additional treatment-related grade 1 and grade 2 AEs that have been reported ≥ 5% of all patients treated with CDX-301 include: injection site reaction (including erythema, rash, reaction or pain; 8%), chills (6%), dyspepsia (6%), fatigue (6%), and hot flush (6%). One case of chills (2%), two cases of fatigue (4%), and two

cases of hot flush (4%) were also attributed to CDX-1140; a single case of fatigue (2%) was also attributed to glembatumumab vedotin. The CDX-301 Investigator Brochure provides additional details.

The safety, biological activity, and preliminary clinical activity of CDX-1140 as monotherapy and in combination with CDX-301 (FLT3 ligand) is being established in an ongoing phase I dose escalation and expansion trial (CDX1140-01; NCT03329950) whose interim results were presented at the 2019 AACR Annual Meeting. CDX-1140 is administered intravenously monthly, and CDX-301 is administered 75 μg/kg subcutaneously daily for 5 days the week prior to CDX-1140 during cycles 1 and 2. As of May 28th, 2020, a total of 89 patients have been administered CDX-1140, with 55 administered CDX-1140 monotherapy, 31 administered CDX-1140 in combination with CDX-301, and 3 patients administered CDX-1140 in combination with pembrolizumab. The Maximum Tolerated Dose (MTD) of CDX-1140 was determined to be 1.5 mg/kg. To date in the CDX1140-01 trial, 23 patients have been administered CDX-1140 monotherapy at 1.5 mg/kg, and 10 have been administered CDX-1140 at 1.5 mg/kg in combination with CDX-301.

Although not the primary objective of the study, evidence of anti-tumor activity has been observed, with an unconfirmed iRECIST partial response in a patient with gastroesophageal adenocarcinoma, treated with CDX-1140 + CDX-301. In addition, 2 patients with HNSCC who received CDX-1140 monotherapy have had early evidence of an anti-tumor effect with, cavitation and/or necrosis of lesions on CT scan.

CDX-1140 is biologically active, with increases in serum cytokine and chemokines observed in the study, as well as increased activation markers on dendritic cells and B-cells. Preliminary data indicates that CDX-301 increased the level of serum IL-12p40.

Most side effects associated with CDX-1140 have occurred in the 24-48 hours following the CDX-1140 infusion, consisted of infusion reactions/cytokine release syndromes, have been mild to moderate in severity, and have resolved with or without medications such as acetaminophen, NSAIDS, and/or anti-nausea medication. In a few cases, the side effects have been severe and have required hospitalization and treatment with corticosteroids or other immunosuppressive medications. Treatment related adverse events that have occurred in > 10% of patients are as follows: fatigue, joint pain, nausea, chills, fever, diarrhea, muscle pain, vomiting. Transient (usually low-grade) increases in liver transaminases have been seen in some patients, but no patient has had to discontinue therapy because of increased liver function tests. Cytokine release syndrome (including symptoms of fever, hypotension, hypoxia, fatigue, headache, and nausea) and pneumonitis have been the most common SAEs reported. Thus far, CDX-301 does not seem to add to the side effect profile of CDX-1140. The CDX-1140 Investigator Brochure provides additional details.

Our recommended phase II dose levels come from a phase I clinical trial that has established a MTD for CDX-1140 (Study CDX1140-01), as well as previous studies that have studied the MTD for CDX-301. These studies show the majority of potential toxicity comes CDX-1140, consistent with the mechanism of action of each drug.

CDX-1140 is being studied in one clinical trial. The first in human (FIH) trial (Study CDX1140-01) is an open-label, non-randomized, multicenter, dose-escalation study with expansion cohorts to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamic, and clinical activity of intravenous CDX-1140 as a monotherapy and in combination with subcutaneous CDX-301 (Flt3L) in patients with advanced solid tumors and hematologic malignancies.

As of a cut-off date of 9/5/2019, a total of 58 patients have been treated; 41 with CDX-1140 monotherapy and 17 patients with CDX-1140 plus CDX-301 combination therapy. The Maximum Tolerated Dose (MTD) and recommended dose and administration schedule for CDX-1140 monotherapy has been defined as 1.5mg/kg every four weeks.

CDX-301 and CDX-1140 had been used previously, alone and in combination, at the doses we are giving without grade 3 or higher AEs. The combination has also been used safely in a dose escalation trial NCT03329950. Few of these prior studies incorporated pancreatic cancer patients, which is why the first six patients on our study will be treated as phase I and assessed for potential toxicity.

Initial studies examined the tolerability of CDX-301 alone. Using a standard 3+3 dose-escalating design, sequential cohorts of 3–6 healthy volunteers received CDX-301 by daily SC injection at a dose level of 1, 3, 10, 25 or 75 μg/kg for 5 days (Cohorts 1–5), 25 μg/kg for 7 days (Cohort 6) or 25 μg/kg for 10 days (Cohort 7). Transient lymphadenopathy (Grade 1) was seen in six subjects (25 or 75 μg/kg/day cohorts) and single cases of diarrhea, injection site erythema, folliculitis and dry mouth (all Grade 1) were observed. A single subject receiving CDX-301 at 75 μg/kg/day for 5 days developed community-acquired pneumonia on day 12. No other AE's were seen.

CDX-301 was given in a subsequent study (25 μg/kg) with a lower dose of RT (2 Gy x 2) and another immune therapy without toxicity in lymphoma patients (Hammerich et al, Nat Med 2019).

1.3.3 Scientific Rationale for Study Design

The key questions for these CDX-1140 and CDX-301 as anti-cancer agents in PDAC patients is what exactly their effects are on tumor infiltrating immune cells. While significant pre-clinical and modest clinical data are already present for both agents; Without fully understanding their effects in human PDAC tissues it is

difficult to predict the optimum ways to employ these agents. In this study for our primary endpoint of changes in intratumoral cDCs we will compare to historical tissues and analysis of untreated PDAC patients. Thus, here-in we will simply run two arms testing CDX-1140 alone and CDX-301 plus CDX-1140.

1.4 Risk/Benefit Assessment

1.4.1 Known Potential Risks

Evidence from mouse and human tolerability studies suggest the study drugs, at the doses we are using, have a safety profile supportive of its further development as an anti-cancer therapeutic.

Treatment related adverse events that have occurred in > 10% of patients are as follows: fatigue, joint pain, nausea, chills, fever, diarrhea, muscle pain, and vomiting. Transient changes in liver function tests, platelet count, and lymphocyte count have been observed with CDX-1140. Transient increases in liver transaminases are expected in the 24-48 hours following the administration of CDX-1140. These changes have been mostly low grade and typically return to baseline within 1-2 week after the infusion. Important observed risks include cytokine release syndrome and pneumonitis. SQ and IV injections may lead to local discomfort or pain, and in some cases, infection.

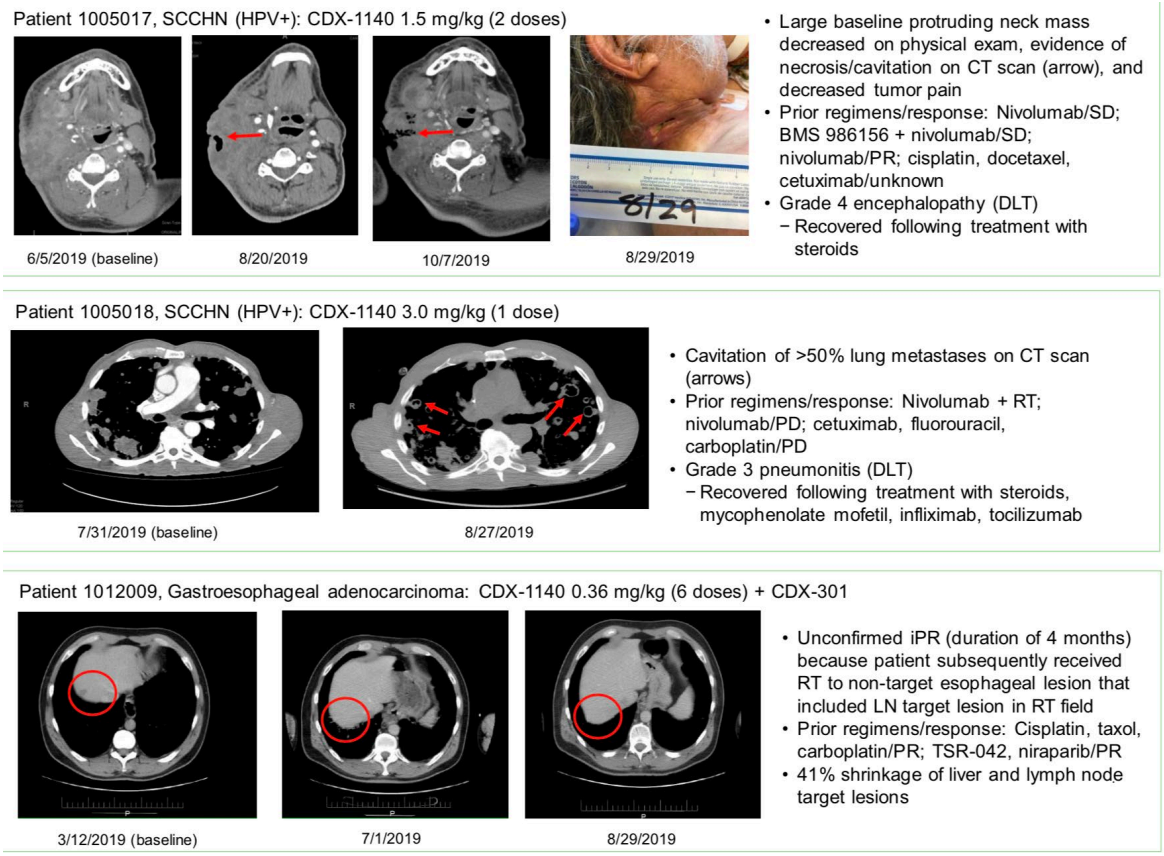
1.4.2 Known Potential Benefits

If the hypothesis of this study is correct, the experimental therapy will initiate a productive immune reaction against the tumor, locally and systemically, which may result in partial or complete tumor elimination and/or prevention of metastatic disease, however the validity of this hypothesis in humans is not currently known.

Thus far preliminary results of the phase I study of CDX-1140 with CDX-301 have been reported in poster form, and show:

- 1 unconfirmed iPR of 4 months duration in combination cohort (CDX-1140 0.36 mg/kg) – see below
- 6 patients with iSD; 4 in CDX-1140 monotherapy and 2 in CDX-1140 + CDX-301 with a duration of 1.8 months to 5.4 months; 1 iUPD in CDX-1140 + CDX301 with a duration of 10+ months
- Of 62 patients, 38 patients with activity assessments (scans) available and 7 have response data pending

Individual patients with encouraging responses are as follows:



While there are no established benefits, results from prior preclinical and clinical work are encouraging for the potential of benefit.

1.4.3 Assessment of Potential Risks and Benefits

The benefit-risk assessment of CDX-1140 with CDX-301 should be taken in the context of a drug in the early stages of development, and therefore is by definition uncertain and evolving. In the early clinical experience to date, this therapy has demonstrated an acceptable toxicity profile with evidence of biologic and clinical activity consistent with the mechanism of action.

In the best-case scenario, and that predicted by prior animal studies, the potential benefit of this therapy is tumor regression. In a population of patients that is overwhelmingly incurable, the potential risk benefit ratio appears very favorable.

2 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints	Justification for Endpoints
Primary		
To determine the amount of intratumor conventional dendritic cells in patients with resectable pancreatic cancer treated with neoadjuvant CDX-1140 vs. patients with resectable pancreatic cancer treated with neoadjuvant CDX-301 + CDX-1140.	intratumoral cDCs in surgical tissues	The immune therapy activates and increases the number of dendritic cells, which in mouse studies correlates with improved clinical outcome.
Exploratory		
To report immunologic correlates in both groups before and after therapy. Immunologic correlates will be assessed by multiplex IHC, FACS, and CyTOF, performed on tumor tissue and blood.	Global immune profiling by CyTOF, single cell RNASeq analysis, and histologic assessments, local control rate, distant metastasis-free survival, overall survival, margin negative resection rate.	Immune correlates are important indicators of therapeutic effect, and may correlate with clinical response.
To assess local control of resectable pancreatic cancer treated with neoadjuvant CDX-1140 vs. resectable pancreatic cancer treated with neoadjuvant CDX-301 + CDX-1140.		
To assess distant metastasis-free survival of patients with resectable pancreatic cancer treated with neoadjuvant CDX-1140 vs. resectable pancreatic cancer treated with neoadjuvant CDX-301 + CDX-1140.		
To assess overall survival of patients with resectable pancreatic cancer treated with neoadjuvant CDX-1140 vs. resectable pancreatic cancer treated with neoadjuvant CDX-301 + CDX-1140.		
To assess extent of resection in patients with resectable		

pancreatic cancer treated with neoadjuvant CDX-1140 vs. resectable pancreatic cancer treated with neoadjuvant CDX-301 + CDX-1140.		
To assess the safety and tolerability profile of CDX-1140 vs. CDX-301 plus CDX-1140 in surgically resectable pancreatic cancer patients.	adverse events	AE profile for this patient population.

3 STUDY POPULATION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed surgically resectable pancreatic ductal adenocarcinoma, but not adenosquamous/squamous pancreas cancers (as determined by operating surgeon or tumor board). Patients who have previously received chemotherapy for his/her pancreas cancer within the past 6 months and who are now deemed resectable are also eligible for this trial.

2. At least 18 years of age.

3. ECOG performance status ≤ 1 (see Appendix A)

4. Normal bone marrow and organ function as defined below:
   a. Absolute neutrophil count ≥ 1,500 /cumm
   b. Platelets ≥ 100,000 /cumm
   c. Hemoglobin ≥ 9.0 g/dL
   d. AST(SGOT)/ALT(SGPT) ≤ 2.5 x IULN
   e. Creatinine clearance ≤ 1.5 x IULN or glomerular filtration rate of ≥ 60 mL/min
   f. INR ≤ 1.5 x IULN unless patient is receiving anticoagulant therapy as long as INR or PTT is within therapeutic range of intended use of anticoagulants
   g. aPTT ≤ 1.5 x IULN unless patient is receiving anticoagulant therapy as long as INR or PTT is within therapeutic range of intended use of anticoagulants
   h. Albumin ≥ 3.0mg/dL

5. The effects of CDX-301 and CDX-1140 on the developing human fetus are unknown. For this reason, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry, for the duration of study participation, and for 3 months after the last dose of either study drug. Should a woman become pregnant or suspect she is pregnant while participating in this study or for 3 months after the last dose of either study drug, she must inform her treating physician immediately.

6. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Immmune deficienties such as HIV.

2. A history of other malignancy with the exception of malignancies for which all treatment was completed at least 2 years before registration and the patient has no evidence of disease.

3. Currently receiving any other investigational agents or has received any other investigational agents within 4 weeks or 5 half-lives of the planned first dose of study treatment.

4. Receipt of chemotherapy within 2 weeks of planned first dose of study treatment.

5. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to CDX-301 or CDX-1140 or other agents used in the study.

6. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (for > 1 month of 10 mg prednisone daily, or equivalent) or any other form of immunosuppressive therapy not routinely associated with chemotherapeutic regimen.

7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, immunosuppression, autoimmune conditions, or underlying pulmonary disease.

8. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, immunosuppression, autoimmune conditions, or underlying pulmonary disease.

9. Has an autoimmune disease requiring systemic treatment within the past 2 years (i.e. with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected).

11. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

12. Has a known history of active TB (bacillus tuberculosis).

13. Major surgery within 28 days prior to the first study treatment.

14. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative pregnancy test within 14 days of study entry.

15. History of bone marrow or solid organ transplant.

16. Patients with a history of myocardial infarction, cerebral vascular accident, thrombosis or pulmonary embolus within 12 months prior to the first dose of study treatment are excluded from this study.

17. Patients with known mutations/amplifications in Flt3

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

4.5 Strategies for Recruitment and Retention

All patients with pancreatic cancer are discussed in our weekly multidisciplinary tumor board and clinical trial options are reviewed. WUSM department of surgery preforms greater than 100 pancreatic cancer resections per year. Many of these patients would be eligible for this trial. We anticipate an accrual rate of approximately 15 patients per year. To have outreach meetings in the community to explain the radiation therapy and clinical trial options available at Washington University. We will accrue without respect to race, gender or socioeconomic background.

4.6 Measures to Minimize Bias: Randomization

Consenting and eligible patients will be randomized on a 1:1 basis to receive CDX-1140 followed by surgery or CDX-301 + CDX-1140 followed by surgery until 12 patients evaluable for the primary objective have been randomized to each arm. The randomization table will be generated by the statistician using a statistical software and will be uploaded to REDCap to randomize patients.

5 TREATMENT PLAN

5.1 Premedication Administration

5.1.1 CDX-1140

Prophylactic premedication is required for all patients: diphenhydramine 25/50 mg (or equivalent anti-histamine), 500 to 750 mg paracetamol (acetaminophen), and naproxen sodium 250 mg (or equivalent NSAID) at least 30 minutes prior to CDX-1140 administrations. Ranitidine 150 mg (or equivalent) may also be incorporated into the premedication regimen. Prophylactic premedication with corticosteroids

is to be avoided because of the potential to attenuate the anti-tumor activity of CDX-1140.

CDX-1140 will be administered intravenously over 90 minutes using a 0.22 micron in-line filter.

CDX-1140 post-infusion medication is also required for all patients. In the 24-48 hours following the CDX-1140 infusion, alternate oral acetaminophen (1000 mg) and non-steroidal anti-inflammatory (e.g., ibuprofen 200 mg) q6H. An anti-histamine and anti-emetic may also be utilized if clinically indicated. Patients should be evaluated to determine if continuation of post-infusion medication is needed on the day after CDX-1140 dosing. Note that the potential for toxicity with these drugs and appropriate precaution should be utilized in patients with risk factors for toxicity, e.g. patients with peptic ulcers, increased LFTs, or increased creatinine. Also, care should be taken to medicate for no longer than is necessary in order to avoid potential confounding factors in determining adverse event causality (e.g. increased LFTs).

All patients should be monitored for 4 to 6 hours post administration of CDX-1140 with standard post-infusion monitoring.

5.1.2 CDX-301

Injection site reactions have been infrequent and mild with CDX-301. Pre-medication with diphenhydramine has been reported to be effective in the prevention of pruritic and erythemic reactions and may be considered for subjects who experience local reactions after treatment with CDX-301. Injection site reactions may also be treated with analgesics (i.e., Tylenol). If there is injection site pain, a numbing cream such as Emla cream can be used prior to administration of CDX-301.

5.2 Study Intervention Administration

Patients randomized to the CDX-1140 monotherapy arm will receive a single IV infusion at a dose of 1.5 mg/kg, with surgery to follow 7-12 days after administration of CDX-1140.

Patients randomized to the CDX-301 + CDX-1140 arm will receive CDX-301 at 75 mcg/kg/day as a subcutaneous injection every day for 5 days (Days 1-5) with CDX-1140 IV at 1.5 mg/kg on Day 8. Patients will be required to be present in clinic for each injection. Surgery will be 7-12 days after administration of CDX-1140.

5.3 Definitions of Evaluability

Patients must undergo collection of blood and tissue at the time of resection in order to be evaluable for the primary objective of determining amount of intratumor cDC. Patients who are not evaluable for the primary objective will not count towards analysis of this

objective and will be replaced. However, these patients will continue on study/in follow-up to be followed for toxicity and local control, DMFS, and OS regardless of whether they had resection.

All patients who receive any study treatment are evaluable for the exploratory objective of safety and tolerability. Patients are evaluated from first receiving study treatment until time of resection, or until 60 days after end of treatment if resection doesn't take place.

In order to be evaluable for the exploratory objective evaluating immunologic correlates, patients must have blood and tissue collected before and after therapy.

In order to be evaluable for the exploratory objectives of assessing local control, DMFS, and OS, patients must have received at least one dose of study treatment.

In order to be evaluable for the exploratory objective of assessing extent of resection, patient must have received at least one dose of study treatment and undergone resection.

5.4 Concomitant Therapy and Supportive Care Guidelines

The investigational drugs are not known or predicted to interact with other drugs, and are not broken down by CYP enzymes.

Infusion reactions may occur when giving any IV medication. Recommendations for the management of peri-infusional reactions are provided below and may be modified based on local treatment standards and guidelines, as appropriate. Infusion reactions should be graded according to NCI-CTCAE guidelines, http://ctep.cancer.gov. Obtain serum at the time of an infusion reaction.

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

Remain at bedside and monitor patient until recovery from symptoms.

For Grade 2 symptoms: (infusion interruption indicated but responds promptly to symptomatic treatment [e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, i.v. fluids]; prophylactic medications indicated for ≤ 24 hours)

Stop the CDX-1140 infusion, begin an i.v. infusion of normal saline, and treat the patient with diphenhydramine 50 mg i.v. (or equivalent) and/or 500 to 1000 mg paracetamol/acetaminophen; remain at bedside and monitor patient until resolution of symptoms. Corticosteroid 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 patient closely. If symptoms recur then no further CDX-1140 will be administered at that visit. The amount of study drug infused must be recorded on the case report form (CRF). Patients who experience an adverse event,

including an infusion reaction of Grade 2, during the 4-6 hour observation period that does not resolve during this time should be observed for 24 hours or until the adverse event resolves with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the adverse event.

For Grade 3 or Grade 4 symptoms: (Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: life-threatening consequences; urgent intervention indicated).

Immediately discontinue infusion of CDX-1140. Begin an i.v. infusion of normal saline, and treat the patient 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 i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed. Patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Patients who experience an infusion reaction of Grade ≥ 3, regardless of resolution, will be observed for 24 additional hours or until the adverse event resolves with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the adverse event. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids). CDX-1140 will be permanently discontinued for patients with Grade 4 infusion reactions or Grade 3 infusion reactions lasting more than 6 hours.

5.5 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum or urine pregnancy test within 14 days prior to the first day of study treatment.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during treatment with the investigational agents.

If a patient is suspected to be pregnant, the study agent should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy with the study agent or 3 months thereafter, the investigator must be notified in order to facilitate outcome follow-up.

5.6 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

Treatment may also be discontinued early for the following reasons:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar.

5.7 Duration of Follow-up

Patients will be followed every 6 months for 2 years or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.8 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for three scheduled visits and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing

address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5.9 Protocol Stopping Criteria

The principal investigator will closely monitor and analyze study data as they become available and will make determinations regarding the presence and severity of adverse events. The administration of study injections and new enrollments will be halted and the QASMC promptly notified if any of the following events occurs:

1. **One** (or more) subject(s) experiences a Grade 3 or 4 adverse event that is classified as probably or definitely related to treatment with CDX-301 or CDX-1140; this excludes Grade 3 arthralgia and myalgia that has been adequately treated with a short course of steroids.

2. **One** (or more) subject(s) experiences a SAE that is classified as probably or definitely related to treatment with CDX-301 or CDX-1140;
3. **Two** (or more) subjects experience the **same** Grade 2 or higher adverse event that is classified as probably or definitely related to study treatment: this criterion applies to cytokine-release syndrome, infusion-related reactions, laboratory abnormalities or other clinical adverse experiences. This excludes adverse events of arthralgia and myalgia that have been adequately treated with a short course of steroids.
4. Any other observation occurs that in the opinion of the PI results in a recommendation to halt enrollment.

If one of these events does occur, study enrollments would only resume if review of the adverse events that caused the halt resulted in a recommendation to permit further study treatment and study enrollments.

6 DOSE DELAYS/DOSE MODIFICATIONS

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 4 weeks of the scheduled interruption, at PI discretion. A hold longer than 4 weeks will be allowed at PI discretion.

There will be no dose modifications for CDX-1140 as it is given as a single dose.

CDX-301 will be discontinued for any grade 3 and grade 4 events that are deemed at least possibly related to it. If discontinued, the patient may still remain on study. Any missing doses are made up, if feasible. Since this is an immune therapy and the dose-response relationship is not likely to be linear, the therapy will be held rather than dose reduced for patients experiencing an AE.

Toxicity Possibly, probably or definitely attributed to CDX-301	Treatment Interruption and Dose Reduction Instructions
Lymphadenopathy	No treatment modification, since lymphadenopathy is not dangerous or indicative of a poor outcome.
Injection site erythema	No treatment modification. Rotate injection site. Treat with topical antibiotic ointment.
Folliculitis	No treatment modification. Treat with topical antibiotic ointment.
Dry mouth	No treatment modification.

Other holds and modifications may be made at the discretion of the PI.

7 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix B for definitions and Appendix C for a grid of reporting timelines.

Adverse events will be tracked from start of treatment through time of surgery (or 60 days after end of treatment if surgery doesn't take place). All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF

Refer to the data submission schedule in Section 10.0 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 Sponsor-Investigator Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Washington University Sponsor-Investigator (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.1.3 Reporting to Celldex Therapeutics

Any serious adverse event (SAE) or follow-up to an SAE, including death due to any cause other than progression of the cancer under study, whether or not related to study drug, must be reported to Celldex Therapeutics within 1 business day.

The investigator must inform Celldex Therapeutics in writing using a MedWatch 3500a form of any SAE within 24 hours of the investigator becoming aware of the event. 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.

"Adverse Event" or "AE" shall mean any untoward medical occurrence in a study subject who is administered the Study Drug regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug.

Celldex Therapeutics, Inc., considers an SAE to be any adverse event that is life-threatening or that results in any of the following outcomes: death; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; or a congenital anomaly/birth defect.

"Suspected Unexpected Serious Adverse Reaction" or "SUSAR" shall mean any Serious Adverse Event, the nature, severity or frequency of which is not consistent with information in the most current investigator's brochure.

Elective or previously scheduled hospitalizations for pre-existing conditions that have not worsened after initiation of treatment should not be classified as SAEs. For example, an admission for a previously scheduled hernia repair would not be classified as an SAE.

Completed SAE reports are to be submitted to:

Celldex Therapeutics, Inc.
Pharmacovigilance
Hotline: 908-323-2233
Fax No.: 781-644-6434
Email: SAE@celldex.com

7.1.3.1 Reporting Pregnancy

Pregnancy per se is not considered an AE unless there is cause to believe that the study drug may have interfered with the effectiveness of a contraceptive medication or if the outcome of the pregnancy meets SAE criteria (miscarriage or congenital anomaly/birth defect), it should be reported as an SAE. Hospitalization for normal delivery of a healthy newborn is not an SAE.

Each pregnancy that occurs in female subjects or female partners of male subjects while on the study drug or within three months following completion of the study drug must be reported to the Celldex within 24 hours of the Investigator becoming aware of its occurrence. If a subject becomes pregnant, drug administration must be discontinued immediately. The pregnancy should be followed up to determine outcome (including spontaneous or voluntary termination), details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal or newborn complications. Follow-up and documentation must occur even if the subject withdraws from the study or the study is completed. Every effort should be made to gather information regarding the pregnancy outcome until 8 weeks postpartum. It is the responsibility of the Investigator to obtain all pregnancy information.

7.1.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Washington University Sponsor-Investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix B for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix B) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix B) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
    - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
    - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8 PHARMACEUTICAL INFORMATION

8.1 CDX-301

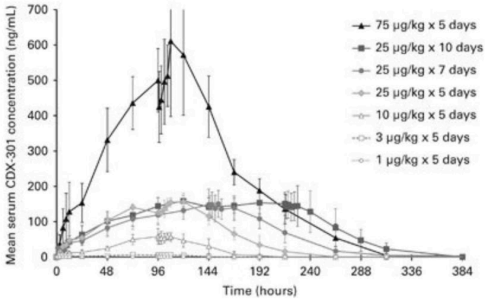
8.1.1 CDX-301 Description

CDX-301 is recombinant human Flt3L, which stimulates dendritic cell development. More specifically, CDX-301 is a soluble glycoprotein, which, after the leader sequence has been cleaved off, consists of 153 amino acids representing most of the protein's extracellular domain except for the C-terminal three amino acids, and whose calculated molecular weight is 17,445 kD ($C_{777}H_{1224}N_{213}O_{229}S_8$). It exists as numerous isoforms, some of which are separated by isoelectric focusing in the pI range of 3.5 to 5.5. There are two N-glycosylation sites (N100 and N123), which are partially occupied by complex carbohydrate structures and five O-glycosylation sites (S136, S137, T138, S144 and T151), three of which are always occupied.

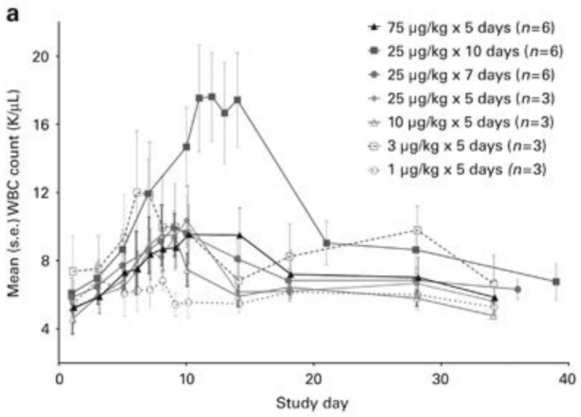
CDX-301 drug product is formulated as a sterile solution intended for single-use parenteral administration. Each vial contains a nominal 2.5 mg/mL CDX-301 protein in a 1 mL volume of buffered solution composed of sodium phosphate and sodium chloride, with a pH of 7.0.

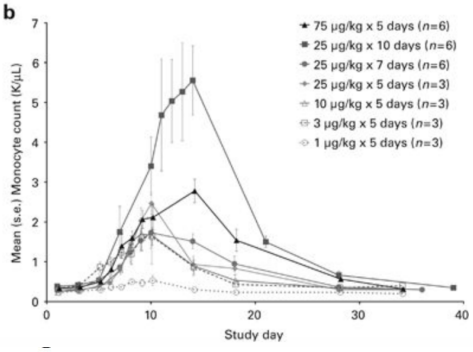
8.1.2 Pharmacokinetics and Drug Metabolism

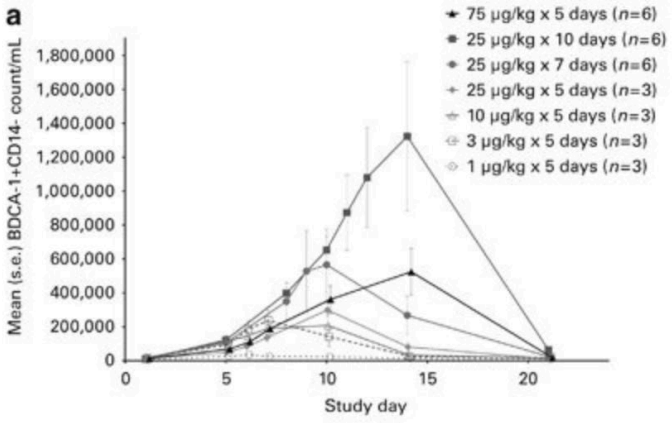
CDX-301 half life, efficacy and safety of CDX-301, recombinant human Flt3L, at expanding dendritic cells and hematopoietic stem cells in healthy human volunteers has been reported [41] and is shown in breif below.

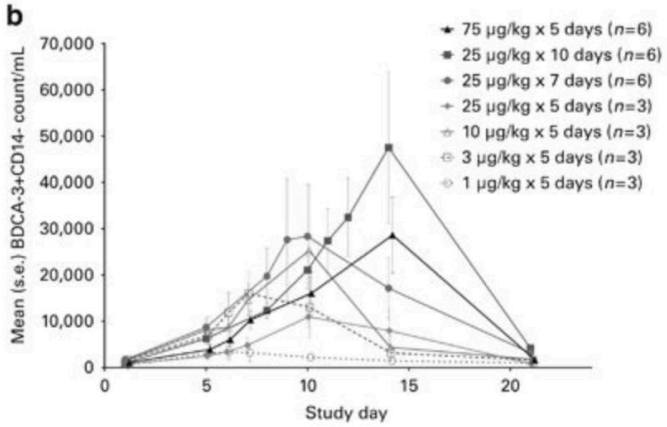


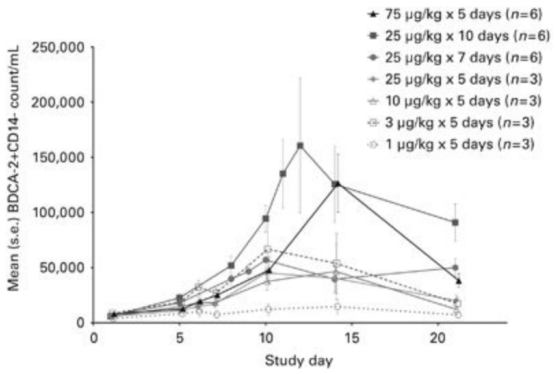
CDX-301 serum concentrations are shown as a function of time following the first dose of CDX-301. CDX-301 concentrations were determined by immunoassay, and mean values (±s.ds.) for each study day are plotted for the cohorts as indicated in the legend.


a
75 µg/kg x 5 days (n=6)
25 µg/kg x 10 days (n=6)
25 µg/kg x 7 days (n=6)
25 µg/kg x 5 days (n=3)
10 µg/kg x 5 days (n=3)
3 µg/kg x 5 days (n=3)
1 µg/kg x 5 days (n=3)
Mean (s.e.) WBC count (K/µL)
Study day


b
75 µg/kg x 5 days (n=6)
25 µg/kg x 10 days (n=6)
25 µg/kg x 7 days (n=6)
25 µg/kg x 5 days (n=3)
10 µg/kg x 5 days (n=3)
3 µg/kg x 5 days (n=3)
1 µg/kg x 5 days (n=3)
Mean (s.e.) Monocyte count (K/µL)
Study day


a
75 µg/kg x 5 days (n=6)
25 µg/kg x 10 days (n=6)
25 µg/kg x 7 days (n=6)
25 µg/kg x 5 days (n=3)
10 µg/kg x 5 days (n=3)
3 µg/kg x 5 days (n=3)
1 µg/kg x 5 days (n=3)
Mean (s.e.) BDCA-1+CD14- count/mL
Study day


b
75 µg/kg x 5 days (n=6)
25 µg/kg x 10 days (n=6)
25 µg/kg x 7 days (n=6)
25 µg/kg x 5 days (n=3)
10 µg/kg x 5 days (n=3)
3 µg/kg x 5 days (n=3)
1 µg/kg x 5 days (n=3)
Mean (s.e.) BDCA-3+CD14- count/mL
Study day



8.1.3 Supplier(s)

The drug will be supplied free of charge by Celldex.

8.1.4 Dosage Form and Preparation

CDX-301 is formulated as an injectable solution, for SQ administration. CDX-301 vials should not be shaken. CDX-301 liquid should be withdrawn from vial gently, avoiding foaming and excess shearing. CDX-301 should be used as soon as possible once drawn into a syringe within 4 hours). Each CDX-301 vial is single use only. Partially used vials or solutions must not be used to prepare another dose and instead should be handled for destruction according to the study sites' regulations for the disposal of biological agents. CDX-301 is injected subcutaneously using standard procedures, in either abdominal or gluteal subcutaneous tissue.

8.1.5 Storage and Stability

CDX-301 will be stored in a refrigerator at 2 to 8°C and protected from light. CDX-301 should not be frozen.

8.1.6 Administration

Patients should be given CDX-301 SQ, in either the stomach or gluteal subcutaneous tissue. The injection can be performed any time during the day, but preferably will be given at roughly the same time each day.

8.1.7 Special Handling Instructions

No special handling instructions.

8.2 CDX-1140

8.2.1 CDX-1140 Description

CDX-1140 is an agonistic antibody against CD40. Specifically, CDX-1140 is a recombinant fully human IgG2 anti-CD40 mAb generated by *in vitro* Chinese Hamster Ovary (CHO) cell culture and using standard mAb purification processes. The product is composed of two identical pairs of polypeptide chains, each pair having one fully-human kappalight (23,227 Da) and one fully-human IgG2 heavy chain (49,172 Da). The heavy and light chains expected molecular weights are based on the amino acid sequence of each chain. The N-terminal amino-acid sequences of the variable regions have been confirmed by sequence analysis.

No animal-derived raw materials are used during the cell culture, purification, and formulation of the drug substance. A low pH step and a nanofiltration step are used for virus inactivation and reduction. Testing for adventitious agents is performed in accordance to the Food and Drug Administration (FDA) Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997).

The Drug Product manufacturing process consists of sterile filtration (2 x 0.22 µm filters in series) of the CDX-1140 formulated bulk Drug Substance, aseptic filling into Type 1 vials, stoppering with gray butyl stoppers, and capped with polypropylene flip-off caps. Each vial contains a nominal 3.0 mg/mL CDX-1140 protein in a 10.0 mL volume of buffered solution composed of sodium phosphate, potassium phosphate, potassium chloride, sodium chloride, and Polysorbate 80, with a pH of 7.0.

The final Drug Product dosage form is provided in a 10-mL Type 1 vial with a gray butyl stopper and a polypropylene flip-off cap, containing a sterile, single-use liquid with a nominal 3.0 mg/mL of CDX-1140 to be used for intravenous administration. The drug product vials are stored at ≤ - 65°C (-85°F). The CDX-1140 formulated drug substance and drug product are identical in terms of formulation and concentration.

8.2.2 Pharmacokinetics and Drug Metabolism

CDX-1140 has previously been described: Vitale et al, *Cancer Immunol Immunother 2019* [42]

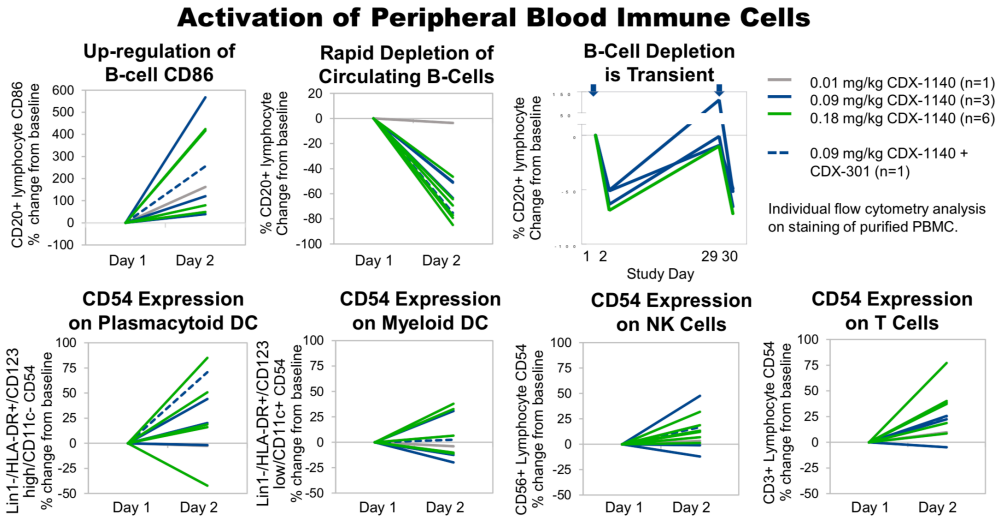
(https://link.springer.com/article/10.1007%2Fs00262-018-2267-0).

Summary of Nonclinical Findings
CDX-1140 is an agonist anti-CD40 human IgG2κ mAb being developed as a cancer therapeutic. The main findings from the *in vitro* pharmacology studies are as follows:

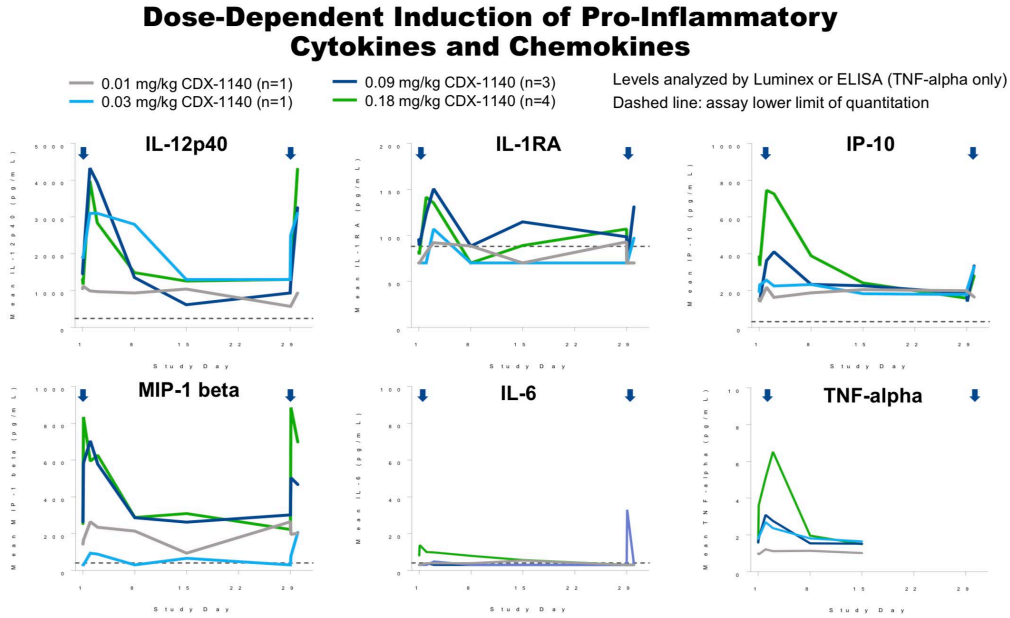
- CDX-1140 bound specifically to human CD40 with high affinity but not to 10 TNFRSF members with the closest homology to CD40.
- CDX-1140 does not block CD40 ligand (CD40L) binding to CD40.
- CDX-1140 bound to human and cynomolgus macaque CD40.

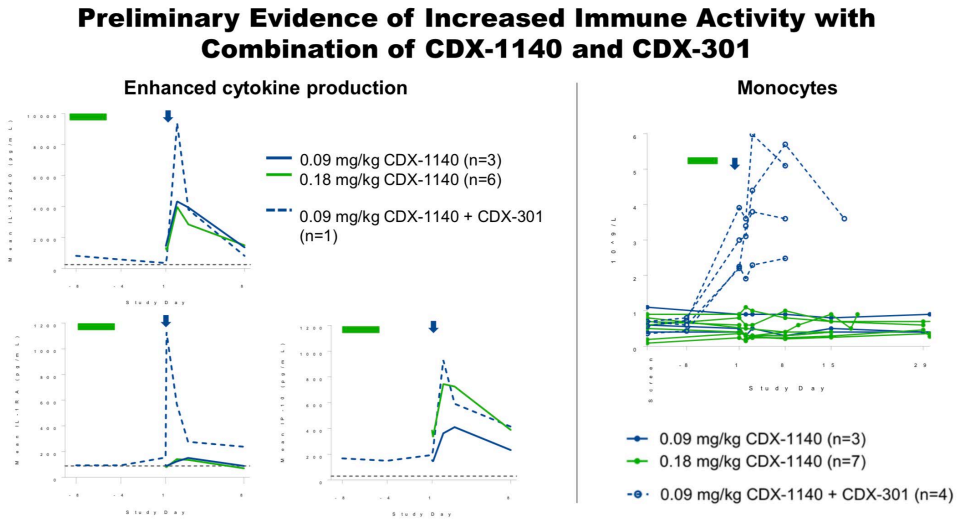
- CDX-1140 activated CD40 signaling in a CD40-expressing HEK-293 NF- kB reporter cell line *in vitro*.
- CDX-1140 promoted B cell activation *in vitro* as measured by proliferation, upregulation of activation markers CD86 and HLA-DR, and induction of IL-12p40 production by dendritic cells (DCs).
- Based on *in vitro* B cell and DC activation, the MABEL is estimated to be approximately 0.004 mg/kg for CDX-1140.
- CDX-1140 agonist activity is independent of Fc receptor (FcR) interactions.
- Prolonged incubation (6 days) of human peripheral blood mononuclear cells (PBMCs) with CDX-1140 led to the accumulation of various cytokines and chemokines, most prominently TNF-α, MIP-1α, and MIP-1β, with lower levels of IL-1RA, IL-6, and IL-10. Depletion of CD14+ monocytes, but not B cells, eliminated the production of TNF-α.
- CDX-1140 was assessed for the capacity to induce cytokines in whole blood from healthy human donors when added in soluble form, or adsorbed to microtiter plates from wet solution, or adsorbed to microtiter plates by drying down completely. Overall, very little specific cytokine induction was observed with CDX-1140 relative to the human IgG2 isotype control under any condition, although donor to donor variability was observed with some activation greater than the negative control.
- CDX-1140 upregulated CD95 on Ramos lymphoma cells and the addition of CD40L enhanced the CD95 expression when combined with suboptimal lower CDX-1140 concentrations. A similar synergy was observed between CDX-1140 and CD40L in DC and B cell activation assays.
- CDX-1140 was compared in vitro to CP*, an mAb having the same amino acid sequence as CP-870,893, an agonist anti-CD40 IgG2 mAb in clinical development by Roche. CDX-1140 was similar, though generally lower compared to CP* in the upregulation of CD86 on B cells and induction of IL-12p40 by DC.
- The main findings from the *in vivo* pharmacology studies are as follows:
- CDX-1140 significantly increased the duration of survival of severe combined immunodeficiency (SCID) mice implanted subcutaneously with human B cell lymphoma Daudi, Ramos or Raji cells.
- When Ramos lymphoma cells were co-implanted with human PBMCs in SCID mice, the survival of the mice was extended further compared to the absence of added PBMCs, suggesting a contribution from immune responses.

Effects of on peripheral blood immune cells have been preliminarily examined, as shown below.



Effects on pro-inflammatory cytokines have been examined, as shown below:





8.2.3 Supplier(s)

The drug will be supplied free of charge by Celldex.

8.2.4 Dosage Form and Preparation

CDX-1140 is formulated as an injectable solution, for IV administration. The morning that a patient is due for treatment, research personnel will remove a vial from the -85°F freezer and place it in the refrigerator at 2-8 degrees °C. When a patient arrives for treatment, research personnel will remove the vial and deliver it to the patient's treatment location. After equilibration to room temperature and before use, the vial should be gently swirled (but not inverted or shaken) to ensure uniform mixing of the contents. Solution should be gently withdrawn (avoiding foaming and excess shearing). Once the sterile vials are entered (i.e., once CDX-1140 is drawn into a syringe), the drug 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). The infusion should take place at a standard rate appropriate for the type of IV access, lasting between 1-15 minutes.

8.2.5 Storage and Stability

Vials of CDX-1140 are shipped in insulated shippers and must be stored at ≤ - 65°C (-85°F) until use and protected from light – storage at -85°F will be done by the primary investigators. The day of treatment, CDX-1140 can be stored at room temperature for up to 3 hours, or refrigerated (at 2-8 degrees) for up to 6 hours if necessary.

8.2.6 Administration

Each vial to be used for intravenous administration contains a premixed solution, containing 3.0 mg/mL CDX-1140 protein in a 10.0 mL volume of buffered solution. Injections can be performed through any standard IV method (peripheral IV, PICC, PORT, or any other IV access that is in place or most convenient for the patient). Patients should be given CDX-1140 IV once per month.

8.2.7 Special Handling Instructions

No special handling instructions.

9 CORRELATIVE STUDIES

9.1 Fresh Tumor Tissue

9.1.1 Collection of Specimen

Tumor tissue will be collected at the time of surgical resection. Tissue received from the OR is brought to the pathology processing table. At this point, the tissue is sectioned and "bread loaved" by a pathologist. Current best practice for correlative studies will take a central plane cross-section from the tumor if not interfering with clinical pathological assessments. Tumor tissue will then be transported to the research labrotory on wet ice in DMEM media. A smaller portion (~20% of available biomarker tissue) will directly cryopreserved in liquid N2 or on dry ice.

Processing labrotory is located at BJCIH 7th floor, room 7202 (DeNardo-lab).

9.1.2 Handling of Specimen(s)

Tumor tissues will be divided into two pieces. Twenty percent of tissue will be directly cryopreserved in liquid N2 or on dry ice, while eighty percent of the tissue will be placed in DMEM Media in wet ice. Samples will be transported on wet and dry ice to the research labrotory for processing. Research processing laboratory is located at BJCIH 7th floor, room 7202 (DeNardo-lab).

9.2 Archived Tumor Tissue

Archival tissue will be retrieved from pathology thru the SCC request system. This will also be used to inspect potential sampling biases or problems.

9.3 Research Blood

Blood will be collected at three time points:

- At screening
- Prior to first therapeutic dose of CDX-1140, on the day of infusion

- At the time of surgery.

For each blood collection three 10ml green-top (sodium heparin) tubes will be collected for PBMCs and plasma along with one red-top sera (no-anticoagulant) tubes. Samples will be transported on wet ice to the research laboratory for processing.

Processing laboratory is located at BJCIH 7th floor, room 7202 (DeNardo-lab).

Additionally, no more than 10 mL of blood will be collected at any standard follow-up visit to analyze for CDX-301 ADAs. This blood will be collected in to a single red top tube, labeled with patient ID, date, and visit time point, and will be taken directly to the DeNardo lab for cryopreservation and batch shipping to Celldex.

9.4 Specimen Analysis

First, we will assess the impact of CDX-1140 compared to CDX-301/CDX-1140 on multiple parameters of PDAC local and systemic tumor immunity. Second, we expect diverse objective responses to therapy; blood and PDAC tissues parameters can be correlated with patient outcomes to identify the biological parameters that indicate therapeutic benefit.

Our tissue collections will include pre- treatment and time of surgery blood and sera, as well as tumor tissue collected at the time of surgery. Tissue collection will be mandatory for all patients. Tumor tissues will be divided into cryopreserved, formalin-fixed paraffin-embedded (FFPE), and flow cytometry/CyTOF samples. We will directly assess how no-treatment vs CDX-1140 vs CDX-301/CDX-1140 alters immune cell tumor infiltration using high-density flow cytometry and CyTOF. We optimized two 14-parameter flow cytometry protocols to assess T-cell infiltration, activation, and exhaustion, and myeloid cell and DC infiltration and two 35 parameter CyTOF panel (see **Figure**). This will be complemented by Single Cell RNA sequencing when tissue it sufficient. Conventional dendritic cells are defined by the lack of expression of CD3, CD19, CD20, CD16, CD56, and the expression of CD45, CD11c, MHCII high and either CD1c or CD141.

On archival FFPE tissues we will complement flow cytometry with multiplex IHC on FFPE tissue. We optimized several multiplex IHC panels using the PerkinElmer OPAL system. These panels can identify changes in T-cell infiltration and proliferation (e.g., $CD3^{+}/CD8^{+}/Ki67^{+}$) and proximity to tumor cells (CK19). For imaging and deconvolution we will capture images and conduct quantitative analysis using HALO pattern recognition software.

We will analyze blood leukocyte populations using two optimized 36-parameter CyTOF panels designed for adaptive and innate immune cells, respectively. We will focus on evidence of increased T-cell activation corresponding with tumor reactivity (similar to results from human checkpoint studies[43, 44]). This will include analyses of T-cell proliferation (Ki67), lineage transcription factors (e.g., GATA3, T-bet, Eomes), effector function (Granzyme B, perforin), memory status (e.g., KLRG1, CD28, CD127), and exhaustion/checkpoint marker expression (e.g., 41BB, LAG3, TCF1 and SLMF6). We will perform unguided analysis of this CyTOF data using PhenoGraph and X-Shift to identify uniquely changing T-cell subsets, and Citirs to determine potential biomarkers of treatment response.

A

Human CyTOF T Cell Pannel			
Marker	**Metal**	**Marker**	**Metal**
CD45	089Y	CCR7	159Tb
open	115In	CD39	160Gd
CCR6	141Pr	Tbet	161Dy
CD19	142Nd	FoxP3	162Dy
ICOS	143Nd	BTLA	163Dy
CD38	144Nd	GITR	164Dy
CD4	145Nd	CD16	165Ho
IgD	146Nd	CD24	166Er
RORgt	147Sm	Gata3	167Er
PD-L1	148Nd	CD8	168Er
open	149Sm	IL-2R	169Tm
CD27	150Nd	CD3	170Er
CD14	151Eu	GranzymeB	171Yb
CTLA-4	152Sm	Ki67	172Yb
TIGIT	153Eu	CXCR4	173Yb
TIM-3	154Sm	PD-1	174Yb
CD45RA	155Gd	Perforin	175Lu
CXCR3	156Gd	NCAM	176Yb
CCR4	158Gd	CD11b	209Bi

B PhenoGraph on α/β T Cells

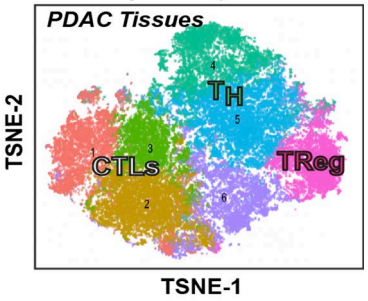


Figure. (A) T-cell CyTOF panel. **(B)** CyTOF data from human PDAC tissues (*n*=6) analyzed for T-cell subsets by PhenoGraph.

10 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to starting treatment
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Surgery Form	Time of surgery
Research Specimen Form	Baseline, time of CDX-1140 treatment, time of surgery
Follow Up Form	Every 6 months for 2 years; 60 days after EOT if surgery is not performed
Progression Form	Time of disease progression
Death Form	Time of death
MedWatch Form	See Section 7.0 for reporting requirements

10.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

11 MEASUREMENT OF EFFECT

Primary Endpoint: This study is powered to detect a two-fold change in intratumoral conventional dendritic cells between CDX-1140 vs. CDX-301 plus CDX-1140 treated patients. This is a critical endpoint to ensure CDX-301 plus CDX-1140 is having its intended biological effect and thus has a likelihood of impacting tumor immunity and patient outcomes.

Correlative Secondary Endpoints: These will include global immune profiling by CyTOF, single cell RNASeq analysis, and histologic assessments. Critical to this assessment will be comparative analysis of the impact of CDX-1140 vs. CDX-301 plus CDX-1140 on T cell and cDC number and phenotype.

Exploratory endpoints: These will include local control rate, distant metastasis-free survival (DMFS), overall survival (OS), and margin negative resection rate. Proportions of local control and margin negative resection for all treated patients.

12 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a two-arm randomized Phase II trial. All the enrolled patients with resectable pancreatic cancer will undergo surgery. Patients will be 1:1 randomized to one of two treatments: neoadjuvant CDX-1140 vs. CDX-301 plus CDX-1140.

13.2 Sample Size Calculation

The primary endpoint is intratumoral conventional dendritic cells (cDCs) at surgery. The sample size calculation is based on the primary endpoint only. Our pilot data in animal models showed that the mean and standard deviation of the number of intratumoral cDCs per gram of tissue in CD40 agonist IgGs was 44726 with a standard deviation of 37895, and for mice treated with CDX-301 plus CD40 agonist, the mean cDCs per gram of tissue was 2716742 with a standard deviation of 1322448. Assuming a similar therapeutic effect on cDCs and similar distribution among samples, 12 patients per arm will have at least 99.9% power to detect the intratumoral cDCs difference as measured by CyTOF between two arms using a two-sided two-group T-test at the type I error of 5%. We plan to enroll 12 patients evaluable for the primary objective per arm for a total of 24 evaluable patients. An interim analysis can be performed at 5 patients per arm or greater; 5 patients per arm will have >80% power to detect changes in cDCs.

13.3 Accrual

We perform surgery in 80-110 patients per year at Washington University with similar characteristics and estimate approximately 30-40 patients/year may be eligible for and will participate in this trial. We anticipate enrollment of approximately 1-3 patients per month.

13.4 Statistical Analyses

13.4.1 Patient Disposition

The number of patients discontinued, the reasons for discontinuation, and the amount of therapy administered will be summarized by patient and by reason for discontinuation by arm.

13.4.2 Protocol Deviations

All significant deviations will be summarized by patient and by type of deviation.

13.4.3 Demographics and Baseline Characteristics

Subject demographic and clinical characteristics will be summarized to characterize the population. Descriptive summaries will include means, standard deviations, medians, ranges for continuous variables and frequency and percentage for categorical variables. They are presented by total and each arm, respectively.

13.4.4 Endpoint Analysis

The primary endpoint is intratumoral cDCs in surgical tissues. Conventional dendritic cells are defined by the lack of expression of CD3, CD19, CD20, CD16, CD56, and the expression of CD45, CD11c, MHCII high and either CD1c or CD141. Kruskal-Wallis test will be used to compare the difference between two

arms.

Exploratory endpoints include global immune profiling by CyTOF, single cell RNASeq analysis, and histologic assessments. Kruskal-Wallis test will be used to compare the difference on T cell and cDC number and phenotype between two arms.

Additional exploratory endpoints include local control rate, distant metastasis-free survival (DMFS), overall survival (OS), and margin negative resection rate. Proportions of local control and margin negative resection for all treated patients and their associated 95% confidence intervals will be calculated assuming a binomial distribution. Chi-square or Fisher's exact test will be used to compare the difference between two arms.

OS is defined as the time from the date of treatment to the date of death, censored at the last follow-up otherwise. DMFS is defined as the time from treatment to the date of distant metastasis or death, whichever occurs first. The alive patients without distant metastasis is censored at the last follow-up. The Kaplan-Meier method will be used to calculate the probability of OS and DMFS. The log-rank test will be considered to compare the difference of OS and DMFS between two arms.

Data on the toxicity in each arm will be collected for each subject, including frequency, type, and severity of adverse events. All analyses will be conducted using SAS (SAS Institute, Cary, NC) at the two-sided 5% significance level.

14 REFERENCES

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APPENDIX A: ECOG Performance Status Scale

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

APPENDIX B: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX C: Reporting Timelines

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Celldex**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	
Serious adverse events regardless of relatedness				Report to Celldex within 24 hours of the investigator becoming aware of the event.
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information	
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment		
Pregnancy				Each pregnancy that occurs in female subjects or female partners of male subjects while on the study drug or within 3 months following completion of the study drug must be reported to Celldex within 24 hours of the investigator becoming aware of its occurrence.
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.			
A series of minor deviations that are	Report within 10 working days.			

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Celldex**
being reported as a continuing noncompliance				
Protocol exception	Approval must be obtained prior to implementing the change			
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Breach of confidentiality	Within 10 working days.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Celldex**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	
Minor deviation	Report summary information at the time of continuing review.			
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			