PHASE I CLINICAL RESULTS COMPARING LOCAL AND SYSTEMIC ADMINISTRATION OF AN APC-TARGETED CANCER VACCINE

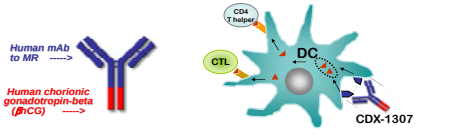
Morse, Michael[1]; Chapman, Robert[2]; Powderly, John[3]; Keler, Tibor[4]; He, Lizhen[4]; Ramakrishna, Venky[4]; Vitale, Laura[4]; Sundarapandiyan, Karuna[4]; Riggs-Garrett, Renee[4]; Clay, Timothy[1]; Davis, Thomas[4]

1. Duke University Medical Center, Durham, NC, USA. 2. Henry Ford Hospital, Detroit, MI, USA. 3. Carolina BioOncology Institute, Huntersville, NC, USA 4. Celldex Therapeutics, Inc., Phillipsburg, NJ, USA

Introduction

Efficient antigen delivery to antigen presenting cells (APCs) is a critical component of effective *in vivo* immunization strategies. Antigens attached to B11 (a human antibody against the mannose receptors expressed on interstitial dendritic cells and macrophages) have been shown to be processed and presented much more efficiently than non-targeted antigens, and generate robust immune responses when combined with toll-like receptor (TLR) agonists. Importantly, this targeted vaccination approach allows potential access to a larger APC population compared to standard protein vaccination strategies. CDX-1307 is a vaccine composed of B11 fused with the β subunit of human chorionic gonadotropin (hCG-β), a tumor-associated antigen that has been correlated with advanced stage of disease and poor prognosis. Initial phase I studies were aimed to investigate dose escalation, and combination with GM-CSF, a cytokine that up-regulates mannose receptors. We have now initiated combination studies with the TLR3 agonist Poly-ICLC (Hiltonol ®) and TLR7/8 agonist (resiquimod). These combinations are expected to maximize the potential for the targeted vaccine strategy.

CDX-1307 – mechanism of action



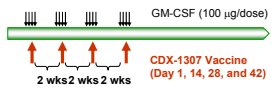
CDX-1307 is a fusion protein of a human mAb to mannose receptor (MR) and the tumor-associated antigen hCG-β

CDX-1307 is targeted to an endocytic pathway in dendritic cells (DCs) that leads to activation of hCG-β-specific CTL and T helper cells

- hCG-β is overexpressed by common cancers and not found in most normal tissues
- Elevated hCG-β expression is associated with a poor outcome in several cancers
- Humoral response to hCG-β is associated with improved survival in colorectal patients (Moultan HM et al., *Clin. Can. Res.* 8: 2044, 2002)
- hCG-β is structurally similar to TGF-β and in vitro studies suggest that it may help prevent apoptosis in bladder cancer cells

Clinical Trial Design

Dose Schedule & Escalation Scheme



	Intradermal Study	Intravenous Study
CDX-1307 (Single Agent)	CDX-1307 0.3 mg → CDX-1307 1.0 mg → CDX-1307 2.5 mg	CDX-1307 1.0 mg → CDX-1307 3.0 mg → CDX-1307 10.0 mg → CDX-1307 30.0 mg
CDX-1307 + GM-CSF	CDX-1307 2.5 mg + GM-CSF	CDX-1307 10.0 mg + GM-CSF → CDX-1307 30.0 mg + GM-CSF (Data too early for inclusion)

Patient Characteristics & Outcome

Patient Characteristics

	Intradermal Study				Intravenous Study				
	0.3 mg (n=6)	1.mg (n=6)	2.5 mg (n=6)	2.5 mg + GM-CSF (n=7)	1 mg (n=4)	3 mg (n=4)	10 mg (n=3)	30 mg (n=3)	10 mg + GM-CSF (n=5)
Median age (years)	64	56	60	63	57	51	53	59	63
Male (N[%])	4(67%)	3(50%)	6(100%)	3(43%)	0	0	0	2(67%)	1(20%)
ECOG 0 1	 2(33%) 4(67%)	 3(50%) 3(50%)	 5(83%) 1(17%)	 2(28%) 5(72%)	 3(75%) 1(25%)	 3(75%) 1(25%)	 3(100%) 0	 0 3(100%)	 3(60%) 2(40%)
Primary Cancer (N[%]) Pancreatic Colorectal Breast Other	 3(50%) 1(17%) 0 2(33%)	 1(17%) 5(83%) 0	 2(33%) 4(66%) 0	 1(14%) 4(57%) 2(29%)	 4(100%)	 4(100%)	 3(100%)	 3(100%)	 1(20%) 4(80%)
Prior Radiotherapy	0	0	0	0	4(100%)	3(75%)	3(100%)	1(34%)	3(60%)
Elevated Serum hCG-β	2(33%)	5(83%)	3(50%)	3(43%)	-	-	-	-	-

Adverse events potentially related to CDX-1307

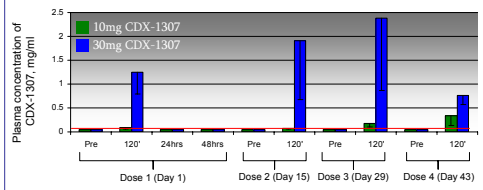
	Intradermal Study				Intravenous Study				
	0.3 mg (n=6)	1 mg (n=6)	2.5 mg (n=6)	2.5 mg + GM-CSF (n=7)	1 mg (n=4)	3 mg (n=4)	10 mg (n=3)	30 mg (n=3)	10 mg + GM-CSF (n=5)
Injection site erythema	2(34%)		2(34%)	5(71%)					
Injection site pain	2(34%)		1(17%)						
Rash	1(17%)			1(14%)					
Diarrhea	1(17%)			1(14%)					
Myalgia					2(50%)	1(25%)	2(67%)		
Fatigue		1(5.6%)[1]	3(50%)	2(29%)	1(25%)	2(50%)	1(33%)		
Fever					1(25%)	1(25%)			
Flu-like symptoms						2(50%)			
Pain					1(25%)	1(25%)			

- Elevated serum hCG-β was seen in 9 / 25 (52%) patients at screening and in 19 (76%) at any time during study
- No Dose-Limiting Toxicities (DLTs) observed
- Treatment-related adverse events were generally mild or moderate in severity
  - Most frequently included injection site reactions, fatigue, and myalgia
  - No obvious dose relationship
  - I.D. injection site reactions more common in patients receiving GM-CSF
  - One patient (1 mg i.d.) experienced a transient Grade 3 generalized allergic reaction possibly related to either a nut allergy or CDX-1307
- Two patients in the i.v. study (at 10 mg and 10 mg plus GM-CSF) experienced stable disease for ≥ 6 months
  - One patient with pancreatic cancer experienced a significant mixed response (26% reduction in lesions)

Targeted delivery in vivo

Skin punch-biopsies taken from injection site and opposite arm 48 hours after CDX-1307 injection (1 mg, i.d.)

CDX-1307 Pharmacokinetics



CDX-1307 plasma concentration determined by functional ELISA measuring active CDX-1307

- Circulating levels of CDX-1307 can be observed only at doses of ≥10 mg i.v.
- Rapid clearance of CDX-1307 (≤ 24 hrs) at 30 mg dose

Anti-hCG-β Immune Response

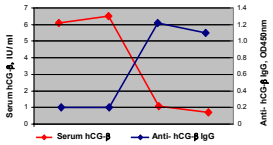
Number of patients developing anti-hCG-β IgG responses (positive/total)

	CDX-1307	Post 1st Dose	Post 2nd Dose	Post 3rd Dose	Post 4th Dose	Retreatment	Cumulative
I.D. Study	0.3 mg	NT	0/5	0/5	0/1	-	0/6
	1 mg	NT	2/6	2/6	2/6	-	2/6
	2.5 mg	NT	0/6	0/6	0/6	-	0/6
	2.5 mg + GM-CSF	NT	3/7	3/7	3/6	-	4/7
I.V. Study	1 mg	1/4	2/4	2/4	1/3	-	2/4
	3 mg	0/4	0/3	0/3	0/2	-	0/4
	10 mg	0/3	0/3	0/3	0/2	0/1	0/3
	10 mg + GM-CSF	1/2	3/5	0/2	0/1	1/1	3/5

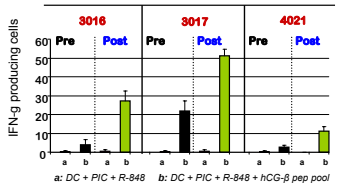
Anti-hCG-b IgG responses measured using an hCG-β ELISA relative to before treatment

- Overall ~ 1/4th of patients developed anti-hCG-β IgG responses on study
- 58% of patients receiving GM-CSF and CDX-1307 had anti-hCG-β IgG responses
- Both i.v. and i.d. administration of CDX-1307 induce anti-hCG-β IgG responses
- Anti-hCG-β IgG could be induce in patients with high levels of circulating hCG-β

Patient 4020
Anti-hCG-β response corresponds with reduction in serum hCG-β levels



T-cell Responses



Example of T-cell response to hCG-β analyzed by expansion and restimulation of CD4 and CD8 T-cells with autologous DCs before and after CDX-1307 vaccination

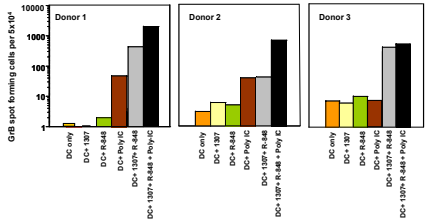
- Several patients had increased IFN-g producing CD8 T-cells post-treatment
- D4 T-cell responses were similar before and after treatment
- GM-CSF did not provide significant improvement in T-cell responses

Future Directions: Addition of TLR Agonists

Addition of toll like receptor (TLR) agonists provide potent adjuvant effects for vaccines. The following compounds will be studied in combination with CDX-1307:

- Poly-IC/LC, also known as Hiltonol®, is a double-stranded RNA that is a synthetic complex of polyinosinic and polycytidylic acid, stabilized with polylysine and carboxymethyl cellulose
- Poly IC/LC is a potent interferon inducer, and activates immune cells via TLR-3
- Resiquimod, is a TLR7 and TLR8 agonist, and an immune response modifier, in the imidazoquinoline class of molecules. Many studies have demonstrated that resiquimod is a potent activator of the innate immune system that also has effects on adaptive immune responses important for both antibody production and cell-mediated immune responses

CDX-1307 mediated hCG-β CTL response is enhanced with TLR agonists



Granzyme B secreting T cell responses to hCG-β were analyzed by expansion and re-stimulation of CD8 T cells with autologous DCs after treatment with CDX-1307 and TLR agonists.

New cohorts under study

Intradermal Study

CDX-1307 2.5 mg + GM-CSF + Poly IC/LC s.c.
Completed enrollment

CDX-1307 2.5 mg + GM-CSF + Resiquimod gel
Currently enrolling

CDX-1307 2.5 mg + GM-CSF Poly IC/LC + Resiquimod gel
Planned

Intravenous Study

CDX-1307 30.0 mg + GM-CSF + Poly IC/LC i.m.
To be enrolled

Summary

- CDX-1307 is designed for efficient local or systemic delivery of hCG-β to antigen presenting cells
- Administration of CDX-1307 is well tolerated
- Intradermal administration of CDX-1307 results in hCG-β localization in antigen-presenting cells of the skin
- In the absence of a strong adjuvant, both local and systemic administration can provide immunity despite advanced disease and high levels of circulating antigen
- anti-hCG-β immune responses were observed more frequently in patients receiving GM-CSF
- Addition of TLR agonists may provide enhanced immunity and improved clinical responses