Preliminary Safety and Efficacy Data using CDX-301 (Flt3 ligand) as a Sole Agent to Mobilize Hematopoietic Cells Prior to HLA-matched Sibling Donor Transplantation

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Abstract # 479

Background

- G-CSF effectively mobilizes donor CD34+ cells for allogeneic hematopoietic cell transplantation (HCT)
- High incidence of chronic graft-versus-host disease (GVHD) with G-CSF mobilized grafts is partly due to the cell composition of the graft
- Flt3 is expressed on hematopoietic stem cells (HSC) and myeloid precursors
- Ligation of Flt3 induces proliferation and mobilization of HSC, which is augmented by other growth factors
- Flt3 ligand (Flt3L) regulates dendritic cell (DC) proliferation and mobilization
- Flt3L-mobilized grafts result in reduced GVHD in a rodent model, and combination with plerixafor enhanced survival (He, et. al., Biol Blood Marrow Transplant. 2014)
- CDX-301 is a recombinant human Flt3L that has been well tolerated in healthy subjects

Methods

- Safety and activity of CDX-301 in mobilizing CD34+ cells in sibling donors for HCT recipients is assessed in pilot study CDX301-03
- Donors received 75 µg/kg/day CDX-301 as a SQ injection for 5 days
- Leukapheresis (LP) began on day 6 if the peripheral blood (PB) CD34+ count was ≥7/µL
- The LP goal CD34+ yield was ≥ 2x10^6/kg recipient weight collected in ≤ 2 days of LP
- Rescue plerixafor was planned if the donor PB CD34+ count was < 7/µL by day 8 or if the total CD34+ yield was < 1x10^6/kg after the second day of LP
- The product was cryopreserved and infused following myeloablative (MA) or reduced-intensity conditioning (RIC)
- Standard GVHD prophylaxis was used
- CDX-301 mobilized cells were analyzed by flow cytometry and compared to historical data for G-CSF mobilized peripheral blood grafts

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View Poster

Results

Table 1. Donor and Recipient Characteristics

Donor	Medical History	Recipient	Medical History	Conditioning Regimen	GVHD Prophylaxis
1	32 y/o male, DM, sleep apnea, HTN, BMI > 30	1	34 y/o male, AML in CR1 (NPM1-, FLT3-)	Myeloablative fludarabine/ busulfan	Tacrolimus, MTX
2	49 y/o female, asthma, shingles, depression	2	50 y/o male, mantle cell lymphoma (MCL), prior auto Tx, Flt3-	Myeloablative fludarabine/ busulfan	Tacrolimus, MTX
3	51 y/o male, HTN, COPD, arthritis, DM	3	48 y/o female, MCL, prior auto Tx, Flt3-	Myeloablative fludarabine/ busulfan	Tacrolimus, MTX
4	28 y/o male, no significant medical history	4	26 y/o male, CML with blast crisis, TKI resistant	Reduced Intensity fludarabine/ melphalan	Tacrolimus, MTX

Table 2. Donor Collection Parameters

Donor	Time Point	WBC	Monocytes	Platelets	CD34+	LP	Total LP
1	Baseline	6.4	0.3	218	4		
	Day 6	8.4	0.8	214	20	2.44M	
	Day 7	9.1	1.3	153	16	2.74M	5.18M
	Day 9	10.7	1.61	111	31		
	Day 33-35	7.7	0.4	230	3		
2	Baseline	6.5	0.5	197	5		
	Day 6	10.5	1.1	207	21	2.03M	
	Day 7	8.8	0.8	114	21	1.67M	3.70M
	Day 8	8.4	1.4	77	15		
	Day 33-35	6.3	0.4	149	<5		
3	Baseline	5.6	0.6	197	2		
	Day 6	7.9	0.71	199	7	1.07M	
	Day 7	7.3	1.1	104	8	1.02M	2.09M
	Day 33-35	4.8	0.3	160	<5		
4	Baseline	9.8	0.9	294	ND		
	Day 6	10.9	1.56	260	10.9	1.5M	
	Day 7	13.7	2.1	193	13.08	1.31M	2.81M
	Day 8	13.5	2.47	145	ND		
	Day 33-35	ND	ND	ND	ND		

ND - not done

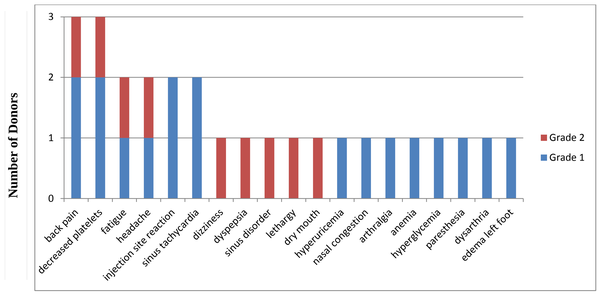
- All donors met the CD34+ cell goal after 2 days of collection
- No donor required rescue with plerixafor

Table 3. Recipient Engraftment Parameters

Recipient	1	2	3
WBC engraftment	Day 17	Day 19	Day 18
Platelet engraftment	Day 14	Day 25	Day 40
Hospital discharge	Day 18	Day 19	Day 21
Day 30 CD3	82%	90%	100%
Day 30 CD33	100%	100%	100%
Day 30 CD4	441	149	390

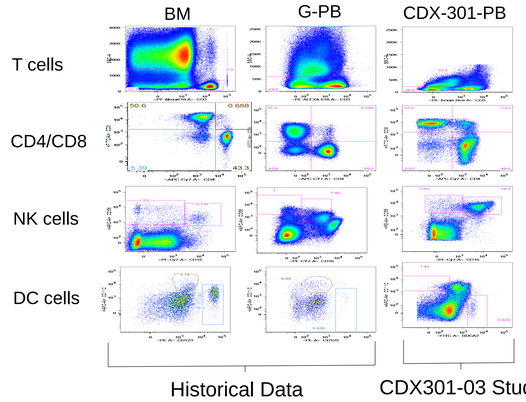
- Four recipients have undergone HCT to date; subject 4 is pre-engraftment
- No unexpected acute toxicities of HCT were seen
- All recipients engrafted neutrophils and platelets (Table 3), but platelet recovery was slow
- Recipients 1 and 3 have not developed GVHD
- Recipient 2 developed steroid-responsive G2 upper GI GVHD on day 18 and grade 1 skin GVHD on day 50 that progressed to stage 3 skin, overall grade 2 GVHD on day 64. Patient has progressive disease.
- There have been no infectious complications

Figure 1. All Adverse Events (AEs) Among Donors



- No grade 3 or 4 AEs were noted among the donors
- CDX-301 related AEs were: dizziness (grade 2), back pain (grade 1), arthralgia (grade 1), injection site reaction (grade 1 x 2), dyspepsia (grade 1 x 1, grade 2 x 1), and decreased platelet count (grade 1 x 2)

Figure 2. Representative Flow Cytometry of Graft Constituents in BM, G-PB and CDX-301-PB products



Flow cytometry was used to analyze frozen aliquots of immune cells in grafts collected following CDX-301 mobilization (n=3) compared with representative samples of BM grafts and G-PB grafts collected from volunteer unrelated donors as reported in Waller et al. JCO 2014 32:3265. Gating for DC subsets from the BM and G-PB samples included a lineage(-), HLA-DR(+) gate; the DC analysis of the CDX-301-PB samples included all nucleated cells.

Table 4. Percentages of Immune Cells in CDX-301-PB Compared with Other Graft Sources

	CDX301-03 Study	Historical Data	
	CDX-301-PB	BM	G-PB
T-Cells	27.4%	8.8%	31.6%
Treg CD4+ foxp3+	1.10%	0.8%	3.8%
γδ TCR T-cells	1.17%	0.2%	0.7%
NK-T-cells	2.28%	1.0%	1.8%
NK cells	9.3%	0.7%	2.3%
B cells	26.0%	3.2%	6.2%
Plasmacytoid DC	1.15%	0.1%	0.1%
Myeloid DC	0.75%	1.6%	0.1%

Median percentages of immune cells in grafts collected following CDX-301 mobilization (n=3, duplicate samples for 2 of 3 subjects) were analyzed by flow cytometry and compared with median percentages of the same cell subsets from BM grafts and G-PB grafts collected from volunteer unrelated donors as reported in Waller et al. JCO 2014 32:3265.

Compared to historical data for G-CSF mobilized peripheral blood grafts, CDX-031 mobilized grafts (Table 4):

- Show an increase in CD127+ (IL-7R) naïve T cells (data not shown), γδ T cells, and NK cells
- Show an increase in B cells
- Are more enriched with plasmacytoid DCs
- DC from the CDX-301 grafts had a more mature phenotype, expressing CD80 and CD86 (data not shown)

Conclusions

- CDX-301 has little toxicity compared to G-CSF and can mobilize CD34+ cells as a single agent for 5 days
- Graft content of immune cells differs significantly compared with G-CSF mobilized cells or BM, including mobilizing more naïve T cells and plasmacytoid DCs which may be associated with better outcomes in recipients
- Neutrophil engraftment occurred in comparable time frame to what would be expected with G-CSF mobilized grafts
- The study will next explore the planned cohort of CDX-301 + plerixafor