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A Phase Ib/II Study of Anti-CD30 Chimeric Antigen Receptor T Cells for Relapsed/Refractory CD30+ Lymphomas

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Introduction: Treatment with chimeric antigen receptor modified T cells targeting CD30 (CD30.CAR-Ts) without lymphodepletion was found to be safe with preliminary efficacy in patients (pts) with relapsed/refractory (r/r) CD30+ lymphomas (Ramos et al., JCI 2017). We report the results of a phase 1b/2 trial of CD30.CAR-Ts infused after lymphodepletion in pts with r/r CD30+ Hodgkin (HL) and Non-Hodgkin lymphoma (NHL).

Objectives: The primary objective of the phase Ib portion of the study was to determine the phase 2 dose of CD30.CAR-Ts using a standard 3+3 design.

Methods: Pts $\geq$ 18 years with r/r CD30+ HL or NHL having failed $\geq$2 prior therapies were eligible. Two dose levels were tested: 1×10^8 CAR-Ts/m^2 (DL1) and 2×10^8 CAR-Ts/m^2 (DL2). The first 8 pts (including the 3 pts on DL1) received bendamustine (benda) 90 mg/m^2 $\times$ 2 days and the remaining 16 pts received benda 70 mg/m^2 and fludarabine (flu) 30 mg/m^2 $\times$ 3 days.

Results: At the time of data cut off (10/1/2018), 24 pts had been treated and undergone response assessment. The median age was 35.5 years (range: 23-70). 22 pts had HL, 1 had enteropathy associated T cell lymphoma and 1 had Sezary syndrome. Pts had undergone a median of 7.5 prior lines of therapy (range: 3-17). 23 pts had received prior brentuximab vedotin. 15 pts had prior autologous stem cell transplant (SCT) and 7 had prior allogeneic SCT.

As there were no dose limiting toxicities, DL2 was administered as the phase 2 dose. 3 pts developed grade 1 cytokine release syndrome (CRS) and 1 pt had grade 2 CRS which responded to tocilizumab.

19 out of 24 pts had evidence of disease prior to lymphodepletion and were included in efficacy analysis. 10 pts had a CR at the 6 week assessment (53%, all in benda/flu cohort), 2 had partial response (11%), 2 had stable disease (11%), and 5 had progressive disease (26%, including all 3 pts treated at DL1). At median follow up of 180 days, the median PFS was 164 days. The median PFS for the 14 evaluable pts who received benda/flu at DL2 was 389 days.

Using peripheral blood PCR, CD30.CAR-Ts peaked at wk 2 post infusion, with increasing CAR-Ts in pts receiving a higher dose or more robust lymphodepletion ($3.4 \times 10^3 \pm 2.9 \times 10^3$ copies/ug of DNA for DL1-beda vs. $61 \times 10^3 \pm 41 \times 10^3$ for DL2-benda vs. $49 \times 10^3 \pm 16 \times 10^3$ for benda/flu). These differences were confirmed by flow cytometry ($CD3^+CAR^+$ cells = 13%±9% for DL1-benda vs 21%±10% for DL2-benda vs 35%±8% for benda/flu). There was also improved persistence at wk4 for higher dose and with addition of flu to lymphodepletion ($0.06 \times 10^3 \pm 0.01 \times 10^3$ vs. $0.44 \times 10^3 \pm 0.41 \times 10^3$ vs. $25 \times 10^3 \pm 11 \times 10^3$/ug of DNA at wk 4 for DL1-benda, DL2-benda, and benda/flu, respectively).

Conclusion: CD30.CAR-Ts administered with lymphodepletion with benda/flu are safe and have promising anti-tumor activity for pts with r/r CD30+ lymphomas. A higher dose of CD30.CAR-Ts and the addition of flu to lymphodepletion increased T cell expansion and persistence and translated to improved efficacy.

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Lentiglobin Gene Therapy for Transfusion-Dependent β-Thalassemia: Outcomes from the Phase 1/2 Northstar and Phase 3 Northstar-2 Studies

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Introduction: Transfusion-dependent β-thalassemia (TDT) is a severe genetic disease characterized by anemia, iron overload and serious comorbidities for which gene therapy may be an effective treatment option. LentiGlobin gene therapy contains autologous CD34+ hematopoietic stem cells (HSCs) transduced *ex vivo* with the BB305 lentiviral vector (LVV) encoding β-globin with a T87Q substitution.

Objective: Evaluate the efficacy and safety of LentiGlobin in patients with TDT in the phase 1/2 Northstar (HGB-204; NCT01745120) and phase 3 Northstar-2 (HGB-207; NCT02906202) studies.

Methods: Patients with TDT ($\geq$100 mL/kg/yr of red blood cells [RBCs] or $\geq$8 RBC transfusions/yr) received G-CSF and plerixafor for mobilization and HSCs were transduced with the BB305 LVV. Patients underwent single agent busulfan myeloablative conditioning, were infused with transduced cells, and were followed for engraftment, safety, and efficacy. Statistics are presented as median (min – max).

Results: As of March 7, 2018, 18 patients (12 – 35 yrs) were treated in Northstar (follow-up 32.1 [23.1 – 41.9] months) and

as of May 15, 2018, 11 patients (12 – 24 yrs) were treated in Northstar-2 (follow-up 8.5 [0.3 – 16.2] months). Patients received a median cell dose of 8.0 (5.0 – 19.4) CD34+ cells × 10^6/kg in both studies. The median time to neutrophil and platelet engraftment in both studies was 19 (14 – 30) days and 44 (19 – 191) days, respectively; 1 patient in Northstar-2 (0.3 months follow-up) had not engrafted at time of analysis. Of 6 patients with platelet engraftment ≥ Day 60, 4 had non-serious bleeding events prior to engraftment. All 6 had intact spleens and 3/6 received G-CSF between Days 0 – 21. Both factors appeared associated with time to platelet engraftment. In Northstar, 8/10 patients with non-β^0/β^0 genotypes and 2/8 patients with β^0/β^0 genotypes achieved transfusion independence (TI; weighted average hemoglobin [Hb] ≥ 9 g/dL without RBC transfusions for ≥ 12 months). Median Hb during TI was 10.0 (9.3 – 13.1) g/dL. In Northstar-2, 7/8 patients with non-β^0/β^0 genotypes and ≥ 6 months follow-up stopped RBC transfusions with Hb of 11.1 – 13.3 g/dL at last visit; the first patient treated achieved TI. Non-hematologic grade ≥ 3 adverse events post-infusion in ≥ 5/29 (15%) patients were stomatitis, febrile neutropenia, and pharyngeal inflammation. Veno-occlusive liver disease attributed to busulfan occurred in 4/29 patients (Table 1). There was no transplant-related mortality, vector-mediated replication competent lentivirus, or clonal dominance.

Conclusion: In Northstar, 80% of patients with non-β^0/β^0 genotypes achieved TI and early Northstar-2 data suggest that patients can achieve near-normal Hb without transfusions. The safety profile of LentiGlobin is consistent with myeloablative busulfan conditioning. Longer time to platelet engraftment was observed in few patients, but no graft failure or deaths were reported.

Table
Veno-occlusive liver disease following treatment with LentiGlobin gene therapy

Parameters	Patients who had a VOD event (N=4)				Patients who did not have a VOD event (N=25)
	Northstar		Northstar-2		
Patient and Treatment Characteristics					
Age at informed consent	20	16	12	12	20 (12 – 35) Median (min – max)
Gender	Female	Female	Male	Female	17 Females 8 Males
VOD prophylaxis	No	No	No	No	48% (12/25)
Liver status at screening					
Imaging LIC, mg Fe/g dw	8.4	10.4	1.0	5.6	5 (0.4 – 41)
AST, U/L	55	26	23	14	23 (9 – 74)
ALT, U/L	121	26	32	7	22 (9 – 164) Median (min – max)
Average busulfan AUC,* µM*min	4374	4025	4595	4471	4205 (3030 – 5789) Median (min – max)
Event Characteristics					
Event grade	Grade 3	Grade 3	Grade 4	Grade 4	
Onset	Day +27	Day +29	Day +34	Day +23	
Outcome	Resolved Day +48	Resolved Day +50	Resolved Day +84	Resolved Day +37	
Attributed to conditioning agent	Yes	Yes	Yes	Yes	
Treatment	Defibrotide, morphine, and vitamin K; Hospitalization was extended	Defibrotide and ursodeoxycholic acid; Hospitalization was extended	Defibrotide; Hospitalization was extended	Defibrotide; Hospitalization was extended	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; LIC, liver iron content; VOD, veno-occlusive liver disease.
*Estimated average daily busulfan exposure over 4 days. Northstar target busulfan: AUC of 1000 (min – max: 900 –1200) µM*min for every 6 hours dosing, or 4000 (min – max: 3600 – 5000) µM*min for once daily dosing. Northstar-2 target busulfan: AUC of 1100 (min – max: 1000 – 1250) µM*min for every 6 hours dosing, or 4500 (min – max: 4000 – 5000) µM*min for once daily dosing

SESSION L. LATE EFFECTS

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Utilization of Fertility Preservation Services By Patients Aged 18-40 Prior to Hematopoietic Cell Transplantation

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Introduction: Survivors of hematopoietic cell transplantation (HCT) often face infertility later in life due to preparative conditioning regimens that are harmful to reproductive function. Current American Society of Clinical Oncology (ASCO) clinical guidelines on fertility preservation (FP) recommend that all patients who are at risk for infertility due to medical treatment should be referred to a fertility specialist for counseling following diagnosis and preferably prior to the start of treatment. Despite HCT physicians' awareness of standard-of-care services for preserving fertility and the psychosocial sequelae resulting from patients losing their fertility, anecdotal evidence indicates that few patients actually receive FP services. National utilization of FP services prior to HCT is currently unknown.

Objective: The goal of this retrospective descriptive analysis is to understand commercially insured and covered FP utilization among HCT recipients and describe patterns of engagement in FP services prior to HCT.

Methods: FAIR Health's national claims database was used to identify HCT recipients and the subgroup of patients who received FP services prior to HCT. Secondary analysis of the FP subgroup included the creation of patient-specific clinical journey timelines that included dates of services associated with diagnosis and procedure codes relevant to HCT and FP (Figure 1).

Results: There were 411 patients aged 18-40 who received HCT. Only 7.1% (N=29) of the HCT cohort had claims for FP services after diagnosis and prior to receiving HCT. Utilization of FP was most common in younger HCT patients, with 69% (N=20) of the FP subgroup being under age 26. The median time between FP services and HCT was 102 days and patients undergoing autologous HCT had longer intervals between FP services and HCT than allogeneic HCT patients (Figure 2).

Conclusion: Despite ASCO guidelines addressing the importance of FP options for cancer patients, results from this administrative claims analysis confirm that utilization of FP services by HCT patients is low. The longitudinally-linked claims allowed for detailed analysis of the FP subgroup which helped inform when patients receive FP services relative to their HCT as well as which FP services are utilized. Analysis of the FP subgroup also showed that the timing between diagnosis, FP services, and HCT may depend on the type of transplant. However, more research is needed to understand the barriers to FP prior to HCT so that targeted tools can be used to increase utilization and improve quality of life for HCT survivors. Future FP service cost and utilization research with an expanded population would be informative for policy-makers, payers, providers and patients. More work is needed to address the difficulty in quantifying FP service utilization that is not processed through commercial payers and as such not included in administrative claims data.

Figs. 1 and 2.

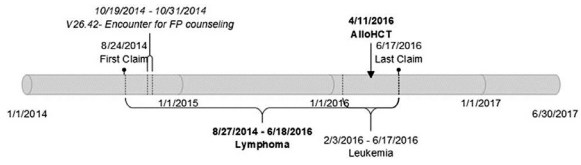

Figure 1. Sample clinical journey map. Includes first and last claim in the analysis window, range of dates of service for each HCT indication, range of dates of service for FP services, and HCT date.