INB-100: Relapse Prophylaxis Post-Haploidentical Bone Marrow Transplantation and Cyclophosphamide (Haplo/Cy) by Infusion of Donor-Derived Expanded/Activated Gamma-Delta (γδ) T Cells: A Phase I Trial

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INTRODUCTION

Effector γδ T cells, can recognize and directly kill malignant cells in an-MHC unrestricted manner. Relapse post Haplo/Cy bone marrow transplantation (BMT) occurs in ~51% of patients within 1 year **(Figure 1)** and may be mitigated by infusing expanded and activated donor-derived haploidentical γδ T cells (EAGD) post-transplant. Additionally, data suggest post-transplant Cy is associated with slower immune reconstitution and higher risk of infections. We report data on the first two dose levels (DL) of a Phase 1 trial assessing the safety and efficacy of allogeneic EAGD cells. Increasing doses of EAGD are administered to patients undergoing haploidentical transplants for underlying hematologic malignancies to prevent relapse, with corresponding preliminary clinical and biologic correlative findings.

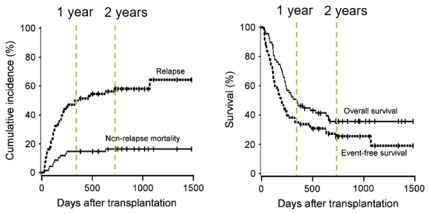


Figure 1: Haploidentical BMT with post-BMT cyclophosphamide GvHD prophylaxis has reduced the rate and severity of GvHD but with a high incidence of relapse (Luznik *et al BBMT* 2008 14: 641-650).

DESIGN AND METHODS

The design of the trial is shown in **Figure 2**. Adult patients with newly diagnosed or relapsed ALL, CML, or AML undergoing consolidative haploidentical transplant with reduced-intensity flu/cy/TBI conditioning received EAGD intravenously within 7 days of neutrophil engraftment. Primary endpoints include dose-limiting toxicities (DLT), grade 3-4 adverse events (AEs) including graft-versus-host disease (GvHD), while secondary endpoints include relapse and overall survival. Peripheral blood for biologic correlative studies was collected at EAGD infusion and monthly thereafter through day +100, 180, and year.

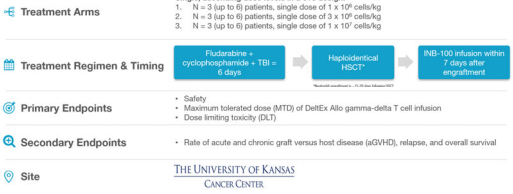


Figure 2: EAGD were manufactured from haploidentical donor apheresis product obtained 7 days prior to BMT harvest and cryopreserved. Patients received standard of care reduced intensity flu/cy/TBI conditioning (RIC) followed by an unmanipulated marrow graft and 50mg/m² Cy on days +3 and +4. Cryopreserved EAGD were thawed and infused intravenously within 7 days of neutrophil engraftment (ANC ≥500/μL X 3d). Peripheral blood for monitoring of immune status was collected at the defined intervals.

RESULTS

Table 1
Status of Patients Currently on Study

Patient	Dose Level	Age / Sex	Cytogenetics	Prior lines	Treatment Related Safety Events	Morphologic CR Duration (mos)
002	1	54 / female	High-risk AML: trisomy 8+ and del7; FLT3 TKD, DNMT3A,	7+3+idasanutlin	Gr.2 skin aGvHD- resolved	36.2+
003	1	45 / female	High-risk AML trisomy 8+ and del7: IDH2	7+3	Gr.2 GI aGvHD and Gr.2 skin rash Remains on Jakafi for skin GvHD	33.9+
006	1	66 / male	Relapsed AML s/p 7+3, ASXL1	7+3	Gr.2 skin aGvHD-resolved	22.2+
007	1	71 / male	Relapsed AML s/p 7+3, ASXL1	Pembrolizumab	Gr.2 skin aGvHD-resolved	7.8+
009	2	68 / male	Ph- ALL; p53 mutated, DNMT3A, GATA2	Induction E1910, blinicyto, inotuzumab x2 cycles, CAR-T with Tecartus	Gr.1-2 skin GvHD within 2 weeks of γδ infusion and Gr.2 diarrhea of unclear etiology	5.8+
010	2	62 / female	Relapsed AML	Hydrea; vidaza/ venetoclax x7 cycles	Gr.2 skin GvHD within 30 days of γδ infusion with undefined GI symptoms	5.6+
011	2	68/ male	ET, triple neg, with MDS/MPN overlap	Hydrea		2.6+
013						

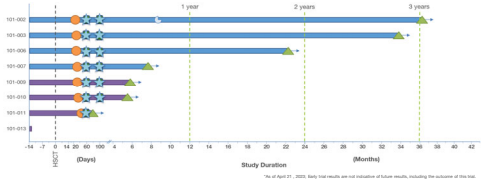


Figure 3: Seven patients have been enrolled and treated on trial, four treated in DL1 at 1 x 10^6 EAGD/kg and three treated in DL2 at 3 x 10^6 EAGD/kg. All patients in DL1 and DL2 remain in morphologic complete remission (CR) at 36.2, 33.9, 22.2, 7.8, 5.8 and 2.6 months post-BMT at data cut-off of Feb. 28, 2023. One patient received intermittent hypomethylating therapy for occurrence of recipient chimerism with time correlation with skin aGvHD. No DLTs, treatment-related ≥Grade 3 AEs, neurotoxicity or cytokine release syndrome were reported. Not shown are off-study patients (one screen failure, one manufacturing failure, one death prior to dosing, and one that received an out of study specification product).

Table 2
Treatment Emergent AE's in >3 patients (n=7)

Adverse Events	Total (%)	Grade 1/2	Grade 3	Grade 4
WBC decreased	100			100
Anemia	100	14	86	
ALC decreased	29			29
ANC decreased	85	14	14	57
Platelet count decreased	100			100
Nausea	85	71	14	
Vomiting	57	57		
Diarrhea	57	57		
Acute GI GVHD	14	14		
Constipation	29	29		
Hypomagnesemia	71	71		
Hypokalemia	71	71		
Fatigue	29	29		
Noninfective cystitis	29	29		
Acute skin GVHD	71	71		
Rash	43	29	14	
Pruritus	29	29		
Creatinine increased	43	43		
Edema	43	43		

- **9 enrolled, N=7 evaluable for safety**
- **No DLT's as of Apr. 21, 2023**
- 2 patients with CMV reactivation
- **Treatment Related SAE's:**
  - Gr.3 Acute Kidney Injury & Gr.2 acute skin GVHD in one patient
  - Gr.3 nausea in another patient
- **Other non-treatment related SAE's include:**
  - 001: Gr.5 multiorgan failure
  - 003: Gr.3 CMV reactivation
  - 004: Gr.5 sepsis and G4 MDS
  - 006: Gr.3 skin infection
  - 011: Gr.2 heart failure, a-fib and hemorrhagic cystitis
- **No treatment related deaths as of Apr. 21, 2023**
- **No SUSAR's or unexpected safety events reported as of Apr. 21, 2023**

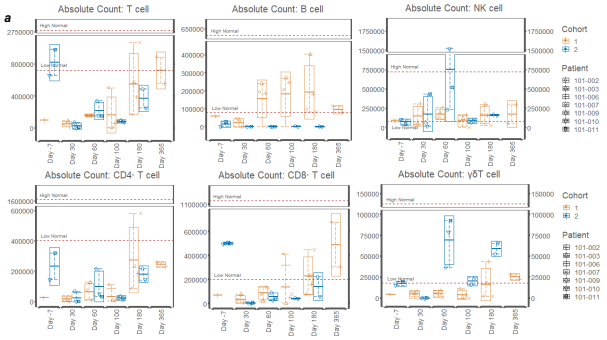


Figure 4: Lymphocyte subset absolute count (***a***) revealed significant T cell depletion through the first 100 days post-BMT followed by slow recovery of αβCD3+CD4+ and αβCD4+CD8+ T cells. In both Cohort 1 and 2 patients, γδ T cells (primarily Vδ2+ subtype) slowly increased toward normal levels. B cell counts recovered in the first 30 days and NK cells remained within the low normal range throughout. NK cells known to be the first to recover in the haploidentical setting, remain generally within normal ranges throughout treatment and are therefore proportionately higher. Interestingly, a significant (p = 0.001) increase in both γδ T cell count and %CD3+ (***b***) was noted at the Day +60, +100, +180 timepoints for Cohort 2 over Cohort 1, potentially a signal of continuing expansion and persistence of γδ T cells with the higher dose.

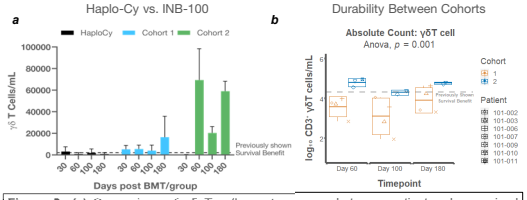
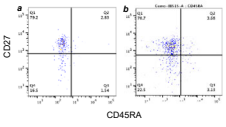


Figure 5: ***(a)*** Comparison of γδ T cell count recovery between patients who received haploidentical BMT + post-BMT Cy without γδ T cell infusion and INB-100 patients from Cohort 1 and Cohort 2. Cohort 2 patients receive 3x the γδ T cell dose as Cohort 1. Dose dependent increase of circulating γδ T cells at Days +60, +100 and +180 for INB-100 treated patients. ***(b)*** Detail of the significant (p = 0.001) increase γδ T cells noted at Day +60, Day +100 and +180 timepoint for Cohort 2 patients over those in Cohort 1. Higher levels of γδ T cells thereby increase the potential for homeostatic reconstitution and durability consistent with numbers previously correlated with improved overall survival (Minculescu *et al Front. Immunol* doi10.3389/fimmu/2019.01997).

Figure 6: Plot is gated on γδ T cells from Cohort 2 patient 010 at ***(a)*** Day +60 and ***(b)*** Day +100. Note the predominance of CD45RA-CD27+ T_{CM} cells that have the potential for persistence and conversion to T_{EM} cells upon re-stimulation with non-peptidic antigens. γδ T cells leading to αβT cell activation, cytokine release, and cytotoxicity



CONCLUSIONS

- **Infusion of expanded and activated γδ T cells following haploidentical bone marrow transplantation shows high potential for prevention of late-term recurrence of hematologic malignancies**
- **All Cohort 1 participants followed for >1 year remain in mCR at an average of 30.7 months and up to 36.2 months**
- **At greater doses, higher levels of γδ T cells are shown to expand in vivo and persist in numbers associated with long-term survival for up to 180 days post-BMT with a manageable safety profile**
- **Given favorable risk:benefit profile, expansion at DL2 is planned without further escalation to DL3**

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