# INB-100: Pilot Study of Donor Derived, Ex-Vivo Expanded/Activated Gamma Delta T Cell Infusion Following Haploidentical Hematopoietic Stem Cell Transplantation and Post-Transplant Cyclophosphamide

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## Background and methods

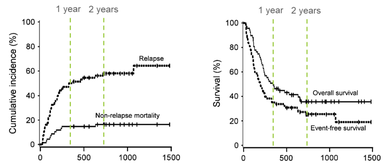
**Background:** Gamma-delta (γδ) T cells immediately recognize and kill malignant cells through MHC unrestricted binding of stress ligands using multiple mechanisms including NKG2D, DNAM-1, and the TCR. As such, γδ T cells do not initiate GvHD. Post-HSCT homeostatic expansion of increased circulating γδ cells in a lymphodepleted environment is associated with improved survival. Haploidentical transplant with PTCy (Haplo/Cy) reduces the risk of GvHD, however, the extended T cell recovery with Haplo/Cy predisposes to an increased risk of relapse approaching 50% in the first year. We sought to determine if early post-transplant infusion of the haploidentical expanded and activated γδ T cells (EAGD) could safely improve PFS and OS in older, high-risk leukemia patients undergoing reduced intensity conditioning (RIC) without increasing the incidence and grade of GvHD.

**Methods:** Adults with newly diagnosed or relapsed ALL, CML, AML undergoing first haploidentical transplant with reduced-intensity flu/cy/TBI conditioning received EAGD intravenously within 7 days of neutrophil engraftment. Peripheral blood was collected at EAGD infusion and monthly through day 90, with additional collections every 6 months through 1 year. Primary endpoints include dose-limiting toxicities (DLT), grade (G) 3-4 adverse events including GvHD with secondary endpoints of PFS and OS. Biologic parameters included multiparameter flow cytometric immunophenotyping and serum cytokine analysis using the Olink® 48 target panel.

## Haploidentical stem cell transplantation (HSCT)

Haplo/Cy increases access and reduces GvHD but also increases early relapse

- Haploidentical transplants have expanded access to stem cell transplantation by increasing the pool of eligible donors
- Post transplant Cy lowers GvHD incidence and grade but increases vulnerability to relapse up to ~50% in the first year
- Infusion of large numbers of γδ T cells may augment the graft-vs-leukemia (GvL) effect and preempt post-BMT relapse without increasing risk of GvHD







## An allogeneic therapy to reduce leukemic relapse

INB-100: Single-center, dose-escalation trial of DeltEx Allo γδ T cells post-haploidentical HSCT

**Treatment Arms**

**Single, ascending dose levels in a 3+3 design:**
1. N = 3 (up to 6) patients, single dose of 1 x $10^8$ cells/kg
2. N = 3 (up to 6) patients, single dose of 3 x $10^8$ cells/kg
3. ~~N = 3 (up to 6) patients, single dose of 1 x $10^9$ cells/kg~~

RP2D*

**Treatment Regimen & Timing**

Fludarabine + cyclophosphamide + TBI = 6 days → Haploidentical HSCT* → INB-100 infusion within 7 days after engraftment

*Neutrophil engraftment is ~15-20 days following HSCT

**Key Eligibility Criteria**

- Adult patients with a haploidentical donor identified
- KPS ≥70
- AML in mCR with intermediate/high-risk features or relapsed disease
- CML in any chronic phase
- MDS with intermediate/high-risk features
- ALL in mCR with high-risk features or relapsed disease

**Primary Endpoints**

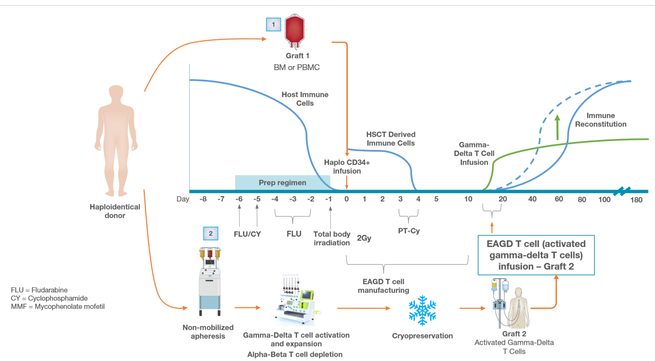
- Safety
- RP2D of DeltEx Allo gamma-delta T cell infusion
- Dose limiting toxicity (DLT)

**Secondary Endpoints**

- Incidence of acute and chronic graft versus host disease (aGVHD), relapse, and overall survival

**Site**

THE UNIVERSITY OF KANSAS CANCER CENTER




## Patient demographics and summary

| Patient | Dose Level | Age / Sex | Prior Therapies | Disease | Acute / Chronic GvHD | CR (mos) | OS (mos) |
|---|---|---|---|---|---|---|---|
| 002 | 1 | 63 / female | Idasanutlin + 7+3 | **High-risk AML trisomy 8+ and del7, FLT3 TKD** | Acute G2 GvHD Chronic limited GvHD | 54.8+ | Alive |
| 003 | 1 | 44 / female | 7+3 | **High-risk AML trisomy 8+ and del7, IDH2** | Acute G2 GvHD | 42.4** LTFU | Alive |
| 006 | 1 | 66 / male | 7+3 IDAC | **High-risk relapsed AML** | Acute G2 GvHD Chronic extensive GvHD | 40.8+ | Alive |
| 007 | 1 | 71 / male | Ven/Aza+Pembrolizumab | AML | Acute G2 GvHD Chronic limited GvHD | 15.5 | 15.5 died due to IPF |
| 009 | 2 | 68 / male | R-CHOP Blinatumomab Inotuzumab Flu/Mel/TBI Vincristine/steroids Flu/cy/brentuximab **CAR-T with Tecartus** | **Relapsed Ph- ALL; TP53 mutated** | Acute G2c GvHD | 14.7 | 20.2 |
| 010 | 2 | 63 / female | 7 cycles Venetoclax/Aza | AML | Acute G2b GvHD | 24.1+ | Alive |
| 011 | 2 | 68 / male | Hydrea/Peg-IFN | ET with **MDS/MPN overlap; TP53 mutated** | | 12.4 | 18.3 |
| 012 | 2 | 69 / male | 2 cycles Venetoclax/Aza | AML | | 17.8+ | Alive |
| 013 | 2 | 71 / female | 1 cycle Ven/aza/gliteritinib 2 cycles Venetoclax/Aza | AML, **FLT3** | | 17.5+ | Alive |
| 014 | 2 | 71 / male | Venetoclax/Dacogen | AML, del20, -Y | | 17.0+ | Alive |

Note: *As of September 30, 2024; Early trial results are not indicative of future results, including the outcome of this trial.

**Average patient age ~68 y/o**

**Majority have AML**

**Received up to 7 prior therapies**

**14 enrolled, n=10 dosed and evaluable for safety**

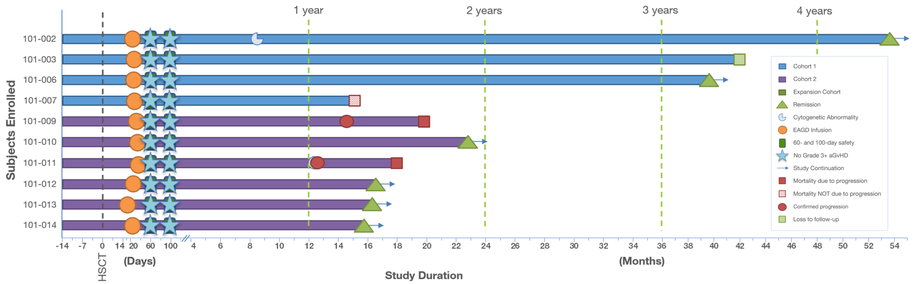
- 1 patient expired prior to dosing
- 1 patient received an out of specification product at 6 x $10^5$ EAGD/kg
- 1 manufacturing failure
- 1 screen failure due to relapse prior to treatment

**Median follow-up = 19.2 mos**

**Median CR of AML patients = 19.7 mos**

## 100% patients remained in mCR ≥ 12 months

Three patients with high-risk disease remain relapse free for >3 years with median follow-up 19.2 months; No AML patients have relapsed to date at a median follow-up of 19.7 months

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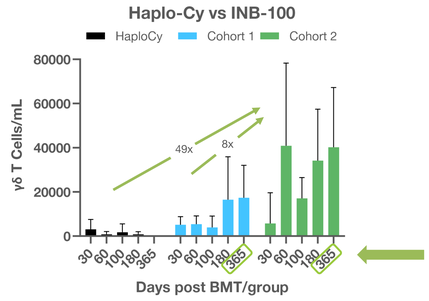
## Treatment emergent AE's in ≥ 20% of patients (n=10)

| Adverse Events | Total (%) | Grade 1/2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Platelet count decreased | 100 | 27.2 | 45.6 | 27.2 |
| WBC decreased | 90.9 | 54.5 | 27.3 | 9.1 |
| Anemia | 100 | 45.5 | 54.5 | 0 |
| ANC decreased | 81.8 | 27.2 | 9.1 | 45.5 |
| Hypomagnesemia | 63.6 | 63.6 | 0 | 0 |
| ALC decreased | 54.5 | 0 | 36.4 | 18.2 |
| Creatinine increased | 54.5 | 54.5 | 0 | 0 |
| Rash maculopapular | 45.4 | 36.3 | 9.1 | 0 |
| Vomiting | 36.3 | 36.3 | 0 | 0 |
| Hypokalemia | 36.4 | 36.4 | 0 | 0 |
| Hyponatremia | 27.3 | 27.3 | 0 | 0 |
| Dyspnea | 27.3 | 27.3 | 0 | 0 |
| Peripheral edema | 27.3 | 27.3 | 0 | 0 |
| Hypertension | 27.3 | 27.3 | 0 | 0 |
| Diarrhea | 27.3 | 27.3 | 0 | 0 |
| Pollakiuria | 18.2 | 18.2 | 0 | 0 |
| Decreased appetite | 18.2 | 0 | 18.2 | 0 |

Note: *As of September 30, 2024; Early trial results are not indicative of future results, including the outcome of this trial.

- **No treatment related deaths**
- **No DLT's to date**
- **2 patients with CMV reactivation**
- **Treatment Related SAE's:**
  - G2/3 Rash maculopapular
  - G3 Nausea
  - G3 Anemia
- **Other non-treatment related SAEs include:**
  - G3 Acute Kidney Injury
  - G3 CMV reactivation
  - G3 Fall
  - G3 Decreased appetite
- **No SUSAR's or unexpected safety events**
- **No change in AE profile from DL1 to DL2**

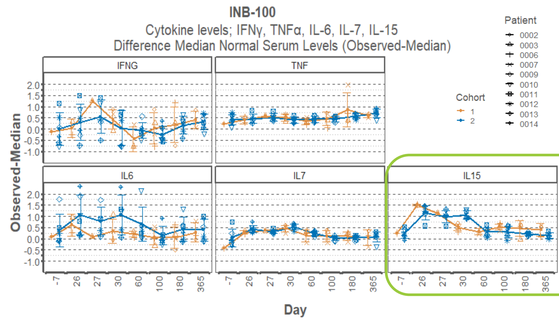
## One–year in vivo persistence and expansion of γδ T cells




Source: IN8bio, Inc. and UAB *previously unpublished data from laboratory of Dr. Lawrence Lamb; as of May 31, 2024 following completion of all time points by patients in dose-level 2

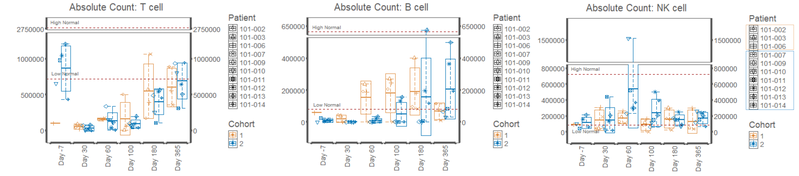
- Comparison of γδ T cell count recovery between patients who received haploidentical BMT + post-BMT Cy without γδ T cell infusion and INB-100 patients from Cohort 1 and Cohort 2
- Dose dependent increase of circulating γδ T cells at Days +60, +100, +180 and +365 for INB-100 treated patients
- Despite Cohort 2 patients receiving 3x the γδ T cell dose as Cohort 1, an 8x increase in γδ T cells was observed at 60 days
- Continued presence at 365 days suggests **in vivo expansion AND persistence** of cells

## Immune recovery: serum cytokine profile




- IL-6 concentration is higher in the second cohort but insufficient to initiate clinical manifestations of CRS. This is also evidenced by decreases of inflammatory cytokines TNF-α, IFN-γ, and IL-7 following transplant and infusion. These data are consistent with a favorable clinical safety profile.
- Initial higher concentrations of serum IL-15 are favorable for homeostatic reconstitution, expansion, and durability of the infused γδ T cell population consistent with the observed intermediate and longer-term efficacy.

## T cell, B cell and NK cell recovery




- T cells recover slowly to low normal values from day 180
- B cell recover slowly to low to normal values from ~ day 60/100
- NK cells recover to low normal to normal levels from day 60 post transplant, with one outlier

## Conclusions & Next Steps

- **There are high rates of relapse in older, high-risk leukemia patients undergoing non-myeloablative, reduced intensity conditioning (RIC), EAGD infusions appear to be tolerable and repeated long-term remissions have been observed with all patients maintaining CR ≥12 months**
- **16.4 months** median duration of **mCR** for 10 evaluable patients at median **19.2 months follow up**
  - **100%** of AML patients remained in **CR after a median 19.7 months of follow-up** with 3 patients with high-risk cytogenetic AML and receiving no maintenance therapy remaining in mCR for >3 years
  - One death in CR attributed to idiopathic pulmonary syndrome not related to EAGD
- This is the first trial to demonstrate **in vivo expansion and persistence of γδ T cells for up to 1-year post-HSCT** suggesting continued γδ T cell surveillance against leukemic relapse
- Safety profile remains manageable and consistent across dose cohorts with primarily grade 2 acute GvHD with no cytokine release syndrome (CRS), neurotoxicity (ICANS), ≥ grade 3 acute GvHD or treatment related deaths reported
- Given favorable risk-benefit ratio and prolonged event free survival (EFS), a Phase 1b expansion of up to 25 total patients is underway to further validate this signal