INB-200: Phase I Study of Gene Modified Autologous Gamma-delta (γδ) T Cells in Newly Diagnosed Glioblastoma Multiforme (GBM) Patients Receiving Maintenance Temozolomide (TMZ)

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Abstract #: CTIM-42

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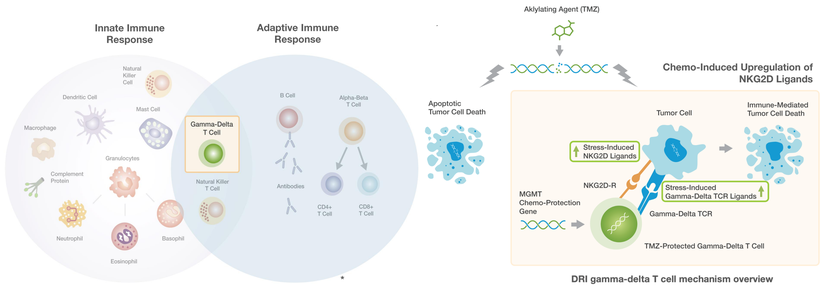
Background

Glioblastoma (GBM) is an aggressive brain tumor that has a high unmet need with one-year overall survival (OS) of 53.7%. Gamma-delta (γδ) T cells are innate immune cells that directly recognize and kill malignant tissue through recognition of Natural Killer Group D Ligands (NKG2D-L) that are expressed on cancer cells. Alkylating chemotherapies such as Temozolomide (TMZ) are lymphodepleting but can also upregulate NKG2D-L expression and amplify the vulnerability of tumor cells to γδ T cell mediated killing, even on TMZ-resistant methylguanine-DNA methyltransferase (MGMT) unmethylated GBM cells. IN8bio's DeltEx Drug Resistant Immunotherapy (DRI), genetically modifies γδ cells with an MGMT chemotherapy resistance gene to permit concomitant administration and the additional targeting of residual TMZ-resistant GBM cells.



DRI gamma-delta T cell mechanism overview

Sources: Ostrom, et al Neuro-Onc 2023; Stupp,et al NEJM 2005; Hottinger, et al Neuro-Oncology 2016, * adapted with permission from Dranoff et al. Nature Rev. Can., Jan. 2004, fig 1., IN8bio, image created with biorender.com

INB-200: Study Design and Treatment Schema

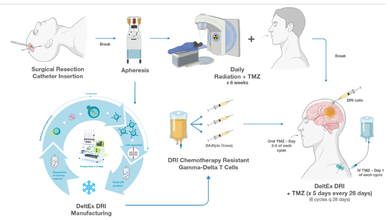
Treatment Arms

Fixed dose level (DL) of DRI in a 3+3 design (N=18):

DL1: N = 3 (up to 6) patients, single dose of 1 x 10^7 cells on C1D1
DL2: N = 3 (up to 6) patients, three doses of 1 x 10^7 cells, one dose every 28 D1 of C1-C3
DL3: N = 3 (up to 6) patients, six doses of 1 x 10^7 cells, one dose every 28 days on D1 of C1-C6

Treatment Regimen & Timing

Surgical resection followed by apheresis → 6 weeks induction TMZ + radiation → 6 cycles maintenance TMZ + DRI



Primary Endpoints

- Safety
- Maximum tolerated dose (MTD) of DeltEx DRI in two dose frequencies

Secondary Endpoints

- Time to progression
- Overall survival
- Biologic response

Site

Source: IN8bio, image created with biorender.com

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Safety and Adverse Events (n=10)

Serious Adverse Events	All Grades	≥ Grade3
Cardiac Arrest	10%	10%
Cardiac Disorder	10%	10%
Platelet Count Decreased	20%	20%
WBC Count Decreased	10%	10%
Hydrocephalus	20%	10%
Dysarthria	10%	10%
Pulmonary Embolus	10%	10%
Cyst Drainaage	10%	10%
Deep Vein Thrombosis	10%	10%

Adverse Events	All Grades	≥ Grade3
Decreased Appetite	20%	
Balance Disorder	20%	
Headache	20%	
Hydrocephalus	20%	10%
Platelet count decreased	30%	30%
WBC count decreased	30%	10%
Lymphocyte count decreased	10%	10%
Neutrophil count decreased	10%	10%
Asthenia	20%	
Fatigue	20%	
Urinary tract infection	20%	

*As of Oct 20, 2023; Early trial results are not indicative of future results, including the outcome of this trial.

- No DRI-related toxicity
- **No DLT's to date**
- **No ICANS/CRS**
- Majority of toxicities are grade 1 or 2 and attributable to TMZ
- Unrelated TESAE's of cardiac arrest, pulmonary embolus, temporal cyst drainage, dysarthria, hydrocephalus
- **No treatment-related deaths**
- **Repeat dosing DOES NOT demonstrate change in toxicity profile to date**

Demographics and Efficacy

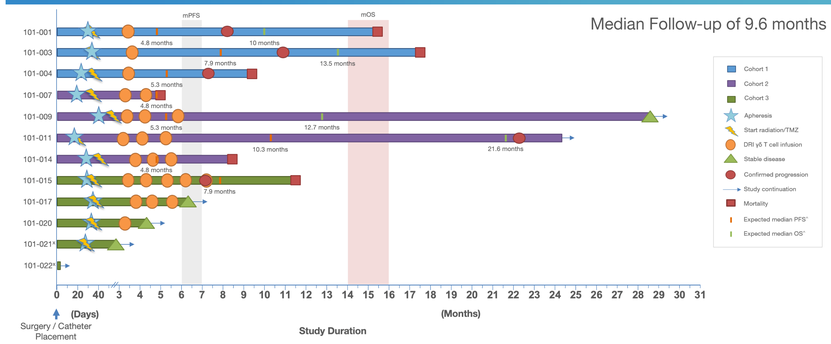
Subject	Age / Sex	Cytogenetics	Dose level	Resection	TMZ Maint. Cycles Received	PFS (mos)	OS (mos)
001	68 / M	IDH-WT, MGMT-unmethylated	1	Total	5	8.3	15.6
003	74 / F	IDH-WT, MGMT-methylated	1	Total	6	11.9	17.7
004	21 / F	IDH-WT, MGMT-unmethylated	1	Total	3	7.4	9.6
007	74 / M	IDH-WT, MGMT-unmethylated	2	Total	2	-	5.1
009	32 / M	IDH-mutant, MGMT-methylated	2	Total	12	28.5+	Alive
011	56 / F	IDH-WT, MGMT-methylated	2	Total	6	22.2	Alive at 24.5
014	73 / F	IDH-WT, MGMT-unmethylated	2	Subtotal	6	8.7	8.7
015	73 / M	IDH-WT, MGMT-methylated	3	Subtotal	5	7.1	11.8
017	74 / F	IDH-WT, MGMT-methylated	3	Subtotal	3	6.3+	Alive
020	66 / M	IDH-WT, MGMT-methylated	3	Subtotal	1	4.4+	Alive
021	57 / M	IDH-WT, MGMT-unmethylated	3	Total	Await Dosing	2.9+	Alive
022	53 / M	IDH and MGMT methylation pending	3	Total	Await Dosing	0.07	Alive

*As of October 20, 2023; Early trial results are not indicative of future results, including the outcome of this trial.

- **22 enrolled, five products unable to be manufactured**
- **Of 10 treated, 4 remain in follow-up**
- **2 await dosing**
- **6 deaths:**
  - 5 due to PD or disease related issues
  - 1 Unrelated:
    - Cardiac event (007)

INB-200: Durability Observed

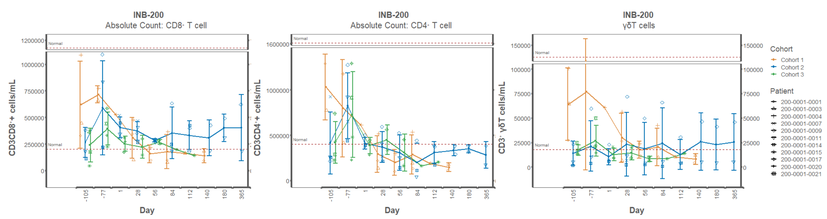
Median Follow-up of 9.6 months



Note: As of Oct. 20, 2023; Source: ^NEJM 2005; 352:987-996 & 352:997-1003 DOI: 10.1056/NEJMoa043330, DOI: 10.1056/NEJMoa043331; NEJM 2017; 376:1027-1037 DOI: 10.1056/NEJMoa1611977; Early trial results are not indicative of future results, including the outcome of this trial.

Peripheral Immunophenotyping

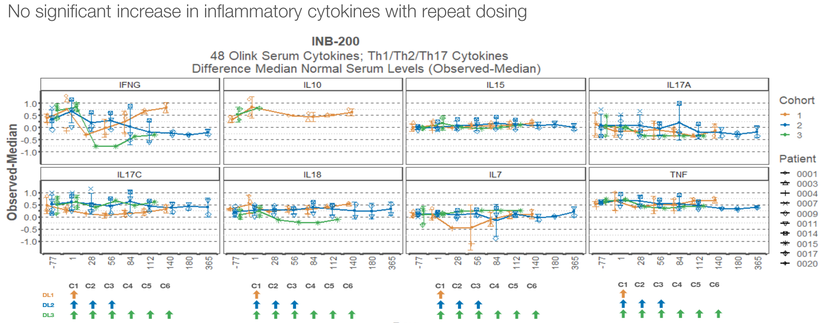
TMZ is an effective lymphodepleting agent for cell therapy



- During TMZ treatment, as expected CD4, CD8 and γδ T cell levels drop to low normal or below low normal values
- The main CD8+ T cells profile is Naïve and Central Memory
- CD8 and γδ T cell level for patient 9 (the only IDH mutant patient) remain at normal levels throughout the study

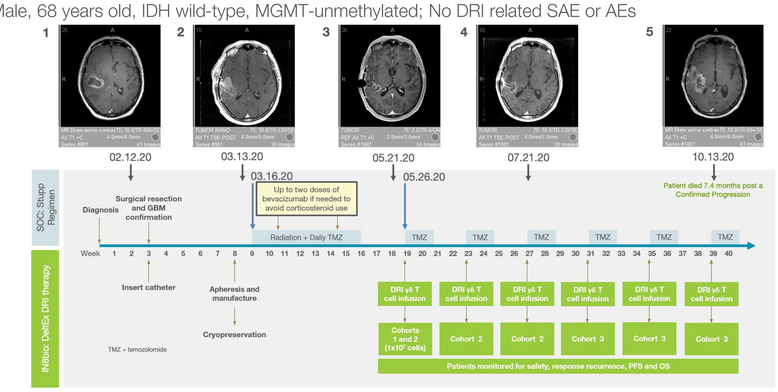
Serum Cytokines

No significant increase in inflammatory cytokines with repeat dosing



First Patient Enrolled and Treated – 001

Male, 68 years old, IDH wild-type, MGMT-unmethylated; No DRI related SAE or AEs

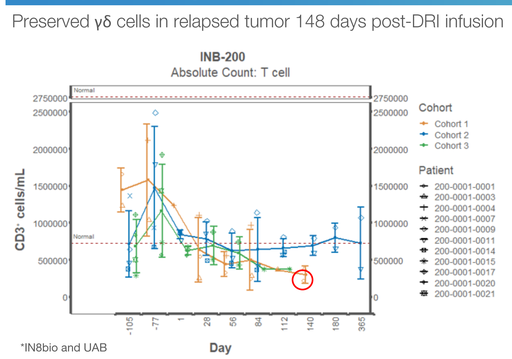


T1 MRI, tumor appears as white; Results from one patient are not indicative of future results including the outcome of this trial

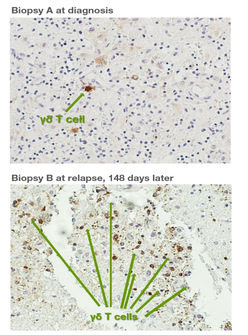
Source: IN8bio and UAB

Peripheral Lymphodepletion in Patient 001

Preserved γδ cells in relapsed tumor 148 days post-DRI infusion



*IN8bio and UAB



Conclusions

- **First study evaluating safety and efficacy of genetically modified γδ T cells**
- **DeltEx DRI γδ T cells have a manageable safety profile with no CRS or ICANS observed**
- **All patients who completed mandated doses surpassed a median PFS of 7 months, with most exceeding the expected PFS based on their age and MGMT status of their tumors**
- **TMZ is an effective lymphodepleting regimen for cellular therapy**
- **DeltEx DRI technology demonstrates preserved γδ T cells in tumor milieu despite significant peripheral lymphodepletion**
- **Promising results indicate DRI γδ T cells could provide treatment options for treating GBM and was granted Orphan Drug Designation by the FDA**
- **Phase 1b/2 trial, INB-400, underway to confirm and validate autologous AND allogeneic DRI γδ T cell therapy in newly diagnosed and relapsed GBM; autologous arm now open for enrollment**

INB-400: NCT05664243; TIPS at CTIM-35

*Arm B and C subject to additional IND for allogeneic drug product (INB-410) as per FDA Guidance for Industry updated Nov. 2022 (https://clinicaltrials.gov/ct2/show/NCT05664243)