INB-400 Phase 1b/2 Drug Resistant Immunotherapy With Activated, Gene Modified Allogeneic or Autologous γδ T Cells in Combination With Maintenance Temozolomide Recurrent or Newly Diagnosed Glioblastoma

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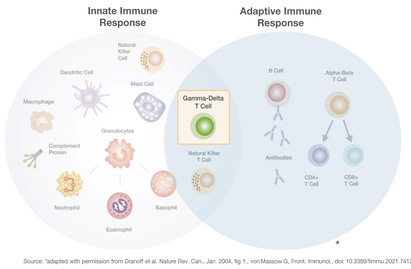
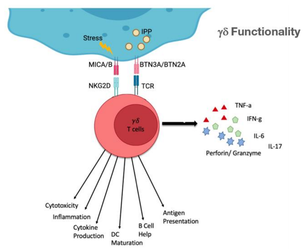
Abstract #: CTIM-35

Background

Gamma-delta (γδ) T cells are powerful immune cells with properties of both the innate and adaptive immune system. They express both a gamma-delta T cell receptor (TCR) and NKG2D-receptor, allowing them to target and kill unhealthy cells, including cancer cells. This is achieved through the recognition of membrane receptors such as the stress-induced NKG2D ligands, which are upregulated on tumor cells after chemotherapy exposure. IN8bio's proprietary DeltEx drug resistant immunotherapy (DRI) platform uses genetic engineering to express the protein O-6-methylguanine-DNA methyltransferase (MGMT) to generate gamma-delta T cells that are resistant to the lymphodepleting effects of alkylating chemotherapies such as temozolomide (TMZ). This approach allows for synergistic combinations of standard-of-care chemotherapy regimens for GBM with DeltEx DRI gamma-delta T cells to potentially strengthen immune response and eliminate cancer cells.



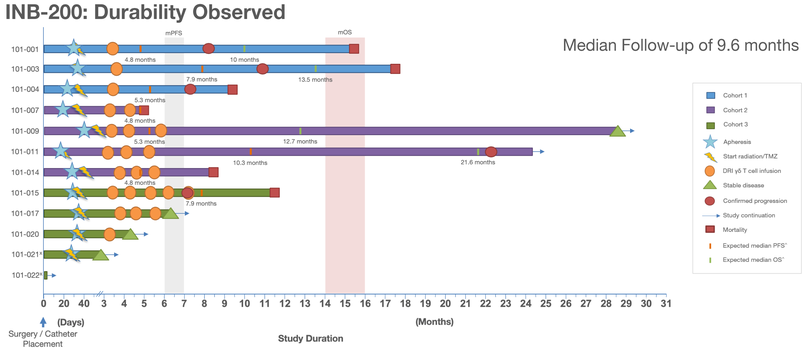
Source: *adapted with permission from Drancff et al. Nature Rev. Can., Jan. 2004, fig 1., von Massow G, Front. Immunol., doi: 10.3389/fimmu.2021.741218



- INB-200, a Phase 1 trial assessing the safety of autologous DeltEx DRI gamma-delta T cells co-administered with maintenance chemotherapy has demonstrated manageable safety and evidence of prolongation of progression-free survival (PFS) in newly diagnosed GBM patients.
- All fully dosed patients have exceeded the median PFS of 7 months for standard-of-care with 1 patient remaining progression free at 28.5 months.
- Furthermore, the majority of treated patients have exceeded their expected PFS based on the age and MGMT status of their tumors.
- Based on this, a Phase 2 corporate sponsored multi-center trial was launched to verify this signal and a Phase 1b/2 trial to assess the safety and efficacy of allogeneic DeltEx DRI from matched related or haploidentical donors in both newly diagnosed and relapsed GBM patients.

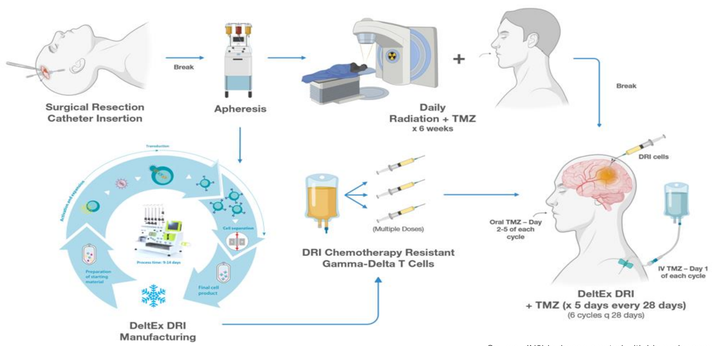
INB-200: Durability Observed

Median Follow-up of 9.6 months



Note: ***POD = progression of disease**; 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.

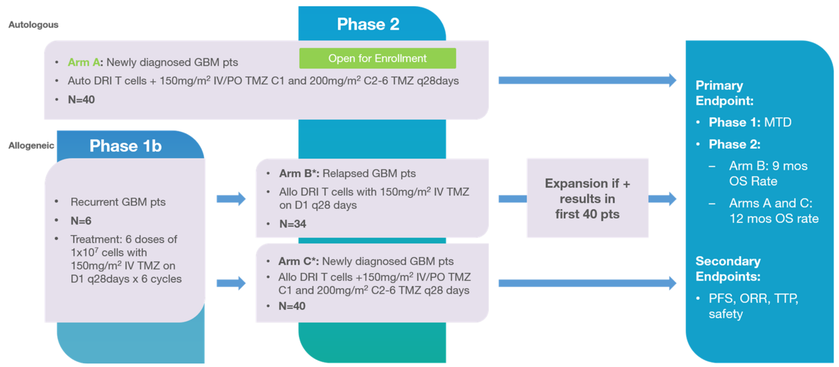
INB-400 - Newly Diagnosed Patient Treatment Protocol



Source: IN8bio, image created with biorender.com

Background (Continued)

INB-400: Study Design and Treatment Schema



*Arm B and C subject to additional IND for allogeneic drug product (INB-400) as per FDA Guidance for Industry updated Nov. 2022 (https://clinicaltrials.gov/ct2/show/NCT05664243)

Primary Objectives

AUTOLOGOUS ARM:

Phase 2 (Arm A):

- To assess the clinical efficacy of autologous DeltEx DRI gamma-delta T cells in subjects with newly diagnosed glioblastoma

ALLOGENEIC ARMS:

Phase 1b:

- To assess the safety and tolerability of allogeneic DeltEx DRI gamma-delta T cells in subjects with relapsed glioblastoma
- To assess the feasibility to manufacture cell product

Phase 2 (Arm B and Arm C):

- To assess the clinical efficacy of DeltEx DRI gamma-delta T cells in subjects with newly diagnosed glioblastoma and relapsed glioblastoma

Secondary and Exploratory Objectives

Secondary: Phase 1b and Phase 2 (Autologous Arm and Allogeneic Arms)

- To assess the safety and tolerability of DeltEx DRI cells
- To assess durability of response
- To assess the feasibility to manufacture cell product in the Phase 2

Exploratory: Phase 1b and Phase 2 (Autologous Arm and Allogeneic Arms)

- To characterize the in-situ biologic activity and immunologic activity of DeltEx DRI T cells
- To characterize the local and systemic immune response to DeltEx DRI T cells

Endpoints

Primary:

Autologous Arm

- Phase 2
  - Arm A: 12 months overall survival (OS) rate

Allogeneic Arms:

- Phase 1b:
  - Establish RP2D for Phase 2 allogeneic arms
  - Define subject or product characteristics that will optimize manufacturing
- **Phase 2**
  - Arm B: 9 months OS rate
  - Arm C: 12 months OS rate

Secondary:

- Autologous Arm and Allogeneic Arms
- Assess adverse events, serious adverse events, vital signs, and laboratory
- ORR, PFS, DOR
- Define subject or product characteristics that will optimize manufacturing in Phase 2

Exploratory:

- Phase 1b and 2 (Arms A to C)
- Changes in cytokines, immune cell reconstitution, composition and functional status over the course of therapy

Inclusion Criteria

1. Adult subjects with histologically or cytologically confirmed history of IDH wild type GBM
2. Phase 1b and Arm B of Phase 2: must have completed no more than 1 standard therapy for glioblastoma, have received no prior Avastin® therapy (unless solely used for edema management) and be eligible for resection
   - Arms A and C: must have newly diagnosed, treatment naïve GBM
   - Phase 1b and Arm B and Arm C: must have a partially matched haploidentical or matched related donor
3. MRI consistent with recurrent malignant glioma in Phase 1b and Arm B
4. Agreeable to inserting and maintaining a Rickham catheter
5. KPS ≥ 70%
6. Life expectancy of greater than 12 weeks
7. Organ and marrow function:
   - WBC > 3,000/μL; ANC> 1,500/μL, Hemoglobin ≥ 9.0 g/dL, Platelets > 100,000/μL
   - ALT/SGPT/AST/SGOT < 2.5 x institutional ULN; Tbili<1.5xULN
   - Normal electrolyte levels
   - INR)/PT)/aPTT≤ 1.5 x ULN
   - CrCl must be ≥ 50 mL/min
   - Normal electrocardiogram (ECG); if abnormal, NCS
   - Appropriate contraception for men and women

Exclusion Criteria

1. Subject in Arm A or donor from Phase 1b, Arms B, and Arm C received vaccinations within 4 weeks or underwent surgery (major or minor) within 72 hours before leukapheresis collection
2. Subjects received/receiving any of the following:
   - Cellular immunotherapy or gene therapy or within 6 weeks prior to entering the study
   - Surgical resection or alkylating agent chemotherapy within 4 weeks prior to entering the study
   - Receiving TTF therapy
   - Have received experimental immunotherapy at any time or other investigational agents concurrently
   - Prior allogeneic therapy with bone marrow or solid tumor transplant
3. Have not recovered from adverse events (≤ Grade 1) from previously administered therapy. Subjects with alopecia unless of immune origin may qualify
4. Concurrent malignancy or 2 years disease free from prior malignancy.
5. Contraindication to the placement of a Rickham catheter
6. Prior history of encephalitis, multiple sclerosis, or other CNS infection <1 year prior to glioblastoma diagnosis
7. Required steroid increase within 2 weeks of scheduled DRI EAGD T cells administration and receiving > 10 mg/day of prednisone or its equivalent
8. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, HIV or active hepatitis or autoimmune disease
9. Allergies/hypersensitivity to amino bisphosphonates such as Zoledronate®, Pamidronate® or similar

Enrolling Centers for INB-400

	Company/Hospital/ Institution	City (Investigator)
1	Board of Regents of the University of Wisconsin	Madison, WI
2	UCLA-Neuro-Oncology	Los Angeles, CA
3	University of Louisville Health Care - James Graham Brown Cancer Center	Louisville, KY
4	OSUWMC--James Cancer Hospital	Columbus, OH
5	The Preston Robert Tisch Brain Tumor Center (Duke)	Durham, NC
6	H. Lee Moffitt Cancer Center and Research Institute	Tampa, FL
7	Cleveland Clinic Foundation	Cleveland, OH
8	University of Alabama at Birmingham UAB - The Kirklin Clinic	Birmingham, AL
9	University of Minnesota	Minneapolis, MN
10	Yale University/Yale New Haven Hospital	New Haven, CT
11	UCSD Medical Center	La Jolla, CA
12	City of Hope	Duarte, CA

- Currently open sites
- Principal investigator site

Source: IN8bio, Inc.