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INB-200: Fully Enrolled Phase 1 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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2024 SNO Annual Meeting

SNO Society for NeuroOncology

Disclosures

LB Nabors

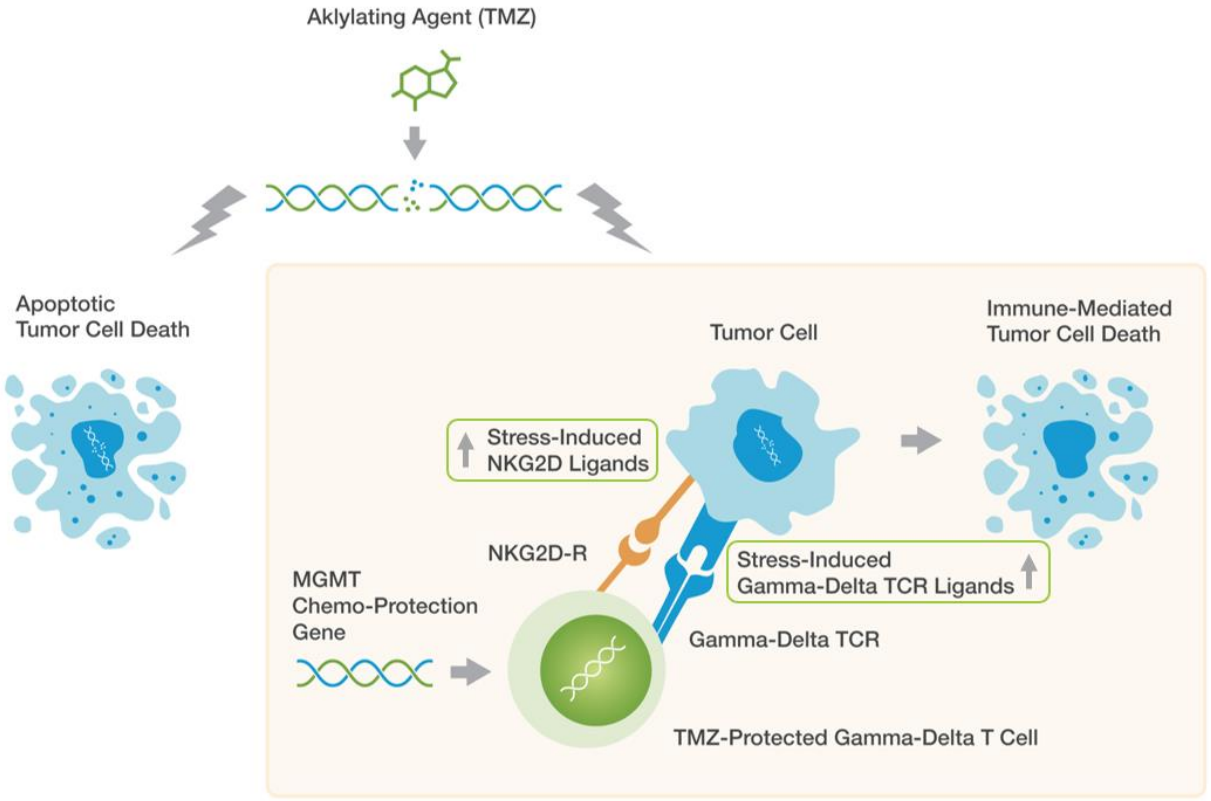
- Scientific Advisory Board for Servier and AnHeart; DSMC for CNS Pharma

LS Lamb, K Rochlin, S Youngblood, M ter Haak

- IN8bio, Inc. employment and equity options

Targeting the DNA Damage Response (DDR) to Kill Tumors

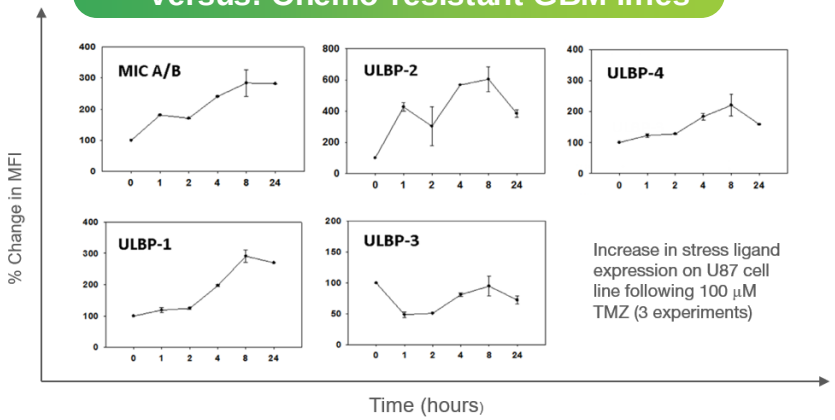
DDR is a biological process that can detect and eliminate cells with DNA damage through increased avidity



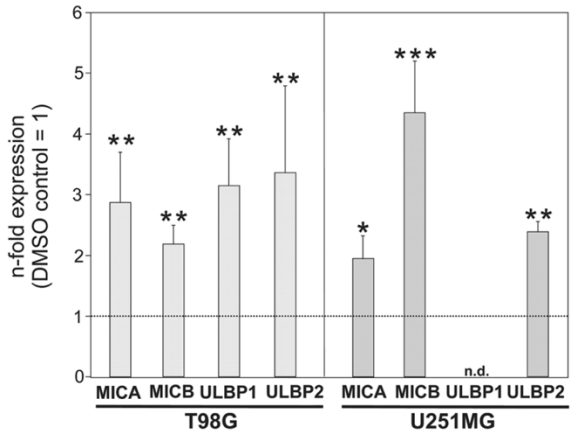
DRI gamma-delta T cell mechanism overview

TMZ Increases NKG2D-L Expression:

Versus: Chemo-resistant GBM lines



Versus: Glioma stem-like cells



Source: IN8bio, Lamb et al. Plos One, (2013) Vol 8., Issue 1, Held-Feindt et al. Histochemistry and Cell Biology, (2018) 149: 2019-233; https://doi.org/10.1007/s00418-018-1633-5

INB-200: Study Design and Treatment Schema

Treatment Arms

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

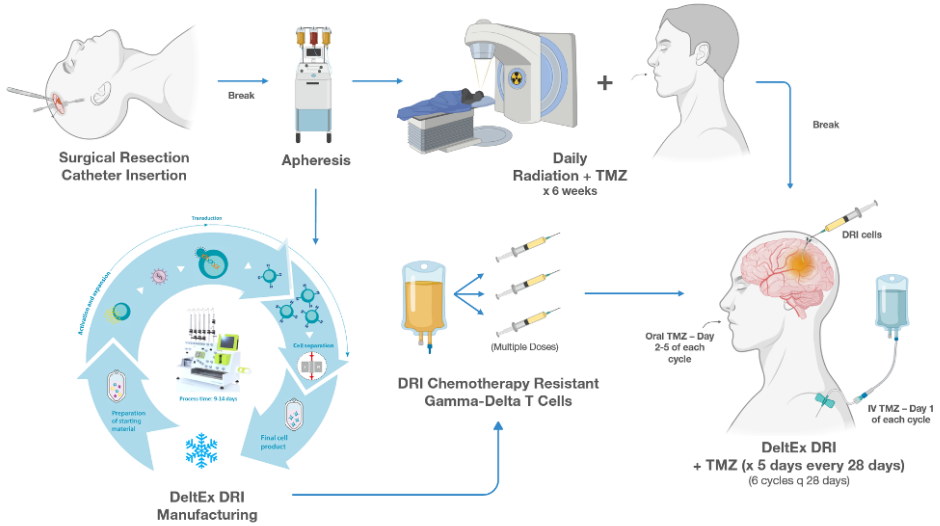
DL1: N = 3 (up to 6) patients, single dose of 1 x 10^7 cells on C1D1
DL2: N = 3 (up to 6) patients, three doses of 1 x 10^7 cells, one dose every 28 D1 of C1-C3
DL3: N = 3 (up to 6) patients, six doses of 1 x 10^7 cells, one dose every 28 days on D1 of C1-C6

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 three dose frequencies

Secondary Endpoints

- Time to progression
- Overall survival
- Biologic response

Site

O'NEAL COMPREHENSIVE CANCER CENTER
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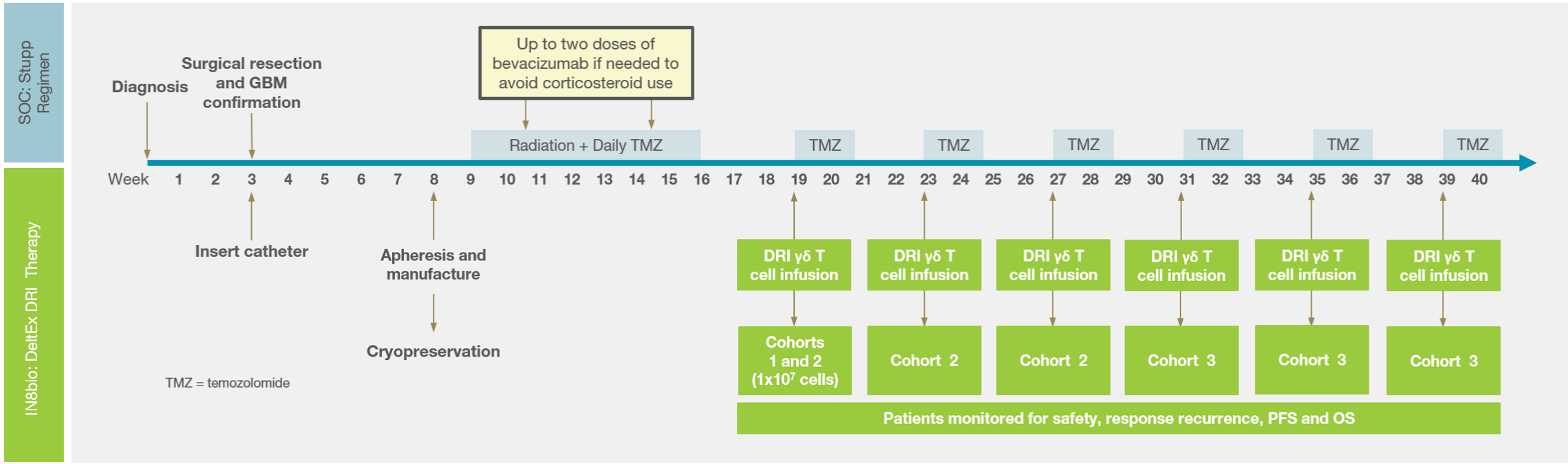
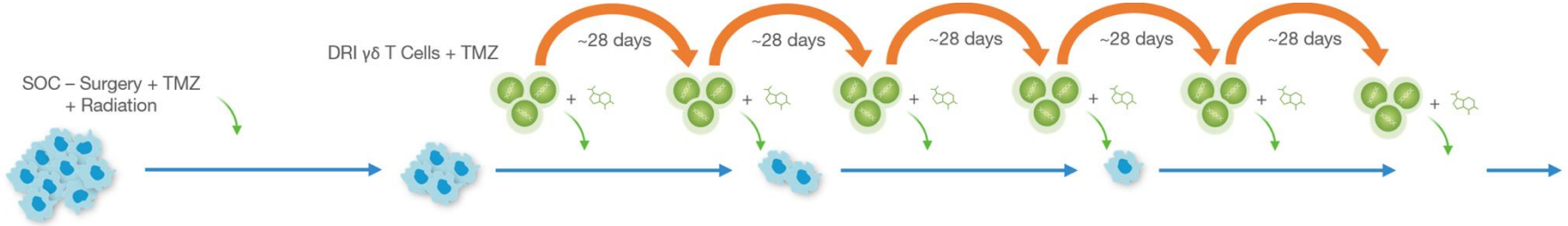
Source: IN8bio, image created with biorender.com

Rationale for Repeat Dosing

INB-200: Phase I trial of intracavitary injection of MGMT-modified autologous γδ T cells for patients with primary, resectable high-grade glioma



TMZ + adjuvant DRI γδ T cells multiple repeat doses



Source: IN8bio; assumptions: GBM doubling time ~50days (Berntsen et al. Neuro-Oncology, 2015), DRI kills ~50% of cells that are resistant to TMZ therapy

Patient Demographics

Subject	Age / Sex	Cytogenetics	Dose level	Resection	TMZ Maint. Cycles Received
001	68 / M	IDH-WT, MGMT-unmethylated	1	Total	5
003	74 / F	IDH-WT, MGMT-methylated	1	Total	6
004	21 / F	IDH-WT, MGMT-unmethylated	1	Total	3
007	74 / M	IDH-WT, MGMT-unmethylated	2	Total	2
009	32 / M	IDH-mutant, MGMT-methylated	2	Total	12
011	56 / F	IDH-WT, MGMT-methylated	2	Total	6
014	73 / F	IDH-WT, MGMT-unmethylated	2	Subtotal	6
015	73 / M	IDH-WT, MGMT-methylated	3	Subtotal	5
017	74 / F	IDH-WT, MGMT-methylated	3	Subtotal	3
020	66 / M	IDH-WT, MGMT-methylated	3	Subtotal	6
021	57 / M	IDH-WT, MGMT-unmethylated	3	Total	6
022	53 / M	IDH-WT, MGMT-unmethylated	3	Subtotal	6
023	52 / M	IDH-WT, MGMT-unmethylated	3	Subtotal	1

- **Median age: 68**
- **54% unmethylated**
- **23 enrolled, five products unable to be manufactured**
- **Of 13 treated, 5 remain in follow-up**
- **8 deaths:**
  - 7 due to PD or disease-related issues
  - Other:
    - Cardiac event (007)

*As of October 18, 2024; Early trial results are not indicative of future results, including the outcome of this trial.

Treatment Emergent Adverse Events (N=13)

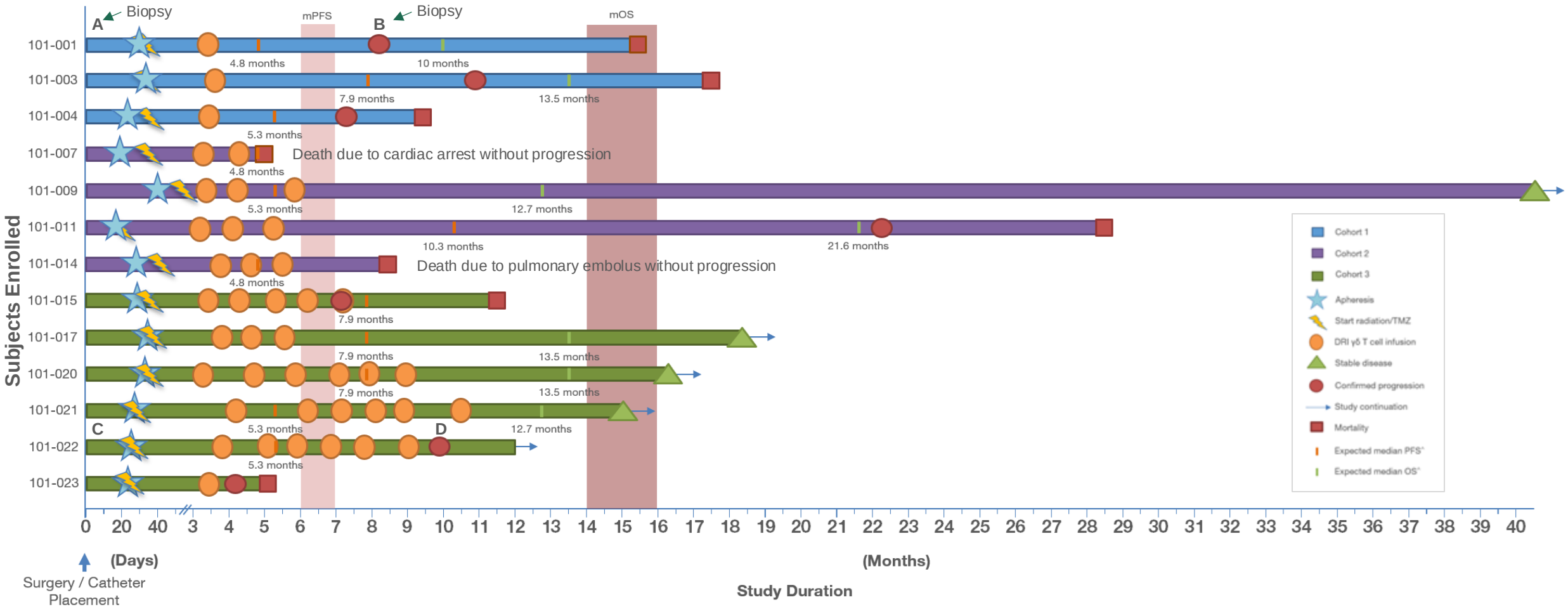
	SAEs	>1 Gr. 1-2	Grade 3	Grade 4	Grade 5	All Grades
WBC count decreased	SAE	2 (15.4)	1 (7.7)	0	0	3 (23%)
Platelet count decreased	SAE		2 (15.4)	1 (7.7)	0	3 (23%)
Hydrocephalus	SAE	1 (7.7)	1 (7.7)	0	0	2 (15.4)
Deep vein thrombosis	SAE	1 (7.7)	1 (7.7)	0	0	2 (15.4)
Dysarthria	SAE		1 (7.7)	0	0	1 (7.7)
Hypertension	SAE		1 (7.7)	0	0	1 (7.7)
Cardiac arrest	SAE		0	0	1 (7.7)	1 (7.7)
Cardiac disorder	SAE		1 (7.7)	0	0	1 (7.7)
Pulmonary embolism	SAE		0	1 (7.7)	0	1 (7.7)
Fall	SAE		1 (7.7)	0	0	1 (7.7)
Cyst drainage	SAE		1 (7.7)	0	0	1 (7.7)
Lymphocyte count decreased			1 (7.7)	0	0	1 (7.7)
Neutrophil count decreased			0	1 (7.7)	0	1 (7.7)
Hypotension			1 (7.7)	0	0	1 (7.7)
Appendicitis			1 (7.7)	0	0	1 (7.7)
Balance disorder		2 (15.4)	0	0	0	2 (15.4)
Urinary tract infection		2 (15.4)	0	0	0	2 (15.4)
Asthenia		2 (15.4)	0	0	0	2 (15.4)
Fatigue		2 (15.4)	0	0	0	2 (15.4)
Headache		2 (15.4)	0	0	0	2 (15.4)
Arthralgia		2 (15.4)	0	0	0	2 (15.4)
Decreased appetite		2 (15.4)	0	0	0	2 (15.4)

*As of October 18, 2024; Early trial results are not indicative of future results, including the outcome of this trial.

- No DRI-related toxicity
- **No DLTs 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**

Improving Outcomes with Increasing Doses of γδ T Cells

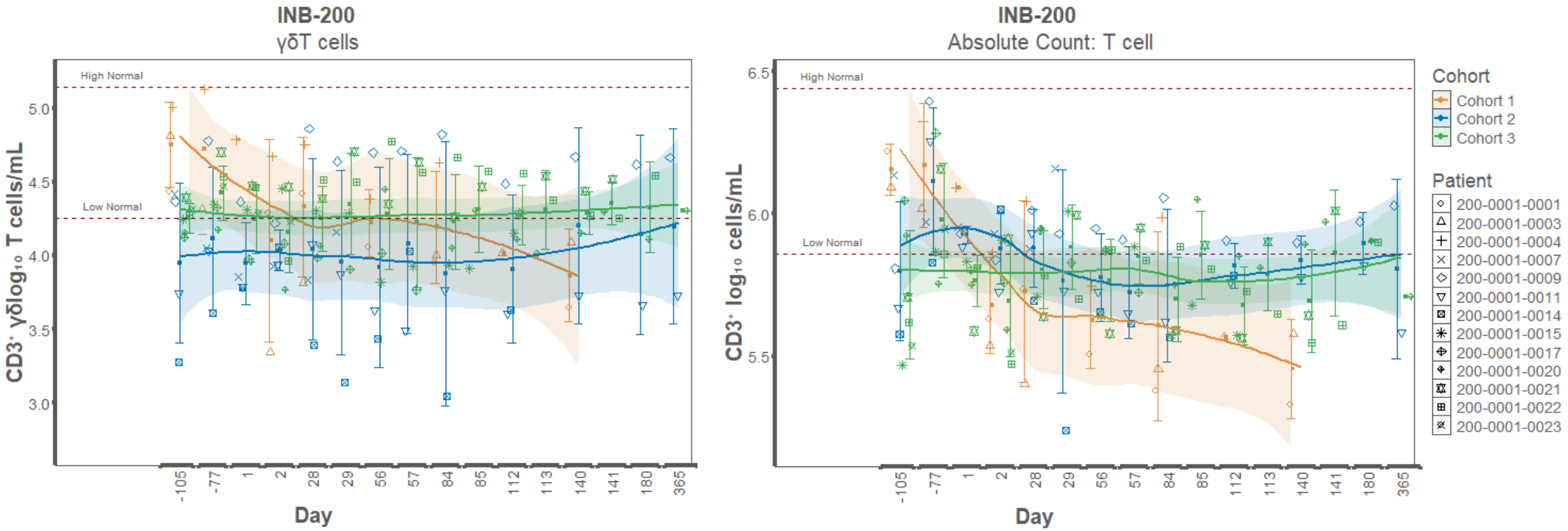
Median Follow-up: 14.8 months



Note: ***POD = progression of disease***; As of October 18, 2024; 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; [X] Not yet treated; Early trial results are not indicative of future results, including the outcome of this trial.

Intracavitary Immunotherapy Influences Global Immunity

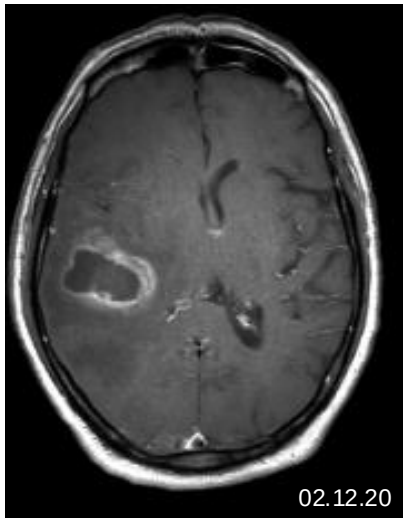
Despite the lymphodepletion with TMZ, intracranial γδ T cell infusions improves both CD3+ T cell and γδ T cell levels peripherally with a dose-response correlated with repeated infusions

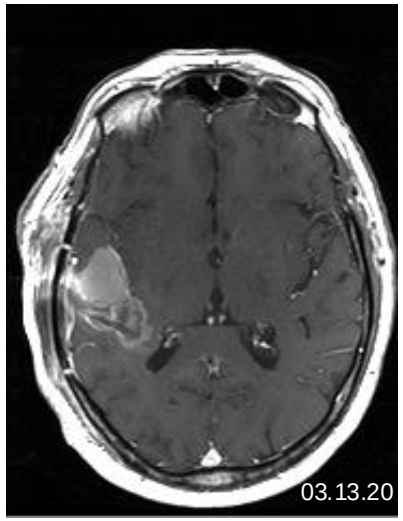


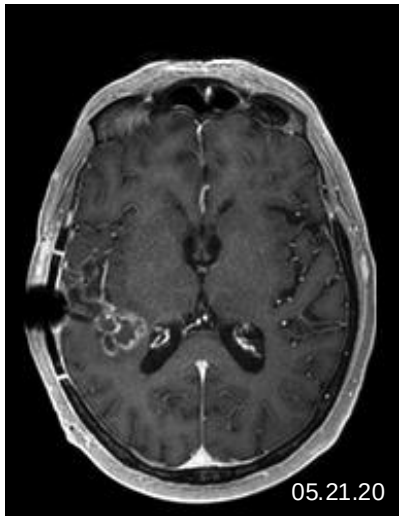
Source: IN8bio and UAB - Results from one patient are not indicative of future results including the outcome of this trial

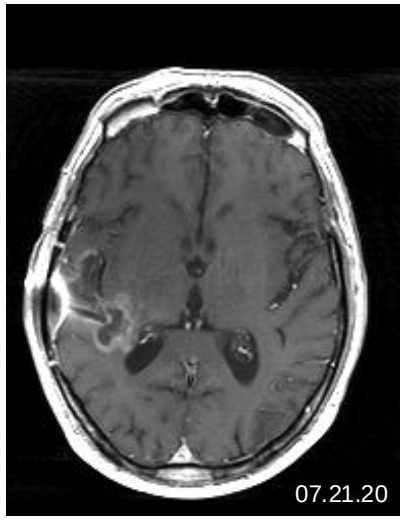
Patient 001 – Male 68y, IDH-wt, MGMT-unmethylated

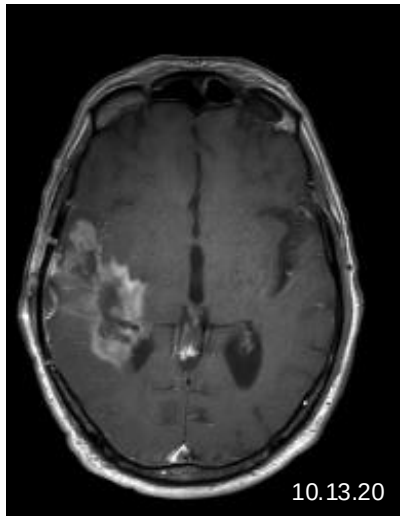
No DRI related SAEs or AEs

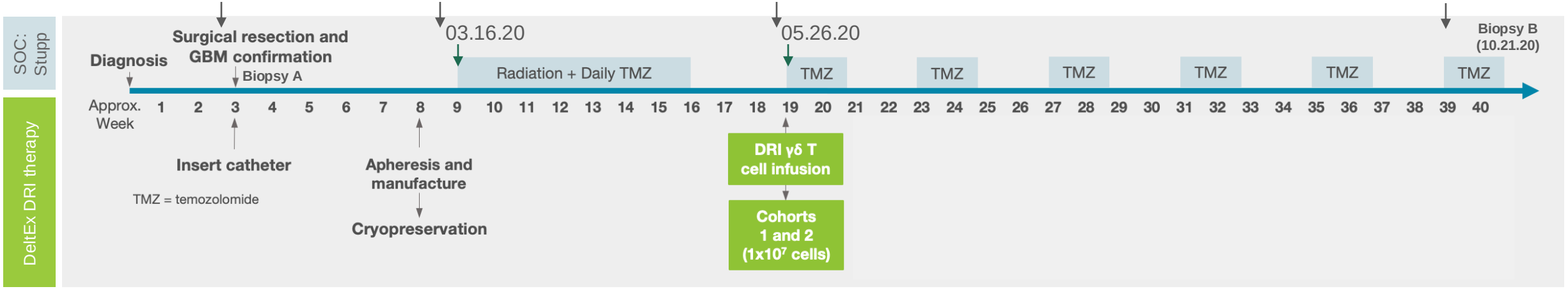










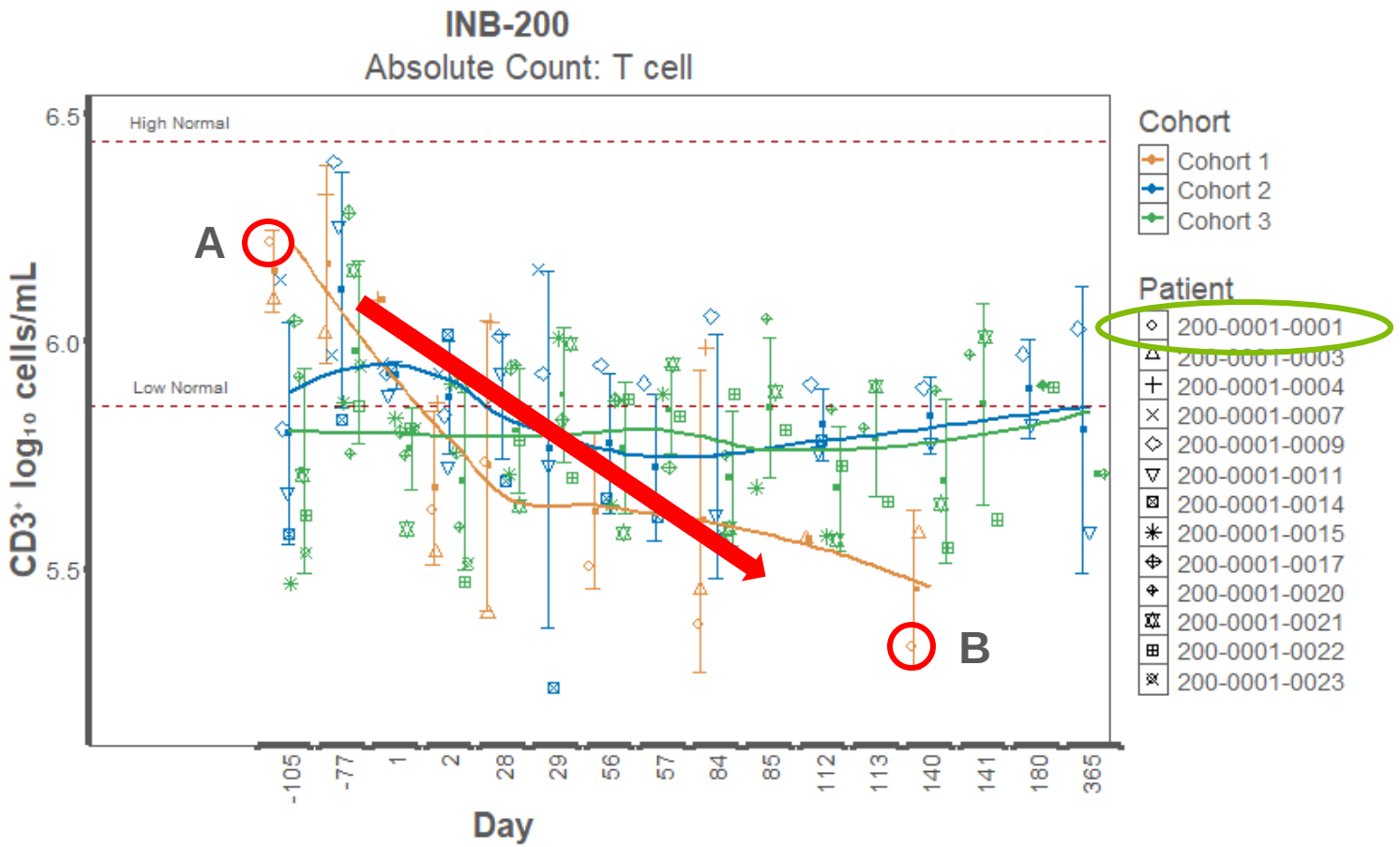


Results from one patient are not indicative of future results including the outcome of this trial

Source: IN8bio and UAB

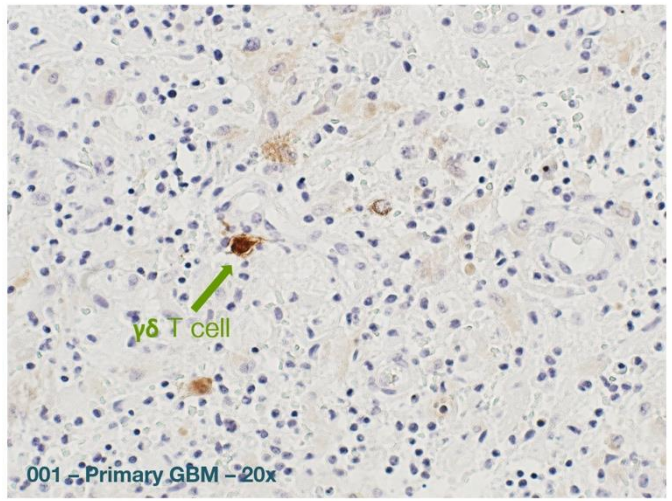
γδ T Cells are Infiltrating and Persisting in Tumor Tissue

Preserved γδ cells in relapsed tumor 148 days post a single DRI infusion despite significant peripheral lymphodepletion in patient 001

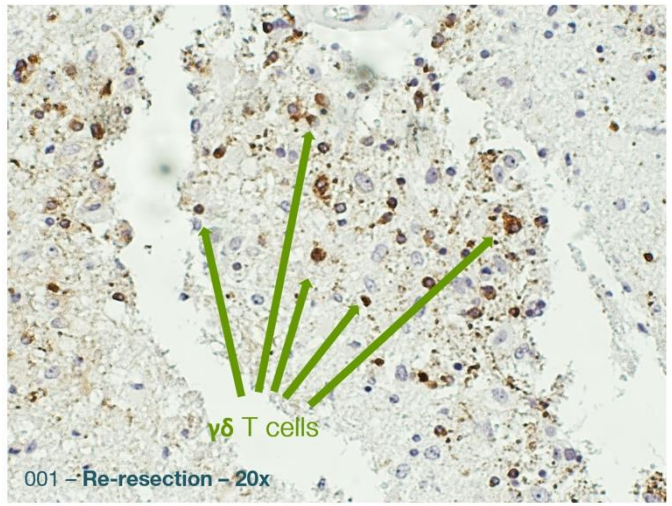


Source: IN8bio and UAB

Biopsy A: at diagnosis

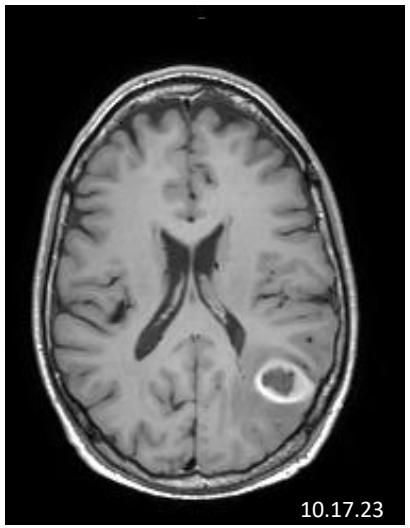


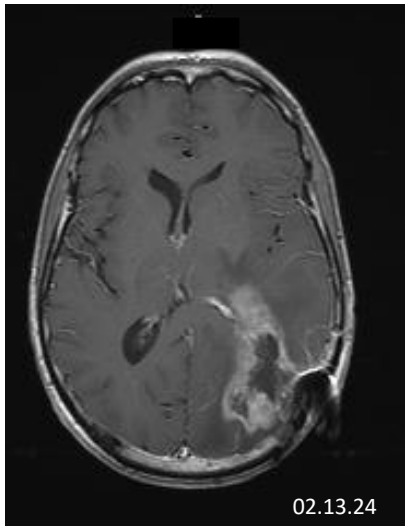
Biopsy B: at relapse, 148 days after single dose

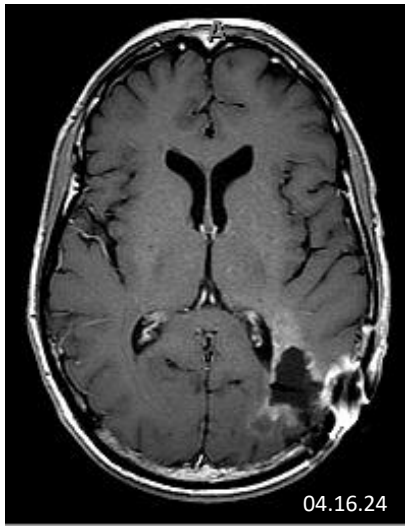


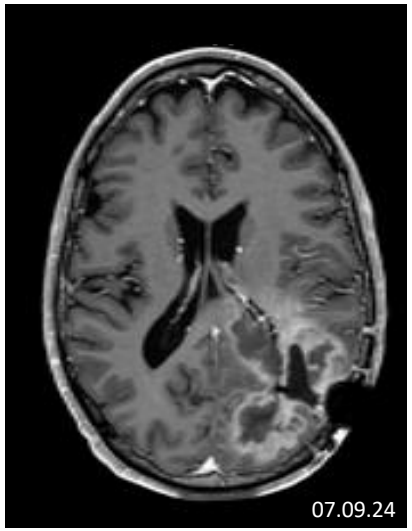
Patient 022 – Male 53y, IDH-wt, MGMT-unmethylated

Sub-total resection at diagnoses, remains alive at 12.0+ months









SOC: Stupp

DeltEx DRI therapy

Diagnosis

Surgical resection and GBM confirmation

Biopsy C

11.14.23

Radiation + Daily TMZ

02.15.24

TMZ

Biopsy D (08.16.24)

Approx. Week 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40

Insert catheter

Apheresis and manufacture

Cryopreservation

TMZ = temozolomide

DRI γδ T cell infusion

Cohorts 1 and 2 ($1x10^7$ cells)

Cohort 2

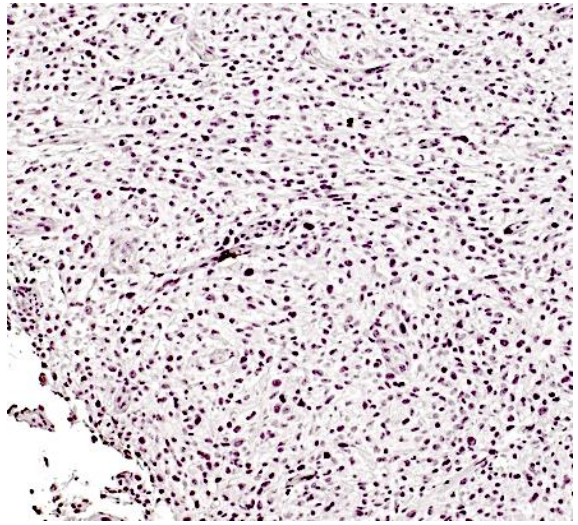
Cohort 3

Source: IN8bio and UAB - Results from one patient are not indicative of future results including the outcome of this trial

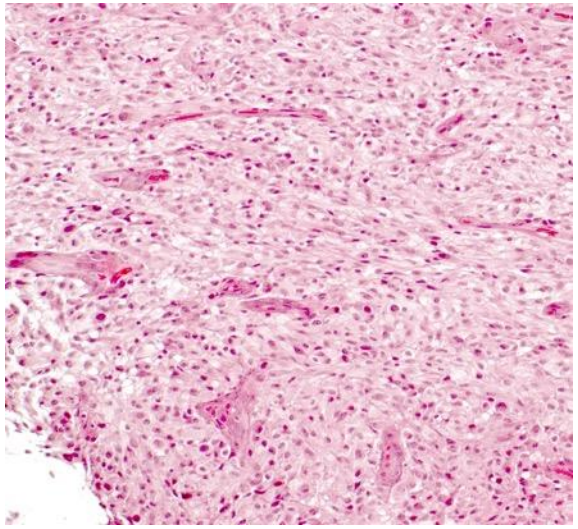
Patient 022 - Confirmation of γδ T Cell Infiltration

Preserved γδ T cells confirmed following six does of DRI infusion + TMZ with presence of necrotic tissue and prominent γδ T cell infiltration of relapsed tumor

Biopsy C: at diagnosis

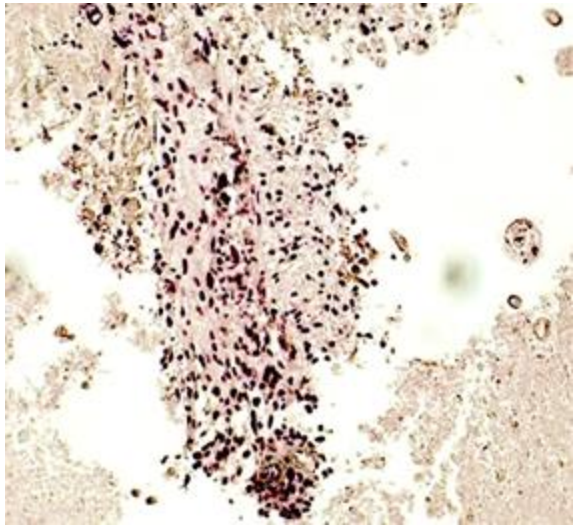


γδ T cell stain (brown)

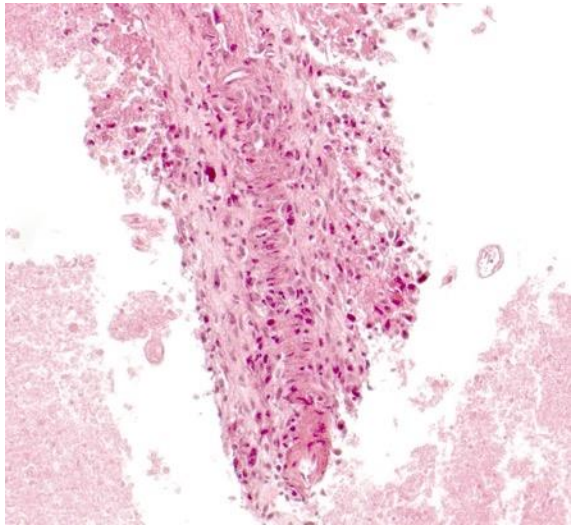


H&E stain

Biopsy D: at relapse



γδ T cell stain (brown)



H&E stain

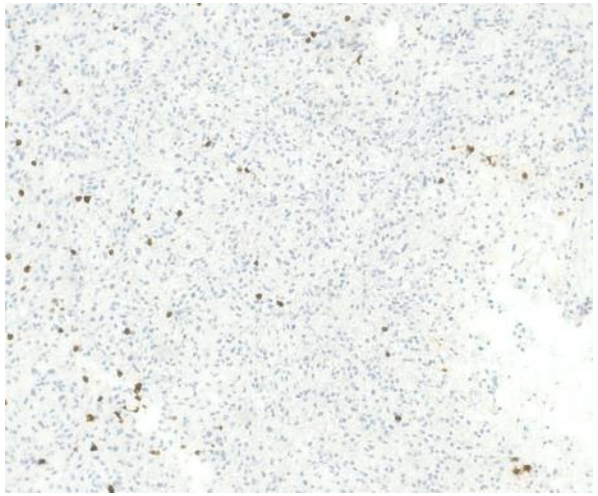
Source: IN8bio and UAB

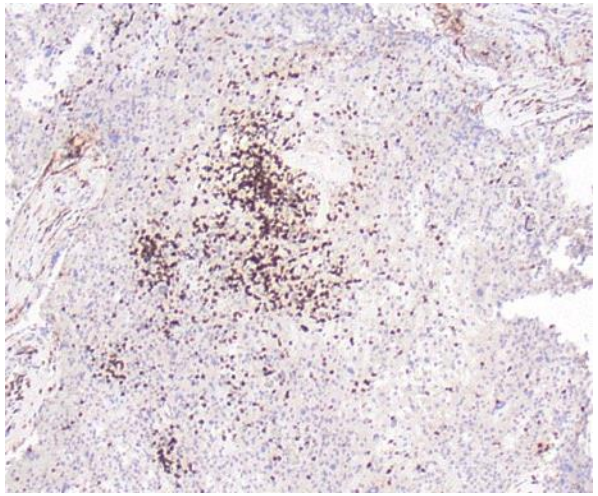
Patient 022 - Confirmation of T Cell Infiltration

Biopsy C: at **diagnosis**

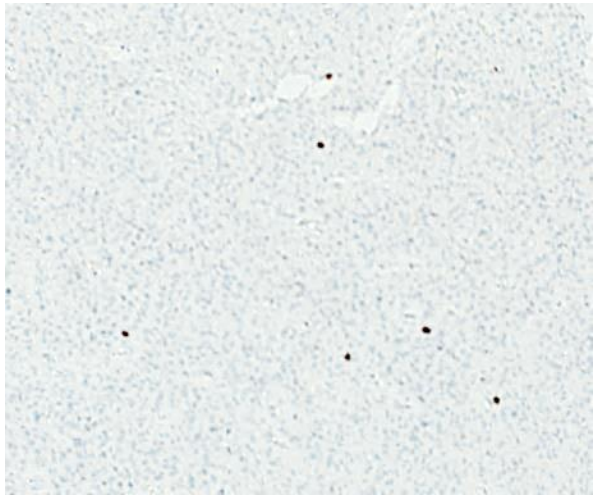
Biopsy D: at **relapse**

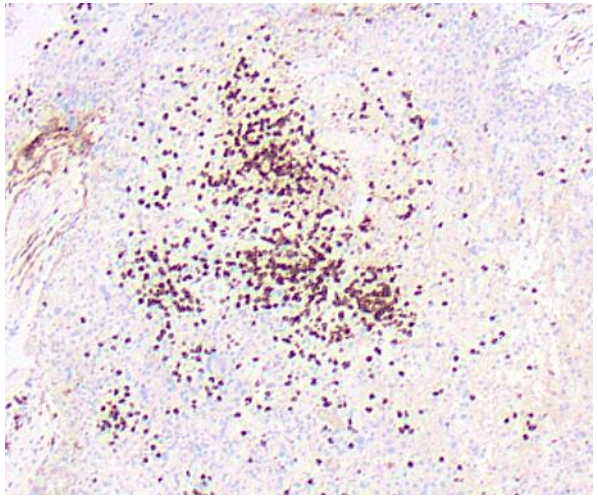
CD3+ T cells





CD8+ T cells





Source: IN8bio and UAB

Conclusions and Future Directions

Outpatient treatment of newly diagnosed glioblastoma patients using an MGMT gene-modified γδ T cell therapy is feasible with a Rickham catheter placed for long-term longitudinal use

- **Safety:** No treatment-related serious adverse events (SAE's), with no observed CRS, ICANs or neurotoxicity and no treatment related deaths
- **Cell Infiltration:** Paired biopsies from two separate patients confirm significant infiltration of γδ T cells, as well as CD3+ and CD8+ T cells
- **Activity and Efficacy: T**here is a discernible dose-response towards longer PFS and OS as patients transition from single to multiple dose cohorts
- **Current Trial Predicament:** INB-400 Phase 2 trial (NCT05664243) suspended due to lack of funding sources
- **Future Directions:** The normal tissue sensing ability and lack of an allogeneic recognition mechanism combined with the CNS immune environment creates an ideal opportunity for allogeneic γδ T cells DRI therapy thereby enabling a potential allogeneic and 'off-the shelf' treatment for multiple patients

Acknowledgements

- All patients and their families!
- UAB Department of Neurosurgery
- Neuro-Oncology Research Staff
- Cell Therapy Laboratory at UAB
- The IN8bio, Inc Team