Unraveling Complexity: The Impact, Interactions and Outcomes of a γδ T Cell Therapy in Glioblastoma

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GBM: High Unmet Clinical Need

Glioblastoma (GBM) is one of the most aggressive cancers with median overall survival (mOS) of only ~12 months(m) and no drug approvals or change to standard-of-care (SOC) in 20+ years. GBM clinical trials face difficult/poor brain imaging and an inability to repeat biopsy. Due to the paucity of treatments, patients undergo limited biomarker stratification with almost all receiving SOC despite biological heterogeneity.

Recent data from INB-200/400 Phase 1/2 trial of DeltExTM Drug Resistant Immunotherapy (DeltEx DRI), demonstrated durable survival improvements in newly diagnosed GBM. DeltEx DRI uses autologous MGMT-modified γδ T cells engineered for temozolomide (TMZ) resistance, enabling intrathecal dosing concomitantly with TMZ.

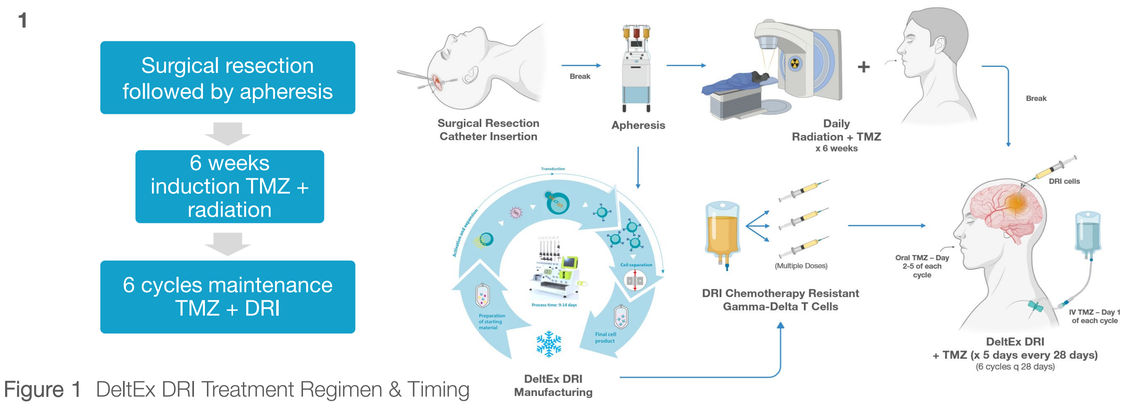


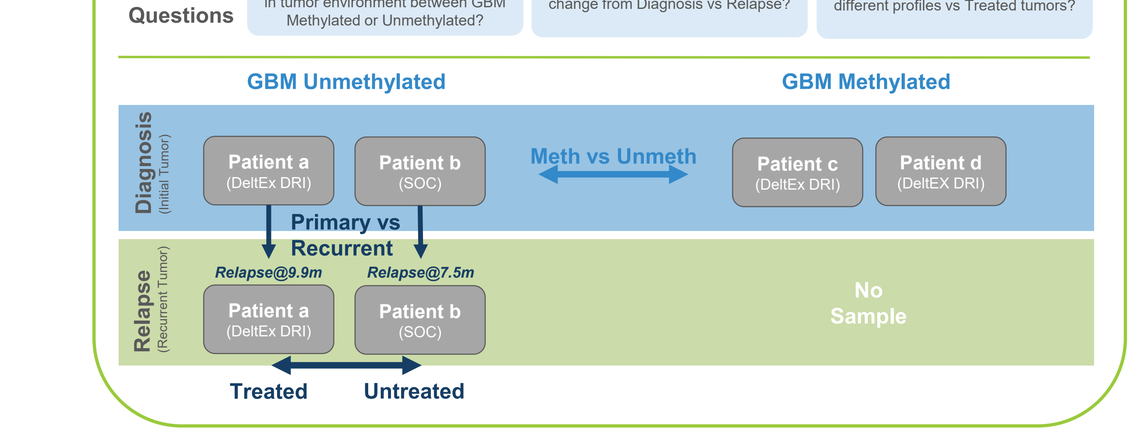
Figure 1 DeltEx DRI Treatment Regimen & Timing

Table I Median Progression Free Survival (PFS) and Overall Survival (OS) for GBM patients either treated with Standard of Care (SOC) only or concomitantly with Multidose DeltEx DRI dose levels.

	MultiDose DeltEx DRI (n=14)	SOC (n=10)	Improvement
Median PFS	13.0m	6.6m	**+97%**
Median OS	17.2m+	13.2m	**≥+30.3%**

Methods: IN8bio Clinical Samples & Elucidate' s Platform

To explore mechanisms underlying tumor response, we initiated a pilot study using paired biopsies at diagnosis and relapse from one SOC patient and one DeltEx DRI multidose patient who, despite exceeding predicted mPFS, showed one of the poorest PFS and OS within the treatment group: an informative outlier for understanding treatment response heterogeneity. Diagnostic biopsies from GBM patients with methylated and unmethylated MGMT promoter status were also included for baseline tumor analysis.



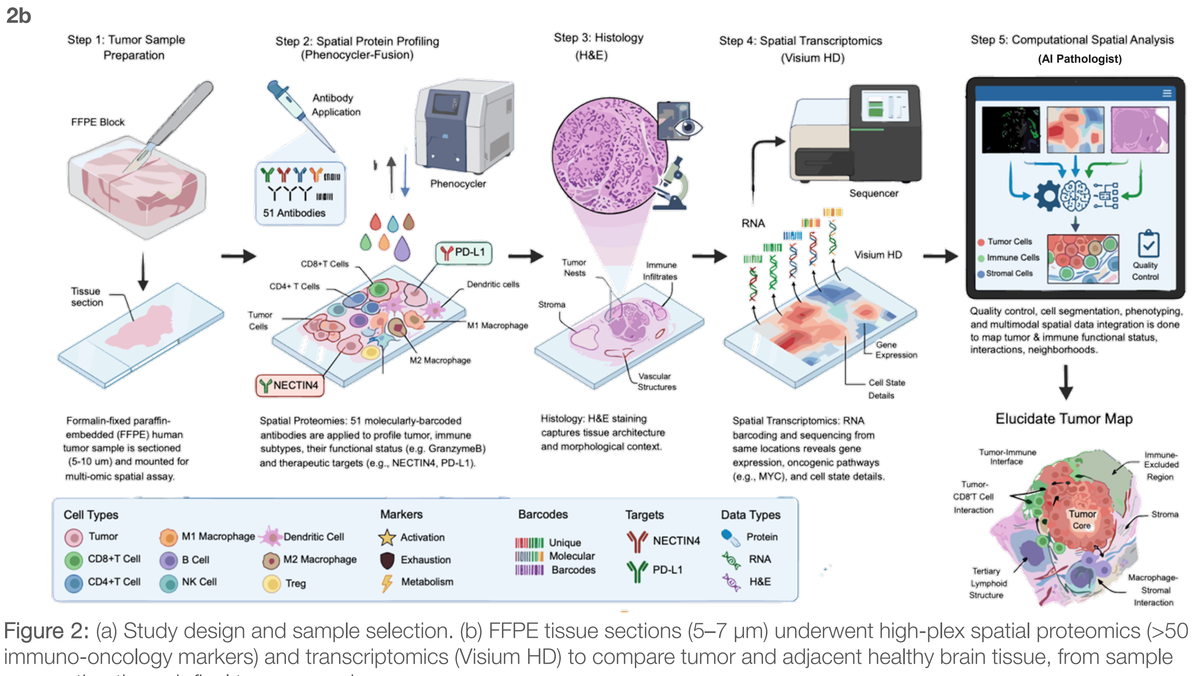


Figure 2: (a) Study design and sample selection. (b) FFPE tissue sections (5–7 µm) underwent high-plex spatial proteomics (>50 immuno-oncology markers) and transcriptomics (Visium HD) to compare tumor and adjacent healthy brain tissue, from sample preparation through final tumor mapping.

Methylated GBM exhibit more cytotoxic CD8 T cells & appear less exhausted

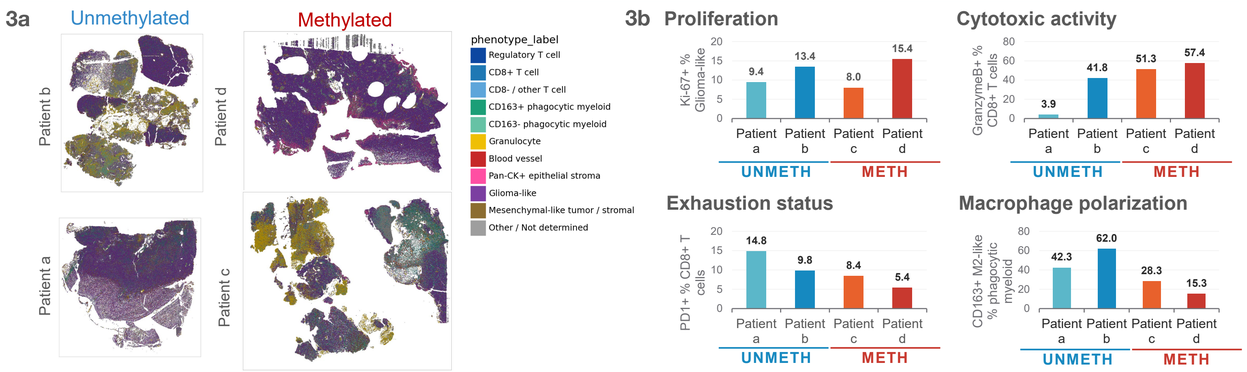


Figure 3 Baseline immune functional state stratified by MGMT methylation status across four initial resection samples (a) Spatially-resolved single-cell phenotype plot from multiplex immunofluorescence (mIF), where each dot represents a cell plotted at its true x/y coordinate, colored by assigned cell type. (b) No consistent separation by methylation status was observed for tumor proliferation (Ki-67+: 9.4–13.4% unmethylated vs. 8.0–15.4% methylated). Cytotoxic activity was directionally higher in methylated samples (GranzymeB+: 51.3% and 57.4%) vs. unmethylated (3.9% and 41.8%), with Patient a representing an outlier of particularly low cytotoxic capacity. Methylated samples showed lower T cell exhaustion (PD1+: 8.4% and 5.4% vs. 14.8% and 9.8%) and lower M2 macrophage polarization (28.3% and 15.3% vs. 42.3% and 62.0%), suggesting a more immunologically permissive baseline microenvironment in MGMT-methylated tumors. Data are descriptive; n=2 per group.

DeltEx DRI treatment induces T cell and reduces granulocyte infiltration

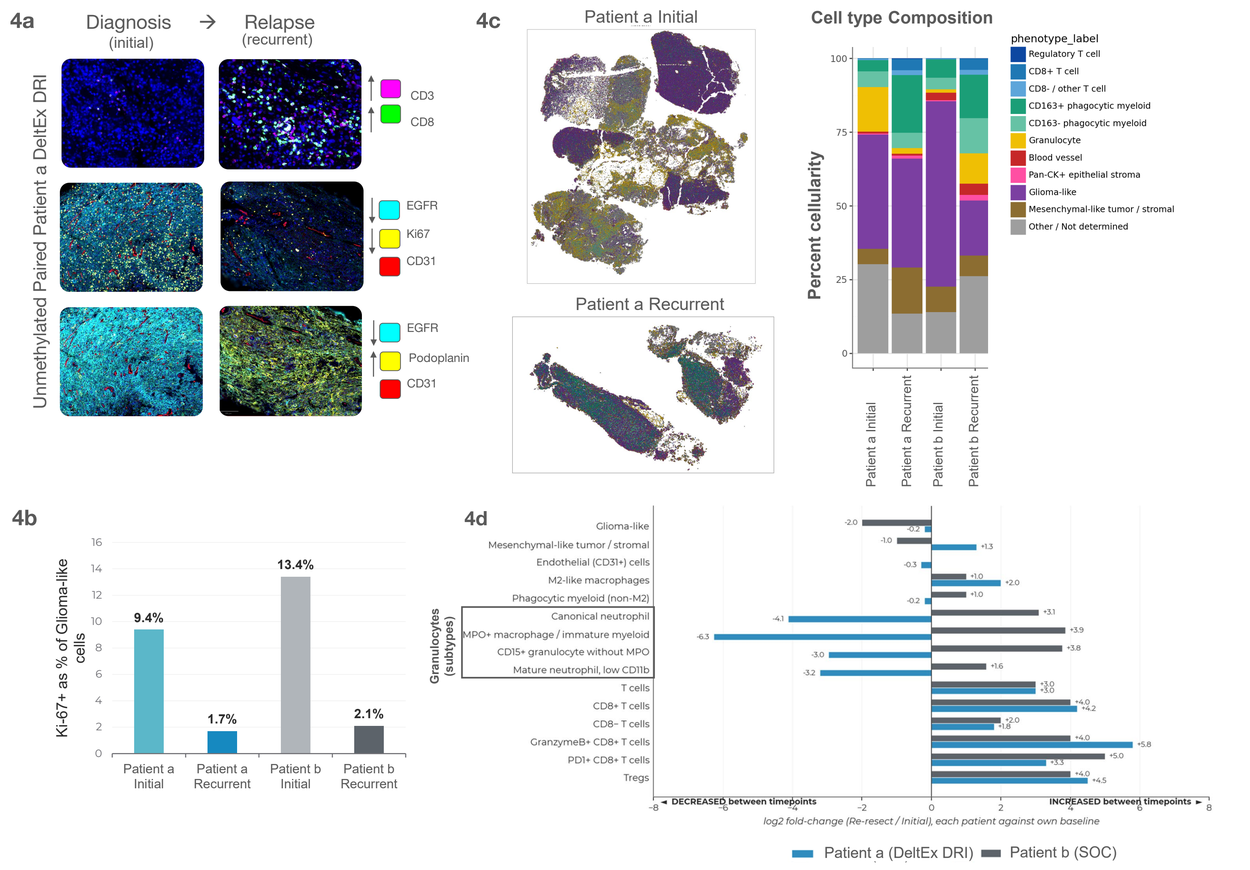


Figure 4 Tumor microenvironment remodeling across treatment arms. (a) In Patient a (DeltEx DRI), the tumor microenvironment shifted from cold to hot, marked by increased T cell infiltration, suppression of proliferation (reduced Ki-67), and signs of immune escape (increased podoplanin). (b) Ki-67+ Glioma-like cells decreased from 9.4% to 1.7% at re-resection in Patient a (DeltEx DRI), an 82% reduction in tumor proliferative fraction. In Patient b (SOC), Ki-67+ Glioma-like cells decreased from 13.4% to 2.1%, an 84% reduction. (c) Spatially-resolved single-cell phenotype plots at initial and recurrent resection for Patient a, with cell type composition overview for Patients a and b. (d) Fold change between initial and recurrent samples shows T cell infiltration across both treatment arms; however, a marked drop in granulocytes, further specified by subtype, was observed only in the DeltEx DRI patient, potentially driven by γδ T cell-mediated clearance. Mesenchymal-like tumor/stromal expansion was also noted, suggesting progressive tumor evasion.

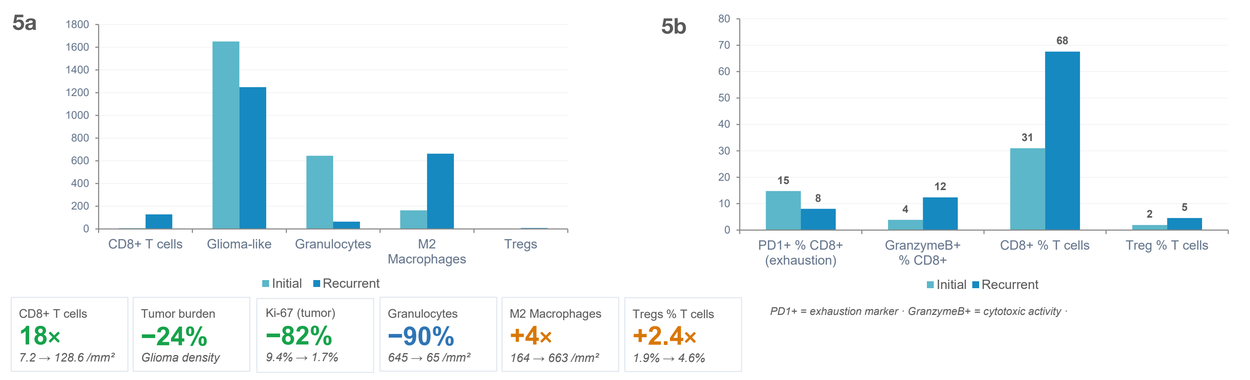


Figure 5 DeltEx DRI influences the GBM tumor microenvironment at the cellular level which is visible at recurrence. Cell type density (cells/mm²) is normalized to tissue area to account for differences in section size between samples. (a) CD8+ T cell density increased 18-fold post-treatment (7.2 → 128.6 cells/mm²), consistent with robust intratumoral T cell infiltration. Ki-67+ Glioma-like cell fraction decreased 82% (9.4% → 1.7%), indicating marked suppression of tumor proliferation. CD163+ myeloid cell density increased 4-fold (164 → 663 cells/mm²), reflecting M2 macrophage expansion and a potentially compensatory immunosuppressive tumor response. Granulocyte density decreased 90% (645 → 65 cells/mm²). (b) PD1+ CD8+ T cells decreased from 14.8% to 8.0%, indicating reduced T cell exhaustion. GranzymeB+ cytotoxic CD8+ T cells increased 3.2-fold (3.9% → 12.4%), while Regulatory T cells expanded 2.4-fold (1.9% → 4.6%), reflecting a net gain in cytotoxic capacity over suppressive pressure, consistent with a functionally active anti-tumor immune response.

Transcriptomics reveal a shift toward M2-like tumor invasion

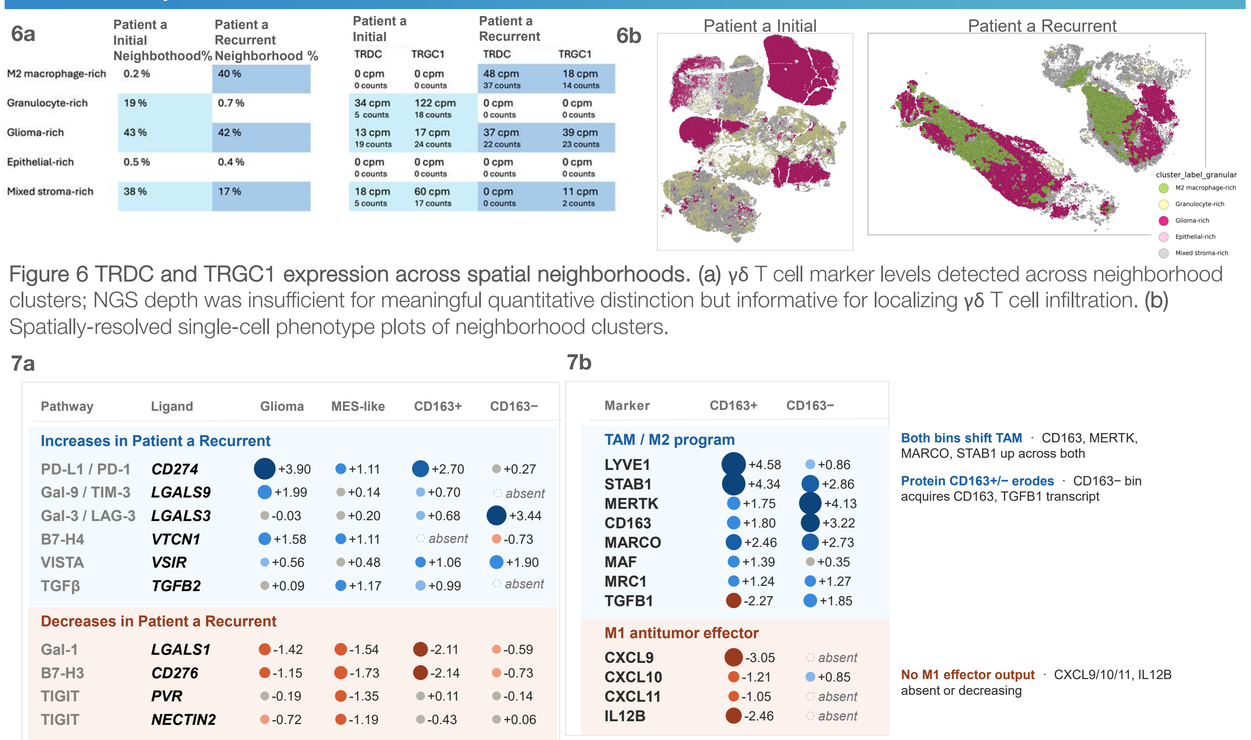


Figure 6 TRDC and TRGC1 expression across spatial neighborhoods. (a) γδ T cell marker levels detected across neighborhood clusters; NGS depth was insufficient for meaningful quantitative distinction but informative for localizing γδ T cell infiltration. (b) Spatially-resolved single-cell phenotype plots of neighborhood clusters.

Figure 7 Glioblastoma cells under DeltEx therapy mount a coordinated transcriptional immune evasion response (a) Under γδ T cell-mediated cytotoxic pressure, glioma-like tumor cells upregulate checkpoint ligands CD274 (PD-L1; +14×), LGALS9 (Galectin-9; +4×), and PDCD1LG2 (PD-L2; +3×), alongside CXCL12-mediated T cell exclusion and IL-10 secretion. Concurrently, proliferative (MKI67; −8×) and stemness (SOX2, NES, NOTCH1) gene expression are markedly suppressed, suggesting the tumor trades proliferative capacity for immune escape under cytotoxic selection pressure. (b) The DeltEx DRI-treated patient shows a shift toward an inhibitory TAM phenotype, with increased M2-like and decreased M1-like polarization.

Conclusions

- DeltEx DRI shows promise in extending mPFS and mOS in patients
- Deeper analysis furthers understanding of the tumor microenvironment, response & DeltEx DRI effects
- Enables biomarker discovery in future DeltEx DRI pivotal studies
- May inform patient stratification for novel GBM therapies, which is currently very limited
- Platform enables future investigation into differential DeltEx DRI response, with early observations suggesting differences in immune escape and baseline tumor aggressiveness

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