Abstract # 2204

Phase I Study of Drug Resistant Immunotherapy (DRI) with Gene Modified Autologous γδ T Cells in Newly Diagnosed Glioblastoma Multiforme (GBM) Patients Receiving Maintenance Temozolomide (TMZ)

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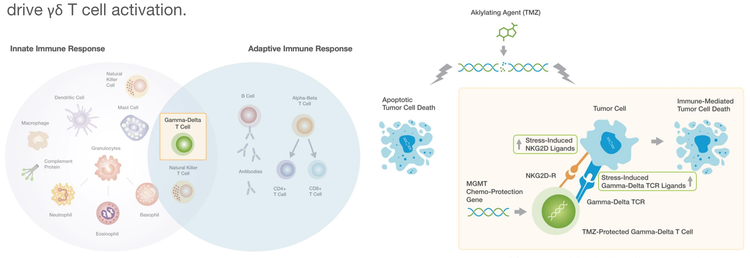
Introduction

CAR-T and immunotherapy have failed to achieve durable responses in most solid tumor cancers. Newly diagnosed glioblastoma multiforme (GBM) has high unmet need with median progression free survival (PFS) of 7 months and overall survival (OS) of 14-19 months. Gamma-delta (γδ) T cells are inherent anti-tumor immune cells that can directly recognize and kill malignant tissue through the recognition of Natural Killer Group D Ligands (NKG2D-L) expressed on tumor cells in an MHC unrestricted manner. Alkylating chemotherapies like temozolomide (TMZ), upregulate NKG2D-L through activation of the DNA-damage response (DDR) pathways and can amplify vulnerability of tumor cells to γδ T cells through an increase in avidity. Co-dosing of chemotherapy and γδ T cells allows the targeting of chemo-resistant and cancer stem cell compartments but such chemotherapies are often lymphodepleting. IN8bio's proprietary platform, DeltEX DRI (drug resistant immunotherapy), has made γδ T cell therapy more effective by transducing them with a construct encoding the DNA repair enzyme O(6)-methylguanine-DNA methyltransferase (MGMT). This resistance gene makes the cells chemotherapy resistant and allowing for concomitant administration with chemotherapy. IN8bio presents updated phase 1 data of autologously derived DeltEX DRI γδ T cells used to treat newly diagnosed GBM patients

The Gamma-Delta (γδ) T cells for Oncology

γδ T cells intrinsically differentiate between healthy and diseased tissues, contributing to direct tumor killing and immune cell recruitment. Alkylating chemotherapy can increase stress ligands that drive γδ T cell activation.



DRI gamma-delta T cell mechanism overview

Clinical Protocol

Trial of autologous, DeltEx DRI gamma-delta T cells in combination with maintenance TMZ following surgical resection

Treatment Arms

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

1. N = 3 (up to 6) patients, single dose of 1 x 10^7 cells (DL1)
2. N = 3 (up to 6) patients, three doses of 1 x 10^7 cells, one dose every 28 days (DL2)
3. N = 3 (up to 6) patients, six doses of 1 x 10^7 cells, one dose every 28 days (DL3)*

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 DRI in two dose frequencies

Secondary Endpoints

- Time to progression
- Overall survival
- Biologic response

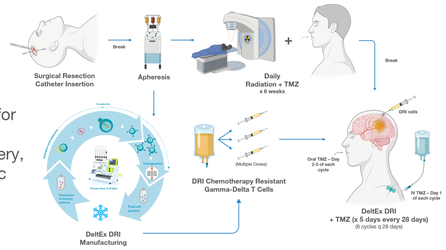
Site

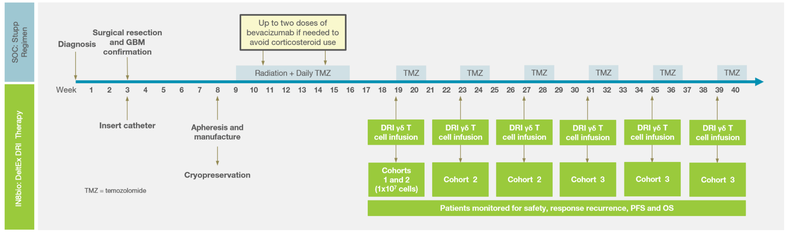
O'NEAL COMPREHENSIVE CANCER CENTER, UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM, UAB HEERSINK SCHOOL OF MEDICINE

Source: ^Created with biorender.com, * Annovazzi et al., Cancers, 2017 Jun; 9(6): 57.

Study Design and Treatment Schema

- 3+3 design with 3 dose schedules
- 28-day DLT period, DLT = any ≥Gr.3 AE possibly attributable to DRI including:
  - Grade 3 or 4 toxicity involving the liver, lungs and heart
  - Any other Grade 4 toxicity that persists for longer than 72 hours
  - Death, stroke, hematoma requiring surgery, CNS hemorrhage, untreatable neurologic deterioration, unresponsive systemic infection
- Neurological deterioration that fails to resolve within 2 weeks





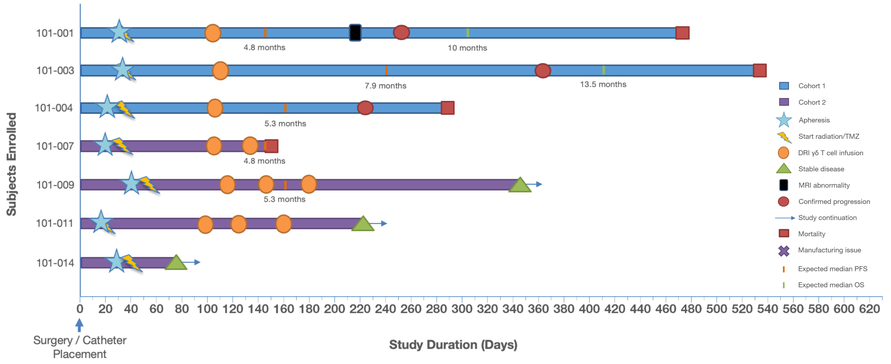
Results: Safety and Efficacy

Adverse Events	Grade 1/2	Grade 3	Grade 4
WBC decreased	29%	14%	
ALC decreased	29%	14%	
Anemia	14%		
ANC decreased			14%
Platelet count decreased	14%		14%
Nausea	29%		
Vomiting	29%		
Constipation	29%		
Anorexia	29%		
Asthenia	43%		
Headache	43%		
Fever/pyrexia	43%		
Urinary tract infection		14%	
Seizures	14%	14%	

Subject	Age / Sex	Cytogenetics	Dose level	Maint. Cycles Received	Response	PFS (mos)	OS (mos)
001	68 / M	IDH-WT, MGMT-unmethylated	1	5	SD	8.3	15.6
003	74 / F	IDH-WT, MGMT-methylated	1	6	SD	11.9	17.7
004	21 / F	IDH-WT, MGMT-unmethylated	1	3	SD	7.4	9.6
007	74 / M	IDH-WT, MGMT-unmethylated	2	2	Unevaluable	-	5.1
009	32 / M	IDH-mutant, MGMT-unmethylated	2	6	SD	11.3+	Alive
011	56 / F	IDH-WT, MGMT-methylated	2	7	SD	7.3+	Alive
014	73 / F	IDH-WT, MGMT-unmethylated	2	To be dosed		2.4+	Alive

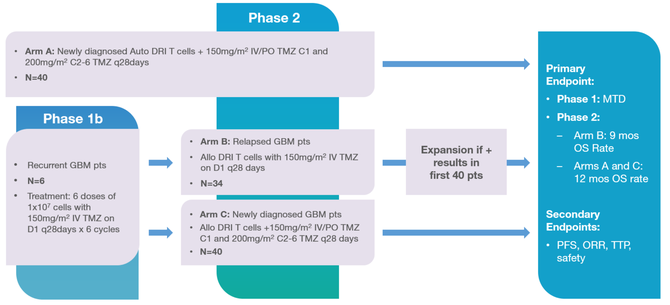
- Median follow-up of 10.45 months
- All Cohort 1 patients exceeded median PFS of 7 months
- Of 7 treated, 3 remain in follow-up
- First patient to receive three repeat doses nearing 1-year PFS
- 4 deaths: 2 due to PD (003 and 004) and 2 unrelated deaths due to sepsis from a pancreatic cyst (001) and cardiac event (007)

Results: Safety and Efficacy



- No DRI related toxicity or DLT's
- No treatment related deaths
- Repeat dosing does not change toxicity profile
- Majority of toxicities are grade 1/2

Future Phase 1b/2 Trial



Conclusions

- DeltEx DRI cells have manageable toxicity with no DLT's, no reports of immune effector cell-associated neurotoxicity syndrome (ICANS) or cytokine release syndrome (CRS) and no treatment related deaths
- Fewer than 30% patients impacted by manufacturing concerns with no upfront selection criteria
- Evidence of persistence of γδ T cells even 148 days after a single infusion and repeat dosing without additional toxicity
- Patients receiving DeltEx DRI cells achieve longer PFS than projected PFS based on age and MGMT status on all patients warranting further study
- All Cohort 1 patients have exceeded 7-month median PFS of standard of care
- Based on this data a phase 2 study will be initiated to further assess efficacy of autologous and allogeneic DeltEX DRI γδ T cells in both the newly diagnosed and relapsed settings