TGF-β2 in DMG

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ABSTRACT

OT-101 is being developed as immunotherapy for a broad range of cancers. Cancers overexpress TGF-β, which suppresses host innate immune response to the cancers. Treatment with OT-101 lifts the TGF-β cloaking effect and allows innate or therapeutic immunity to attack and eliminate the cancers. OT-101 completed phase 2 for pancreatic cancer and melanoma and phase 2 in glioblastoma with robust efficacy and safety. Here we are presenting data and clinical trial design for OT-101 in DMG (Diffuse Midline Glioma). ADME studies were performed on OT-101 demonstrating perfusion of the brain including the midline by either intracerebral or intraventricular administration. The studies allowed us to bridge intraventricular administration to corpus of CED administered OT-101. Safety studies were performed in two species supporting the safety of OT-101 intraventricular administration. Expression analyses of pediatric brainstem cases of the TCGA database yielded highly significant survival benefit across all four quartiles of TGF-β2 expression. This was not observed for either TGF-β1 and less so for TGF-β3. Expression analyses of all gliomas treated with radiation yielded highly significant survival benefit across all four quartiles of TGF-β2 expression. This was not observed for either TGF-β1 nor TGF-β3. In adult gliomas, OT-101 is noninferior to the most active drugs (TMZ, BCNU, or PCV) in both chemo naïve and chemo-resistant patients. In terms of overall survival when compared to standard chemotherapy (TMZ, BCNU, or PCV) in both G004 and G005 as both the hazard ratio, which was 0.9168, and the 90% upper limit of the confidence interval, which was 1.2245, were both less than the initial non-inferiority bound of 1.25. Together the data support the development of OT-101 for DMG. The phase 2 clinical trial design is being presented for OT-101 in DMG administered using Ommaya reservoir following radiation in newly diagnosed DMG

BACKGROUND

OT-101: Antisense oligodeoxynucleotides are short strings of DNA that are designed to downregulate gene expression by interfering with the translation of a specific encoded protein at the mRNA level. Several RNA therapeutics, including anti-sense oligonucleotides have been evaluated in clinical trials and some approved. OT-101 is a synthetic 18-mer phosphorothioate oligodeoxynucleotide (S-ODN) in which a non-bridging oxygen of each phosphate moiety is substituted by a sulfur atom. OT-101 was designed to be complementary to a specific sequence of human TGF-β2 mRNA following expression of the gene. It is a first-in-class RNA therapeutic designed to abrogate the immunosuppressive actions of TGF-β2 and reduce the level of TGF-β2 in malignant gliomas, and thereby delay the progression of disease.

Diffuse midline glioma (DMG) is a highly morbid pediatric central nervous system (CNS) tumor for which there is currently no effective treatment. DMG is responsible for 50% of all childhood HGG. Due to their anatomic location and infiltrative nature, DMGs are not amenable to surgical resection and are most often diagnosed radiographically and treated with radiation therapy, with no effect on survival. The median age at diagnosis is 5 to 11 years with tumors that arise in the pons occurring at a younger age (~7 years) than those that arise in the thalamus (~11 years). DMG patients face a very poor median overall survival (OS) of just 9–11-months, with <10% of patients with pontine tumors surviving two years post-diagnosis. Radiation remains the mainstay of therapy, though it is only palliative, and is expected to increase survival by an average of 3 months.

RATIONALE FOR USE OF OT-101 IN DMG

- It is safe and effective during extended (7-day) high flow perfusion of the brain in adult gliomas. As single agent it is as effective as the most active drug in adult gliomas – TMZ for chemo naïve patients BCNU/CCNU in chemo failure patients. [Uckun, F.M.; Qazi, S.; Hwang, L.; Trieu, V.N. Recurrent or Refractory High-Grade Gliomas Treated by Convection-Enhanced Delivery of a TGFβ2-Targeting RNA Therapeutic: A Post-Hoc Analysis with Long-Term Follow-Up. Cancers 2019, 11, 1892. https://doi.org/10.3390/cancers11121892]
- TGF-β2, is expressed at high levels in both pediatric GBM (WHO Grade IV) and pediatric DIPG (WHO Grade IV) patients. [Uckun FM, Trieu V, Hwang L, Qazi S. In silico Molecular Target Validation Demonstrates Transforming Growth Factor Beta 2 is Strongly Expressed in Pediatric Diffuse Intrinsic Pontine Glioma and Glioblastoma Multiforme. Clin Res Pediatr 2019;2(1):1-10]

GLIOMA PHASE 2 DATA

OT-101 Single Agent Activity in Recurrent/Refractory High-Grade Glioma Patients

Phase 2 clinical data showing remarkable single agent activity of OT-101 in recurrent/refractory high-grade glioma patients with more than a third of patients (26 of 77) receiving the intended 4-11 cycles of therapy achieving durable complete responses, partial responses, or prolonged stable disease and a median OS of 1280 days [95% CI: 1116 - >1743 days].

The median PFS for these 77 patients was significantly better than the PFS for the 12 patients treated with 1-3 cycles of OT-101 (86 days vs. 32 days, Log-rank P-value < 0.0001). Likewise, the median OS of the 77 patients who were treated with 4-11 cycles of OT-101 was significantly better than the median OS for the 12 patients who were treated with 1-3 cycles (432 days vs. 128 days, Log-rank P-value < 0.0001).

19 achieved durable objective responses (CR: 3, PR: 16). The median time for 90% reduction of the baseline tumor volume was 11.7 months (Range: 4.9-57.7 months). The mean log reduction of the tumor volume in these 19 patients was 2.2 ± 0.4 (Median = 1.4: Range: 0.4-4.5) logs.

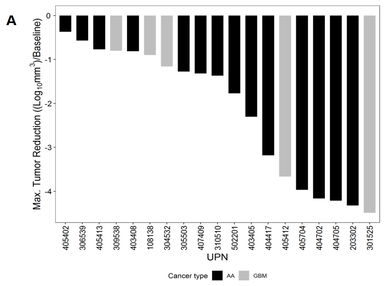
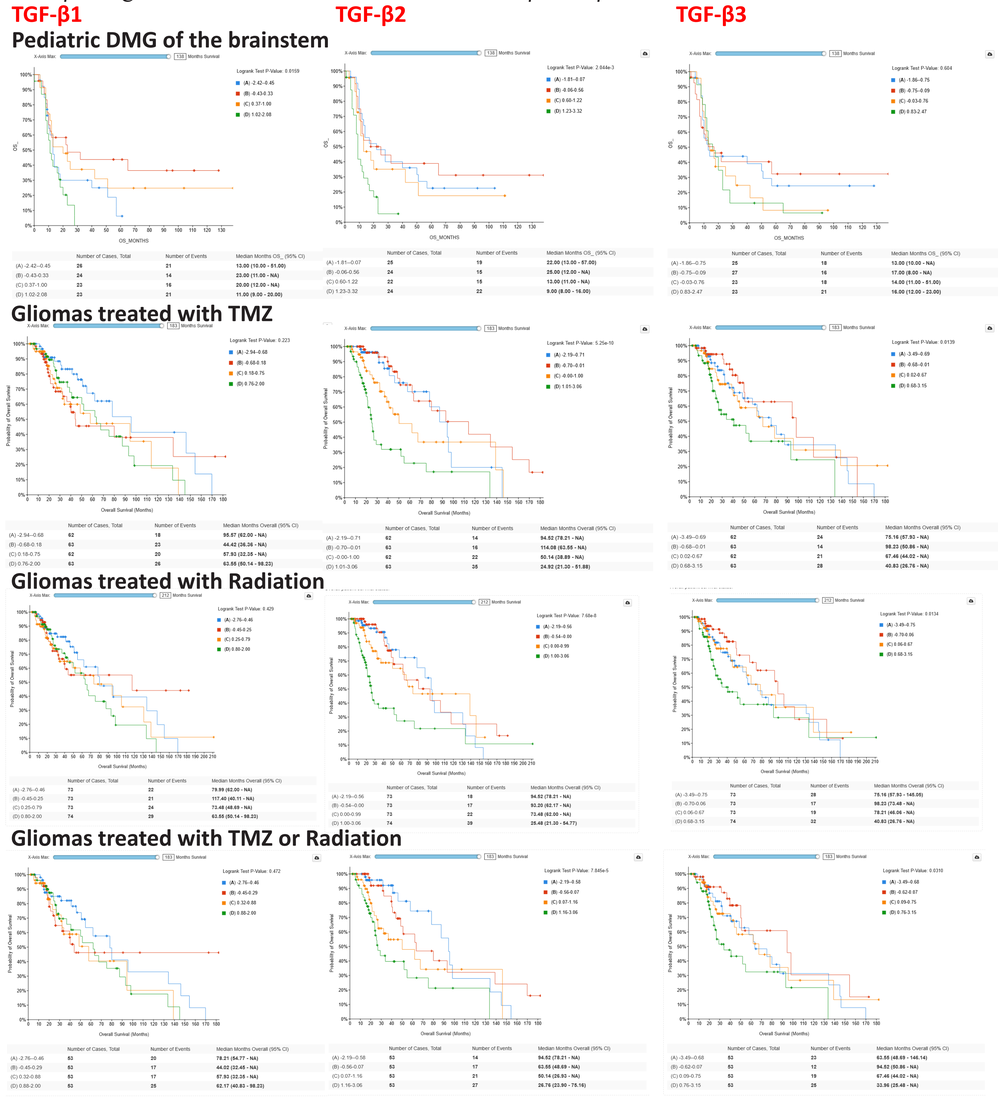


Figure 1. Imaging Responses in R/R High-Grade Glioma Patients Treated with OT-101 Monotherapy Who Achieved a CR or PR. [A] A waterfall plot depicting the maximum log_{10} reduction values for the tumor volumes. [B] A semi-log plot of the combined 3-D tumor volume reduction curve for the 19 patients.

TGF-β2 AND POOR SURVIVAL IN DMG

The Cancer Genome Atlas (TCGA) collected, characterized, and analyzed cancer samples from over 11,000 patients over a 12 year period. All data collected and processed by the program is currently available at the Genomic Data Commons (GDC). This is a joint effort between NCI and the National Human Genome Research Institute since 2006. All pediatric brainstem patients, excluding spinal cord patients, were analyzed. High TGF-β2 (and not β1 nor β3) is associated with poor overall survival (OS) across all quartiles. TMZ only, Radiation only, or TMZ or Radiation for all adult and pediatric gliomas also exhibited poor OS with high TGF-β2 – again- no such association was found with β1 nor β3.



DMG PHASE 1 STUDY DESIGN

Study Title: An Open-label Dose Escalation Study to Evaluate the Safety and Tolerability of Repeated Cycles of OT-101 in Pediatric Diffuse Midline Glioma (DMG) Patients, Administered Intraventricularly over A 7 Day Period at Weekly Intervals

Study Population:

Pediatric (≥ 2 to < 18 years) patients with Diffuse Midline Glioma (DMG)

Sample Size:

In general, a cohort of 3 evaluable patients has to be enrolled per treatment group. In the case of 2 patients experiencing dose-limiting toxicity, the number of evaluable patients may be increased to six to further evaluate toxicity.

Study Objectives

Primary Objective: To determine the maximum tolerated dose (MTD) by assessing the dose-limiting toxicity (DLT) of two cycles of OT-101, administered intraventricularly at weekly intervals

Secondary Objectives:

- To determine the safety and tolerability of at least two cycles of OT-101, administered intraventricularly at weekly intervals
- To determine the change in tumor size measured in patients treated with at least two cycles of OT-101, administered intraventricularly at weekly intervals
- To determine the time to progression of patients treated with at least two cycles of OT-101, administered intraventricularly at weekly intervals
- To determine plasma concentration levels of OT-101

Group	Conc.	Treatment Period (OT-101-infusion)		Flow Rate		Dose			Rest Period (no infusion)	
No.	µM	days	h/day	µl/min	ml/day	nmol/day	nmol/cycle	mg/cycle*	weeks	µl/min
1	10	7	24	4	5.76	57.6	403.2	2.476	1	0
2	80	7	24	4	5.76	460.8	3225.6	19.811	1	0