Clinical Potential of Targeting Transforming Growth Factor β2 with OT-101 for Post-Radiation Consolidation in Diffuse Intrinsic Pontine Glioma

Abstract# RTID-04

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ABSTRACT

Diffuse intrinsic pontine glioma (DIPG) in children has a dismal prognosis with a median overall survival (OS) of 10 months and a 2-year overall survival rate of < 10% after standard radiation therapy. Chemotherapy does not offer clinically meaningful benefits. Therefore, there is an urgent need for therapeutic innovations for treatment of pediatric DIPG.

High-grade glioma cells, including pediatric glioblastoma and DIPG cells have been shown to produce transforming growth factor beta 2 (TGF-β2) which has been implicated both as promoter of glioma cells and as a key contributor to the T-cell hyporesponsiveness of the tumor microenvironment (TME) towards glioma cells.

OT-101 is a first-in-class RNA therapeutic designed to abrogate the immunosuppressive and tumor promoting actions of TGF-β2. At low micromolar concentrations, OT-101 reduces the TGF-β2 secretion by human glioma cells, blocks their proliferation as well as migration, and restores the anti-glioma cytolytic function of patient-derived T-cells. In a Phase 2 clinical study, intracerebrally applied OT-101 administered via convection-enhanced delivery showed promising single agent activity in Recurrent/Refractory (R/R) high-grade glioma (HGG) (Uckun et al., Cancers. 2019 28;11(12):1892).

The intrathecal/intraventricular administration of antineoplastic drugs directly in the CSF allows to bypass the selective filter of BBB, achieving significant concentrations of the antineoplastic agents in CSF, while reducing the likelihood of systemic toxicity. Informed by favorable safety pharmacology studies of intrathecally delivered OT-101 in rabbits and primates and encouraged by its single agent activity in adult patients with HGG, we decided to embark upon a multi-center, two-part, randomized Phase 1-2 study of OT-101 in pediatric patients with DIPG. Multiple doses of OT-101 will be administered after completion of radiation therapy as intrathecal/intraventricular bolus injections. The study is designed to determine: 1) the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of OT-101, and 2) its efficacy in children with DIPG.

BACKGROUND AND RATIONALE 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.

NONCLINICAL PROOF OF CONCEPT

Functional in vitro assays showed that:

- OT-101 exhibits an efficient time-dependent uptake into human tumor cells in the presence as well as in the absence of the carrier liposome Lipofectin®.
- OT-101 reduces the TGF-β2 secretion by human tumor cells without the use of any carrier.
- At the clinically used OT-101 concentrations up to 80 μM over 7 days in A 172 human high-grade glioma cells, 10 μM is the most effective concentration for inhibition of the TGF-β2 production.
- OT-101 reduces proliferation of human tumor cells while at the same time stimulating PBMC proliferation. OT-101 does not affect viability of human PBMC.
- OT-101 restores immune function of human PBMC derived from high grade glioma patients demonstrated by immune cell-mediated cytotoxicity assay.
- OT-101 inhibits human tumor cell migration.

NONCLINICAL SAFETY & PHARMACOLOGY

OT-101 has been subjected to a series of nonclinical safety and pharmacology studies. The salient features of the conclusions from these studies were as follows:

- Prolonged local administration of OT-101/AP 12009 may result in local tissue inflammation There was mild to moderate local toxicity observed in animals after infusion of a concentration of 500 μM without any macroscopic changes.
- When administered to 3 kg male or female rabbits as a bolus IT injection at a 0.12 mg/kg dose level (500 μM solution; 0.1 mL) with an estimated CSF concentration of 4.16 μM, OT-101 did not cause any clinical toxicity or drug-related macroscopic/microscopic changes consistent with sub-clinical toxicity.
- When administered to 6-7 kg cynomolgus monkeys as a bolus IT injection at a 0.05 mg/kg dose level (500 μM solution; 0.1 mL) with an estimated CSF concentration of 0.46 μM, OT-101 did not cause any clinical toxicity or drug-related macroscopic/microscopic changes consistent with sub-clinical toxicity.
- When given to rats via intraventricular administration, radiolabeled OT-101 (0.18 mg/kg) was detected within 1 hour after administration not only in the CSF but also in the cerebrum, cerebellum and pineal body. The CSF and brain tissue half-lives were <24 hours with <15% residual OT-101 remaining at 72 hours.

CLINICAL PROOF OF CONCEPT

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.

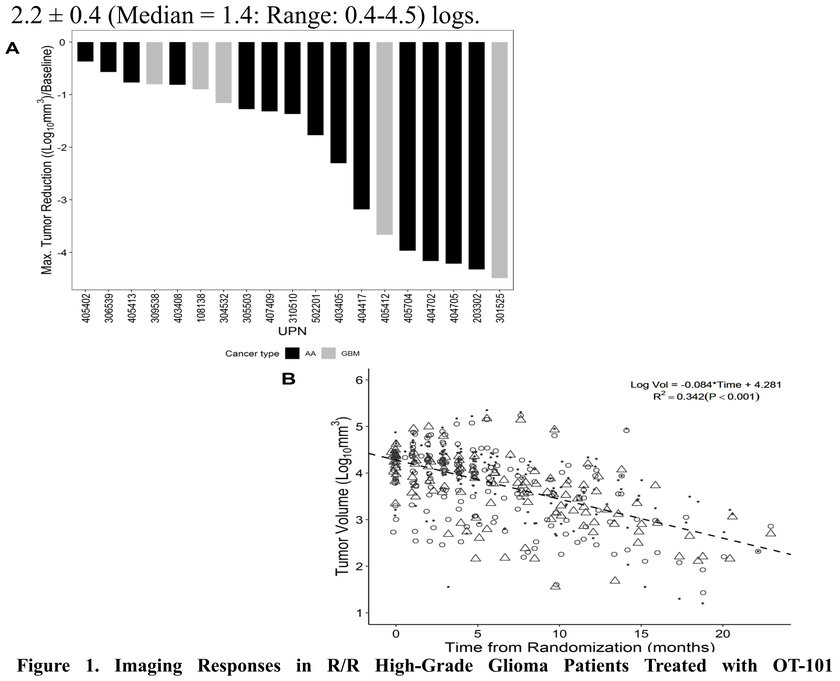

Figure 1. Imaging Responses in R/R High-Grade Glioma Patients Treated with OT-101 Monotherapy Who Achieved a CR or PR. [A] A waterfall plot depicting the maximum log_{10} reduction values for the tumor volumes. [B] A semi-log plot of the combined 3-D tumor volume reduction curve for the 19 patients.

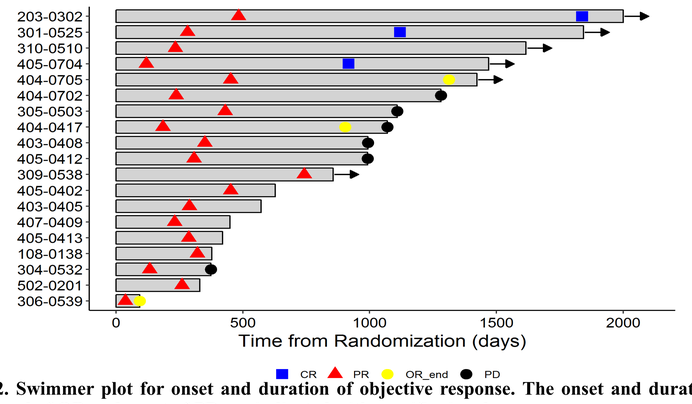

Figure 2. Swimmer plot for onset and duration of objective response. The onset and duration of CR/PR, end of OR and onset of PD are indicated with specific signals.

OT-101 induces durable CR and PR in R/R GBM as well as AA patients. 19 patients had objective responses. 16 had a partial response with an onset at 307 ± 159 days (mean ±SE). The median time to onset of PR was 287 days (Range: 37-742). 3 patients had a PR first which deepened to a CR at 917, 1120 and 1838 days, respectively. Six of these 16 patients developed a PD at 970 ± 126.7 days (mean ± SE) (Median = 1032 days, Range: 374 – 1281 days).

DRAFT STUDY DESIGN

Study title: Phase 1/2 Study to Determine the Safety, Pharmacokinetics and Efficacy of the TGFB2 Targeting Anti-sense ODN OT-101 in Pediatric Patients with Newly Diagnosed DIPG

Planned Sample Size:
Part 1, Cohort 1: 9 patients
Part 1, Cohort 2: 9 Patients
Part 2: 108 Patients (81 patients treated with OT-101 and 27 Patients treated with Placebo)

Part 1 is designed as a two-cohort dose finding study and Part 2 is designed as a randomized (3:1 ratio) placebo-controlled study. OT-101 will be administrated via intraventricular injections into an Ommaya reservoir.

Study Objectives

Part 1 Dose Escalation/Finding Phase:
- Primary Objectives
  - To estimate the MTD and/or RP2D of OT-101
  - To define and describe the toxicities associated with OT-101
  - To characterize the systemic and CSF PK of OT-101
- Secondary Objectives
  - To determine the clinical efficacy of repeated administration of OT-101 given by IT bolus injection
- Exploratory Objectives
  - To assess Quality of Life (QOL)
  - To perform central review of imaging to explore MR qualitative and quantitative measures as markers of disease response and/or progression

Part 2 Dose Expansion Phase:
- Primary Objectives
  - To determine the 12-month overall survival (OS12) and progression-free survival (PFS)
- Secondary Objectives
  - To estimate the progression-free survival (PFS)
  - To define and describe the toxicities associated with OT-101 at the RP2D level after radiation therapy
  - To estimate the proportion of newly diagnosed DIPG patients to have experienced pseudo-progression
  - To characterize the systemic and CSF PK of OT-101
- Exploratory Objectives
  - To assess Quality of Life (QOL)
  - To perform central review of imaging to explore MR qualitative and quantitative measures as markers of disease response and/or progression

Study Endpoints
Part 1 Dose Escalation/Finding Phase:
- Cumulative incidence of DLTs and drug-related SAEs (viz., sum of DLT + SAEs) reported within 4 weeks of first dose of OT-101

Part 2 Dose Expansion Phase:
- Overall survival at 12 months (OS12)

We will assess the preliminary efficacy using overall survival at 12 months (OS12) in 108 evaluable DIPG patients (81 treated with OT-101 and 27 treated with placebo) treated within the expansion cohort. With a null hypothesis that OS12 is 40%, accrual of 108 patients with a 3:1 randomization ratio provides 80% power with a target overall two-sided type I error of 0.05 to detect a 30% difference in OS12 using a two-arm binomial test. A null OS12 rate of 40% was chosen on the basis of prior studies and review of outcomes of DIPG patients.

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