OT-101/Chemotherapy- A novel mechanism of action (MOA) in gliomas immunization therapy

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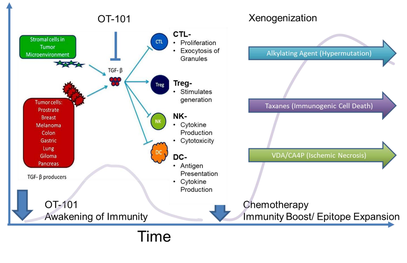
ABSTRACT

Background: Escalating Intratumoral heterogeneity (IH) resulting in xenogenization which is countered by overexpression of TGF-β2. OT-101 is a TGF-β2-specific Phosphorothioate Antisense. Here we report the results of a randomized Phase 2b clinical trial (NCT00431561) comparing the safety and efficacy of OT-101 versus temozolomide (TMZ) in adult patients with WHO grade III/IV high-grade glioma. We took advantage of the known xenogenization activity of alkylating agent such TMZ to explore the impact of xenogenization on survival on treatment with OT-101.
Methods: This is a phase 2b, multi-national, multi-center, open-label, active-controlled, randomized parallel group dose-finding study to evaluate the efficacy and safety of OT-101 in adult patients with recurrent high-grade glioma, administered intratumorally as continuous high-flow microperfusion over a 7-day period every other week.
Results: A total of 144 patients, 97 patients in the OT-101 test group and 47 patients in the temozolomide (TMZ) group. OT-101 was superior to TMZ in doubling the number of pts in the good survival group, 64 of 97 pts (66%); whereas, only 15 of 47 pts (32%) treated with TMZ did (p=0.0001). There were two cases of neutropenia in the 90 pts treated with OT-101 versus 8, 10, and 8 pts with leukopenia, neutropenia, and thrombocytopenia, respectively, among 45 pts treated with TMZ (2% vs. 56%, p<0.0001).
Conclusions: Improved survival was achieved by repeated exposure to TMZ/alkylating agent. This was further enhanced by OT-101 and consistent with the proposed MOA of OT-101/Chemo as reactivation of immunity during TGF-β suppression and subsequent xenogenization by TMZ.

INTRODUCTION

Trabedersen (AP12009, OT-101) is a novel antisense oligodeoxynucleotide (ODN) developed by Oncotelic Inc., CA (USA), for the treatment of patients with pancreatic carcinoma, malignant melanoma, colorectal carcinoma, high-grade glioma (HGG), and other transforming growth factor beta 2 (TGF-β2) overexpressing malignancies (e.g. prostate carcinoma, renal cell carcinoma etc.). Trabedersen is a synthetic 18-mer phosphorothioate oligodeoxynucleotide (S-ODN) complementary to the messenger ribonucleic acid (mRNA) of the human TGF-β2 gene.

TGF-β is a multifunctional cytokine with a key role in promoting tumor growth and progression including cell proliferation, cell migration, and angiogenesis. Above all, TGF-β is a highly potent immunosuppressive molecule. Thus, inhibition of TGF-β overexpression in tumor tissue represents a novel multimodal treatment principle leading to the reduction of tumor growth, inhibition of metastasis, and restoration of host antitumor immune responses. Despite its recognized pivotal role in cancer- therapeutics targeting TGF-β have not been successful and many have failed due to toxicity issues related to inhibition of TGF-β1 essential functions. The high level of homology between the various TGF-β isoforms is making it impossible to create mAb or small molecule inhibitor without TGF-β1 cross inhibition, therefore, we chose to target TGF-β2 only using OT-101 antisense approach. Here we report on clinical testing of OT-101 in Phase IIb G004. The data validated our proposed Mechanism of Action (MOA) of OT-101/Chemotherapy as an in situ cancer vaccine (SIP®).



Proposed MOA for SIP® (OT-101/Chemotherapy Combination): TGF-β inhibitor (ie. OT-101) alleviates the immunosuppression and primes the innate immune system against the tumor. Subsequent chemotherapy boost further expands the neoepitopes via chemotherapy-induced immunogenic cell death (ICD)

METHODS

G004 is a multinational, multicenter, open-label, randomized, active-controlled, parallel-group study in adult patients with either recurrent or refractory AA (WHO grade III) or recurrent or refractory GBM (WHO grade IV). There were 3 treatment groups: 1) 10 µM Trabedersen, 2) 80 µM Trabedersen, and 3) standard chemotherapy (mostly TMZ). Tumor control rate at 6 months was the primary endpoint and OS as a secondary endpoint. The analyses here were performed per Statistical Analysis Plan: analyses of other subpopulations were performed to identify activity in specific subgroups (i.e. indications or subsequent chemotherapy) and to allow for post-hoc, comparative outcome analyses (e.g. against historical controls), further patient subpopulations may be defined, requiring selection of patients fulfilling specific subcriteria. All patients had previous tumor surgery, almost all patients had previous radiation therapy, and more than half of the patients had received previous chemotherapy.

RESULTS

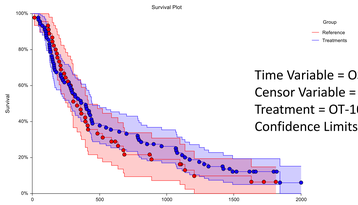
Non-Inferior for OS / Superior for Myelosuppression vs. TMZ

- OT-101 is non-inferior to TMZ using Wald Test (10uM and 80uM dose levels were treated as one group since they exhibited similar efficacy and survival).
- TMZ (Temozolomide) is an alkylating agent approved for the treatment of adults with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment. It is also indicated for the treatment of adults with refractory anaplastic astrocytoma (ie, patients with disease progression on a drug regimen containing nitrosourea and procarbazine).
- Non-Inferiority Bound of 1.25. Higher hazards were considered to be worse if they were greater than the bound for the non-inferiority hypothesis. Kaplan Meier survival analysis and Chi-square tests were used for statistical evaluation.

100(1 - 2α)% Confidence Interval Test for Non-Inferiority (Wald Test)
Hazard Ratio (HR) = Hazard(Group="Treatment") / Hazard(Group="Reference")
Higher Hazards are Worse
Non-Inferiority Hypothesis: HR < 1.25

Alternative Hypothesis	Hazard Ratio HR*	Lower 90.0% C.L. of HR	Upper 90.0% C.L. of HR	Wald Z-Value	Wald Prob Level	Conclude Non-Inferiority at α = 0.05?
HR < 1.25	0.8739	0.6325	1.2074	-1.8211	0.0343	Yes

* In Cox Regression, the Hazard Ratio (HR) is commonly referred to as the Risk Ratio and is equal to Exp(B), where B is the estimated regression coefficient.



Time Variable = OS
Censor Variable = Censor. Group Variable = Group
Treatment = OT-101; Reference = Chemotherapy/TMZ
Confidence Limits Method = Linear (Greenwood)

Myelosuppression Analysis

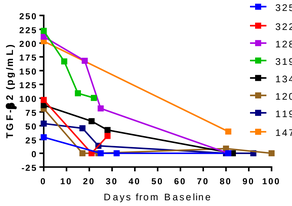
- AEs that occurred in a greater proportion of patients in the chemotherapy group included leukopenia, neutropenia, and thrombocytopenia.
- N: number of patients in the treatment group; n (%): number of patients with AEs (percent, based on N); n§: number of AEs

	OT-101 (N = 90)	TMZ (N = 45)
Patients with at least one AE	n(%)n§	n(%)n§
Leukopenia	0	8 (17.8) 9
Neutropenia	2 (2.2) 2	10 (22.2) 25
Thrombocytopenia	0	8 (17.8) 28

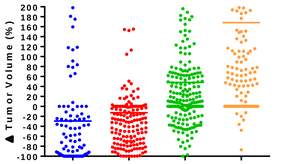
RESULTS

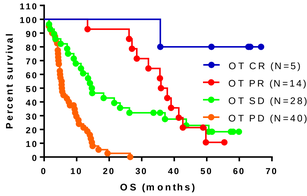
OT-101 Single Agent Activity (Priming of Immunity)

- **Target Engagement- TGF-β2 Knockdown**
- Plasma samples were analyzed for TGF-β2 using the Quantikine® Human TGF-β2 ELISA assay. The assay was a difficult assay with limited detection –42% of patients tested (9 of 22) did not have detectable TGF-β2 by this assay
- Among the 13 pts with detectable plasma level by the assay: 9 (69%) decrease and 4 (31%) increase/unchange following treatment with OT-101.

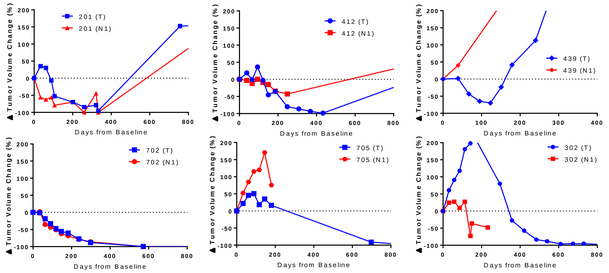


- **Clinical Efficacy- Objective Tumor Response**
- Objective responses were observed among the 87 evaluable patients treated with OT-101:
- Best Objective Responses were: 5 CR (5.9%), 14 PR (16.5%), 28SD (31.8%), and 40 PD (45.9%)
- Confirmed Best Objective Responses were: 4 CR (4.7%), 12 PR (12.9%), 31 SD (36.5%), and 40 PD (45.9%)
- Best Objective Responses were confirmed with deeper tumor reduction.
- Best Objective Responses were confirmed with improved OS: CR: >66mos, PR: 36.9 mos, SD: 14.7 mos, and PD: 5.5mos.



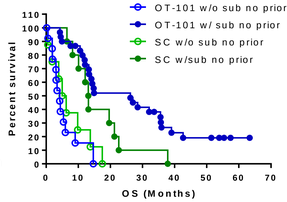


- **Clinical Efficacy- Bystander Effect**
- Both Treated and nontreated tumors were affected showing that the effect was not due to local administration of OT-101 but a systemic response to the tumor (T= Treated/ N1= Not treated.
- Of six pts with evaluable multiple lesions- 4 exhibited clear bystander effect
- Pt 302 treated tumor was exhibiting pseudoprogression with robust immune response per immuno-histochemistry

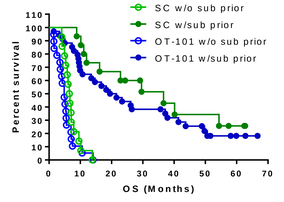


OT-101/Chemo Combination Activity (Immunity Boost)

- Subsequent chemotherapy after OT-101 should release neoantigen via immunogenic cell death and thereby reeved up immunity against the tumors
- **Chemo Naïve Pts.**
- There were 18 and 44 chemo naïve pts treated with SC (Standard Chemotherapy – mostly TMZ) and OT-101.
- OT-101 treatment nearly doubled the ratio of patients being able to go onto subsequent chemotherapy vs. not being able: 10:8 (1.25) vs. 30:14 (2.14)
- OT-101/Chemo pts doubled their mOS from 13.1 mos to 26.2 mos
- More importantly, OT-101/Chemo pts more than doubled their 2 yr and 4 yr survival: 20% and 0% versus 53% and 20%



- **Non Chemo Naïve Pts**
- There were 29 and 53 non chemo naïve pts treated with SC (either PCV or TMZ dependent on prior exposure to TMZ) and OT-101.
- OT-101 treatment nearly doubled the ratio of patients being able to go onto subsequent chemotherapy vs. not being able to: 15:14 (1.07) vs. 34:19 (1.78)
- mOS, 2yr and 4 yr survival (20.5 mos, 47%, and 26%) were similar to that observed for chemo naïve pts as reported above
- Surprisingly, the SC pts treated with subsequent chemotherapy (chemotherapy across 1st, 2nd, and 3rd line exhibited robust mOS, 2yr and 4yr survival (36.6 mos, 67%, and 33%)



CONCLUSIONS

- OT-101 is an effective agent against recurrent gliomas without the myelosuppression effects of chemotherapy which is hitherto unavailable
- OT-101 single agent activity is consistent with the proposed MOA for OT-101 in SIP®: 1) TGF-β2 knockdown was demonstrated. 2) Objective tumor responses were demonstrated and confirmed with improved survival and tumor reduction. 3) Bystander effect was demonstrated. Tumor reduction was observed in both treated and untreated tumors consistent with the mounting of immunity against the tumor.
- OT-101/Subsequent chemotherapy is also consistent with the proposed MOA for OT-101/Chemo in SIP®: 1) mOS, 2yr and 4 yr survival increased above and beyond that of subsequent chemotherapy alone without OT-101 treatment. 2) Activity was independent of prior treatment with chemotherapy
- Rather than being inactive on 3rd line, 1st, 2nd, and 3rd lines of chemotherapy resulted in robust mOS, 2yr and 4 yr survival with the survival curve exhibiting characteristics of immunotherapy
- Alkylating agents such as TMZ possess high DIX properties, being by far more potent as compared to a number of other antitumor mutagenic compounds.(Franzese O et al., 2018, Pharmacological Research 131:1). It is possible that what we observed here is due to the Xenogenization activity of TMZ.
- This improvement in OS survival by overtreatment with alkylating agent must be weighed against the increase incidence of secondary hematological malignancies especially when long term survival is feasible due to new agents such as OT-101