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Non-inferiority of OT-101 (TGF-β2 Specific Inhibitor) versus Standard Chemotherapy in Glioma

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ABSTRACT

Background: OT-101 (Trabedersen) is an 18-mer phosphorothioate antisense oligodeoxynucleotide designed to specifically target the human TGF-β2 messenger RNA. On the basis of data showing that TGF-β2 is overexpressed in multiple cancers and that its levels are closely related to tumor progression, OT-101 has been clinically evaluated in patients with high-grade glioma, pancreatic and colorectal cancers as well as melanoma. Furthermore, inhibition of TGF-β2 in tumor tissue leads to reversal of tumor-induced immune suppression as well as inhibition of tumor growth, invasion, and metastasis. Here, we report the analysis of responders in the clinical Phase II studies with the treatment of OT-101 compared to standard chemotherapy in glioma patients.

Methods: Active-controlled, open-label, randomized parallel group glioma clinical trials were performed with intracranial delivery of OT-101. Patients with high-grade glioma were treated with OT-101 (7 days-on, 7 days-off regimen for up to 11 cycles) versus standard chemotherapy and their overall survival (OS) and censor data were extracted from the raw data of each clinical trial. NCSS 12 Data Analysis (Kaysville, Utah) was used for Two-Sample Non-Inferiority Tests for Survival Data using Cox Regression and Nonparametric Survival Analysis for analysis of non-inferiority of OT-101 to standard chemotherapy regimen. The overall survival was plotted utilizing the Kaplan Meier curve utilizing the same software as well.

Results: A total of 134 patients, 89 patients in the OT-101 test group and 45 patients in the standard chemotherapy control group were assessed. Test for Non-Inferiority was used to see if the Upper 90.0% Confidence Limit (C.L) of the Hazard Ratio (HR) is within the non-inferiority hypothesis. The α-level was set at 0.050 with a hazard ratio (Hazard Ratio [HR] = Hazard [Treatment Group] / Hazard [Reference Group]) 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. The result of this study demonstrated non-inferiority of OT-101 versus TMZ (Temodar/Temozolomide) chemotherapy (HR<1.25, p= 0.0343). Furthermore, it was found that OT-101 treatment resulted in similar tumor shrinkage as chemotherapy – however, OT-101 does take longer than chemotherapy to achieve the tumor shrinkage (Median time to maximum reduction at 176 days for chemotherapy versus 456 days for OT-101, p = 0.0428. log-rank statistics).

Conclusion: A TGF-β2 specific inhibitor is the only viable product targeting the TGF-β pathway. Our drug candidate- OT-101/Trabedersen was built around this concept and is the only one with advance safety data across 6 clinical trials including two phase II trials. Furthermore our drug candidate is the only one with clear clinical efficacy in multiple indications including non-inferiority to chemotherapy in glioblastoma from in our phase II trial comparing OT-101 versus TMZ. As OT-101/Trabedersen is not a cytotoxic chemotherapeutic agent and does not cause myelosuppression, and its use is compatible with other immunotherapeutic agents and passive immune inducers.

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 possibly due 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 specific without TGF-β1 cross inhibition, therefore, we chose to target TGF-β2 only using OT-101 antisense approach. Here we report on the post-hoc efficacy analyses of a Clinical Phase IIb Study AP12009-G004 of OT-101 in glioblastoma in order to identify the target population and clinical pathway for OT-101 in glioblastoma.

METHODS

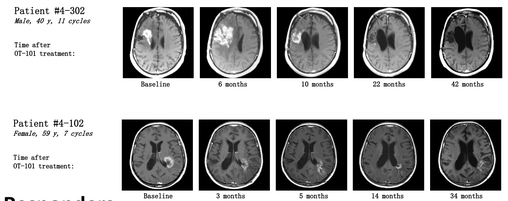
G004 is a multinational, multicenter, open-label, randomized, active-controlled, parallel-group study in adult patients with either recurrent or refractory AA (WHO grade III) or recurrent or refractory GBM (WHO grade IV). There were 3 treatment groups: 1) 10 µM Trabedersen, 2) 80 µM Trabedersen, and 3) standard chemotherapy (mostly TMZ). Tumor control rate at 6 months was the primary endpoint. Response assessment included the tumor control rate and the overall response rate, which were assessed at 6, 12, and 14 months by central MRI reading. The tumor control rate was defined as the percentage of patients with either CR (complete response), PR (partial response), or SD and the overall response rate was defined as percentage of patients with either CR or PR. An independent blinded central MRI reading was performed to obtain a standardized response assessment for the efficacy analysis. Central reading was performed by 2 independent neuroradiologists with an additional adjudicator deciding in case of conflicting opinions.

All patients had previous tumor surgery, almost all patients had previous radiation therapy, and more than half of the patients had received previous chemotherapy. The median time from the first diagnosis of AA or GBM until baseline in Study G004 as well as KPS values at baseline were similar in the 3 treatment groups. In the 10 µM Trabedersen group, a higher percentage of patients was older than 55 years (43%) compared to the 80 µM Trabedersen (18%) or the standard chemotherapy group (29%). There was no clinical significant differences between 10 µM and 80 µM groups and they were treated as one group for this post-hoc analysis.

Two-Sample Non-Inferiority Tests for Survival Data using Cox Regression was performed to evaluate non-inferiority versus TMZ. Kaplan Meier survival analysis and Chi-square tests were used for statistical evaluation.

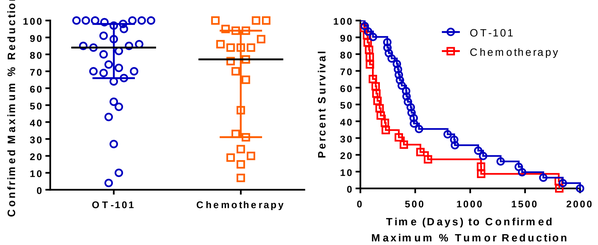
RESULTS

Typical late tumor reduction with OT-101



Analyses of Responders

1. **OT-101 has comparable Tumor Response and Tumor Control Rate as TMZ chemotherapy. Potentially more CR (100% reduction) with OT-101**
2. **Time to maximum tumor reduction is slower for OT-101 versus TMZ**
3. **Slower time to response is typical for immunotherapy. Median time to maximum reduction at 176 days for chemotherapy versus 456 days for OT-101 (p=0.04, Log rank statistic)**



RESULTS

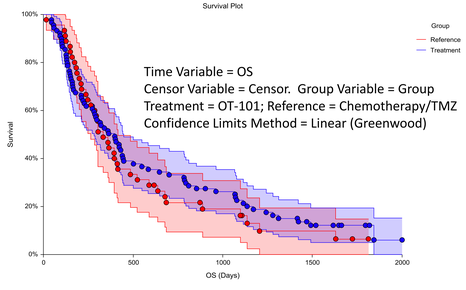
Non-Inferiority Analysis

1. **OT-101 is non-inferior to TMZ using Wald Test**

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

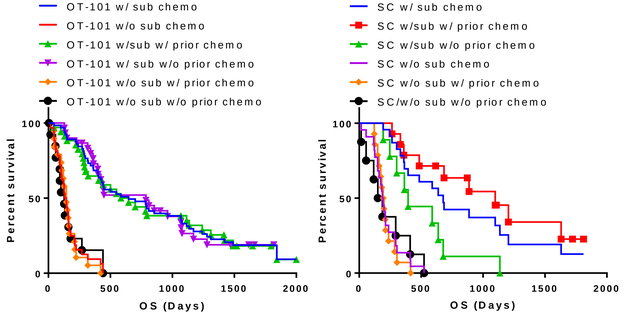
Alternative Hypothesis	Hazard Ratio HR*	Lower 90.0% C.L. of HR	Upper 90.0% C.L. of HR	Wald Z-Value	Wald Prob Level	Conclude Non-Inferiority at α = 0.05?
HR < 1.25	0.8739	0.6325	1.2074	-1.8211	0.0343	Yes

* 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.



Subgroup Analyses

1. **All patients benefited from subsequent chemotherapies following treatment with either OT-101 or TMZ**
2. **TMZ treated group bifurcated into two distinct groups- those receiving prior chemotherapy has survival advantage over those did not received prior chemotherapy (p=0.02, Log rank statistic)**
3. **OT-101 treated group did not bifurcated as expected for its non-chemotherapeutic nature (p=ns, Log rank statistic)**



Target Population

1. **Target Population which would benefit the most from OT-101 is chemo naïve patients with recurrent glioblastoma**
2. **OT-101 in this target population was superior to TMZ with 33.3% survival when the TMZ group has only 5.6% survival at 2 yr (p=0.0258, Fisher exact test, two-sided)**

Events	w/prior chemo	w/prior chemo + OT101	w/prior chemo + TMZ	w/o prior chemo	w/o prior + OT101	w/o prior + TMZ
# censored	11	6	5	9	9	0
# deaths	71	47	24	54	36	18
Total	82	53	29	63	45	18
mOS (days)	**301.5**	**292**	**305**	**365**	**398**	**334**
2 yr Survival						
Alive	25	16	9	16	15	1
Dead	57	37	20	47	30	17
%	30.5%	30.2%	31.0%	25.3%	33.3%	5.6%

Myelosuppression Analysis

1. **AEs that occurred in a greater proportion of patients in the chemotherapy group included leukopenia, neutropenia, and thrombocytopenia in the SOC blood and lymphatic disorders.**
2. **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

CONCLUSIONS

1. **Post-hoc efficacy analyses of a Clinical Phase IIb Study AP12009-G004 of OT-101 in glioblastoma in order to identify the target population and clinical pathway for OT-101 in glioblastoma.**
2. **In this study the comparator arm is standard chemotherapy with majority of the patients on TMZ (Temodar/Temozolomide)**
3. **The following findings are being reported here**
   a. **OT-101 demonstrated clear clinical efficacy**
   b. **OT-101 tumor reduction is delayed versus TMZ**
   c. **OT-101 is noninferior to TMZ**
   d. **OT-101 does not bifurcated based on prior chemo as TMZ did**
   e. **OT-101 in subgroup chemo naïve pts is superior to TMZ**
   f. **OT-101 is non myelosuppressive whereas TMZ is myelosuppressive**
4. **Based on these findings it is clear that OT-101 exhibits many of the characteristics of immunotherapeutic agents with activity on par with chemotherapeutic agents (TMZ)**
5. **OT-101 did not demonstrate cytotoxic activity in vitro nor does it resulted in myelosuppression and should not interfere with immunotherapy agents**
6. **Therefore OT-101 is an ideal drug to use in combination with immunotherapy agents**
7. **The use of chemotherapy together with OT-101 is also warranted however proper sequencing is needed.**
8. **The use of agents to increase passive immune response is also suggested**

In conclusion. OT-101 is a promising novel agent against TGF-β2 with clear clinical efficacy and potential superiority to TMZ. Further testing of OT-101 against glioblastoma is warranted.