Clinical efficacy of Intratumoral OT-101 a TGF-β2 antisense and proposed confirmatory phase 2/3 trial in glioma

Larn Hwang, David Nam, Vuong Trieu
Oncotelic Inc., Agoura Hills, CA, USA

ONCOTELIC

ABSTRACT

Background: G004 is a multi-national, multi-center, open-label, active-controlled, randomized parallel group dose-finding study to evaluate the efficacy and safety of two doses 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.

Methods: A total of 134 patients, 89 patients in the OT-101 treatment groups and 45 patients in the standard chemotherapy (TMZ) group were assessed. All patients previously underwent surgery followed with radiation, with half treated with TMZ/radiation.

Results: Primary Objective of G004 was to evaluate the efficacy of two doses (10 μM and 80 μM) of OT-101 on the tumor control rate (CR+PR+SD) at six months based on central MRI assessment in comparison to standard treatment (predominantly Temozolomide [TMZ]). Efficacy was similar between doses of OT-101, therefore they were pooled for subsequent analyses. Non-inferiority of OT-101 versus TMZ chemotherapy (HR<1.25, p= 0.0343) was demonstrated. For OT-101, mOS were 21.6 months and 4.6mos of patients with and without subsequent Chemo, p<0.0001, respectively; for TMZ, mOS were 22.6 months and 6.4 months of patients with and without subsequent Chemo, p<0.0001, respectively. Treatment sequencing was important as lead-in OT-101 followed with subsequent Chemo was more effective than Chemo prior to OT-101 (26.2mos vs. 4.8 mos, p<0.0001). TMZ required both prior and subsequent Chemo for successful outcome; no prior Chemo decreased mOS from 36.6mos to 13.1mos, p=0.0061. OT-101 was superior to TMZ in doubling the number of pts in the good outcome group, 64 of 97 pts (66%); whereas, only 14 of 45 pts (31%) 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: OT-101 is as effective as TMZ in recurrent high grade glioma. More importantly, OT-101 efficacy is superior to TMZ in chemo naïve patients and OT-101 also safer due to absence of myelosuppression. Treatment will consist of 4 cycles of OT-101 followed with Chemo. As G004 allowed pts to go on either subsequent Chemo or Best Supportive Care, mOS is expected to further improve when Chemo is a required component of OT-101 treatment.

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 glioma in order to identify the target population and clinical pathway for OT-101 in glioma.

11th AACR-JCA, February 8 - 12, 2019, Maui, Hawaii, USA

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.

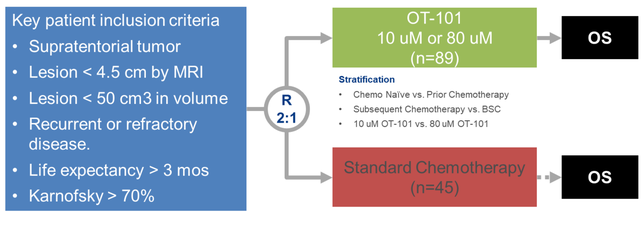
Following the initial report on G004 in 2010, a prolonged follow up study was performed. The intention of the prolonged follow-up of phase IIb study AP 12009-G004 was to collect long-term efficacy and safety data in patients with high-grade glioma who had received treatment during the core study with either one of two doses of AP 12009 (10 μM or 80 μM) or standard chemotherapy (TMZ or PCV). For all patients who entered the prolonged followup, additional MRI data were collected at 6-monthly visits and assessed by Central MRI Reading. The core study ended when the last patient finished the 6 month treatment period. It should be noted that there was a considerable time lag of 15 months between the last visit of the core study and the first visit of the prolonged follow-up. Therefore, only a limited number of patients could enter the prolonged follow-up. Of the 134 patients treated during the core study, 34 patients were alive at the end of the core study. Of these, 27 patients entered the prolonged follow-up study.

All patients had previous tumor surgery, almost all patients had previous radiation therapy, and more than half of the patients had received previous chemotherapy. 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. Kaplan Meier survival analysis and Chi-square tests were used for statistical evaluation.

Trial Design

Secondary Endpoints for G004 (Core + Prolonged Studies)

1. **Study objective: To assess OS as approvable endpoint to define the target population for subsequent confirmatory phase 2/3 trial.**
2. **Primary Objective has been reported previously: To evaluate the efficacy of two doses (10 μM and 80 μM) of AP 12009/ OT-101 on the tumor control rate (CR+PR+SD) at six months based on central MRI assessment in comparison to standard treatment (Temozolomide [TMZ] or combination of Procarbazine, CCNU [Lomustine], and Vincristine [PCV]).**
3. **SECONDARY ENDPOINTS: OS and Myelosuppression**



RESULTS

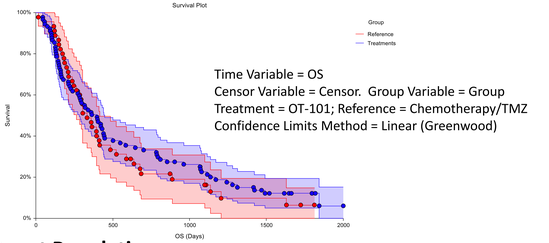
Non-Inferiority Analysis

1. **OT-101 (10uM or 80 uM) is non-inferior to TMZ using Wald Test**
2. **OS was similar between the 10 uM dose and the 80 uM dose**

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)

Target Population

1. **Target Population which would benefit the most from OT-101 is chemo naïve patients with recurrent glioma**
2. **All patients benefited from subsequent chemotherapies following treatment with either OT-101 or TMZ. At least 4 cycles of OT-101 is needed for the observed benefit.**
3. **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)**
4. **OT-101 treated group did not bifurcate (p=ns, Log rank statistic)**
5. **OT-101 was superior to TMZ in doubling the number of patients in the good outcome group. As shown below, 64 of 98 pts (65.3%) in OT-101 arms showing considerable improved mOS; whereas, only 15 of 47 pts (32%) treated with TMZ did (P=0.0002, Fisher's exact test, Two-tailed).**
6. **OT-101 in this target population was superior to TMZ with 33.3% survival (15 of 45 pts alive) when the TMZ group has only 5.6% survival (1 of 18 pts alive) at 2 yr (p=0.0258, Fisher exact test, two-sided). This was further improved with subsequent chemotherapy to 50% (15 of 30 pts alive) (p = 0.0015, Fisher exact test, two sided)**

Table 1. Median Overall Survival and 2 yr Survival of Subjects Receiving OT-101 or TMZ, based on Prior or Subsequent Chemotherapy

mOS	OT-101		TMZ	
	Subseq. TMZ		Subseq. TMZ (or other alkylating agent)	
Prev. TMZ	No	Yes	No	Yes
No	4.2mos (N=14)	26.2mos (N=30)	5.6mos (N=8)	13.2mos (N=10)
Yes	4.8mos (N=19)	29.5mos (N=34)	6.6mos (N=14)	36.6 mos (N=15)

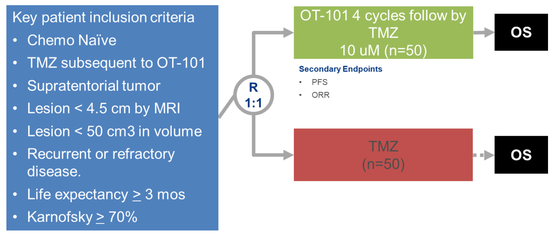
Myelosuppression Analysis

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

Proposed Phase 2/3 Confirmatory Trial

1. **Primary Endpoints : Improved OS vs. TMZ**
2. **Target Pts Population: Chemo naïve recurrent glioma pts**
3. **Treatment: 4 cycles of OT-101 followed with TMZ.**
4. **Biomarker: IL-8 spike**



CONCLUSIONS

1. **Secondary Endpoint Analyses Clinical Phase IIb Study AP12009-G004 of OT-101 in glioma in order to identify the target population and clinical pathway for OT-101 in glioma.**
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 is noninferior to TMZ**
   b. **OT-101 does not bifurcated based on prior chemo as TMZ did**
   c. **OT-101 in subgroup chemo naïve pts is superior to TMZ**
   d. **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 a promising 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.**

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 glioma is warranted.