Clinical efficacy of Intravenous OT-101 a TGF-β2 antisense and proposed confirmatory phase 2/3 trial in Pancreatic Cancer (PC)

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ABSTRACT

Background: P001 is an Open-Label, Multicenter Dose-escalation Study to Evaluate the Safety and Tolerability of OT-101 (TGF-β2-specific Phosphorothioate Antisense Oligodeoxynucleotide), Administered Intravenously (IV) in Adult Patients with Advanced Tumors Known to Overproduce TGF-β2, who are Not or No Longer Amenable to Established Therapies.
Methods: Total 61 pts enrolled in the study of which 37 were with pancreatic cancer (PC) whom received OT-101 with option to go on subsequent Chemo (OT-101/Chemo) or Best Supportive Care (BSC) (OT-101/BSC). Overall survival (OS) was compared using log-rank statistic. Stratification by treatment line, schedule, metastasis location, disease control (DC), and baseline CA19-9, was performed.
Results: The primary objective of P001 was to determine the maximum tolerated dose (MTD) and the dose limiting toxicities (DLTs) of two cycles of IV OT-101 administered for 7 days or for 4 days every other week. MTD was not reached on 4 days on 10 days off schedule. Dose was selected at 140 mg/m^2 and expanded into phase 2 for the full cohort. OT-101 was well tolerated. Among 61 pts in the safety populations, there were 2 SAEs which were considered as possibly related (1 SAE of gastrointestinal hemorrhage, 1 SAE of pyrexia, in which both have recovered). Median OS (mOS) of the 18 pts receiving OT-101/Chemo was 9.4mos vs. the 19 pts on OT-101/BSC (2.8mos, p=0.0004). The survival benefit of subsequent Chemo was evident after at least 4 cycles of OT-101. No significance was observed on stratification except in pts with only liver metastasis (met) (n=15) had a mOS of 9.5mos while those with liver met plus others only (n=22) had a mOS of 4.7mos (p=0.0077). Among the former, one patient has Complete Response for over 77.3mos and one patient had Stable Disease with OS of 40.3mos. OS was higher for liver met only group with OT-101/Chemo – 12.4mos (n=10) versus 1.9mos (n=4) without chemo, p=0.0006, respectively. There were 16 of 37 pts with DC, with mOS of 9.7mos vs. 3.0mos (p<0.0001). OS was higher for DC group with OT-101/Chemo – 11.8mos (n=13) vs. 5.0mos (n=6), p=0.0021.
Conclusions: The clinical data support the development of OT-101 in pancreatic cancer. Target population was defined as advanced treatment failure PC with liver involvement only. Treatment will consist of 4 cycles of OT-101 followed with Chemo, based on physician's choice.

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.

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METHODS

The P001 trial was an open-label, multicenter dose-escalation study to evaluate the safety and tolerability of OT-101 (TGF-β2-specific Phosphorothioate Antisense Oligodeoxynucleotide) in adult patients with advanced tumors known to overproduce TGF- β2, while are not or no longer amenable to established therapies. The primary objective of the study was to determine the maximum tolerated dose (MTD) and the dose limiting toxicities (DLTs) of two cycles of trabedersen administered intravenously (i.v.) on a 7-days-on/7-days-off or 4-days-on/10-days-off schedule.

Secondary objectives included were: 1) Determining the safety and tolerability of OT-101 administered intravenously at weekly intervals for four days every other week. 2) Assessing the plasma pharmacokinetic profile of OT-101 administered intravenously at weekly intervals and for four days every other week. 3) Establishing a suitable determination method and to assess the urine pharmacokinetic profile of OT-101 administered intravenously for four days every other week. 4)Determining the effect of OT-101 administered intravenously at weekly intervals and for our days every other week on TGF-β2 plasma concentration levels. 5) Assessing the potential antitumor activity of OT-101 administered intravenously at weekly intervals and for four days every other week, as assessed by the effect on tumor size and tumor markers.

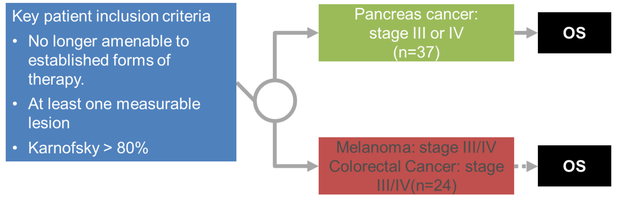
Primary and Secondary objectives were met and are part of the core CSR for P001. The purpose of this secondary endpoint analysis is to assess the various subgroups of the pancreatic cancer patients in the P001 trial to define the clinical development pathway for OT-101; focusing on maximizing tumor reduction while extending the overall survival of patients is an approvable endpoint. Overall survival (OS) in terms of subsequent chemotherapy, line of treatment, CA19-9 values, status of metastasis, as well as number of cycles was reviewed.

GraphPad Prism 6 (La Jolla, California) was used to prepare Kaplan-Meier curves for overall survival and corresponding logrank tests. Patient data such as overall survival and censor data were obtained from SAS datasets generated during the clinical trial. Due to concerns about possible bias in the clinical data, a comparator drug with similar propensities was added in the analysis to act as a control for OT-101.

Trial Design

Secondary Endpoints for P001

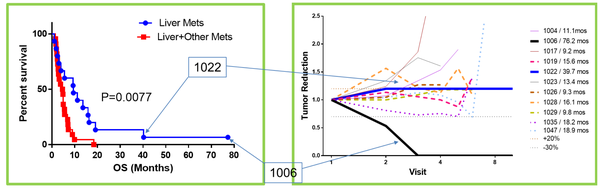
1. **Study objective: To assess OS as approvable endpoint to define the target population for subsequent confirmatory phase 2/3 trial.**
2. **Primary Objective has been reported previously: to determine the maximum tolerated dose (MTD) and the dose limiting toxicities (DLTs) of two cycles of trabedersen administered intravenously (i.v.) on a 7-days-on/7-days-off or 4-days-on/10-days-off schedule**
3. **SECONDARY ENDPOINTS: OS**



RESULTS

Target Population

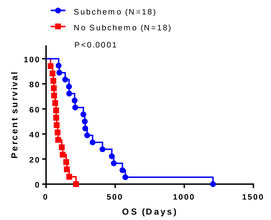
1. **OT-101 exhibited promising single agent clinical activity as second line therapy in patients with advanced metastatic pancreas cancer with a mOS of 14.5 mos for 6.1 mos for Onivyde+5FU/LV in NAPOLI-1.**
2. **Target Population which would benefit the most from OT-101 was defined as end stage pancreatic cancer pts with only liver mets**
3. **1 yr survival was 19% (7 of 36 pts alive) which is significantly higher than the 7% (8 of 117 pts alive) and 6% (7 of 119 pts alive) among comparable populations treated with Onivyde+5FU/LV and 5FU/LV of NAPOLI-1, respectively, (p<0.05).**
4. **1 yr survival was improved to 35% (5 of 14 pts alive) among pts with liver metastasis only (p=0.0035 and p =0.0032 vs. Onivyde+5FU/LV and 5FU/LV of NAPOLI-1, respectively)**

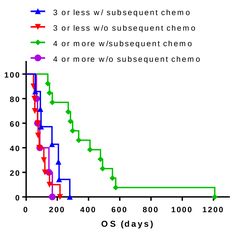


Patient 1006: CR as far out as 77 mos. 1) Surgery: Whipple's procedure, **2)** 1st line: 5-FU/LV, Dose 425 mg/m2, **3)** 2nd line: 5-FU/LV, Dose 2600 mg/m2/24hr, **4)** 3rd line: Gemcitabine, Dose 1000 mg/m2/week, **5)OT-101-Liver mets/ Complete Response (Black Line). Patient 1022: OS of 40 months. 1)** Surgery: Whipple's procedure, **2)** 1st line: Radiation therapy (50 Gy), **3)** 2nd line: 5FU, **4) OT-101- Liver Mets/ Stable Disease (Blue Line)**

Subsequent Chemotherapy and Improved OS

1. **Subjects receiving subsequent chemotherapy had extended OS compared to no subsequent chemotherapy. Median OS (Excluding 1006)With Subsequent Chemo: 282 days, Without Subsequent Chemo: 77 days. Logrank P-Value: P<0.0001**
2. **At least 4 cycles of OT-101 is needed for the observed improvement in OS with subsequent chemotherapy. Subjects that received three or less cycles of OT-101 reported a median overall survival of 166 days compared to 80.5 days of the subgroup that did not receive subsequent chemotherapy (P=0.1302).**
3. **For patients that received four or more cycles of OT-101, those that received subsequent chemotherapy had a median overall survival of 337 days, while those that did not receive subsequent chemotherapy had a median overall survival of 88 days (P=0.0001).**
4. **Disease Control also improved OS significantly. Disease control (CR+PR+SD) was 19 of 35 evaluable pts (54%).**
5. **Subjects with disease control as best response had extended OS with subsequent chemotherapy compared to those without subsequent chemotherapy. Median OS (Excluding 1006) With Subsequent Chemo: 337 days, Without Subsequent Chemo: 133 days. Logrank P-Value: P=0.0004.**



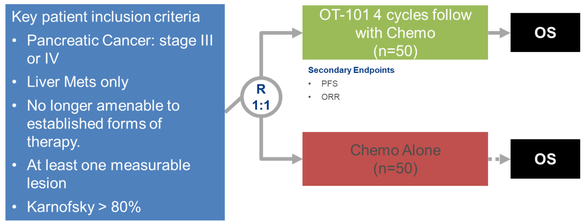


Safety Analysis

1. **About 18% (107 of 600 AEs) of all AEs that have been reported during the treatment phase of this study were assessed by the investigator to be either related (20 AEs) or possibly related (87 AEs) to the study medication trabedersen, while 82% (493 of 600 AEs) were assessed by the investigator to be either unlikely (205 AEs) or not related (283 AEs) to trabedersen, or not assessable (5 AEs).**
2. **Amongst the 107 AEs considered as related or possibly related there were 2 SAEs which were considered as possibly related (1 SAE of gastrointestinal hemorrhage, 1 SAE of pyrexia, both with outcome recovered). The remaining 105 AEs that were assessed as (possibly) related to trabedersen were non-serious.**

Proposed Phase 2/3 Confirmatory Trial

1. **Primary Endpoints : Improved OS vs. Standard Chemotherapy (physician choice)**
2. **Target Pts Population: End stage Pancreatic Cancer Pts with liver mets only**
3. **Treatment: 4 cycles of OT-101 followed chemotherapy**
4. **Biomarker: IL-8 spike**



CONCLUSIONS

1. **Secondary Endpoint Analyses Clinical Phase I/II Study AP12009-P001 of OT-101 in pancreatic cancer in order to identify the target population and clinical pathway for OT-101 in pancreatic cancer.**
2. **The following findings are being reported here**
   a. **Target population was identified as end stage pancreatic cancer pts with liver mets only**
   b. **OT-101 treatment exhibited exceptional OS when followed with subsequent chemotherapy**
   c. **Minimum of 4 cycles of OT-101 is needed for the observed effect with subsequent chemotherapy**
   d. **Minimum toxicity is associated with intravenous delivered OT-101**
3. **Based on these findings it is clear that OT-101 exhibits many of the characteristics of immunotherapeutic agents**
4. **OT-101 did not demonstrate cytotoxic activity in vitro nor does it resulted in myelosuppression and should not interfere with immunotherapy agents**
5. **Therefore OT-101 is a promising drug to use in combination with immunotherapy agents**
6. **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 pancreatic cancer is warranted.