Breaking immune tolerance for the treatment of pancreatic cancer. Phase I/II clinical experience.

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ABSTRACT

Background: Escalating Intratumoral heterogeneity results in xenogenization which is countered by overexpression of TGF-β. Here we report on the use of OT-101/Chemo to break immune tolerance to cure pancreatic cancer (PC). OT-101 is an antisense against TGF-β2.

Methods: Total of 37 pts 2nd line and beyond received OT-101 with option to go on subsequent Chemo (OT-101/Chemo) or Best Supportive Care (BSC) (OT-101/BSC). Stratification by treatment line, schedule, metastasis location, disease control (DC), and baseline CA19-9, was performed. Plasma levels of 31 cyto-/chemokine were measured in a subset of 12 pts.

Results: mOS of the 18 pts receiving OT-101/Chemo was 9.4mos vs. OT-101/BSC (2.8mos, p=0.0004). No significance was observed on stratification. However, pts with only liver metastasis had a mOS of 9.5mos while those with liver metastasis and others only had a mOS of 4.7mos (p=0.0077). Among the former, 1006 has Complete Response beyond 77.3mos and 1022 had Stable Disease with OS of 40.3mos; and OS was higher with OT-101/Chemo – 12.4mos versus 1.9mos, p=0.0006. There were 16 of 37 pts with DC, with mOS of 9.7mos vs. 3.0mos (p<0.0001); and OS was higher with OT-101/Chemo – 11.8mos vs. 5.0mos, p=0.0021. Pts exhibited spike in IL-8 level which returned to basal level at treatment stop. R squares relating the IL-8 spike and OS were 0.8522 and 0.9895 and p values were 0.0011 and 0.0053 for OT-101/Chemo and OT-101/BSC, respectively. Preclinically, OT-101 enhanced PBMC activity in cell kill assay and in vivo xenograft.

Conclusions: The MOA for OT-101/Chemotherapy is consistent with the reactivation of immunity during TGF-β suppression and subsequent boosting/expansion of immunity during Chemo. Contrary to traditional tumor vaccine- this is universally applicable to all patients.

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.

We previously have shown that suppression of TGF-β2 by OT-101 followed with Drug-Induced Xenogenization (DIX) by temozolomide resulted in improved OS and 2 yr survival among gliomas. The data validate the concept that lifting immunosuppression by OT-101, a TGF-β inhibitor immune booster, followed with treatment with a xenogenization agent, TMZ, is an effective treatment protocol for recurrent gliomas. Data are available now to support that the antitumor activity of conventional cancer chemotherapy results in part from its ability to harness the innate and adaptive immune systems by inducing immunologically active tumor cell death. In this study we examined whether chemotherapy through chemotherapy induced antigen release could work in the same context in pancreatic cancer. **Hypothesis: Lifting the TGF-β mediated immunosuppression with OT-101 followed by chemotherapy among treatment failure pts is an effective treatment combination to stimulate immunity against their tumors despite the fact that chemotherapy is no longer effective against their tumors as traditional cytotoxic.**

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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.

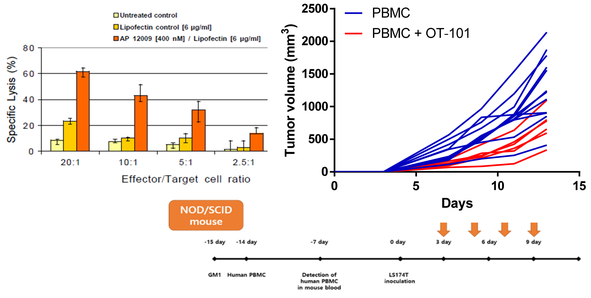
Secondary objectives included were: 1) Determining the safety and tolerability of OT-101 administered intravenously at weekly intervals for four days every other week. 2) Assessing the plasma pharmacokinetic profile of OT-101 administered intravenously at weekly intervals and for four days every other 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 four 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 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 historic controls), further patient subpopulations may be defined, requiring selection of patients fulfilling specific subcriteria.

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.

OT-101 as Immune Booster

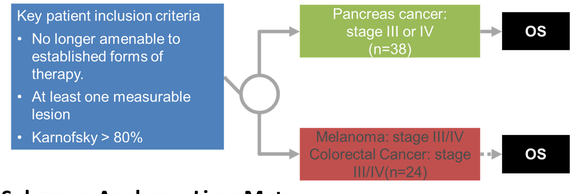
1. In vitro - OT-101 (AP 12009) reduced TGF-β2 secretion and increased LAK cell-activity against all tumor lines by 400% and 364% in comparison to the untreated control and compared to the Lipofectin control, respectively.
2. Addition of active rh-TGF-β2 protein restored suppression of the cytotoxic activity of the immune cells in a dose dependent manner.
3. Preclinical- LS174T xenograft was treated with PBMC or PBMC + OT-101. OT-101 significantly enhanced the activity of PBMC against the xenograft.



RESULTS

Trial Design

1. A total of 62 patients were enrolled, which consisted of 38 patients with pancreatic cancer, 19 with malignant melanoma, and 5 with colorectal cancer. The efficacy-evaluable population (EE-Pop) had a total of 60 patients, which were 36 patients with pancreatic cancer, 19 with malignant melanoma, and 5 with colorectal cancer. The subgroup analyses of the EE population are as below.

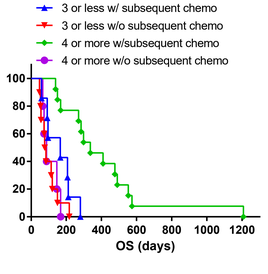


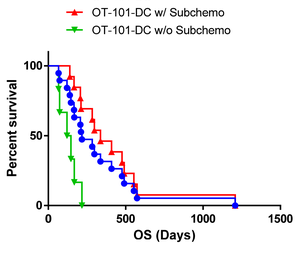
Subgroup Analyses- Liver Mets

1. Patients receiving OT-101 as a second-line of treatment had a higher mOS of 270 days vs. 120 days for those receiving OT-101 as a third-line or greater, but was not statistically significant (P=0.1295).
2. Patients with a baseline CA19-9 level less than median had a higher mOS of 214 days vs. 94 days of those with a CA19-9 level that is higher than the median, but was not statistically significant (p=0.1266).
3. Patients with liver metastasis only, had a higher mOS of 284 days vs. 139 days for those with liver metastasis to the liver and/or other sites including the lungs (P=0.0087)
   - ❖ 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.
   - ❖ 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

Subgroup Analyses- Subsequent Chemotherapy

1. Patients with subsequent chemotherapy had higher mOS of 282 days vs. 81 days of those without subsequent chemotherapy (P=0.0026). At least 4 cycles of OT-101 was needed for the observed improvement in OS with subsequent chemotherapy.
2. Patients with Disease Control (CR+PR+SD) had a higher mOS of 217 days vs. 86 days of those with PD (p<0.0001). Subjects with disease control as best response had extended OS with subsequent chemotherapy compared to those without subsequent chemotherapy.





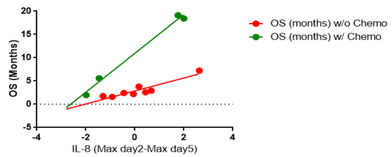
1 yr Survival Superiority for OT-101 vs. Chemotherapy

1. Pts population in P001 was extracted for those with metastatic pancreatic cancer only to match that of Napoli-1 and MPACT
2. mOS improved from 6.1 to 9.3 / 9.4 months
3. As typical for immunotherapies, long term survival was highly significant, with 1 yr survival increased to 33.3% for OT-101/Chemotherapy versus 6.8% for Onivyde + 5FU/LV and 5.9% for 5FU/LV reported for Napoli-1 (Wang-Gillam A. et al., 2016, Lancet 387: 545).
4. More importantly, among liver mets only patients, OT-101 single agent 1 yr survival was 46.7% and was superior to those reported for 2nd line and greater in Napoli-1 and even 1st line in MPACT (von Hoff DD et al., 2013, N Engl J Med 369:1691).

1 yr survival	Metastatic Pancreatic Cancer					mOS
P001	# At Risk	Dead	%	p vs. Subseq Chemo	p vs. Liver	
Subseq. Chemo	6	12	33.3%			9.4mos
Liver only	7	8	46.7%			9.3 mos
Napoli-1						
Onivyde+5FU/LV	8	109	6.8%	0.0038	0.0002	6.1 mos
5FU/LV	7	112	5.9%	0.0022	0.0001	4.2 mos
MPACT						
ABX+Gem	108	323	25.1%	ns	0.0729	8.5 mos
Gem	69	361	16.0%	ns	0.0066	6.7 mos

OT-101/Chemo IL-8 Linkage

1. Patients exhibited variable dynamics in IL-8 levels whereby increases were observed during cycles 1 (days 2, 5), 2 (days 1, 2, 5) and 3 (day 5). R squares were 0.8522 and 0.9895 and p values were 0.0011 and 0.0053 for pts treated subsequently with chemo and without chemo, respectively.



CONCLUSIONS

1. The following findings are being reported here
   a. OT-101 exhibit exceptional single agent activity in 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. OT-101 single agent and OT-101/Chemotherapy combination is operating through a common mechanism- as defined by IL-8 through the cytokine nexus
   e. It is our hypothesis that OT-101 lifted the immunosuppression exerted by TGF-β allowing the priming of immunity. Subsequent chemotherapy via its chemotherapy induced immunogenic cell death further expanded the immunity against the tumor

In conclusion. OT-101 is a promising novel agent against TGF-β2 with clear clinical efficacy. Further testing of OT-101/Chemotherapy against pancreatic cancer is warranted.