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

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ABSTRACT

Background: OT-101 is a phosphorothioate antisense oligodeoxynucleotide targeting the human TGF-β2 mRNA. OT-101 breaks down immune tolerance and activates immunity against the tumor. The Subsequent Chemotherapy (SC) releases tumor antigens and boosts the immunity response along with further epitope expansion. The phase 1/2 clinical data for OT-101/SC is presented here along with supporting preclinical MOA studies.

Methods: Total of 37 pts, 2nd line and beyond received OT-101 with option to go on SC (OT-101/SC) or Best Supportive Care (BSC) (OT-101/BSC). Overall survival (OS) was compared using log-rank statistics. Stratification by treatment line, schedule, metastasis location, disease control (DC), and baseline CA19-9, was performed. For cytokine analysis, plasma levels of 31 cyto-/chemokine were measured over 8 time points during 3 cycles of intravenous OT-101 therapy and a subset of 12 patients.

Results: In vitro cell kill assay and in vivo xenograft study were performed with human PBMC and OT-101. OT-101 reduced TGF-β2 secretion and increased LAK cell-activity against all tumor lines by 400% and 364% in comparison to the untreated control and the Lipofectin control, respectively. Addition of active rh-TGF-β2 protein suppressed the cytotoxic activity of the immune cells in a dose dependent manner. Preclinical- LS174T xenograft was treated with PBMC or PBMC + OT-101. OT-101 significantly enhanced the activity of PBMC against the xenograft. Median OS (mOS) of the 18 pts receiving OT-101/SC was 9.4mos vs. the 19 pts on OT-101/BSC (2.8mos, p=0.0004). Pts with only liver mets had a mOS of 9.5mos while those with liver mets and others only had a mOS of 4.7mos (p=0.0077). Among the former, one patient had complete response beyond 77.3mos and another had stable disease with OS of 40.3mos. OS was higher for liver mets. only group with OT-101/SC - 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). OS was higher for DC group with OT-101/SC - 11.8mos vs. 5.0mos, p=0.0021. Patients exhibited transient spike in IL-8 level on treatment with OT-101. R^2 relating the IL-8 spike and OS were 0.8522 and 0.9895 and p values were 0.0011 and 0.0053 for pts treated subsequently with SC and BSC, respectively. The two lines intersect at the origin with higher response for those with OT-101/SC, suggesting exaggerated response expected for antigen boost during the SC phase.

Conclusions: Escalating Intratumoral heterogeneity (IH) resulting in xenogenization, which is countered by overexpression of TGF-β. Here we report on the use of OT-101/SC to break immune tolerance to pancreatic cancer (PC) for the cure. The MOA for OT-101/SC is consistent with the reactivation of immunity during TGF-β suppression and subsequent boosting/expansion of immunity during SC. 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.

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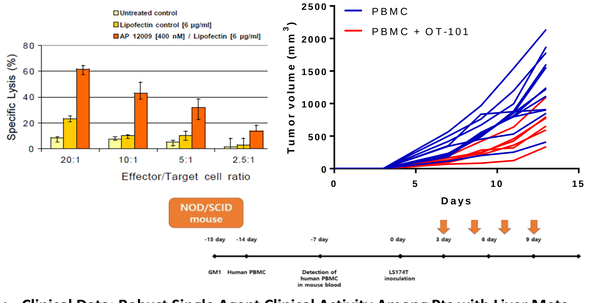
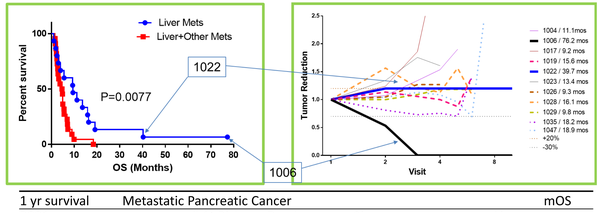
RESULTS

OT-101 Single Agent Activity (Priming of Immunity)

- **PBMC Data: OT-101 Enhances Immune Cell Anti-Tumor Activity**
- 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.
- Addition of active rh-TGF-β2 protein restored suppression of the cytotoxic activity of the immune cells in a dose dependent manner.
- Preclinical- LS174T xenograft was treated with PBMC or PBMC + OT-101. OT-101 significantly enhanced the activity of PBMC against the xenograft.



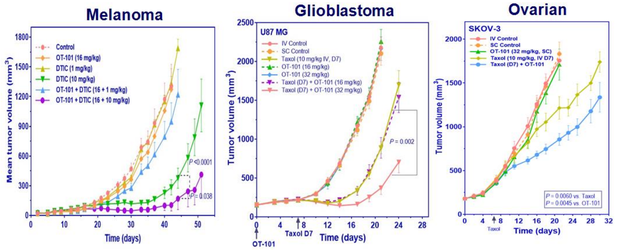
- **Clinical Data: Robust Single Agent Clinical Activity Among Pts with Liver Mets**
- Patients with liver metastasis only, had a higher mOS of 284 days vs. 139 days for those with liver metastasis to the liver and/or other sites including the lungs
- OT-101 single agent 1 yr survival was 46.7% and was 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).
  - Patient 1006: CR as far out as 77 mos. 1) Surgery: Whipple's procedure, 2) 1st line: 5-FU/LV, Dose 425 mg/m^2, 3) 2nd line: 5-FU/LV, Dose 2600 mg/m^2/24hr, 4) 3rd line: Gemcitabine, Dose 1000 mg/m^2/week, 5) OT-101- Liver mets/ Complete Response.
  - Patient 1022: SD with 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



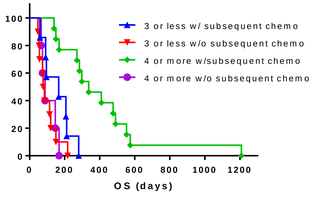
1 yr survival	Metastatic Pancreatic Cancer				mOS
P001	# At Risk	Dead	%	p vs. Liver	
Liver only	7	8	46.7%		9.3 mos
Napoli-1- 2nd line					
Onivyde+5FU/LV	8	109	6.8%	0.0002	6.1 mos
5FU/LV	7	112	5.9%	0.0001	4.2 mos

OT-101/Chemo Combination Activity (Immunity Boost)

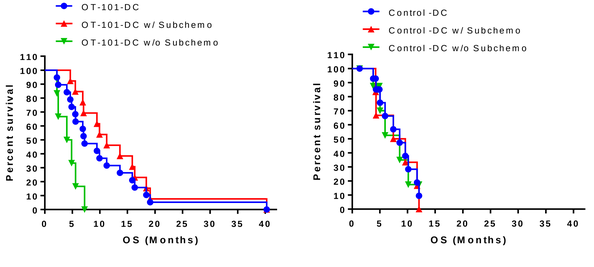
- Subsequent chemotherapy after OT-101 should release neoantigen via immunogenic cell death and thereby reeved up immunity against the tumors
- **Xenograft Data: Sequencing is Crucial**
- In three xenograft models, OT-101 displayed a significant synergistic relationship in vivo with a schedule of OT-101 followed by chemotherapy that enhanced antitumor activity and increased survival in mice.



- **Clinical Data: 4 Cycles of OT-101 Required**
- 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.

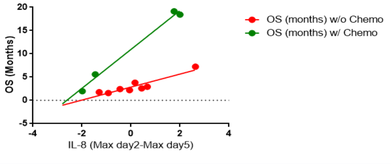


- **Clinical Data: Superiority to Controls**
- Only pts with disease control (DC) were entered into the analysis to eliminate as they are healthy enough to able to enter subsequent chemotherapy if they desired
- OT-101 treatment more than doubled the ratio of patients being able to go onto subsequent chemotherapy vs. not being able: 6:9 (0.67) vs 13:6 (2.17)
- OT-101/Chemo had increased mOS compared to the control, from 8.5 mos to 11.2 mos
- More importantly OT-101/Chemo pts more than doubled their 1 yr survival: 16% vs. 54%



IL-8 Nexus Between OT-101 and OT-101/Chemo

- 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.
- OT-101 single agent and OT-101/Chemotherapy combination is operating through a common mechanism- as defined by IL-8 through the cytokine nexus



CONCLUSIONS

- OT-101 single agent activity is consistent with the proposed MOA for OT-101 in SIP®: 1) Preclinical data showing OT-101 enhancement of immune cells both in vitro and in vivo 2) Strong single agent activity especially against those with liver mets only
- OT-101/Subsequent chemotherapy is also consistent with the proposed MOA for OT-101/Chemo in SIP®: : 1) mOS, 1yr survival increased above and beyond that of subsequent chemotherapy alone without OT-101 treatment. 2) Minimum of 4 cycles of OT-101 is needed for the observed effect with subsequent chemotherapy 3) OT-101 single agent and OT-101/Chemotherapy combination is operating through a common mechanism- as defined by IL-8 through the cytokine nexus

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)