Mechanism of Action for OT-101 TGF-β Immunotherapy

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ONCOTELIC

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ABSTRACT

Background: OT-101 is being developed as immunotherapy for a broad range of cancers that overexpress TGF-β, which suppresses host innate immune response to the cancers. Treatment with OT-101 lifts the TGF-β cloaking effect and allows innate or therapeutic immunity to attack and eliminate the cancers. OT-101 completed Phase II for pancreatic cancer and malignant melanoma and Phase II in glioblastoma with robust efficacy and safety.

Methods: Pharmacokinetic (PK) analysis of OT-101/Trabedersen for P001 study was assessed over the first 2 cycles of 7- or 4-day intravenous infusions, separated by 7- or 10-day treatment-free interval, respectively, at doses of 40, 80, 140, 160, 190, 240, 250, and 330 mg/m^2/day to for dose exposure response. Xenograft studies were performed across immunocompetent mice (C57Bl6), humanized immune mice (SCID), and T-cell deficient immune mice (nude) to demonstrate immune cell responses.

Results: The median AUClast was 232 ug*h/mL (29.7-834) across the three tumor types (pancreatic cancer [PC], malignant melanoma [MM], and colorectal cancer [CRC]). OT-101 PK is dose proportional (p<0.0001). The PK is highly variable between patients with the AUClast of 140 mg/m^2 spanning the range of observed values for the four dose levels examined for 4 days on 10 days off schedule (140, 190, 250, 330). Patients with AUC > median exhibited improved PFS for MM and CRC but not for PC with median PFS of 67 *vs.* 49 days, p=0.005, 84 *vs.* 40 days, p=ns, and 55 *vs.* 56 days, p= ns, respectively. More than half of the OT-101 treated PC patients went into long term disease control (21 of 37 pts, 55%) allowing them to enter into subsequent chemotherapy which has an unexpected benefit of more than doubling their median OS, 9.3 *vs.* 2.6 mos, p<0.0001. Among those who underwent subsequent chemotherapy, high AUC was associated with improved OS, 9.6 *vs.* 2.4 mos, p=0.0006. Animal xenograft studies demonstrated robust immune cell infiltration of the tumors. Synergy was demonstrated when OT-101 was combined with immunotherapy or chemotherapy.

Conclusions: Suppression of the TGF-β resulted in conversion of cold to hot tumors with dose dependent relationship. The synergy between OT-101 chemotherapy is similar to OT-101 immunotherapy suggesting that chemotherapy is inducing immune response amplified with prior treatment of OT-101. OT-101 is currently being combined with IL-2, PD-1, and PDL-1 agents in multiple Phase II trials.

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.

OT-101 has been evaluated in over 200 patients treated across 7 clinical trials- 6 in oncology and 1 in COVID. Clinical efficacy demonstrated in treatment failure patients- glioblastoma, pancreatic, melanoma with no known safety issues. OT-101 was granted orphan designation status for three tumor indications in US & EU/ Rare Pediatric Designation in the US for DIPG.

The Society for Immunotherapy of Cancer's (SITC) 37th Annual Meeting, Nov 8-12, Boston, MA.

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.

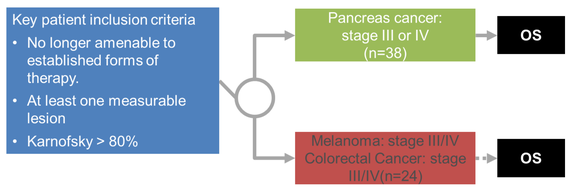
Safety

In this first intravenous administration, open-label, dose escalating phase I/II study, a total of 61 patients with pancreatic cancer (N=37), melanoma (N=19), or colorectal cancer (N=5) were treated with different doses of OT-101 through continuous IV infusion with either a 7 days on, 7 days off or a 4 days on, 10-days-off schedule. The following dose levels were explored 40, 80, 160 or 240 mg/m^2/day for 7/7 cycle and 140, 190, 250, and 330 mg/m^2/day for 4/7 cycle.

Three of these patients treated at 240 mg/m^2/day in the 7 days on, 7 days off schedule (2 Grade 3 thrombocytopenias, 1 Grade 3 maculo-papular rash). Therefore, a dose of 160 mg/m2/day was declared to be the MTD for the 7-days-on, 7 days off schedule.

Only one patient experienced a DLT at 140 mg/m^2/day in the 4-days-on, 10-days-off schedule (Grade 3 upper gastrointestinal hemorrhage). No other DLTs were observed in this schedule even at the higher doses and consequently, no MTD was identified for the 4 days on, 10 days off schedule and the dose of 140 mg/m^2/day for the 4-days-on, 10-days-off schedule was chosen as safe dose for the expansion cohort. There were total 33 patients treated at 140 mg/m^2/day (N=5 from dose escalation cohort and N=28 from the expansion cohort).

There was no major difference in AEs or their frequency regardless of treatment schedule or dose. The most frequent TEAEs observed are similar to what can be seen with late-stage cancer patients and in particular GI malignancies (nausea, abdominal pain), and consequently may not be linked to OT-101 itself.

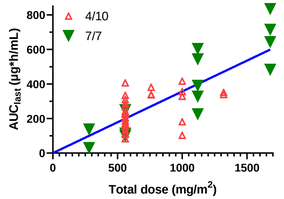


PHARMACOKINETICS AND EFFICACY

Pharmacokinetics

Pharmacokinetic analysis of trabedersen for P001 study was assessed over the first two cycles of 7- or 4-day intravenous infusions, generally separated by 7- or 10-day treatment-free interval, respectively, at doses of 40, 80, 140, 160, 190, 240, 250, and 330 mg/m^2/day. Plasma concentrations of OT-101 and five metabolites (n-1 to n-5 shortened from either end of the parent compound) were determined. Some subjects underwent more than two cycles of treatment, where only 2 time points/cycle were collected and therefore no PK analysis was performed for cycles beyond Cycle 2.

PK profiles of OT-101 showed sustained plasma concentrations throughout the dosing period (4 or 7 days) with similar PK exposure parameters (Cmax and AUC) between Cycle 1 and 2. OT-101 PK was dose proportional for OT-101 over the 7-day dose range (40, 80, 160 and 240 mg/mg^2/day) and the 4-day dose range (140, 190, 250, and 330 mg/m^2/day). The PK profile of OT-101 is in line with the the short half-life expected for this class of agents. Observed plasma T1/2 was between 1 to 2 hrs. This naturally requires a prolonged infusion as employed for this study to ideally achieve extended target suppression.



Bivariate Fit of AUClast By Total Dose. Linear Fit. AUClast = 0 + 0.3568*Total Dose. Dose proportionality of OT-101.

AUC and PFS

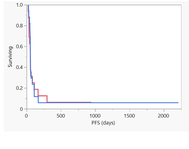
With the AUClast information we explored the effect of drug exposure versus PFS. The median AUClast value of each indication was used to divide the treated patients into high and low AUClast groups. As shown in the Figure below, there was no differences between the AUClast high versus AUClast low among pancreatic cancer patients , whereas the melanoma patients and colorectal patients exhibited improved PFS with high OT-101 exposure.

The data would suggest that tumor types known to have high mutational burden (Melanoma > CRC > Pancreatic) are responsive to OT-101 at the tested dose of 140 mg/m^2 with those exhibiting high AUClast having high PFS.

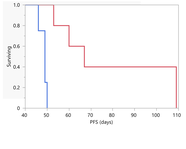
	PFS- median in days (95% interval)		
AUClast	Pancreatic Cancer (N=33)	Melanoma (N=10)	Colorectal (N=5)
High	55 (35-85)	67 (53-109)	84 (56-112)
Low	56 (49-84)	49 (46-50)	40 (26-70)
P value	ns	0.0029	ns

PFS plots. HighAUC = red / Low AUC = blue

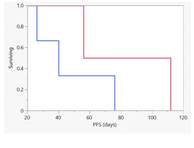
Pancreatic Cancer



Melanoma



Colorectal Cancer



Pancreatic Cancer Survival Analysis

1. Patients with subsequent chemotherapy had higher mOS of 282 days vs. 81 days of those without subsequent chemotherapy (P=0.0026).
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).
3. More than half of the OT-101 treated pancreatic cancer patients went into long term disease control (21 of 37 pts, 55%) allowing them to enter into subsequent chemotherapy which has an unexpected benefit of more than doubling their median OS. As these patients have already failed chemotherapy, the increase in OS was surprising and not replicated when another agent was used i.e. anti-CA19.

	Disease Control vs PD	Subsequent Chemo vs. No subsequent Chemo	Both DC and subsequent chemo vs all others
PFS	2.2 vs. 1.3 mos (p=0.0002)	1.8 vs. 1.9 mos (p=ns)	2.5 vs. 1.9 mos (p=0.04)
OS	9.3 vs. 2.9 (p<0.0001)	9.3 vs. 2.6 mos (p<0.0001)	12.2 vs. 3.0 (p=0.0002)

	DC High vs. Low AUC	w/Chemo High vs. Low AUC
PFS (mos)	2.4 vs. 2.2 , p = ns	1.8 vs. 1.6 , p = ns
OS (mos)	11.6 vs. 6.8 p = ns	9.6 vs. 2.4, p=0.0006

Comparison to Onivyde

OT-101 single agent activity is at minimum on par with Onivyde monotherapy and 5FU/LV monotherapy and close to the approved combination Onivyde + 5FU/LV. This is further explored by subgroup analysis where DC group analysis is comparable to reported for Onivyde. OS among OT-101 treated patients was highly dependent on drug exposure as determined by sample dense pharmacokinetics. OS comparable to that of Onivyde + 5FU/LV was observed when patient with high AUC was examined.

OS Analysis – OT-101 vs. Onivyde					
Su et al. DC	Su et al. PD	OT-101 DC	OT-101 PD	OT-101 High AUC	OT-101 Low AUC
(n = 19)	(n = 25)	(n = 18)	(n = 14)	(n = 19)	(n = 13)
8.4	3.2	9.3	2.9	8.9	3.7

CONCLUSIONS

1. **OT-101 is safely administered in P001 clinical trial**
2. **OT-101 against Melanoma and Colorectal Cancer is drug exposure dependent with improved PFS with high AUC**
3. **In the immunologically cold tumor, pancreatic cancer, the majority of the patients achieved disease control allowing them to go onto subsequent chemotherapy**
4. **Patients able to go on subsequent chemotherapy exhibited higher OS with high AUC**
5. **OT-101 activity is comparable to Onivyde+5FU/LV the most active FDA approved product for treatment failure pancreatic cancer patients.**