599 MECHANISM OF ACTION FOR OT-101 TGF-ß IMMUNOTHERAPY

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Background OT-101 is being developed as immunotherapy for a broad range of cancers. Cancers 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 2 for pancreatic cancer and melanoma and phase 2 in glioblastoma with robust efficacy and safety.

Methods Pharmacokinetic analysis of OT-101/trabedersen for P001 study was assessed over the first two 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 demonstrated 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 AUC_{last} was 232 ug*h/mL (29.7-834) across the three tumor types (pancreatic cancer (PC), melanoma (Mel), and colorectal cancer (CRC)). OT-101 PK is dose proportional ($p<0.0001$). The PK is highly variable between patients with the AUC_{last} 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 Mel 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 demonstrated when OT-101 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 responds amplified with prior treatment of OT-101. OT-101 is currently being combined with IL2, PD-1, and PDL-1 agents in multiple phase 2 trials.

Trial Registration NCT00844064- Safety and Tolerability of AP 12009, Administered I.V. in Patients With Advanced Tumors Known to Overproduce TGF-beta-2

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