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PK/PD Analysis For P001 – Phase 1/2 Clinical Trial For OT-101 Against Pancreatic Cancer, Melanoma, and Colorectal Cancer

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COI Disclosure Information

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Lead Presenter/Principal Researcher:

Vuong Trieu

I have the following financial relationships to disclose.

✔ **Leadership position/advisory role for:** CEO of Sapu Bioscience

Introduction

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- Elevated levels of TGF-β2 in tumor tissue or plasma have been associated with poor survival in patients with advanced pancreatic carcinoma. Since numerous mechanisms of malignant progression in pancreatic cancer are closely related to the expression of TGF-β2, attempts to block the activity of this factor may represent a novel promising therapy, aiming at both the enhancement of the antitumor immune response and reduction of tumor growth. Inhibition of tumor invasion and metastasis should be an additional effect, resulting in improved clinical outcome.
- OT-101 is being developed as immunotherapy for the treatment of TGF-β2 overexpressing malignancies.
- OT-101 (trabedersen) is a novel antisense oligodeoxynucleotide undergoing clinical development for the treatment of TGF-β2 overexpressing malignancies.
- OT-101 is a synthetic 18-mer phosphorothioate oligodeoxynucleotide, complementary to part of the messenger ribonucleic acid (mRNA) of the human TGF-β2 gene.
- OT-101 has demonstrated direct inhibition of TGF-β2 and indirect inhibition of TGF-β1
- Treatment with OT-101 lifts the TGF-β cloaking effect and allows innate or therapeutic immunity to attack and eliminate the cancers.
- In this open-label, multicenter dose-escalation study, plasma PK profile of OT-101 administered intravenously was evaluated in patients with advanced tumors.

Phase I/II P001 trial of Trabedersen (OT-101)

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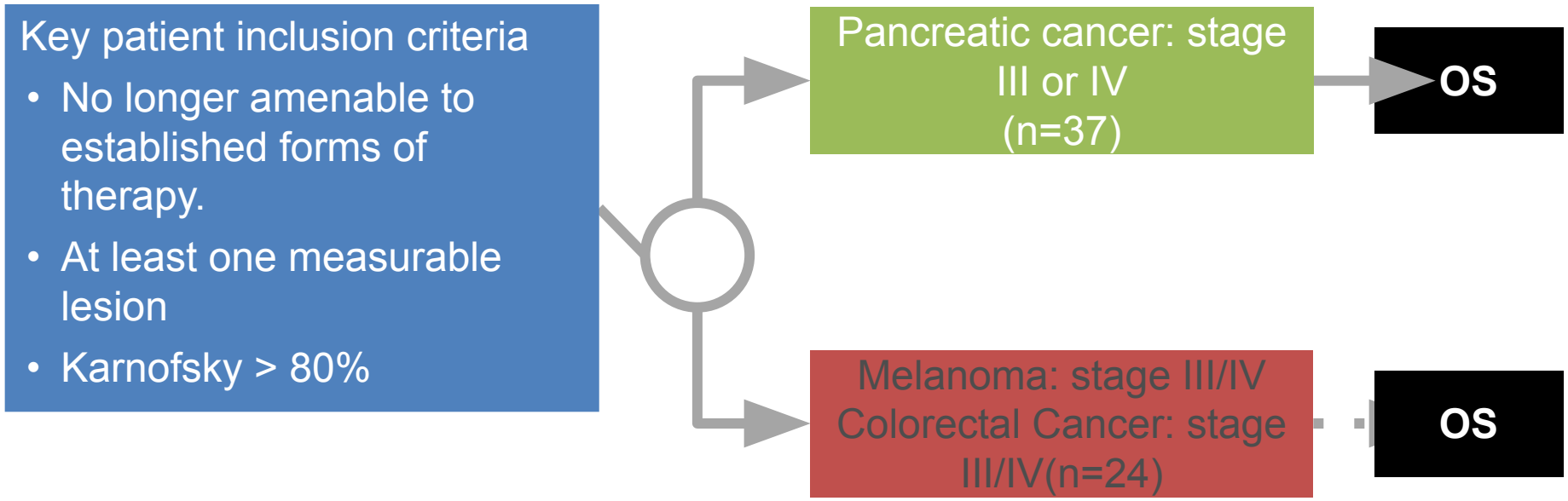
- Study objectives
- To determine the safety, pharmacokinetics and activity of OT-101 in patients with pancreas cancer, malignant melanoma, or colorectal cancer when administered intravenously



* Primary objective met. An effective dose for Phase II/III registration study has been identified

Promising Clinical Activity in Advanced Pancreas Cancer

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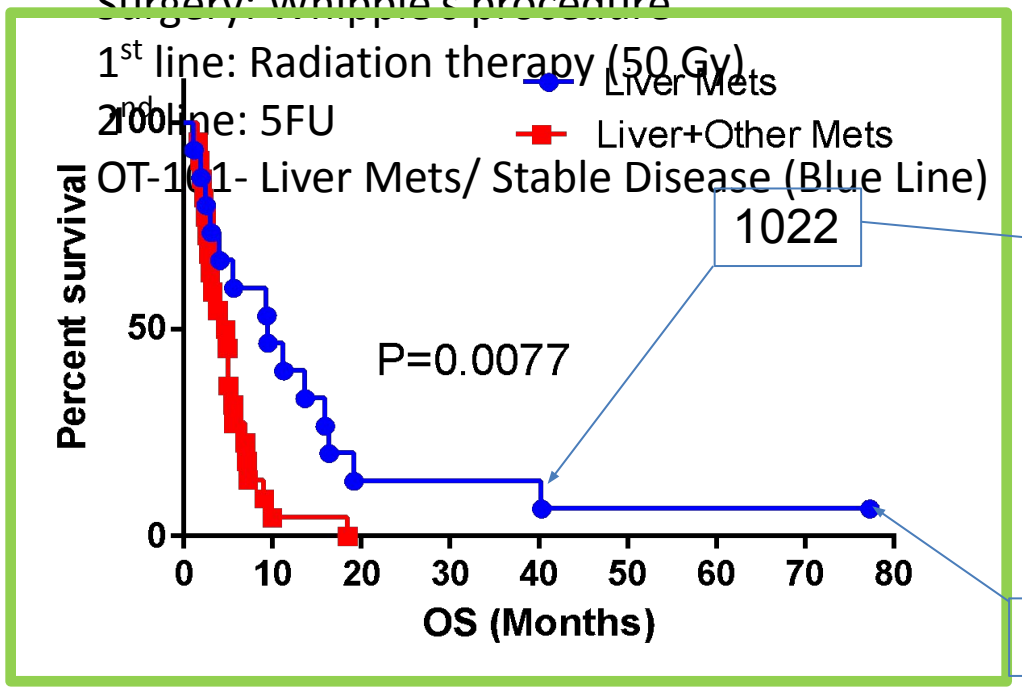
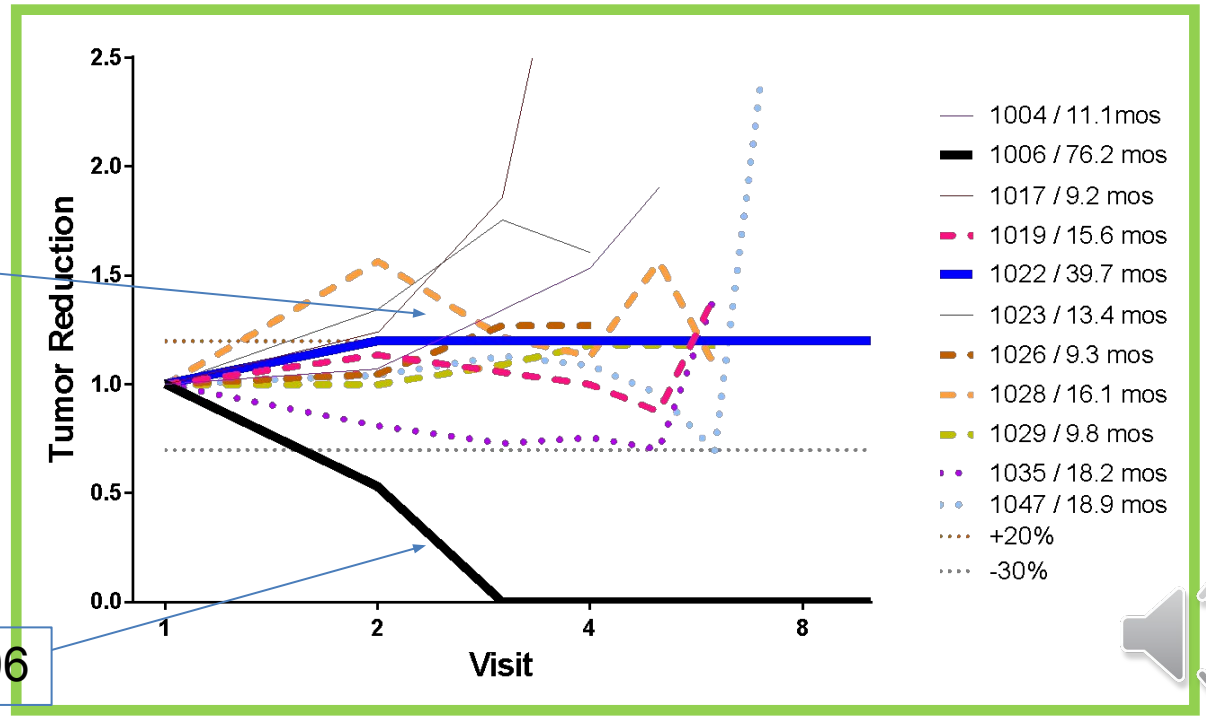
Patient 1006: CR as far out as 77 mos

Surgery: Whipple's procedure
1st line: 5-FU/LV, Dose 425 mg/m2
2nd line: 5-FU/LV, Dose 2600 mg/m2/24hr
3rd line: Gemcitabine, Dose 1000 mg/m2/week
OT-101- Liver mets/ Complete Response (Black Line)

Patient 1022: OS of 40 months

Surgery: Whipple's procedure
1st line: Radiation therapy (50 Gy)
2nd line: 5FU
OT-101- Liver Mets/ Stable Disease (Blue Line)





Dosing and Sampling

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Table 1. Dosing Scheme			
Schedule	**Dose (mg/m^2/day)**	**Infusion Duration**	**Number of Subjects**
7-days-on, 7-days-off	40	7 days (168 h)	3
	80	7 days (168 h)	3
	160	7 days (168 h)	5
	240	7 days (168 h)	4
4-days-on, 10-days-off	140	4 days (96 h)	33
	190	4 days (96 h)	3
	250	4 days (96 h)	5
	330	4 days (96 h)	3

- The PK population consisted of 57 patients from the Phase I/II study treated with OT-101 using either 7-days-on/7-days-off or 4-days-on/10-days-off schedule.
- Six subjects were removed from analysis due to a deviation from the clinical study protocol regarding the dosing or plasma sampling procedure.

Table 2. Blood sampling schedule

	Pharmacokinetic Time Points (Cycle 1 and Cycle 2)																
	Post start of infusion								Post stop of infusion								
Normal time (h)	Prior to Start	1	2	4	6	24	>29	0.5 h prior to stop	Stop[a]	0.5	1	2	3	4	6	24	7 days
Actual Time (h) for PK Analysis (7- days infusion)[b]	0	1	2	4	6	24	29	-	168	168.5	169	170	171	172	174	192	336[c]
Actual Time (h) for PK Analysis (4- days infusion)[b]	0	-	-	4	6	24	29	95.5	96	96.5	97	98	99	100	102	120	336[d]

- Not collected.
[a] Immediately prior to stop.
[b] Time points for PK analysis are expressed relative to the start of infusion.
[c] Collected 7 days after stop of infusion in Cycle 2.
[d] Generally collected 10 days after stop of infusion in Cycle 2.

Demographic and Population PK

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Table 3. The demographic and indication index of the patients. Mean ± SD.

Characteristics	7-d-on/7-d-off	4-d-on/10-d-off
Demographic		
Male	9	18
Female	6	18
Age, year	58.2 ± 10.3	60.8 ± 9.8
BW, kg	70.7 ± 12.9	68.6 ± 12.5
Height, cm	171.0 ± 8.4	171.0 ± 9.6
BMI, kg/m^2	24.1 ± 3.4	23.4 ± 3.6
Indication		
Pan/Mel/Col Cancer	9/2/4	24/11/1

BW, body weight; BMI, body mass index; Pan, pancreatic cancer; Mel, melanoma; Col, colorectal cancer.

Table 4. Parameter estimates of population PK model for OT-101

Parameters	Base model Estimate	Final Model Estimate	Bootstrap Median (95%CI)
V (L)	4.89	4.69	4.50 (3.46 - 5.85)
V2 (L)	5236.3	5046.4	5064.3 (3909.0 - 6546.0)
Cl (mL/h)	156.8	0.17	0.17 (0.16 - 0.18)
Cl2 (L/h)	3.3	3.31	3.32 (2.76 - 4.02)
Cl2_BodyWeight	-	-1.48	-1.43 (-2.38 - 0)

- The final analysis dataset contained 92 patient cycles and 1444 plasma samples. Twenty-six patient cycles were from 7-days-on/7-days-off schedule and 66 were from 4-days-on/10-days-off schedule.
- Demographic characteristics were relatively consistent between the subjects in the two treatment schedules.
- The concentration time course of OT-101 was best described by a two- compartment model.
- The influence of age, gender, body mass index (BMI), body weight (BW), height, cancer type, and treatment schedule as covariates on PK was evaluated. BW was identified as a covariate.

PK/PD Analysis

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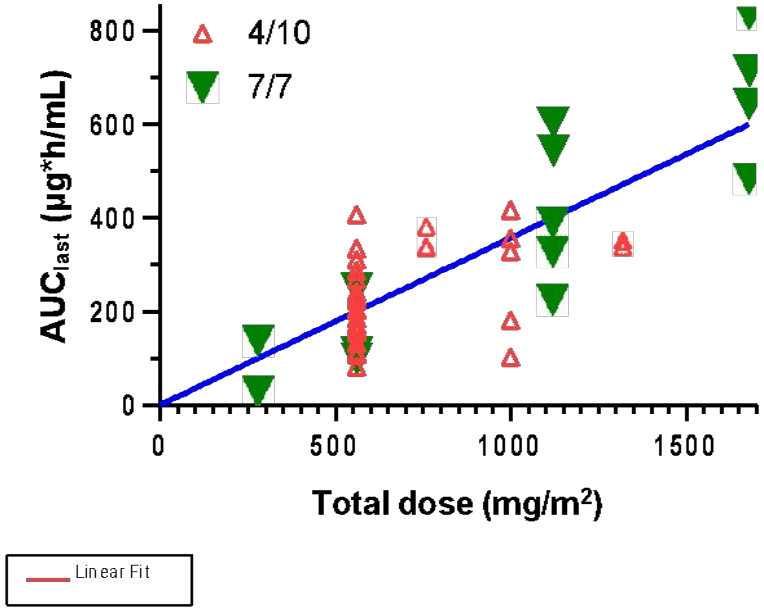
Figure 2: Bivariate Fit of AUC_{last} By Total Dose



Linear Fit

$AUC_{last} = 0 + 0.3568*Total\ Dose$

- OT-101 PK is dose proportional (p<0.0001) (Figure 2).
- 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.

	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	2.4 vs. 2.2 , p = ns	1.8 vs. 1.6 , p = ns
OS	11.6 vs. 6.8 p = ns	9.6 vs. 2.4, p=0.0006

Conclusions

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- 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/m2/day. Plasma concentrations of trabedersen and five metabolites (n-1 to n-5 shortened from either end of the parent compound) were determined.
- Clinical efficacy as disease control was demonstrated
- The median AUClast 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 ($p<0.0001$).
- In Mel and CRC, tumours with high mutational load, high AUC was associated with improved PFS.
- 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.
- PC patients exhibited improved OS with subsequent chemotherapy which improved with high AUC.
- It is our hypothesis tumor response following TGF-β suppression is related to mutational load and can be further enhance by subsequent chemotherapy probably through xenogenization.
- Therefore the combination of OT-101 with pembrolizumab should be effective and clinical trials are underway to test this concept.

OT-101 Clinical Trials

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	Discovery	Preclinical	Phase 1	Phase 2	Phase 3
	Oncology				
	OT-101 -IV	Solid Tumors	Proleukin/ Clinigen		
	OT-101-IV	Mesothelioma	Keytruda/ Merck		
	OT-101- IV	NSCLC	Tecentriq/ Genentech		
SAPU BIOSCIENCE	OT-101- IV	PDAC	Sapu Bioscience	P001– Good efficacy signal	
SAPU BIOSCIENCE	OT-101- CED	DIPG/ RPD Voucher	Sapu Bioscience		
SAPU BIOSCIENCE	OT-101- CED	GBM	Sapu Bioscience	G004 – Good efficacy signal	
	Virology				
SAPU BIOSCIENCE	OT-101- IV	COVID	Sapu Bioscience	C001- Good efficacy signal	
	Discovery				
	OT-101/LNP				
	OT-101/Intranasal				

Thank you

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