OT-101 FOR PDAC

PANCAN 2-26-2023

SAPU BIOSCIENCE

REDEFINING TUMOR-ASSOCIATED MACROPHAGE SUBPOPULATIONS AND FUNCTIONS IN THE TUMOR MICROENVIRONMENT

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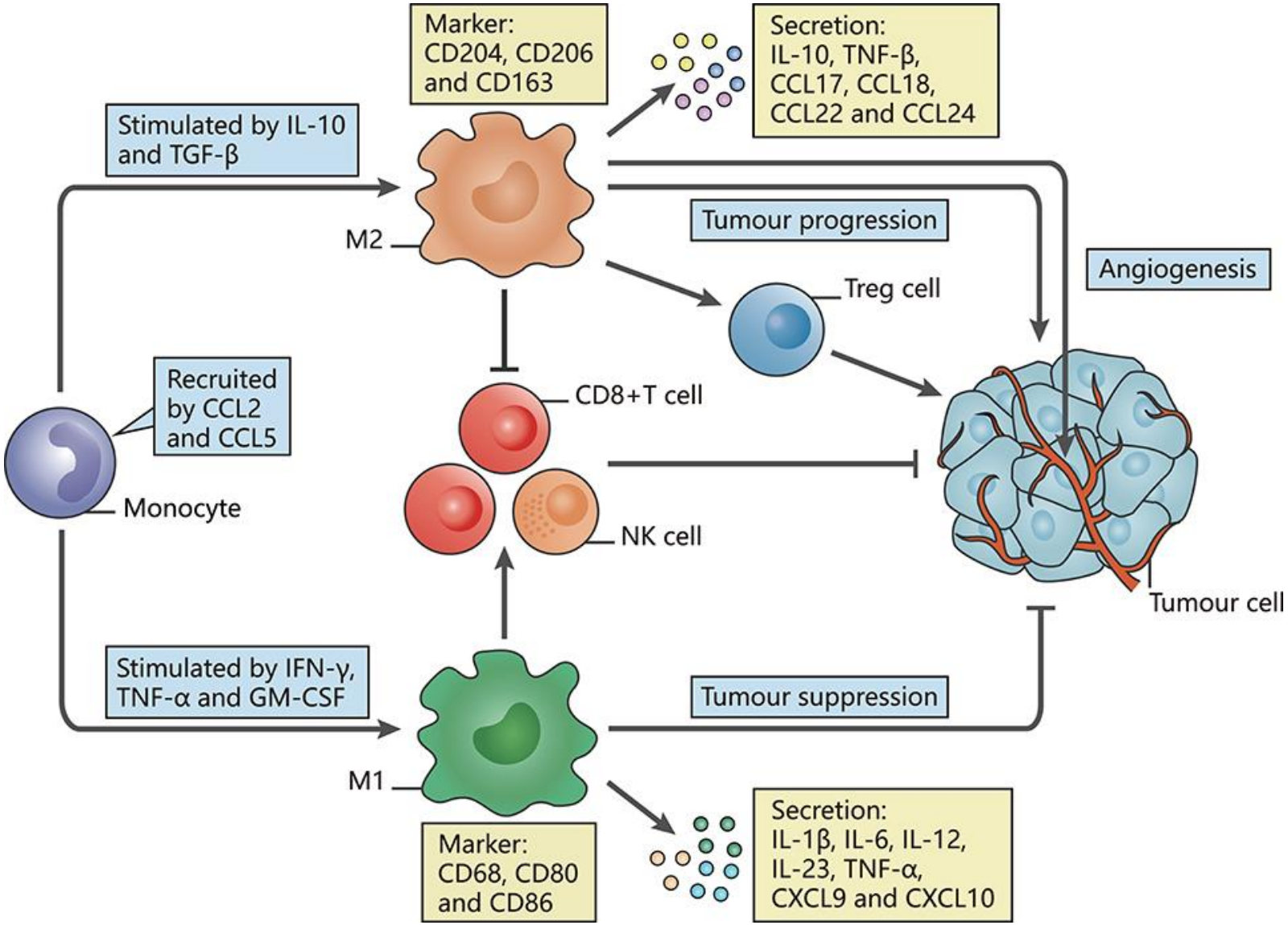
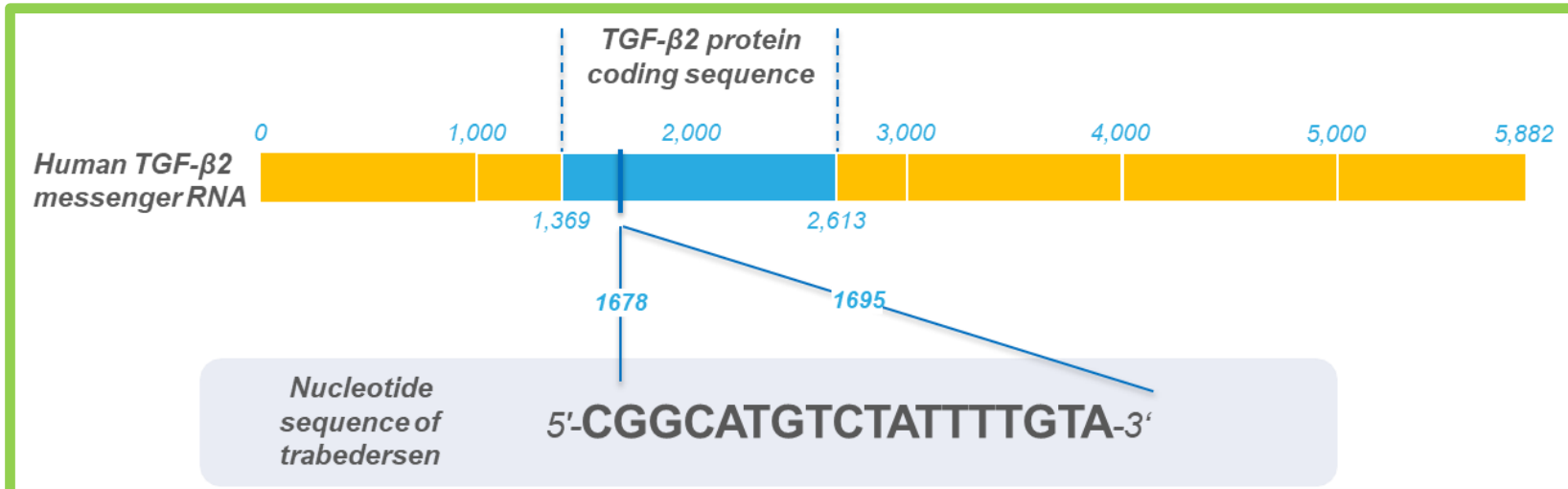
The polarization of TAMs and their characteristics. The figure displays a general principle of polarized M1-like and M2-like phenotypes. M1-like and M2-like phenotypes represent two extremes of TAM polarization and display distinct functions. In response to different stimuli in the TME, TAMs undergo M1-like, or M2-like activation. M1-like TAMs are stimulated by IFN-γ, TGF-α, or GM-CSF, express CD68, CD80, and CD86, secrete IL-1β, IL-6, IL-12, IL-23, CXCL9, and CXCL10, and exert anti-tumor effects. In contrast, M2-like TAMs are activated by IL-10 or TGF-β, express CD163, CD204, and CD206, secrete IL-10, TNF, CCL17, CCL18, CCL22, and CCL24 and promote tumor progression.



OT-101: DRUG PRODUCT

- Trabedersen (OT-101) is a single-stranded phosphorothioate antisense oligodeoxynucleotide (18-mer) designed to specifically target the human TGF-β2 messenger RNA
- Ready for registration trials--Over 200 patients treated across 6 clinical trials
- Potential for breakthrough designation for early approval
- Strong Patent protection until 2037
- Orphan designation granted for three tumor indications in US & EU
- Manufacturing process optimized and scaled up sufficient drug to treat over 10,000 GBM patients/ sufficient for current IIS program



OT-101 / VALIDATION OF TGF-B2 AS THE TARGET

OT-101 IS THE ONLY TGF-B2 INHIBITOR IN CLINICAL DEVELOPMENT

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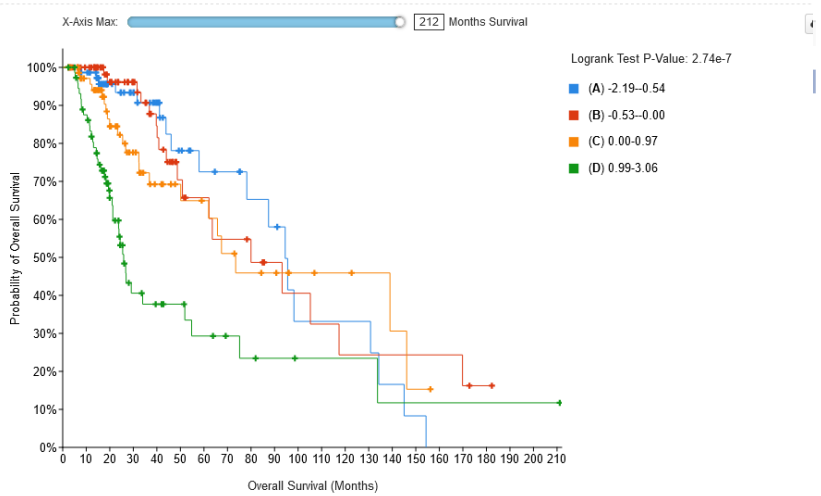
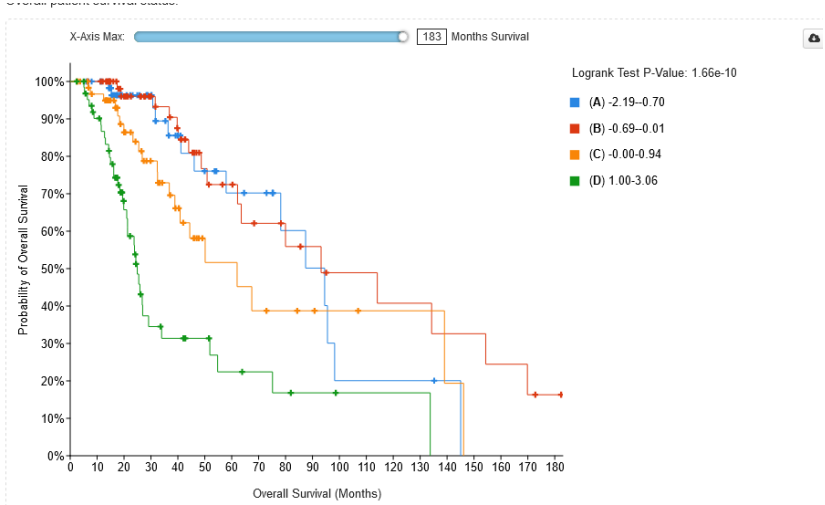
TGF-B2 IS A NEGATIVE PROGNOSTIC FACTOR IN ADULT GLIOMAS TREATED WITH RADIATION OR CHEMOTHERAPY (TMZ) OR BEVACIZUMAB (AVASTIN)

- Gliomas treated with Radiation, TMZ, and Avastin exhibited increasing OS with decreasing TGF-B2 suggesting that OT-101 would be synergistic with these only available treatments for gliomas
- No effect was observed for TGF-B1 nor TGF-B3 validating TGF-B2 as the correct target.
- OT-101 is the only TGF-B2 inhibitor in clinical development



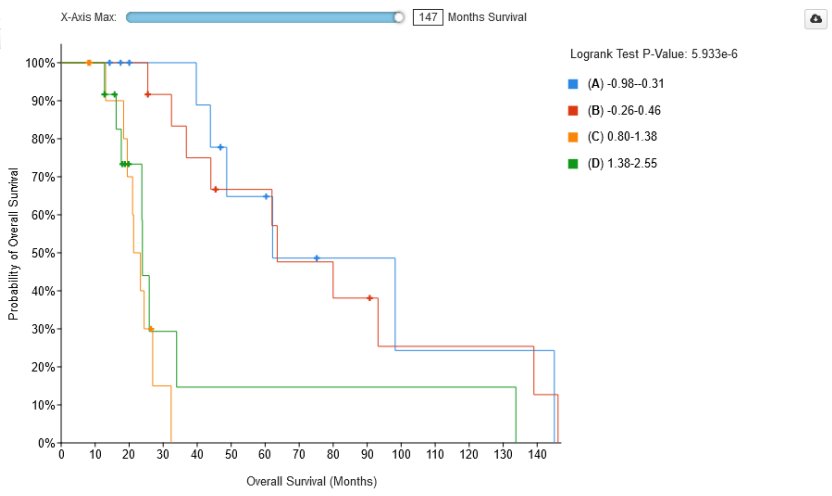
	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
(A) -2.19--0.54	**74**	**18**	**94.52 (78.21 - NA)**
(B) -0.53--0.00	**75**	**18**	**79.99 (62.17 - NA)**
(C) 0.00-0.97	**75**	**22**	**73.48 (62.00 - NA)**
(D) 0.99-3.06	**75**	**39**	**25.91 (21.30 - 54.77)**

Radiation



	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
(A) -2.19--0.70	**63**	**14**	**94.52 (78.21 - NA)**
(B) -0.69--0.01	**64**	**17**	**93.20 (63.55 - NA)**
(C) -0.00-0.94	**64**	**21**	**62.00 (40.83 - NA)**
(D) 1.00-3.06	**64**	**36**	**24.92 (21.30 - 33.96)**

TMZ

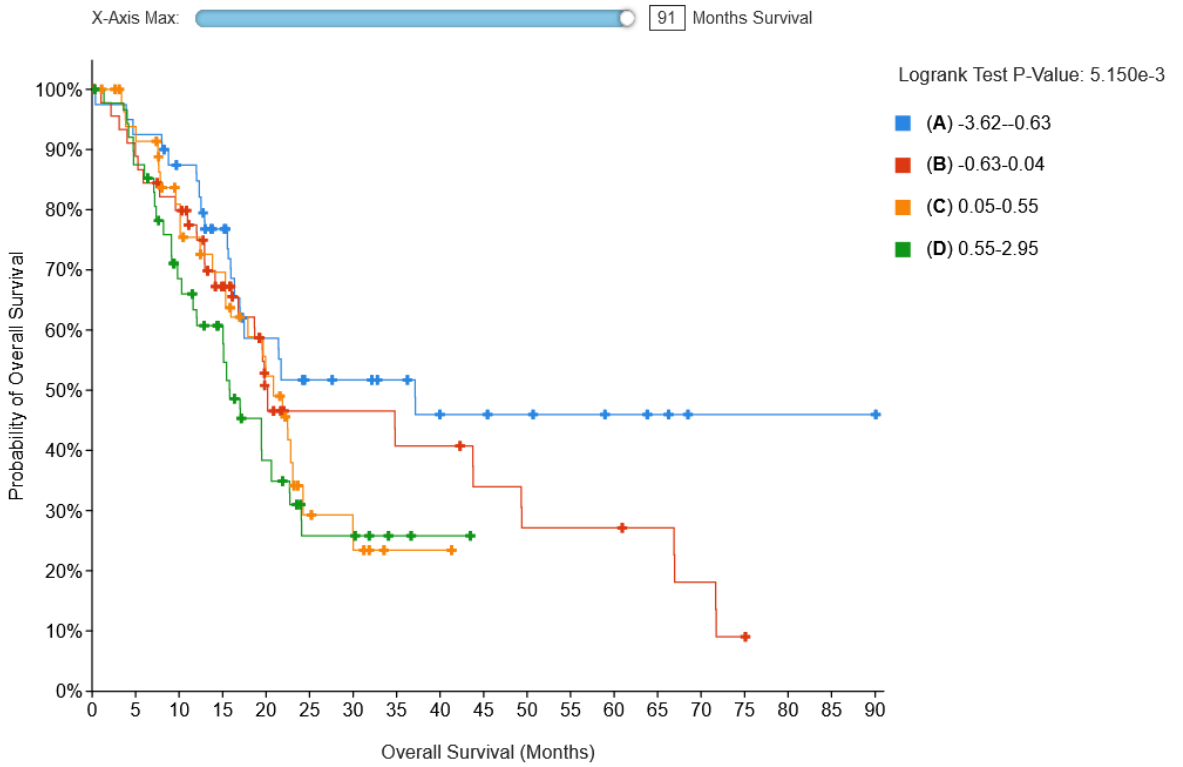


	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
(A) -0.98--0.31	**12**	**6**	**62.17 (48.69 - NA)**
(B) -0.26-0.46	**12**	**10**	**63.55 (44.02 - NA)**
(C) 0.80-1.38	**12**	**9**	**21.30 (19.46 - NA)**
(D) 1.38-2.55	**12**	**8**	**23.90 (23.74 - NA)**

Avastin

TGF-B2 IS NEGATIVE PROGNOSTIC INDICATOR FOR OS IN PDAC

- PDAC has worse OS with high TGF-B2. Suggesting that treatment with OT-101 should be effective
- No impact of TGF-B1 nor TGF-B3
- Again validating TGF-B2 as the target
- Note the >2X improvement in OS (15 mos with high TGF-B2 versus 37 mos with low TGF-B2)



	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
(A) -3.62--0.63	**82**	**35**	**37.12 (17.48 - NA)**
(B) -0.63-0.04	**96**	**49**	**20.17 (18.67 - 49.34)**
(C) 0.05-0.55	**87**	**48**	**20.84 (17.92 - 23.08)**
(D) 0.55-2.95	**90**	**53**	**15.81 (15.05 - 20.61)**

OT-101 FOR GBM

CED DELIVERY

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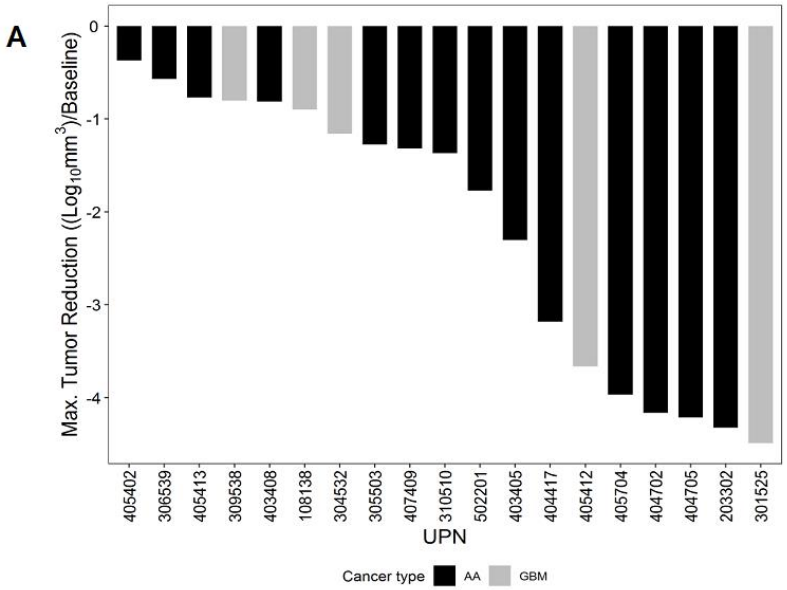
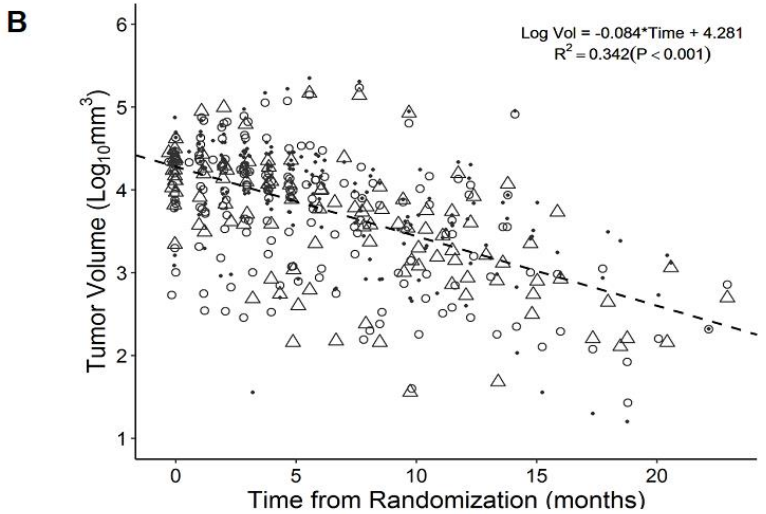
G004-PHASE 2B GBM TRIAL

- Title: A multi-national, multi-center, open-label, active-controlled, randomized parallel-group dose-finding study to evaluate the efficacy and safety of two doses of OT-101 in adult patients with recurrent high-grade glioma, administered intratumorally as continuous high-flow microperfusion over a 7-day period every other week.
- Pts#: N = 145. OT-101 10 µM, N = 40; OT-101 80 µM, N = 49; Control, N = 45
- Single agent activity on par with TMZ- the most active agent against glioblastoma.
- Objective responses were observed among the 87 evaluable patients treated with OT-101:
- Best Objective Responses were: 5 CR (5.9%), 14 PR (16.5%), 28 SD (31.8%), and 40 PD (45.9%)
- Confirmed Best Objective Responses were: 4 CR (4.7%), 12 PR (12.9%), 31 SD (36.5%), and 40 PD (45.9%)
- Best Objective Responses were confirmed with deeper tumor reduction.
- Best Objective Responses were confirmed with improved OS: CR: >66mos, PR: 36.9 mos, SD: 14.7 mos, and PD: 5.5mos.





OT-101 GLIOMA TRIALS : G001-G005

Parameter	Study No.					
	G001	G002	G003	G004	G005	
Aim	Determination of the MTD/MTC, safety, and efficacy			Evaluation of efficacy and safety compared to standard chemotherapy	Evaluation of efficacy and safety compared to standard chemotherapy	
Clinical phase	I/II			IIb	III	
Study design	Randomized, multicenter, open-label, dose escalation			Randomized, active-controlled, open-label, parallel-group, multi-national, multicenter,	Randomized, active-controlled, open-label, parallel-group, multi-national, multicenter	
Patient population	Adult patients with either recurrent/refractory AA or recurrent/refractory GBM, i.e. patients previously treated with standard therapy (surgery, radiotherapy, and/or chemotherapy)			Same as G001 to G003, but patients with no more than 2 previous (radio) chemotherapies	Same as G004	
Administration of trabedersen	Intratumorally, using CED via 1 single intratumoral catheter			Same as G001 to G003	Same as G001 to G004	
Dose of trabedersen	2.5, 10, 40, and 80 µM at 4 µL/min for 4 d	2.5 µM at 4 µL/min for 4 d	80 µM at 8 µL/min for 4 d	10 µM at 4 µL/min for 7 d	10 µM at 4 µL/min for 7d	
	80 µM at 8 µL/min for 4 d	80 µM at 8 µL/min for 4 d	80 µM at 8 µL/min for 7 d	80 µM at 4 µL/min for 7 d		
Duration of treatment per treatment cycle	4 d	4 d	4 d or 7 d [a]	7 d [a]	7d[a]	
No. of treatment cycles	1	1	At least 2 and up to 10	At least 4 and up to 11 [b]	Up to 11	
No. of patients Enrolled (AA/GBM) Safety (AA/GBM) Efficacy (AA/GBM)	(6 [c]/13) (6/13) (5/11)	(2 [d]/1 [e]) (2/0) (2/0)	(1 [f]/6) (1/6) (1/5)	10 µM 80 µM Control [g] (14/34) (16/34) (12/35) (12/29) (15/34) (12/33) (12/28) (15/34) (12/33)	10 µM (14/0) (12/1) (13/0)	Control (10/1) (12/0) (9/1)

OT-101 FOR PDAC

IV DELIVERY

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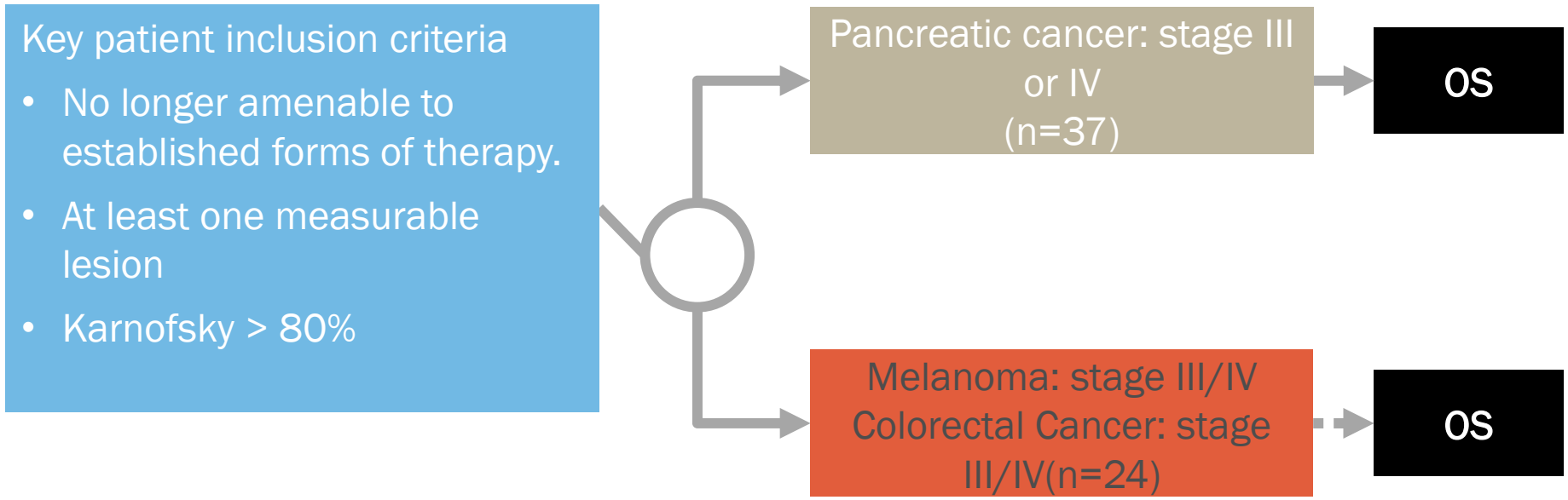
INTRODUCTION

- 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)

- 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

DOSING AND SAMPLING

Table 1. Dosing Scheme

Schedule	Dose (mg/m²/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.

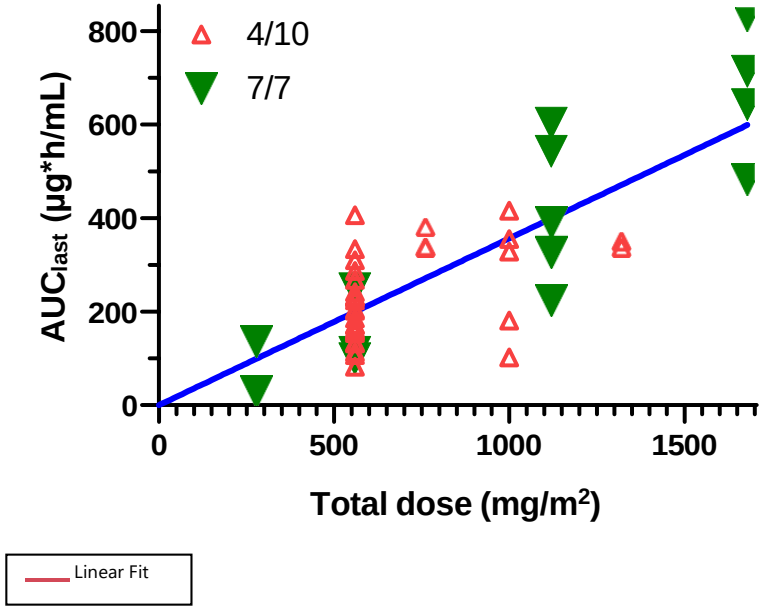
Table 2. Blood sampling schedule

	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.

PK/PD ANALYSIS

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

P001- PHASE 1/2 PDAC & MELANOMA TRIAL

- Title: An Open-Label, Multicenter Dose-escalation Study to Evaluate the Safety and Tolerability of OT-101 (TGF-β2-specific Phosphorothioate Antisense Oligodeoxynucleotide), Administered Intravenously in Adult Patients with Advanced Tumors Known to Overproduce TGF-β2, Who are Not or No Longer Amenable to Established Therapies.
- Pts#: 61 (37 with pancreatic cancer; 19 with malignant melanoma; 5 with colorectal cancer)
- Primary Objective: To determine the maximum tolerated dose (MTD) and the dose limiting toxicities (DLTs) of two cycles of trabedersen administered intravenously (i.v.) for 7 days or for 4 days every other week.
- OT-101 was well tolerated. MTD not reached and Efficacy Demonstrated
- Efficacy was on par with Onivyde- recently approved against PDAC.

End-point	Onivyde + 5-FU/LV [5]	Onivyde [5]	5-FU/LV [5]	OT-101	Su et al. DC	Su et al. PD	OT-101 DC	OT-101 PD	OT-101 High AUC	OT-101 Low AUC
	(n = 117)	(n = 151)	(n=149)	**(n = 36)**	(n = 19)	(n = 25)	**(n = 18)**	(n = 14)	**(n = 19)**	(n = 13)
OS, mos	6.2	4.9	4.2	**5.2**	8.4	3.2	**9.3**	2.9	**8.9**	3.7

PIPELINE HIGHLIGHTS

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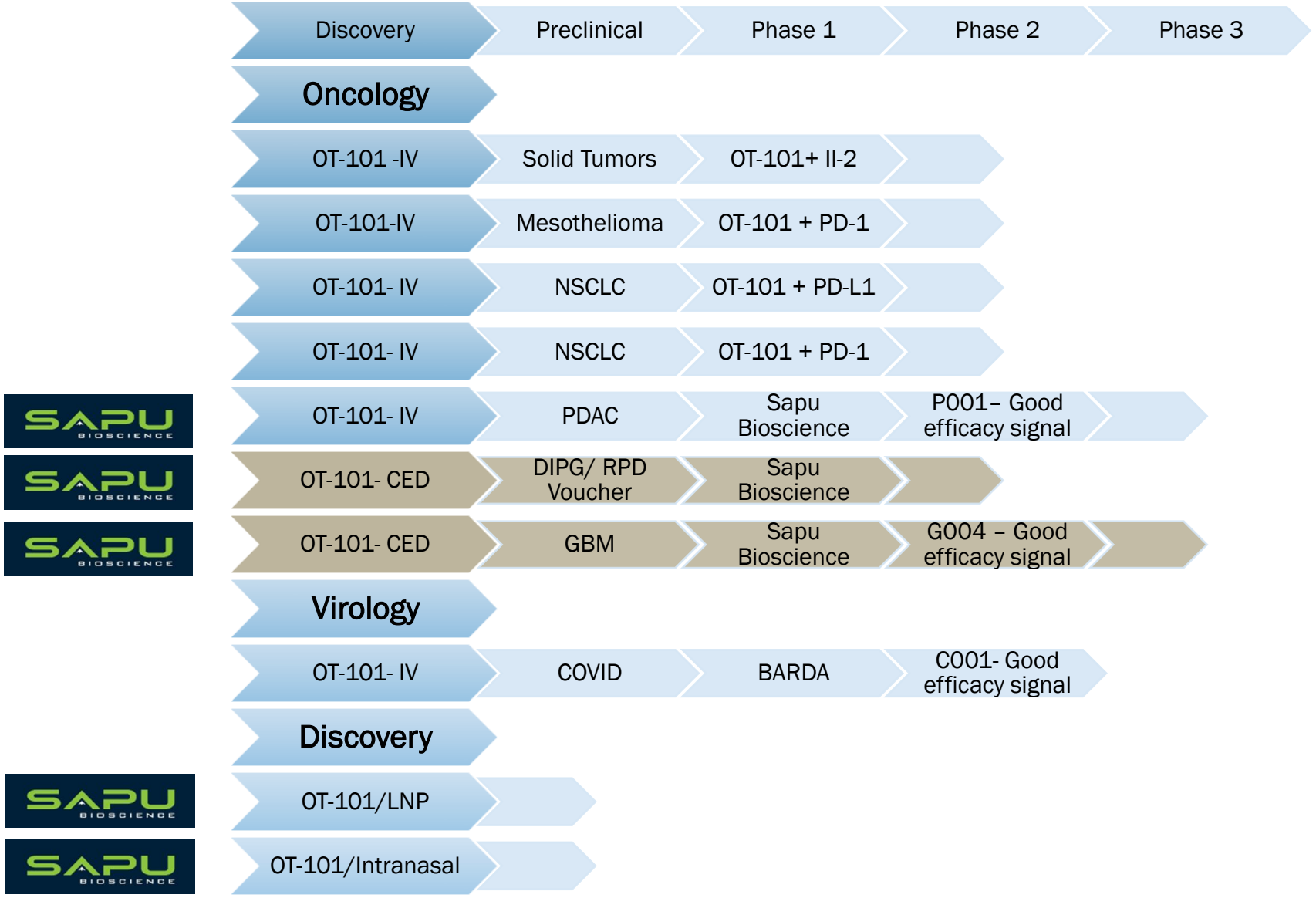
PIPELINE



- Strong pipeline in collaboration with global pharmas and US BARDA
- Seeking local collaborators
- Immune Checkpoint Inhibitor Program- collaborative efforts ongoing with global pharma including Merck, Genentech, Astra Zenica, and Clinigen
- DIPG & PDAC - Global pivotal registration trial in planning phase.
- COVID- Collaboration with BARDA.

NANOMEDICINE PLATFORM

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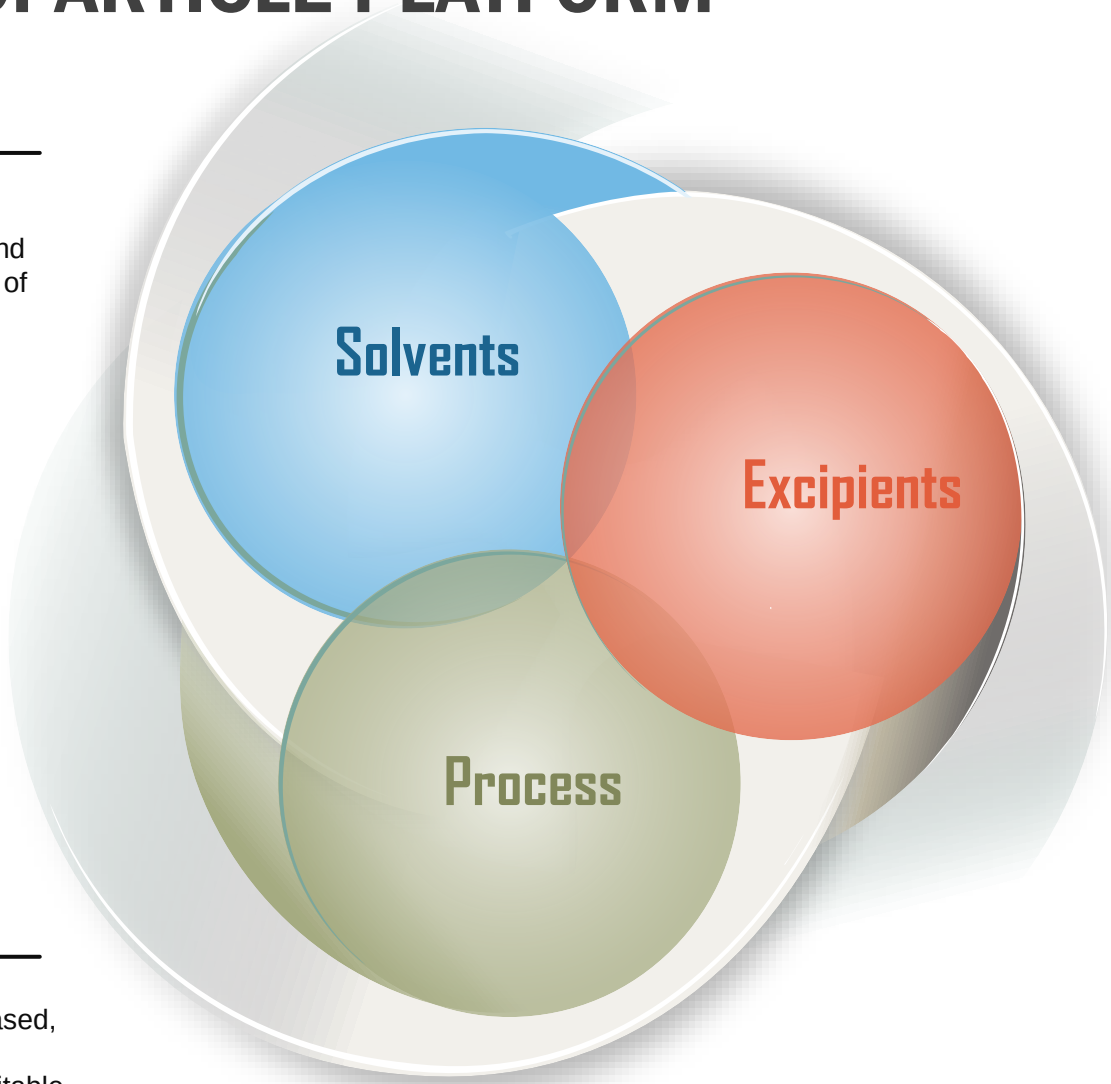
AI GUIDED NANOPARTICLE PLATFORM

Solvent

- Proprietary Ternary systems to achieve stability of the API and facilitating formation of nanoparticles



Excipient

- Proprietary excipients to stabilize the nanoparticles during manufacturing – at least 24 hrs at room temperature to allow for sterile processing

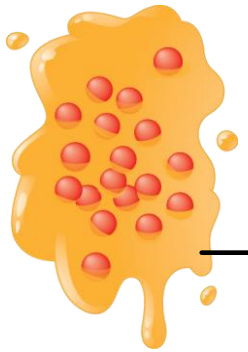
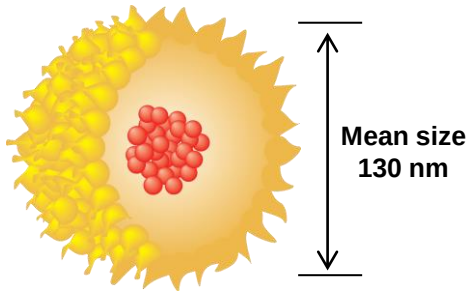
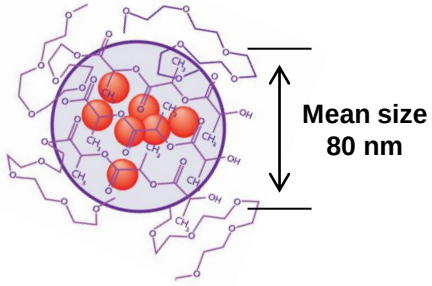
Process

- Multiple processes including albumin based, polymer based, lipid based to achieve suitable nanoparticle characteristics

Bring us your molecule

- We will be your partner from concept to clinic to marketing
- We will invest if it is aligned with our pipeline

END PRODUCT- SUPERIOR CLINICAL PERFORMANCE

Generation		Formulation	Maximum Tolerated Dose (MTD)
1st	**Taxol®** paclitaxel	 **Cremophor EL** excipient**:** Polyoxyethylated castor oil - Adverse reactions, including anaphylactic shock	**175 mg/m²**
			↓ *+ 48% dose increase*
2nd	**Abraxane®** *nab*-paclitaxel	 **Biological** polymer: Donor-derived human serum albumin (HSA) - Tedious reconstitution / foaming - Human donor components - Ambient temp storage required	**260 mg/m²**
			↓ *+ 15-30% dose increase*
3rd	**Cynviloq™** paclitaxel polymeric micelle	 **Chemical** polymer: Poly-lactide and polyethylene glycol diblock copolymer - Same MOA as Abraxane® - Free of biological ingredients - Simple handling and preparation	**≥ 300 mg/m²**

THANK YOU

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