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Vuong Trieu PhD/ CEO of Oncotelic Therapeutics and Sapu Bioscience

"TRANSFORMING GROWTH FACTOR BETA 2 IN AGING, CANCER, LUPUS, AND IMMUNO-ONCOLOGY: A CONVERGENCE OF DISEASE PATHWAYS AND THERAPEUTIC POTENTIAL"

THE 5TH SYMPOSIUM ON WORLD CANCER RESEARCH (SWCR 2025). MAR 24TH-26TH, 2025; KYOTO, JAPAN

SWCR

Oncotelic is Focusing on Antisense (ASO) as Next Generation Drugs

Attributes	Small Molecules	mAb	Antisense
Inception	1850s to present	1920s to present	**1990s to present**
Size	200-500	>150,000	**5,000 to 7,000**
Drug Discovery	Random screening	Focused screening	**Rationally designed**
Success Rate	Low-~5%	Moderate-~50%	**High-~90%**
Predictable PK	No	Yes	**Yes**
On Target Safety	Target Specific	Target Specific	**Target Specific**
Off Target Safety	Nonspecific Targets	Cross Reactivities	**Sequence Homology**
Risk Profile	High >50%	Moderate =< 40%	**Low ~1%**
Speed of Development	15-20 years	10-15 years	**5-10 yrs**
Manufacturing Cost	Low	High	**Low**
Amenable to Individual Therapy	No	No	**Yes**

ASO is drug platform of the future because time gene identification to treatment can be a short as 1 year.

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Approved oligonucleotide drugs (between 1998 and 2024)

ASO 1998
CMV Retinitis

Aptamer 2004
Age-Related Macular Degeneration (AMD)

ASO 2013
Familial Hypercholesterolemia

SSO 2016 **SSO 2019**
Duchenne Muscular Dystrophy

SSO 2016
Spinal Muscular Atrophy

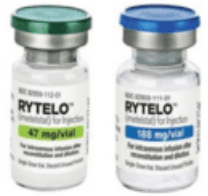
2023

Qalsody: ALS

Izervay: Geographic Atrophy

2024

Rytelo: MDS



Tryngolza: Familial chylomicronemia syndrome

Vaccine Adjuvant 2017
HBV

siRNA 2018
TTR Polyneuropathy

ASO 2018
TTR Polyneuropathy

ASO 2019 EU
Familial Chylomicronemia Syndrome

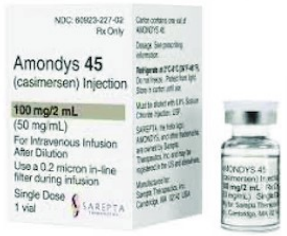
siRNA 2019
AHP Porphyria

siRNA 2020
Primary Hyperoxaluria type 1

Rivfloza: primary hyperoxaluria

WAINUA: amyloid polyneuropathy

SSO 2020
Duchenne Muscular Dystrophy



SSO 2021

siRNA 2021
LDL-C reduction "siRNA statin"

siRNA 2022
TTR Polyneuropathy

mRNAs 2021/2022
Covid-19 Vaccines

Nucleic Acids Res, Volume 51, Issue 6, 11 April 2023, Pages 2529–2573, https://doi.org/10.1093/nar/gkad067

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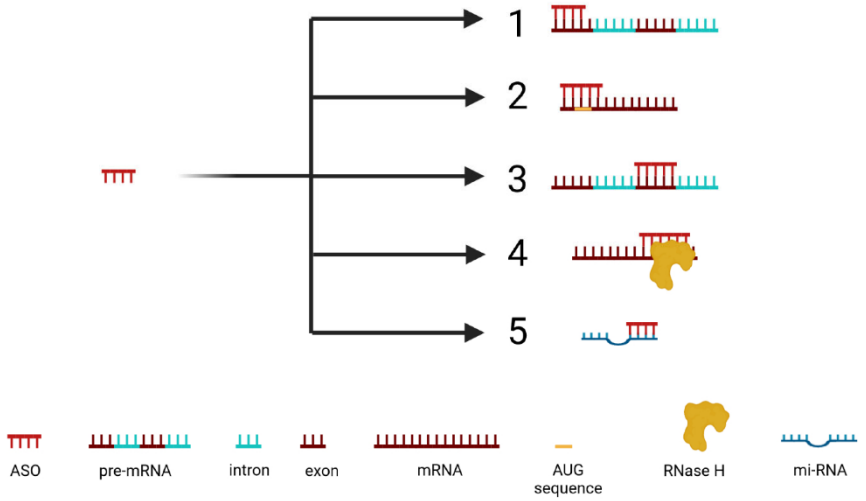
TGFB2 ASO

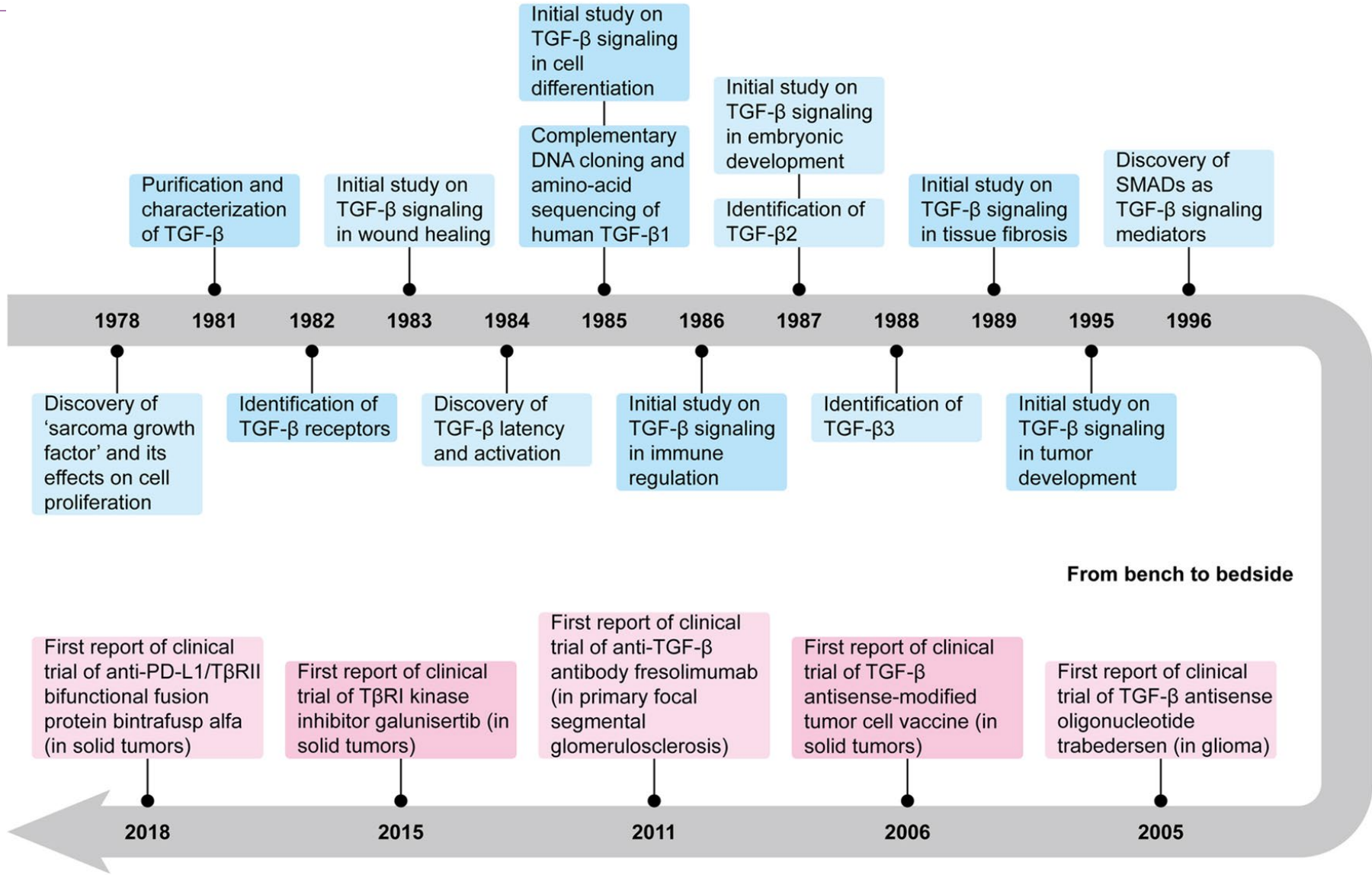
OT-101



Mechanisms of ASOs. 1—inhibition of 5′ cap formation, 2—steric blocking of translation, 3—alteration of splicing, 4—activation of RNase H, and 5—inhibition of miRNA. Created with BioRender.com(accessed on 16 August 2024). Çakan, E.; Lara, O.D.; Szymanowska, A.; Bayraktar, E.; Chavez-Reyes, A.; Lopez-Berestein, G.; Amero, P.; Rodriguez-Aguayo, C. Therapeutic Antisense Oligonucleotides in Oncology: From Bench to Bedside. Cancers 2024, 16, 2940. https://doi.org/10.3390/cancers16172940

TGF-beta has a long history

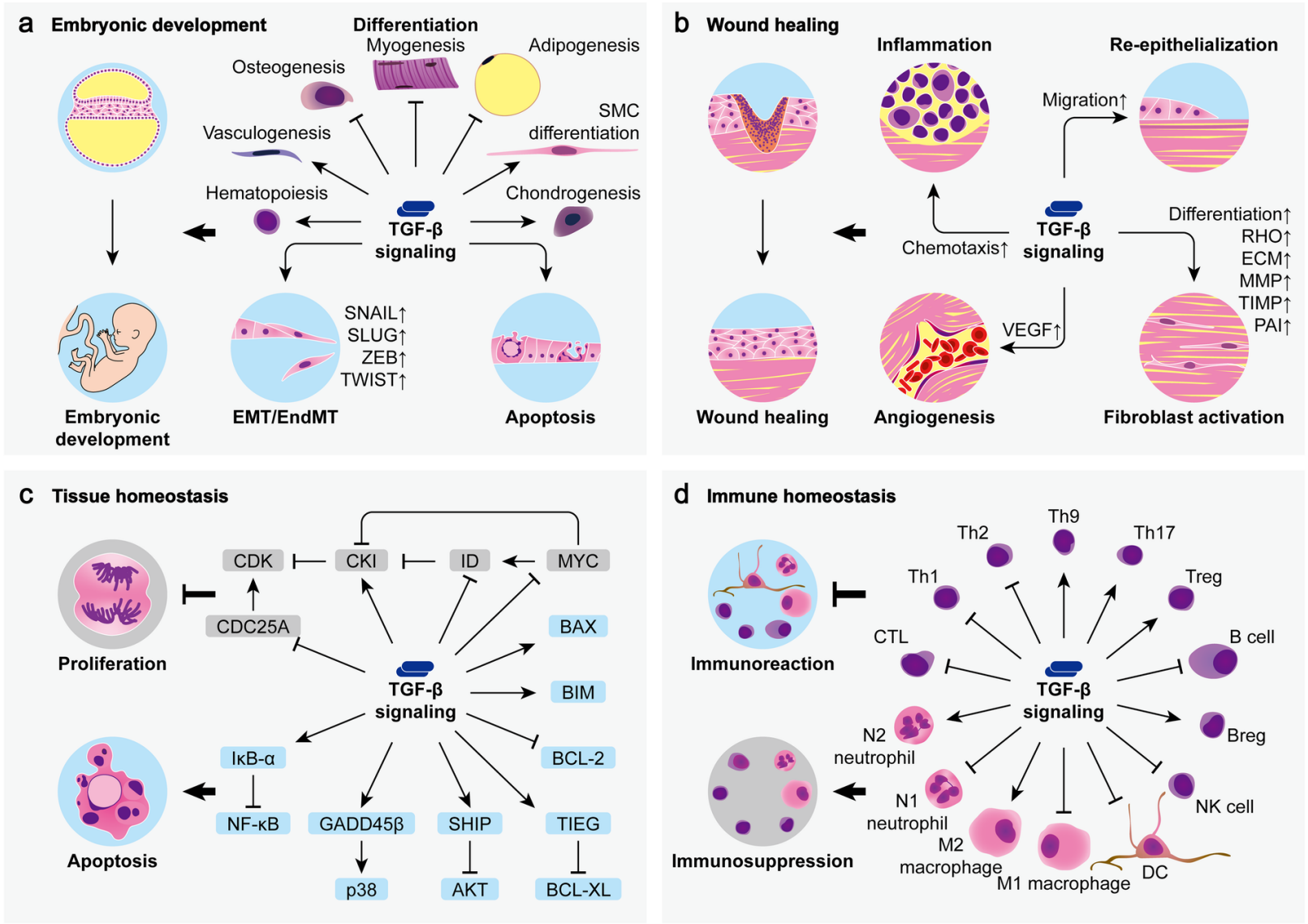
Deng, Z., Fan, T., Xiao, C. et al. TGF-β signaling in health, disease, and therapeutics. Sig Transduct Target Ther 9, 61 (2024). https://doi.org/10.1038/s41392-024-01764-w



TGF-beta is involved in many biological processes

Deng, Z., Fan, T., Xiao, C. et al. TGF-β signaling in health, disease, and therapeutics. Sig Transduct Target Ther 9, 61 (2024). https://doi.org/10.1038/s41392-024-01764-w

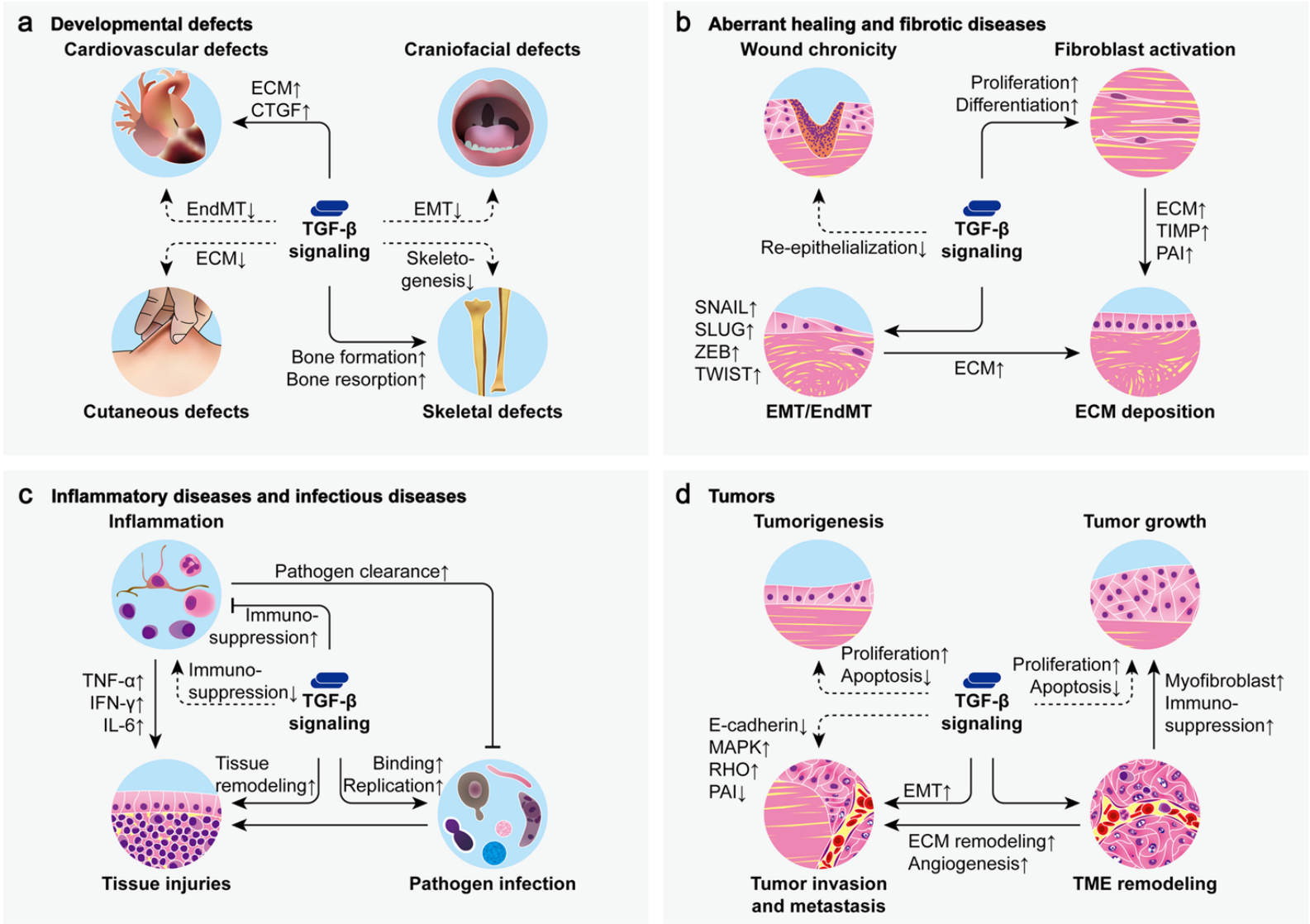
TGF-β signaling in health. TGF-β signaling plays a critical role in physiological conditions. a During embryonic development, TGF-β regulates cell differentiation, epithelial/endothelial-mesenchymal transition (EMT/EndMT), and apoptosis to ensure proper histogenesis and organogenesis. b TGF-β promotes wound healing by participating in inflammation, re-epithelialization, angiogenesis, and fibroblast activation. c TGF-β is indispensable for tissue homeostasis as it generally suppresses cell proliferation and induces cell apoptosis through various mechanisms. d TGF-β functions to suppress the activity of multiple immunocompetent cells while inducing the phenotypes of several immune immunosuppressive cells to maintain immune homeostasis.



TGF-beta is involved in many diseases

Deng, Z., Fan, T., Xiao, C. et al. TGF-β signaling in health, disease, and therapeutics. Sig Transduct Target Ther 9, 61 (2024). https://doi.org/10.1038/s41392-024-01764-w.

TGF-β signaling in disease. Dysfunctional TGF-β signaling is involved in numerous pathological processes. a Mutations that lead to decreased or increased TGF-β signaling can cause various developmental defects. b Deficient TGF-β signaling contributes to wound chronicity while excess TGF-β signaling leads to wound scarring and tissue fibrosis by stimulating ECM deposition through fibroblast activation and EMT/EndMT. c Dysfunctional TGF-β signaling exacerbates tissue injuries in inflammatory diseases and infectious diseases by promoting inflammation, pathogen infection, and tissue remodeling. d Aberrant TGF-β signaling is implicated in all aspects of tumor development including tumorigenesis, tumor growth, tumor invasion, tumor metastasis, as well as tumor microenvironment (TME) remodeling.



Ongoing early clinical development of TGF-β-targeting therapies

Targets	Strategies	Treatments	Diseases	Clinical trials
Latent TGF-β complex	Monoclonal antibody	SRK-181	Solid tumors	NCT04291079 (phase 1)
GARP	Monoclonal antibody	HLX60	Solid tumors and lymphoma	NCT05483530 (phase 1) and NCT05606380 (phase 1)
TGF-β	Monoclonal antibody	SAR439459	Multiple myeloma and osteogenesis imperfecta	NCT04643002 (phase 1/2) and NCT05231668 (phase 1)
TβR	Dominant-negative TβR	TGF-β-resistant cytotoxic T lymphocytes	Lymphoma	NCT00368082 (phase 1)
TβRI	Kinase inhibitor	Galunisertib/ Development of galunisertib by Eli Lilly was discontinued in January 2020. Galunisertib had been in a trial for both lung and liver cancers, including a combo test starting in 2015 with Bristol-Myers Squibb's Opdivo. "wound down and terminated as part of our effort to focus the pipeline on higher conviction programs with the greatest potential for patients and pipeline assessment is ongoing." https://www.fiercebiotech.com/biotech/eli-lilly-cuts-three-cancer-drugs-amid-q4-clear-out	Nasopharyngeal carcinoma, prostate cancer, colorectal cancer, and glioma	NCT04605562 (phase 2), NCT02452008 (phase 2), NCT02688712 (phase 2), NCT01582269 (phase 2), NCT05700656 (phase 1/2), and NCT01682187 (phase 1)
TβRI	Kinase inhibitor	Vactosertib/ Vactosertib pharmacokinetics were dose-proportional within tested dose range with negligible accumulation when administered once daily for five days. Considering the short half-life, it seems necessary to administer vactosertib twice- or thrice-daily to maintain its concentrations above minimum effective level over a dosing interval.	Solid tumors and myeloproliferative neoplasm	NCT04515979 (phase 2), NCT04064190 (phase 2), NCT05436990 (phase 2), NCT04103645 (phase 2), NCT05588648 (phase 1/2), NCT03802084 (phase 1/2), etc.
TβRI	Kinase inhibitor	LY3200882	Solid tumors	NCT02937272 (phase 1)

Ongoing Phase 3 of TGF-β-targeting therapies

Targets	Strategies	Treatments	Diseases	Clinical trials
TGF-β2 mRNA	Antisense oligonucleotide	OT-101 - TGFB2	Pancreatic ductal adenocarcinoma	NCT06079346 (phase 3) and NCT04862767 (phase 1)
TGF-β	Monoclonal antibody	NIS793- TGFB1,2,3	Pancreatic cancer, colorectal cancer, and MDS	NCT04935359 (phase 3), NCT04390763 (phase 2), NCT04952753 (phase 2), NCT05417386 (phase 1), and NCT04810611 (phase 1)
TGF-β	Ligand trap	Bintrafusp alfa- TGFB1	Solid tumors	NCT05061823 (phase 3), NCT03436563 (phase 2), NCT04396886 (phase 2), NCT05005429 (phase 2), NCT04708470 (phase 1/2), NCT04574583 (phase 1/2), etc.

- Based on a benefit-risk assessment, Novartis discontinued the NIS793 program in metastatic pancreatic ductal adenocarcinoma. https://endpts.com/novartis-cuts-tgfs-antibody-licensed-from-xoma-ends-phii-studies/. More patients died of pancreatic cancer, the indication being studied, in the NIS793 arm of the study than in the comparator arm. No specific pattern of adverse events was identified that would explain the increased number of deaths, additionally there was no suggestion of any of the secondary efficacy endpoints being met.
- After two years and multiple trial failures, Merck KGaA, Darmstadt, Germany and GlaxoSmithKline have terminated a nearly $4 billion development agreement that centered on the experimental immunotherapy drug bintrafusp alfa. Phase III was terminated as the Independent Data and Safety Monitoring Board determined the study was not likely to meet its primary endpoint of progression free survival.
- OT-101 phase 3 is still ongoing. A case of TGFB2 specific inhibition

OT-101 Summary

- Novel antisense oligodeoxynucleotides (ODNs) - for the treatment of patients with pancreatic cancer, malignant melanoma, colorectal cancer, high-grade glioma (HGG), and other malignancies overexpressing transforming growth factor β2 (TGF-β2).
- A single-stranded phosphorothioate antisense oligodeoxynucleotide (18-mer) that directly targets human TGF-β2 messenger ribonucleic acid mRNA and indirectly targets TGF-β1.
- Treated more than 200 patients in 7 clinical trials - 6 oncology clinical trials (Glioblastoma: 3 Phase 1 trials, 1 Phase 2 trials; Anaplastic Astrocytoma: 1 Phase 3 trial; Pancreatic cancer, melanoma and colorectal cancer: 1 Phase 1/2 clinical trial) and 1 COVID-19 clinical trial (Phase 2 clinical trial)
- Clinical efficacy demonstrated in patients with glioblastoma, pancreatic cancer, melanoma after treatment failure
- no known safety issues
- **Orphan drug designation for three tumor indications in the United States and the European Union / Rare pediatric disease designation for diffuse pontine glioma (DMG) in the United States (PRV).**
- Manufacturing process optimized for commercialization

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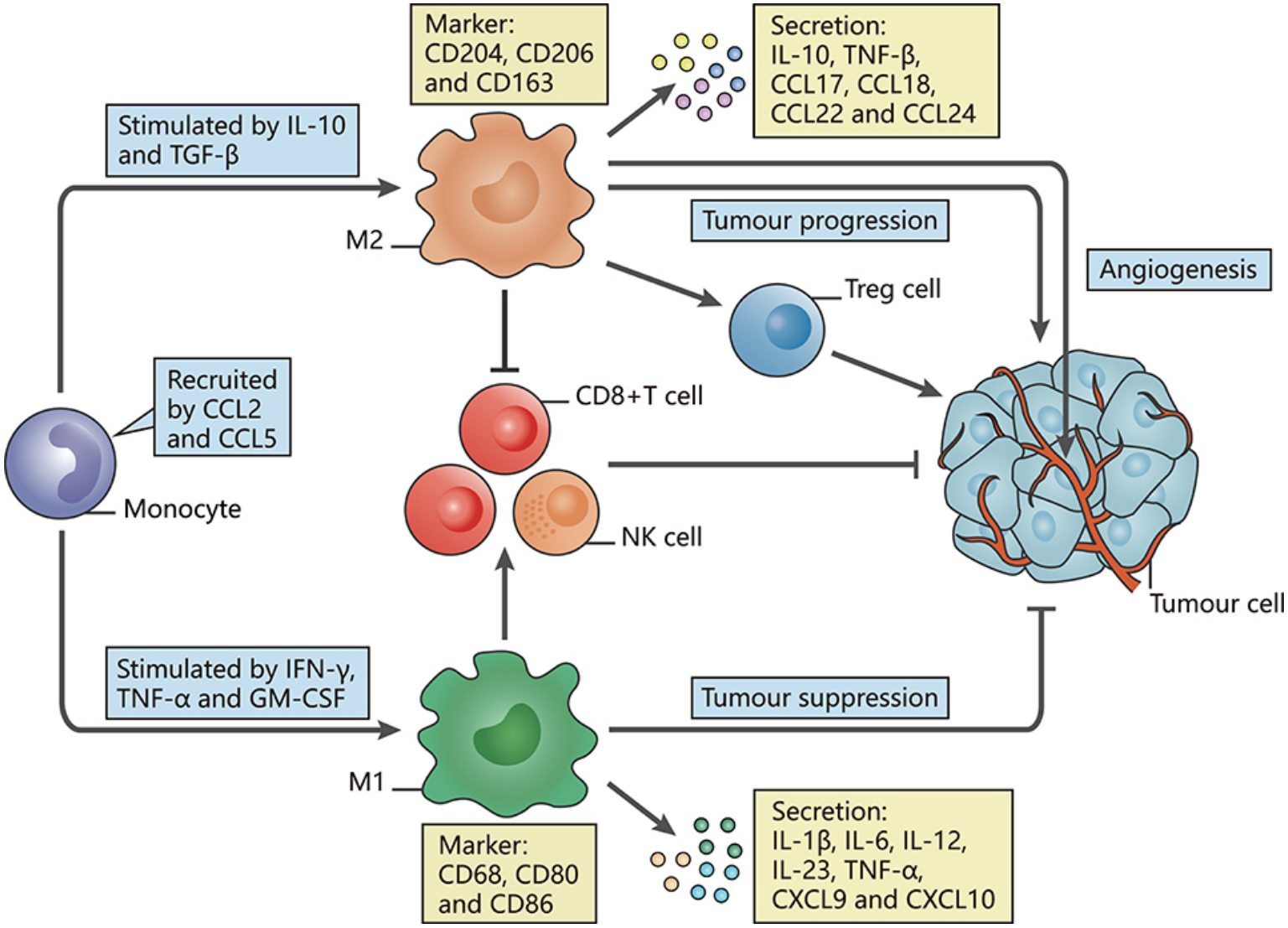
OT-101 is designed to direct M2- tumor promoting- to M1 – Tumor suppressing.

The polarization of Tumor-Associated Macrophages (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. Redefining Tumor-Associated Macrophage Subpopulations and Functions in the Tumor Microenvironment Kaiyue Wu



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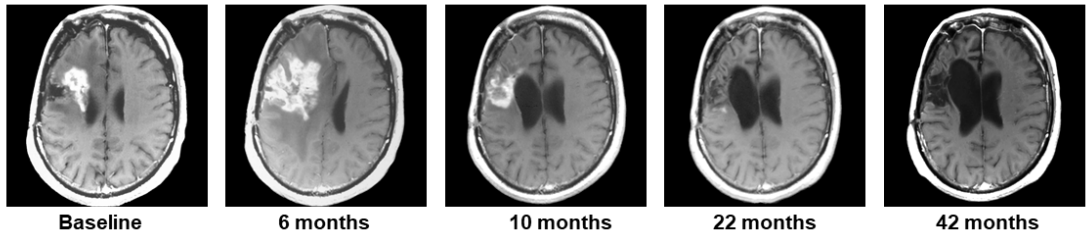
Intracranial delivery

OT-101 FOR GBM

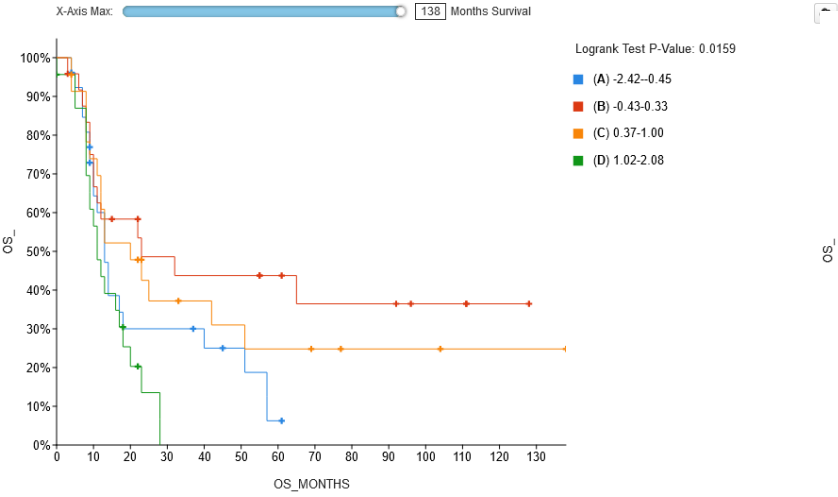
Patient #4-302
Male, 40 y, 11 cycles

Time after OT-101 treatment:



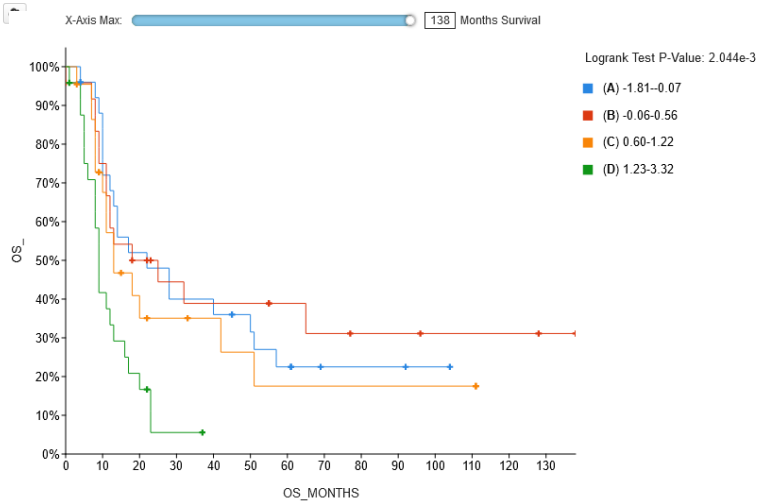
TGF-B2 is a negative prognostic factor for survival in pediatric DMG

- The Cancer Genome Atlas (TCGA) collected, characterized, and analyzed cancer samples from over 11,000 patients over a 12 year period. All data collected and processed by the program is currently available at the Genomic Data Commons (GDC). This is a joint effort between NCI and the National Human Genome Research Institute since 2006. All pediatric brainstem patients, excluding spinal cord patients, were analyzed. High TGF-β2 (and not β1 nor β3) is associated with poor overall survival (OS) across all quartiles.



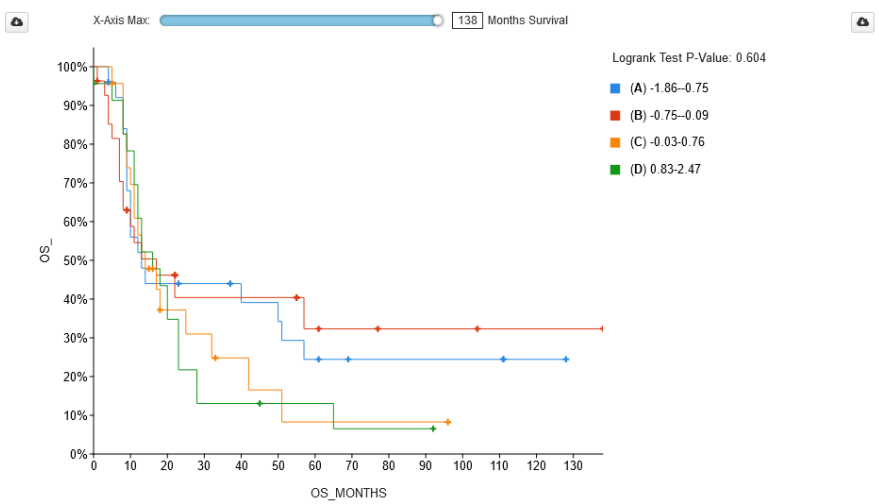
	Number of Cases, Total	Number of Events	Median Months OS_ (95% CI)
(A) -2.42--0.45	**26**	**21**	**13.00 (10.00 - 51.00)**
(B) -0.43-0.33	**24**	**14**	**23.00 (11.00 - NA)**
(C) 0.37-1.00	**23**	**16**	**20.00 (12.00 - NA)**
(D) 1.02-2.08	**23**	**21**	**11.00 (9.00 - 20.00)**

TGF-B1



	Number of Cases, Total	Number of Events	Median Months OS_ (95% CI)
(A) -1.81--0.07	**25**	**19**	**22.00 (13.00 - 57.00)**
(B) -0.06-0.56	**24**	**15**	**25.00 (12.00 - NA)**
(C) 0.60-1.22	**22**	**15**	**13.00 (11.00 - NA)**
(D) 1.23-3.32	**24**	**22**	**9.00 (8.00 - 16.00)**

TGF-B2

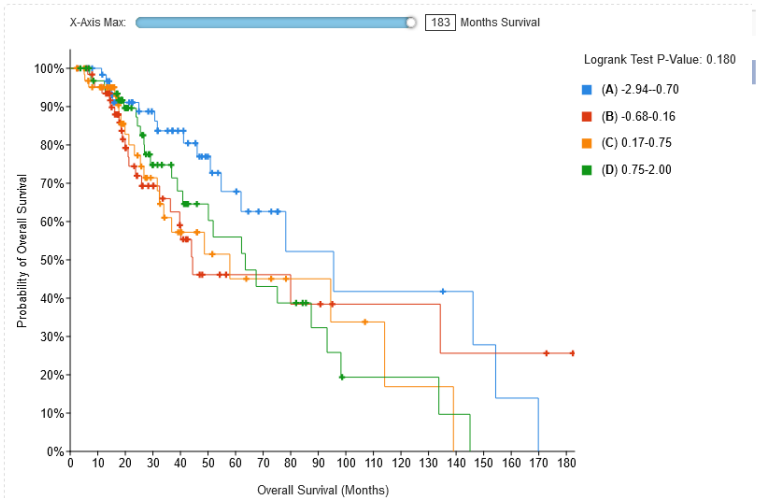


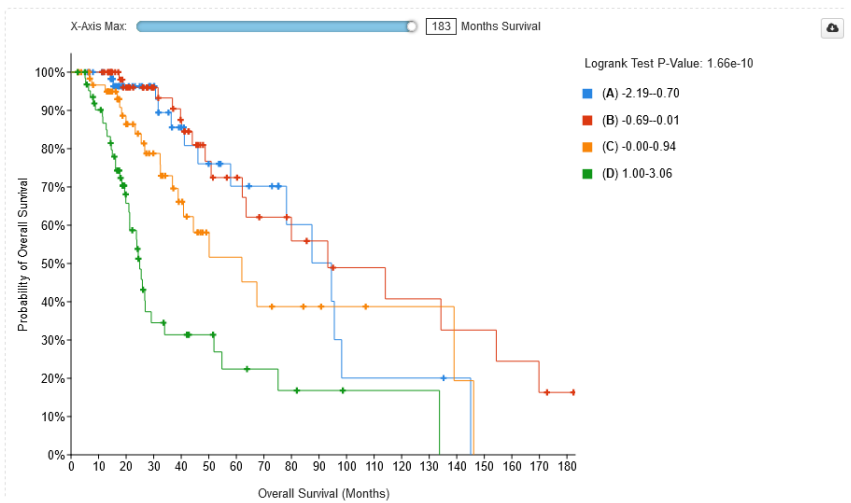
	Number of Cases, Total	Number of Events	Median Months OS_ (95% CI)
(A) -1.86--0.75	**25**	**18**	**13.00 (10.00 - NA)**
(B) -0.75--0.09	**27**	**16**	**17.00 (8.00 - NA)**
(C) -0.03-0.76	**23**	**18**	**14.00 (11.00 - 51.00)**
(D) 0.83-2.47	**23**	**21**	**16.00 (12.00 - 23.00)**

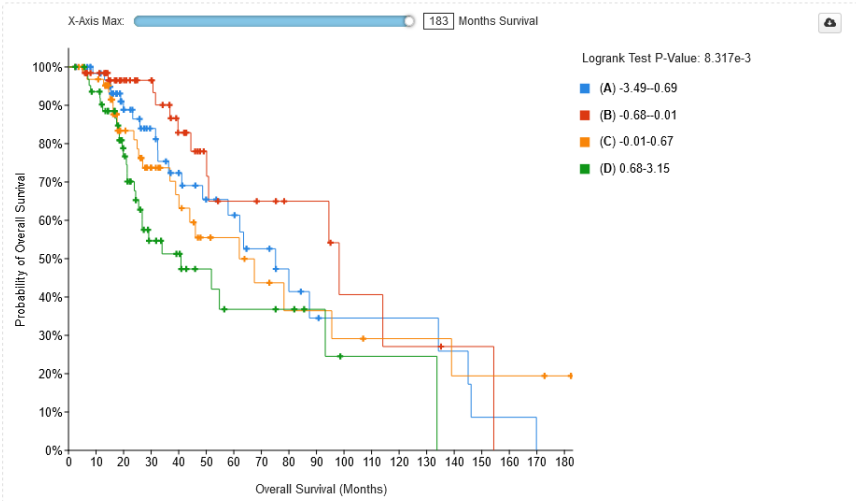
TGF-B3

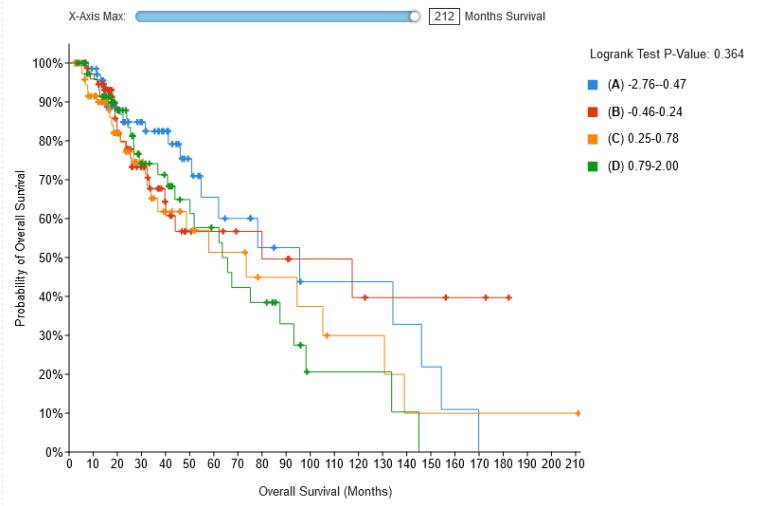
TGF-B2 is a Negative Prognostic Factor in Adult Gliomas + TMZ or Radiation

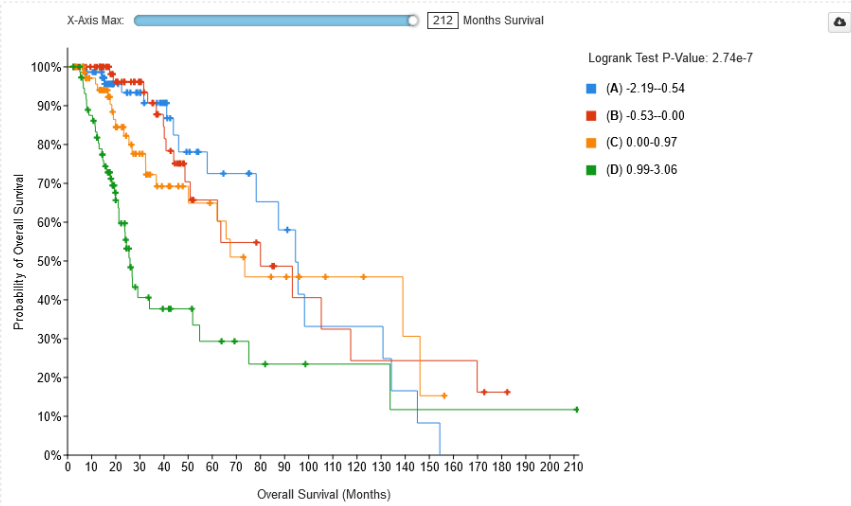
- Gliomas treated with TMZ or Radiation exhibited increasing OS with decreasing TGF-B2

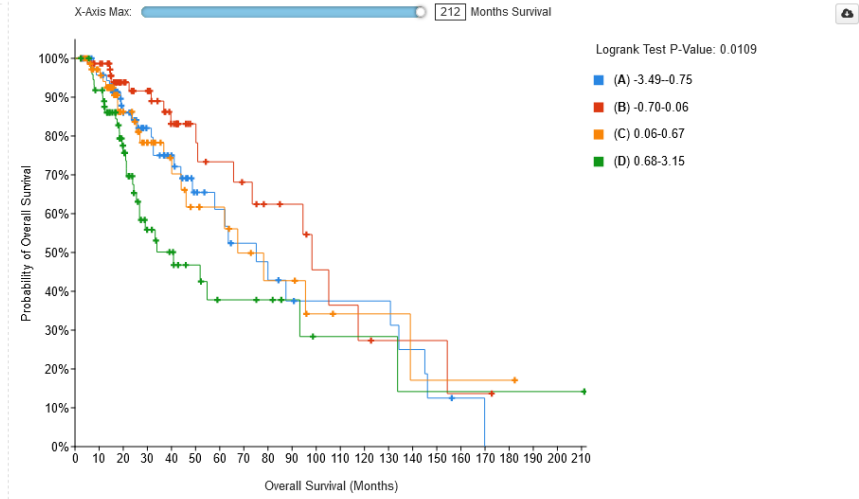












TGF-B1 TGF-B2 TGF-B3

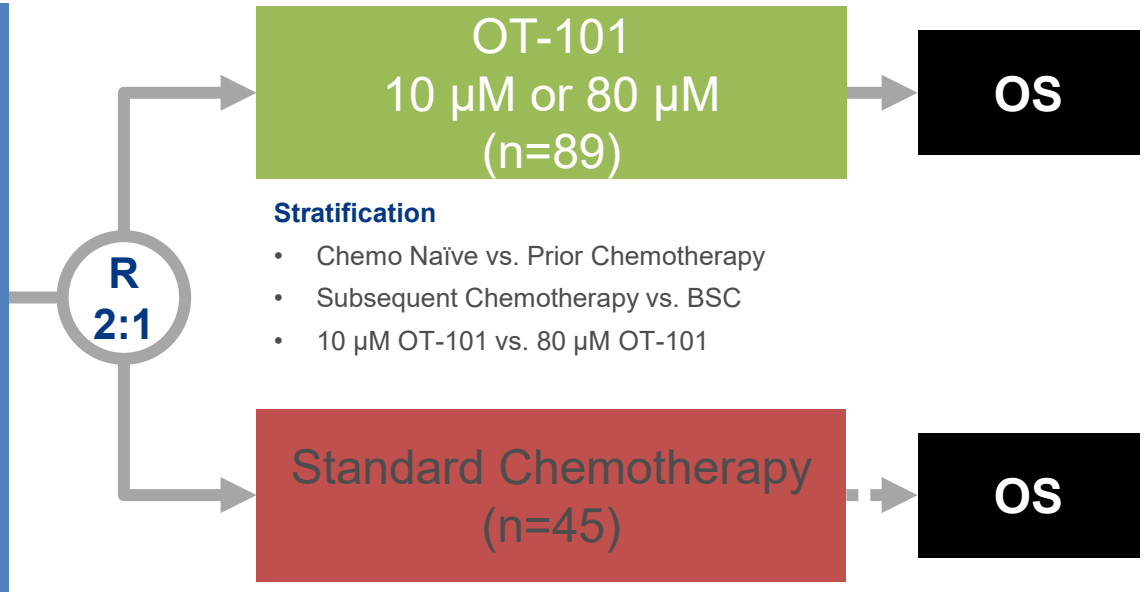
Phase IIb G004 trial of Trabedersen (OT-101) in High Grade Gliomas

Study Objectives

- To identify the target patient population most likely to benefit from OT101 for subsequent confirmatory Phase II/III registration trial

Key patient inclusion criteria

- Supratentorial tumor
- Lesion < 4.5 cm by MRI
- Lesion < 50 cm3 in volume
- Recurrent or refractory disease.
- Life expectancy > 3 mos
- Karnofsky > 70%



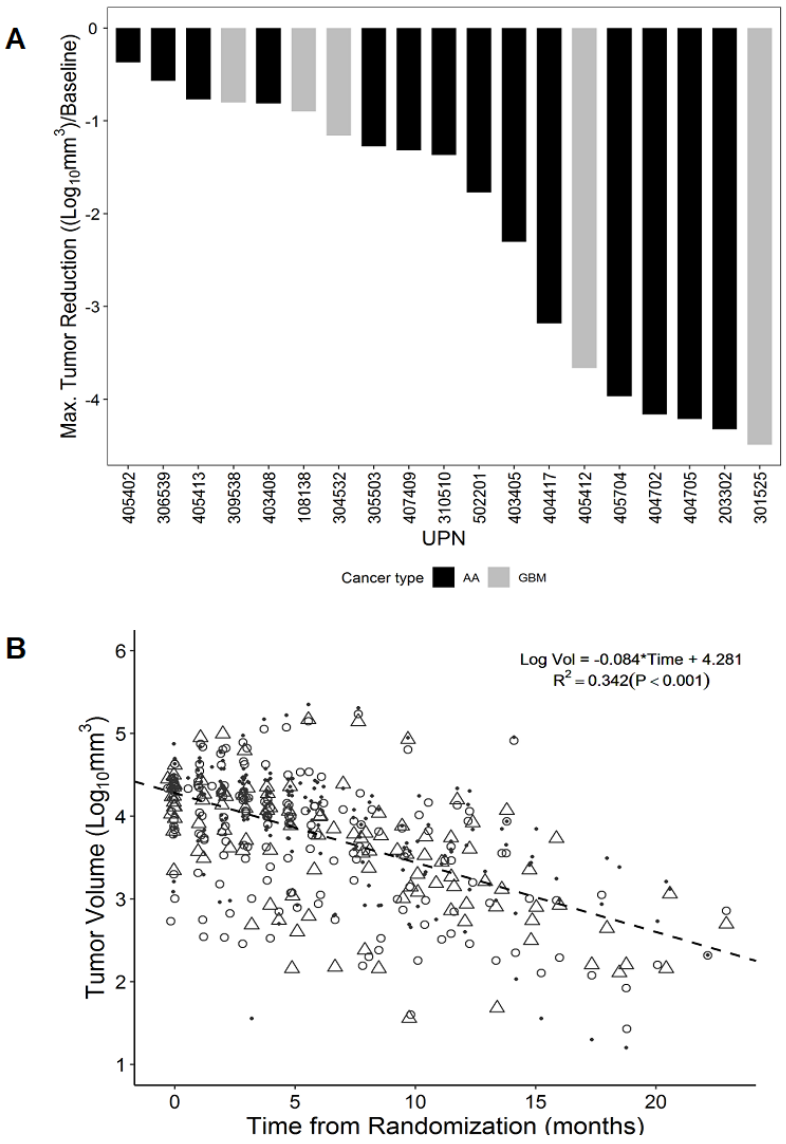
SECONDARY ENDPOINTS*

- OS and Myelosuppression

***The trial met its Primary Objective:** To evaluate the efficacy of two doses (10 µM and 80 µM) of AP 12009/ OT-101 on the tumor control rate (CR+PR+SD) at six months based on central MRI assessment in comparison to standard treatment (Temozolomide [TMZ] or combination of Procarbazine, CCNU [Lomustine], and Vincristine [PCV]).

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 dos of OT-101 in adult patients with recurrent high-grade glioma, administered intratumorally as continuous high-flow microperfusion over a 7-day period ever 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 glioblastom
- Objective responses were observed among the 87 evaluable patients treated wi OT-101:
- Best Objective Responses were: 5 CR (5.9%), 14 PR (16.5%), 28 SD (31.8%), and 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: 3 mos, SD: 14.7 mos, and PD: 5.5mos.

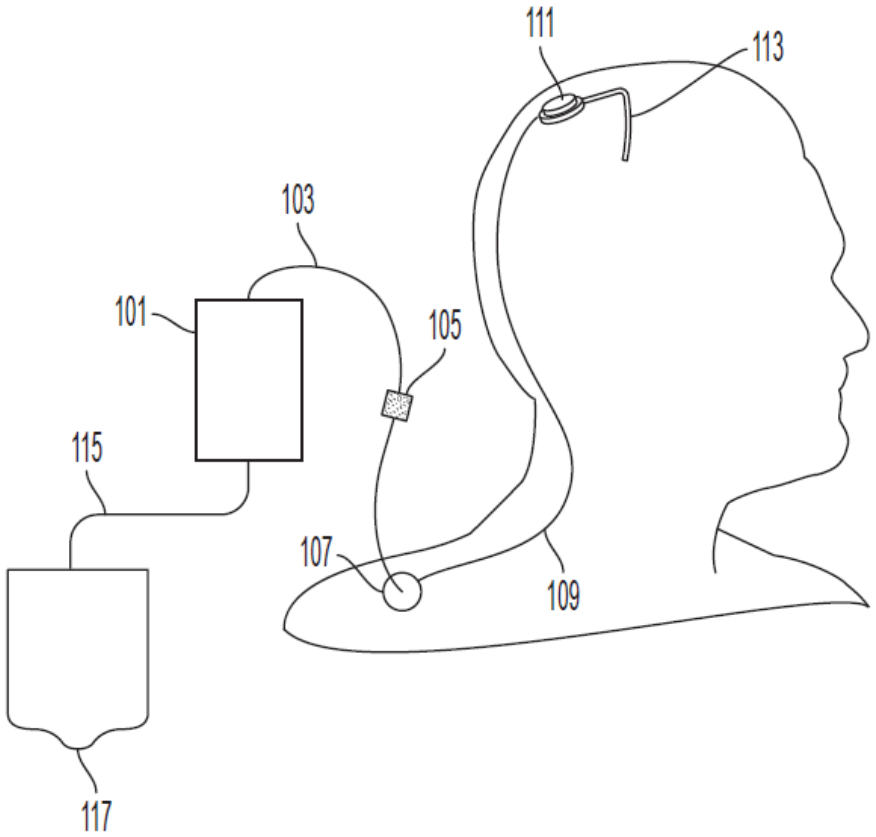


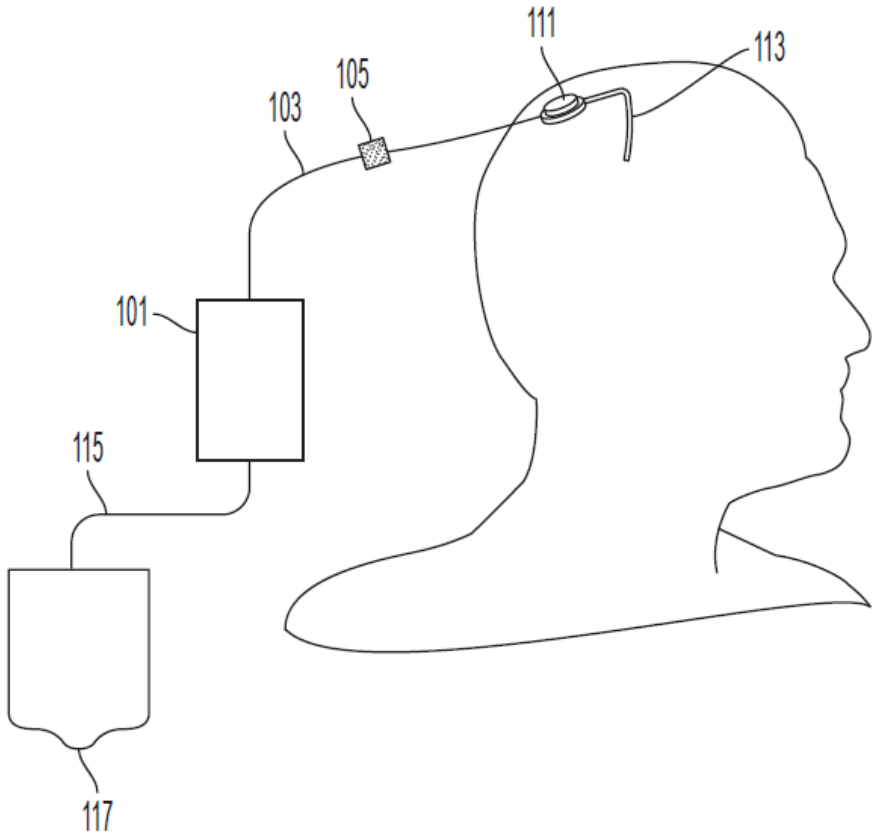
OT-101 Glioma Trials : G001-G005

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 (14/34) (12/29) (12/28)	80 µM (16/34) (15/34) (15/34)	Control [g] (12/35) (12/33) (12/33)	10 µM (14/0) (12/1) (13/0)	Control (10/1) (12/0) (9/1)

Central Nervous System Drug Delivery Technology

- Meant for either long infusion with inwelling tubing or short (4.5 hr) infusion with external tubing
- Neurological diseases including Alzheimer, Parkinson, Baten.
- Neurological cancers including DIPG, DMG, Leptomeningeal metastases
- Patent issued March 2025





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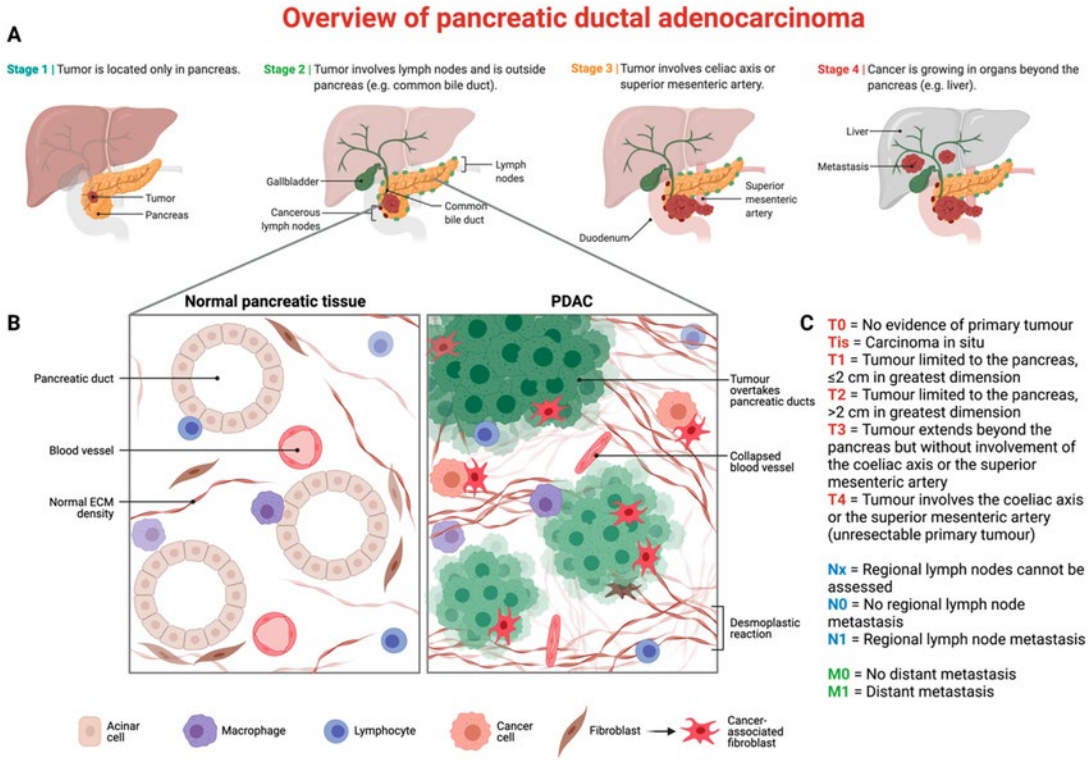


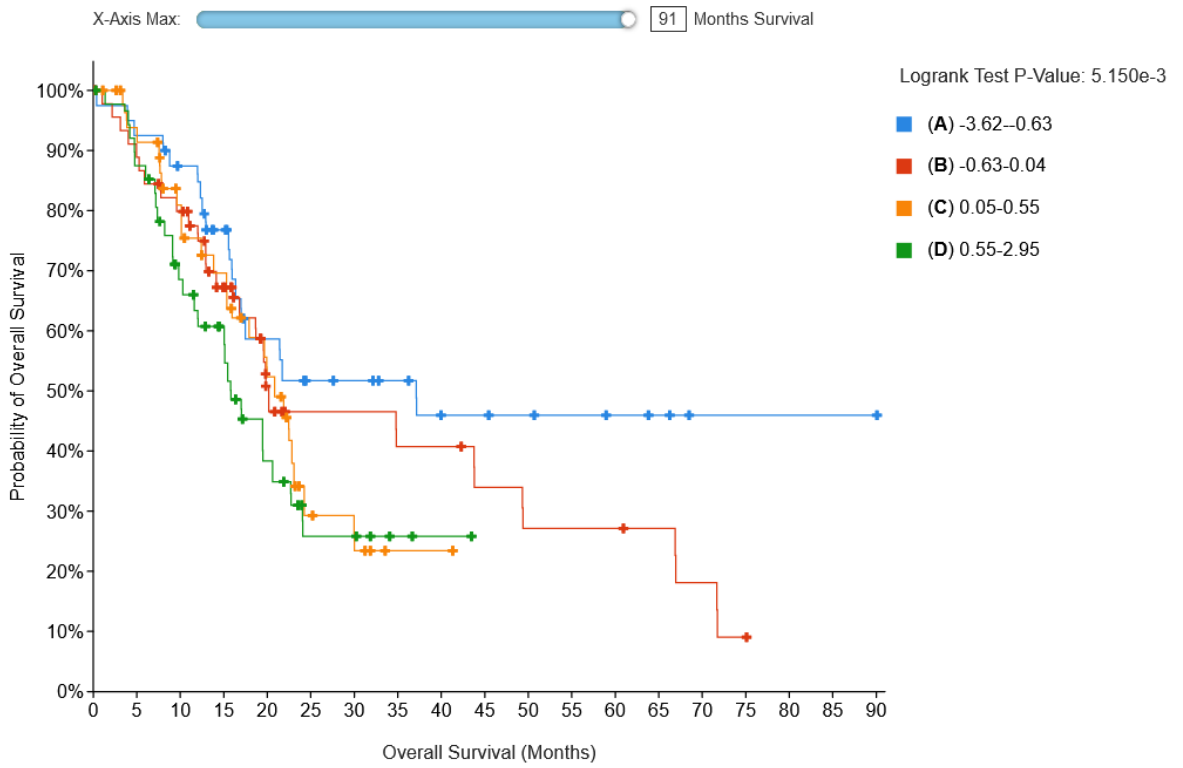
Where Do We Stand with Immunotherapy for Advanced Pancreatic Ductal Adenocarcinoma: A Synopsis of Clinical Outcomes
MDPI Biomedicines. December 202210(12):3196.
DOI:10.3390/biomedicines10123196

IV delivery

OT-101 + mFOLFIRINOX FOR PDAC

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)

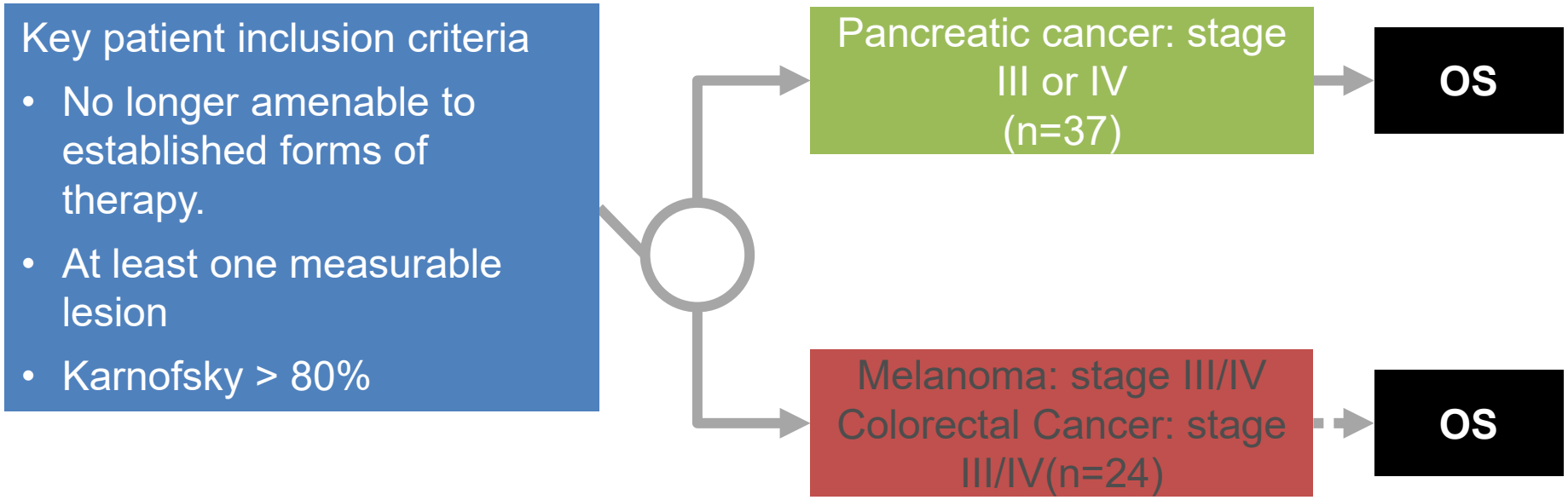


	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
(A) -3.62--0.63	**82**	**35**	**37.12 (17.48 - NA)**
(B) -0.63-0.04	**96**	**49**	**20.17 (18.67 - 49.34)**
(C) 0.05-0.55	**87**	**48**	**20.84 (17.92 - 23.08)**
(D) 0.55-2.95	**90**	**53**	**15.81 (15.05 - 20.61)**

Phase I/II P001 trial of OT-101

Study objectives

- 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.

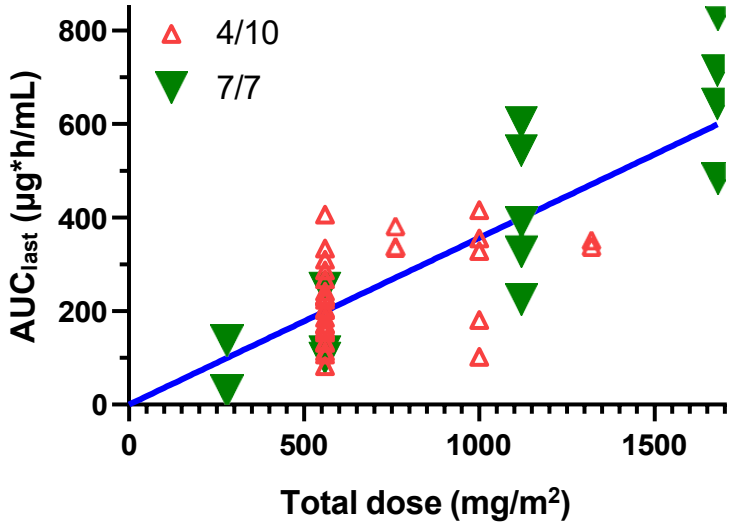


Pts#: 61 (37 with pancreatic cancer; 19 with malignant melanoma; 5 with colorectal cancer)
Primary Objective: To determine the maximum tolerated dose (MTD) and the dose limiting toxicities (DLTs) of two cycles of OT-101 administered intravenously (i.v.) for 7 days or for 4 days every other week.
OT-101 was well tolerated. MTD not reached and Efficacy Demonstrated. Efficacy was on par with Onivyde.

PK/PD Analysis

- 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.
- PFS changes for the three indications are:
  - 56 vs. 55 days (PDAC)
  - 40 vs. 84 days (CRC)
  - 49 vs. 67 days (Melanoma)

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

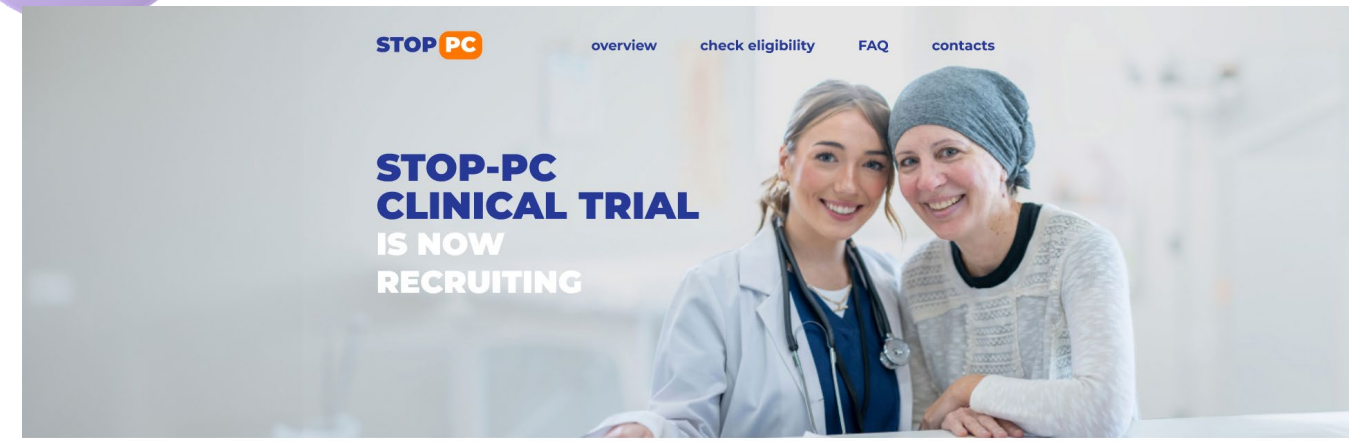


Linear Fit

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

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

P201 STOP-PC Trial



OVERVIEW

A Randomized Phase 2b/Phase 3 Study of the TGF-β2 Targeting Antisense Oligonucleotide OT-101 in Combination with mFOLFIRINOX Compared with mFOLFIRINOX Alone in Patients with Advanced and Unresectable or Metastatic Pancreatic Cancer.

The transforming growth factor-β (TGF-β for short) is a protein that modulates the activity of immune cells. In cancer tissue it suppresses immune cell response and contributes to tumor growth and spread.

OT-101 is a first-in-class RNA therapeutic designed to fight the immunosuppressive actions of TGF-β2, reduce the level of TGF-β2 in malignant tumors, and thereby delay the progression of disease.

OT-101 has demonstrated notable single-agent activity, consistently surpassing reported literature data for overall survival. Importantly, the overall survival increased in a dose-dependent manner at the levels of 140mg/m2 and higher.

The Phase 2/3 trial that you are being asked to participate in will compare OT-101 plus mFOLFORINOX with mFOLFORINOX alone as second line therapy in patients whose cancer progressed.

The trial will have 2 parts:

- **The goal of Part 1** is to estimate the maximum tolerated dose (MTD) of OT-101. After completion of Part 1, a justification for the dose regimen of OT-101 for Part 2 will be discussed with FDA.
- **The main goal of Part 2** is to compare the efficacy of OT-101 in combination with mFOLFORINOX versus mFOLFORINOX alone in patients with metastatic pancreatic cancer by measuring the overall survival (OS).

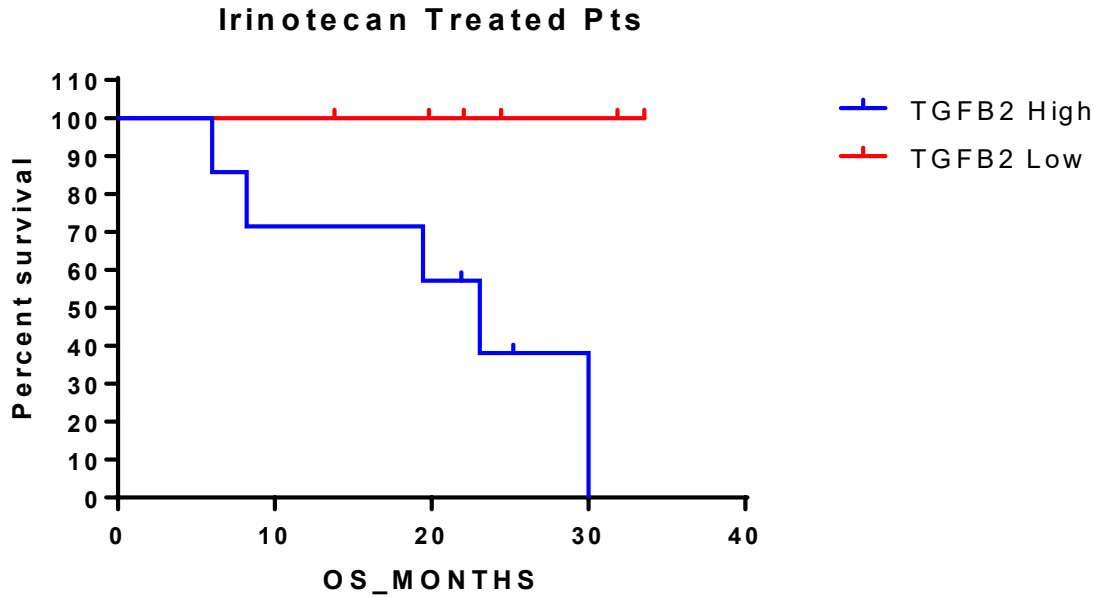
- **P201: A Randomized Phase 2b/Phase 3 Study of the TGF-β2 Targeting Antisense Oligonucleotide OT-101 in Combination with mFOLFIRINOX Compared with mFOLFIRINOX Alone in Patients with Advanced and Unresectable or Metastatic Pancreatic**
- **NCT06079346**
- **Patient population**
  - Adult patients with advanced and unresectable or metastatic pancreatic
    - OT-101 + mFOLFIRINOX
    - mFOLFIRINOX alone
- Cromos as CRO
- https://stop-pc.com/

Phase 3 Trial Design: OT-101 + mFOLFIRINOX

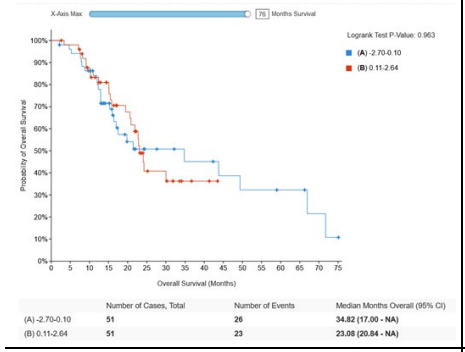
TGFB2 suppression synergizes only with Irinotecan – not paclitaxel nor gemcitabine. Note- NIS793 chose ABX/Gem.

Subsets of pts treated with various drug/drug combinations were examined for synergy with TGFB2 inhibitor.

There is a progressive increase in OS as we narrow in on patient population treated with irinotecan. The FOLFIRINOX seems to be the most affected by TGF-beta2 level. [Log rank p = 0.0174]

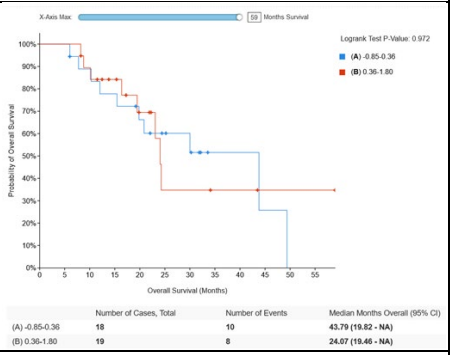


Gemcitabine (11% pts treated with irinotecan)



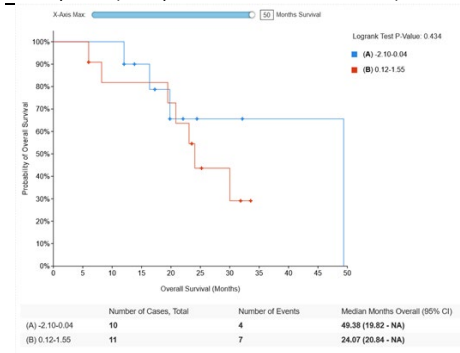
	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
(A) -2.70-0.10	51	26	34.82 (17.00 - NA)
(B) 0.11-2.64	51	23	23.08 (20.84 - NA)

Fluorouracil (35% pts treated with irinotecan)



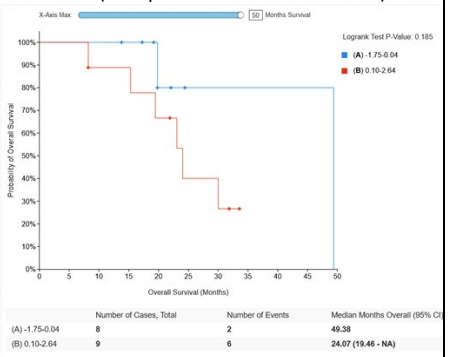
	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
(A) -0.85-0.36	18	10	43.79 (19.82 - NA)
(B) 0.36-1.80	19	8	24.07 (19.46 - NA)

Oxaliplatin (57% pts treated with irinotecan)



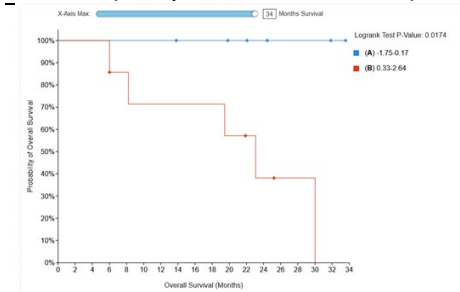
	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
(A) -2.10-0.04	10	4	49.38 (19.82 - NA)
(B) 0.12-1.55	11	7	24.07 (20.84 - NA)

Leucovorin (65% pts treated with Irinotecan)



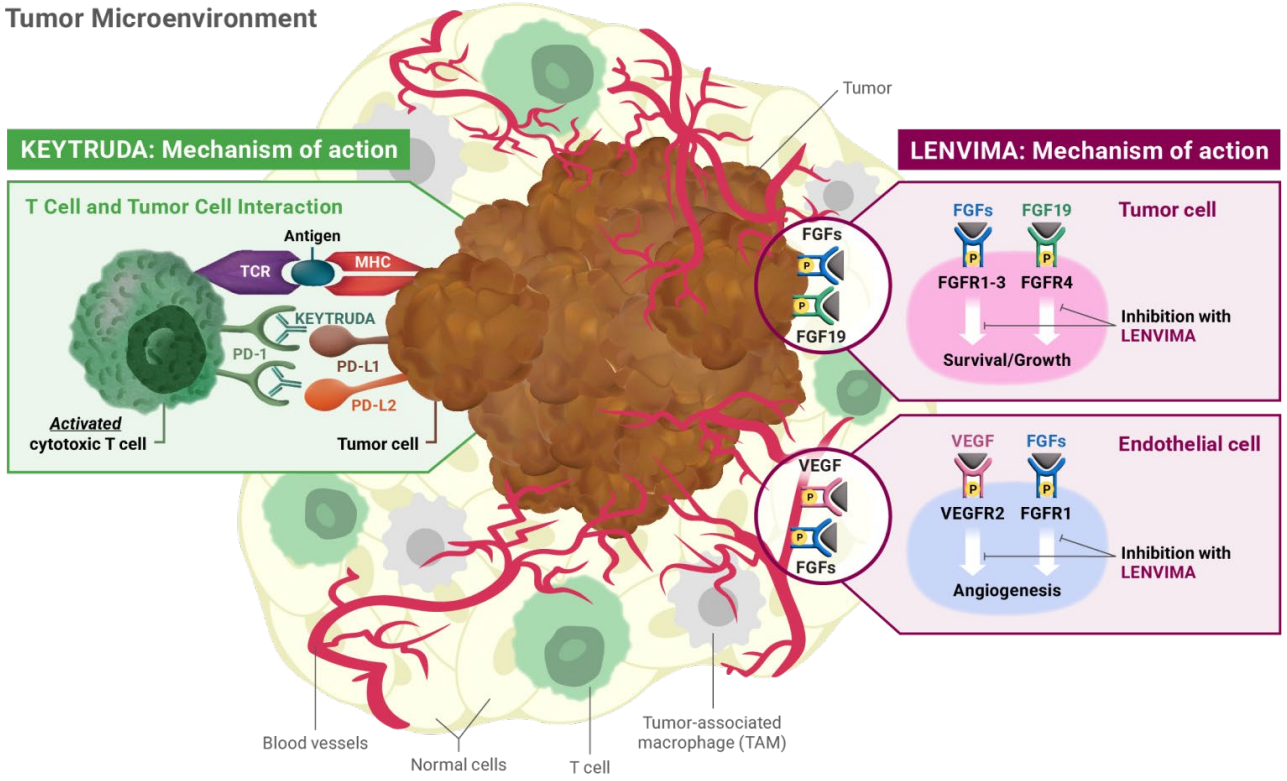
	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
(A) -1.75-0.04	8	2	49.38
(B) 0.10-2.64	9	6	24.07 (19.46 - NA)

Irinotecan (100% pts treated with irinotecan)



	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
(A) -1.75-0.17	6	0	NA
(B) 0.33-2.64	7	5	23.08 (8.22 - NA)

ONCOTELIC



IV delivery

OT-101 + KEYTRUDA FOR LUNG CANCER AND MELANOMA

OT-101 Checkpoint inhibitor combination therapies

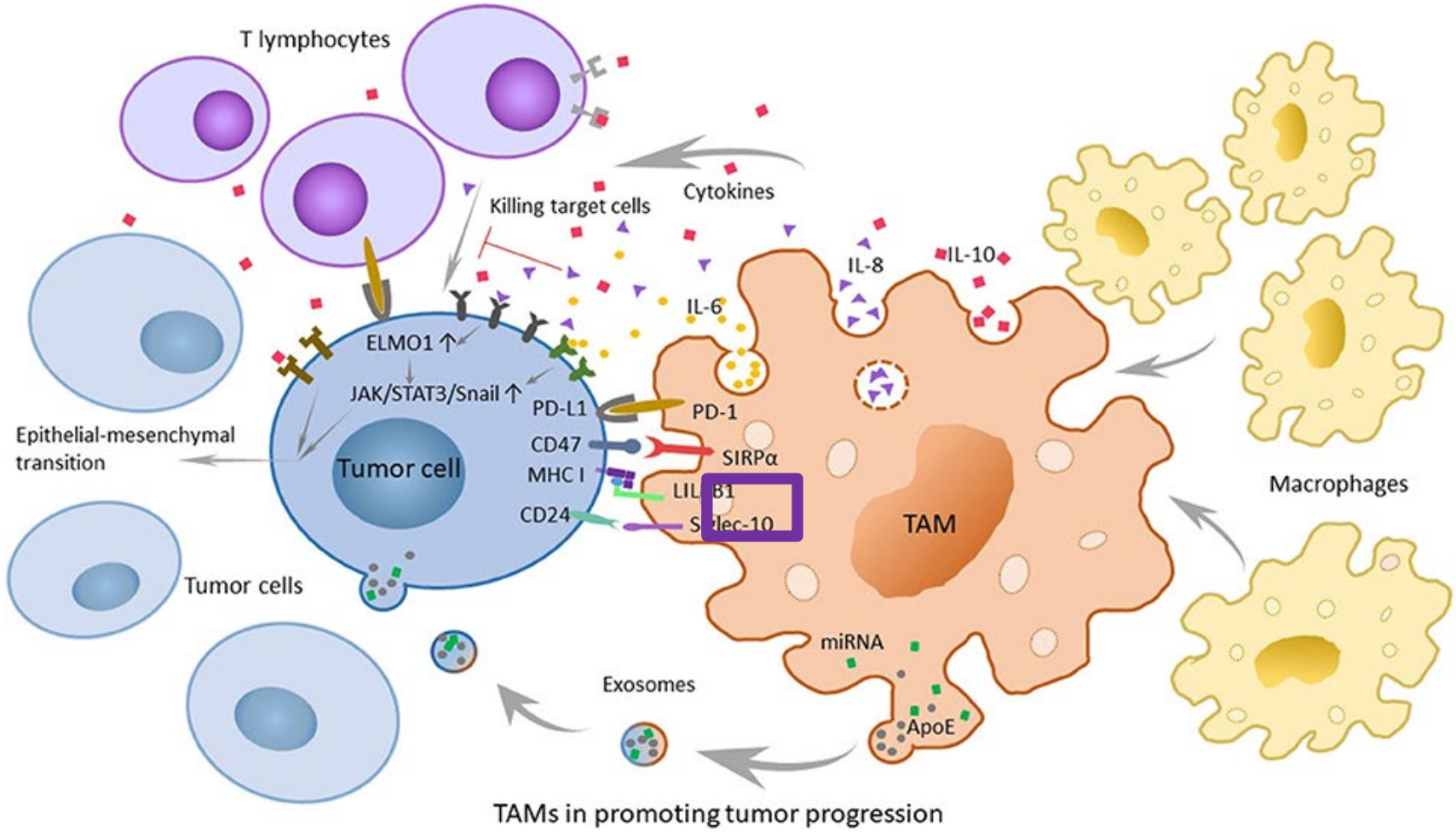
Box = PD-1 which is only present in M2 TAMs

OT-101 + PD1 Inhibitor combination / External collaborations with Merck and others.

OT-101 + PD1 Inhibitor + IL-2/ External collaborations with Regneneron and others

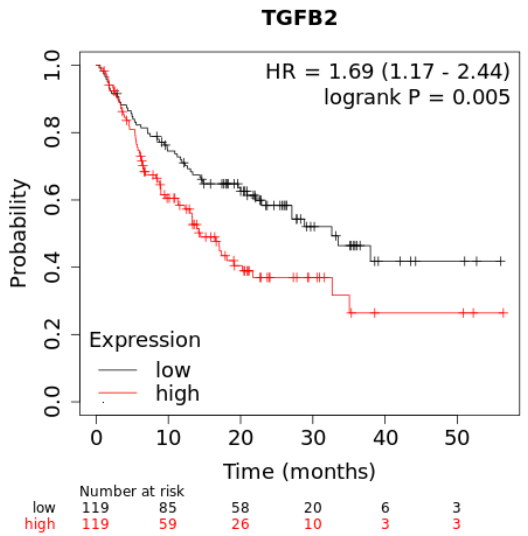
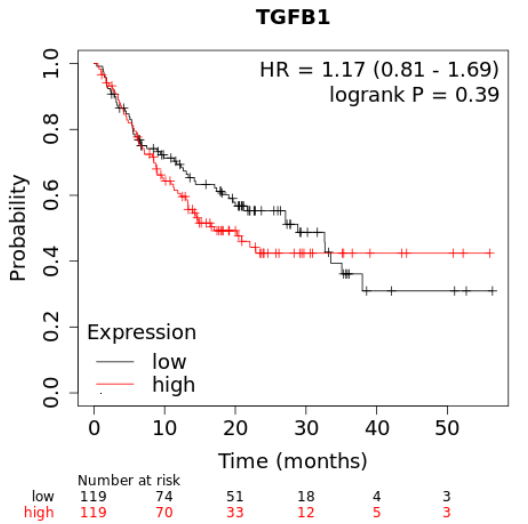
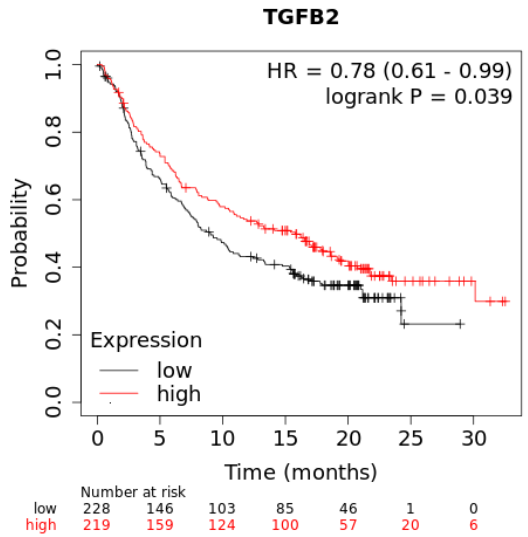
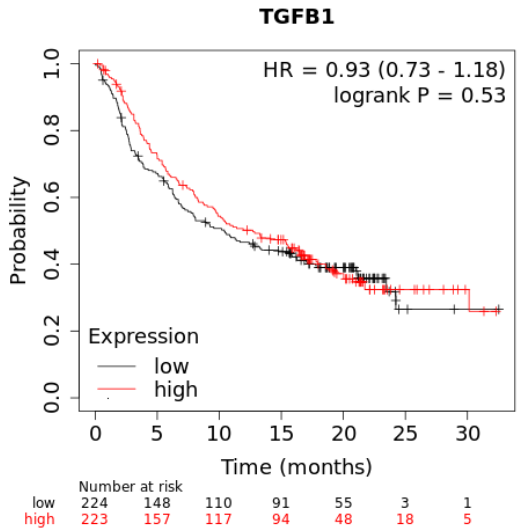
OT-101 suppression of TGF-B2 suppresses and repolarizes M2 to M1 and tumor regression

OT-101 is working on the same target as PD-1 inhbitor



A case for PD-1 Combination

- **TGFB1 versus TGFB2:** Bintrafusp alfa is inhibiting TGF-beta 1 by binding to the TGFB1 protein only with no affinity for TGFB2. TGFB2 (not TGFB1)- is upregulated in advance stage tumors; TGFB2 (not TGFB1) is associate with worse prognosis across multiple cancer types; TGFB2 (not TGFB1) synergizes with PD1 checkpoint inhibitor such as pembrolizumab

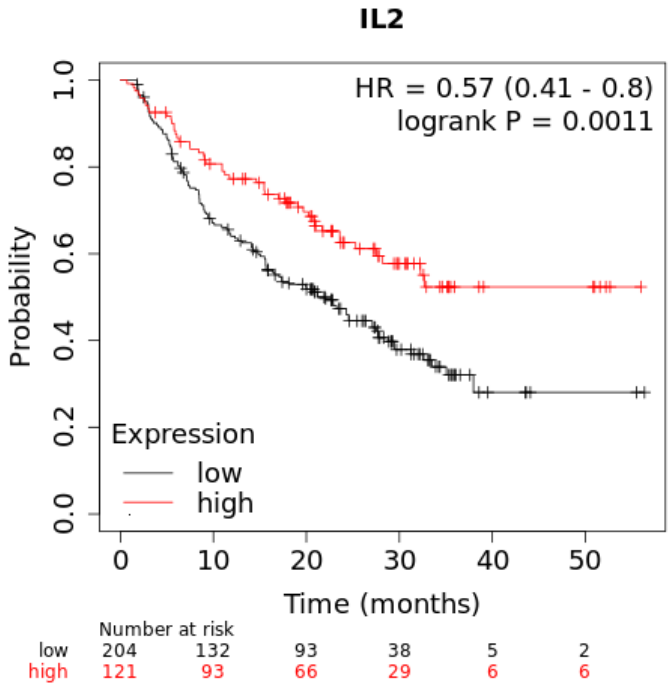
TGFB2/ Pembrolizumab treated pts	TGFB1/Pembrolizumab treated pts	TGFB2/ Atezolizumab	TGFB1/ Atezolizumab
P value: 0.005	P value: 0.3938	P value: 0.0385	P value: 0.5327
			
Median survival	**Median survival**	**Median survival**	**Median survival**
Low expression cohort (months): 32.62	Low expression cohort (months): 28.85	Low expression cohort (months): 9.03	Low expression cohort (months): 10.41
High expression cohort (months): 14.46	High expression cohort (months): 17.02	High expression cohort (months): 15.8	High expression cohort (months): 12.71

OT-101 With Pembrolizumab for Newly Diagnosed Advanced NSCLC and Positive PD-L1/ ClinicalTrials.gov ID NCT06579196/ University of Nebraska

- FPI expecting April 2025
- Phase I: Dose Finding. Dose Limiting toxicity (DLT) and Maximum Tolerated Dose (MTD)
- Experimental: Arm I: Dose Finding: Participants receive either 140, 190, or 250 mg/m2 intravenous OT-101/Trabedersen for up to 12 weeks using a 4 days on 10 days off dosing schedule. The dose level is determined according to the Bayesian optimal interval (BOIN) design with cohort size 3. Participants receive concurrent administration of 400 mg intravenous Pembrolizumab every 6 weeks.
- Phase II: Progression-Free Survival (PFS). Progression-Free Survival (PFS) defined as first therapy until the first documentation of clinical progression, relapse, or death due to any cause. Participants not experiencing an event of interest will be right-censored at last known disease status
- Experimental: Arm II: Treatment: Participants receive the recommended phase II dose of intravenous OT-101/Trabedersen (140, 190, or 250 mg/m2) until progression using a 4 days on 10 days off dosing schedule. Participants receive concurrent administration of 400 mg intravenous Pembrolizumab every 6 weeks.

Synergy of TGFB2 low (OT-101) and IL2 high (IL2)

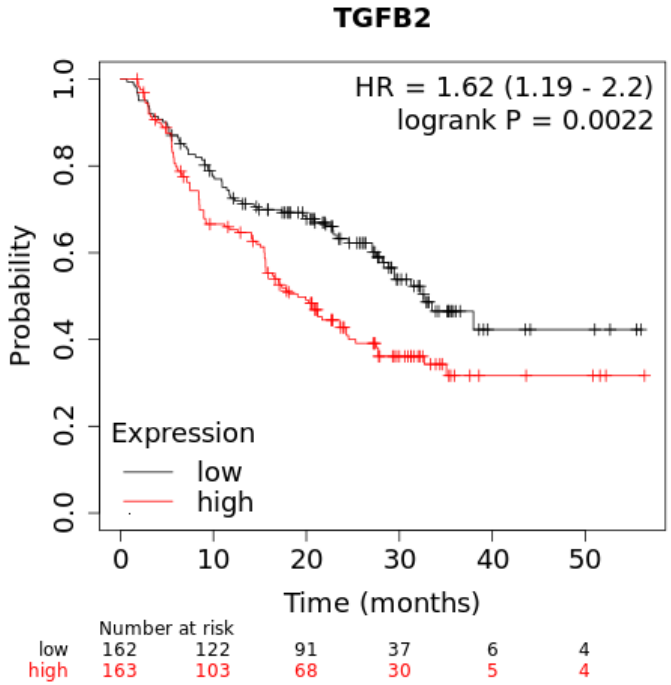
- Combining low TGFB2 (denominator) to show effect of OT-101 suppression of TGFB2 and high IL2 (as numerator) to show effect of IL-2 therapy clearly demonstrate synergy between the two therapeutics when used in conjunction with CKIs – specifically PD-1 inhibitors such as Keytruda
- Melanoma only PD1: Survival advantage increased from 7mos to 8 mos



Download plot as a PDF

Upper quartile survival

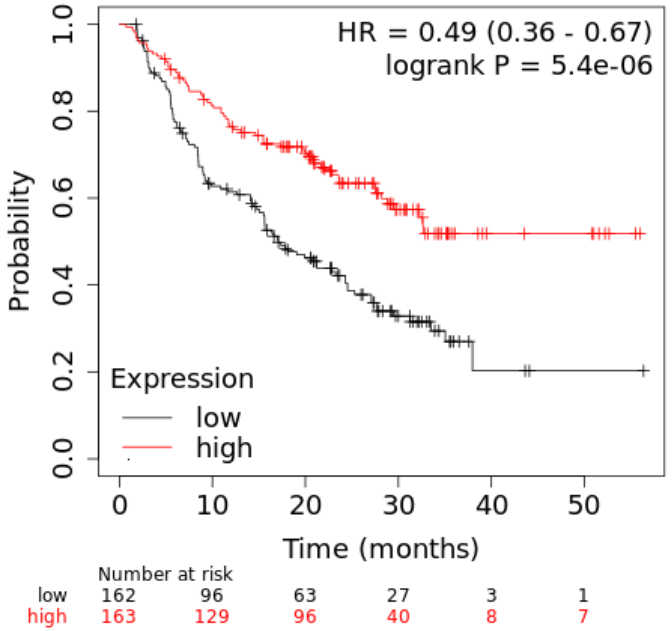
Low expression cohort (months)	High expression cohort (months)
8.07	15.47



Download plot as a PDF

Median survival

Low expression cohort (months)	High expression cohort (months)
32.62	19.07



Download plot as a PDF

Upper quartile survival

Low expression cohort (months)	High expression cohort (months)
6.7	14.63

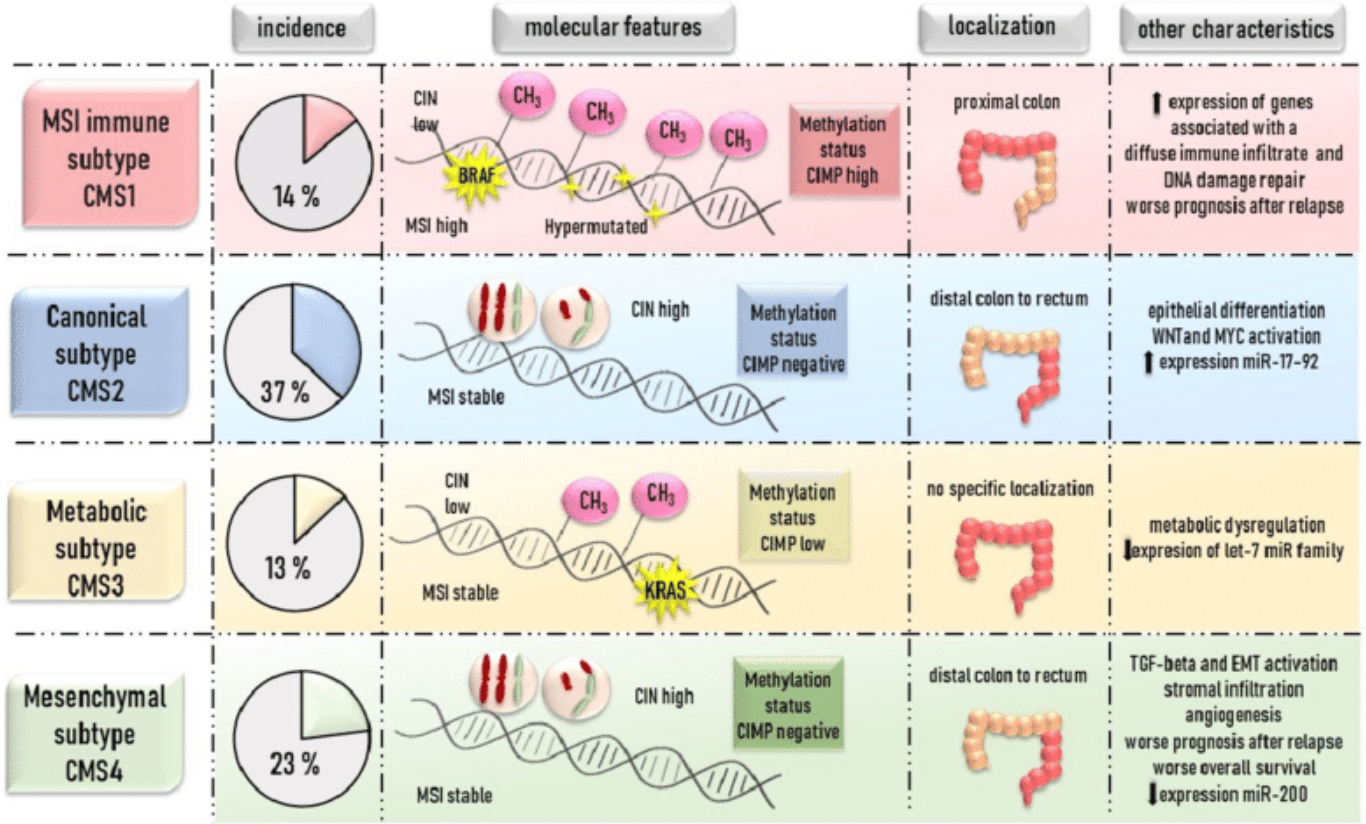
OT-101 in Combination With Recombinant Interleukin-2(Aldesleukin) in Advanced or Metastatic Solid Tumor. ClinicalTrials.gov ID NCT04862767

- Study Completed
- The study was divided into two cohorts based on the dosage of the investigational product. It started with Cohort 1 (Level 1: TASO-001 140 mg/m²/day). The occurrence of dose-limiting toxicities (DLT) was assessed up to day 14 after the start of the second cycle of investigational product administration. Based on the decision of the Data Monitoring Committee (DMC), dosage for Cohort 2 was planned to proceed at either Level 2 (TASO-001 190 mg/m²/day) or Level -1 (TASO-001 110 mg/m²/day). The 3+3 design was applied for participant recruitment in each cohort.
- Incidence of MTD (Tolerability) [Time Frame: 4weeks(DLT)]
- ORR(objective response rate) [Time Frame: every 8 weeks, and up to 14 days after the last dose of OT-101]. In case the best overall response expressed as CR or PR by RECIST v1.1 and iRECIST, the rate of subjects should be presented for each dose group.
- The combination therapy of OT-101 at 140 mg/m²/day with IL-2 can proceed to a Phase 2 clinical trial to evaluate its efficacy in patients with advanced or metastatic solid tumors.

ONCOTELIC

IV delivery

OT-101 FOR CRC



Cervena, Klara & Siskova, Anna & Buchler, Tomas & Vodicka, Pavel & Vymetalkova, Veronika. (2020). Methylation-Based Therapies for Colorectal Cancer. Cells. 9. 1540. 10.3390/cells9061540.

Synergistic effect of TGFB2 and TGM6 on survival in CRC

- Bioinformatic analyses were performed to determine the impact of TGFB2 expression on survival in CRC.
- TGFB2 exhibits sexual dimorphism in CRC patients; Its impact on OS was minimal except for RFS.
- The impact of combined TGFB2 and TGFM6 were synergistic and robust
- The activity was specific to mesenchymal form of CRC

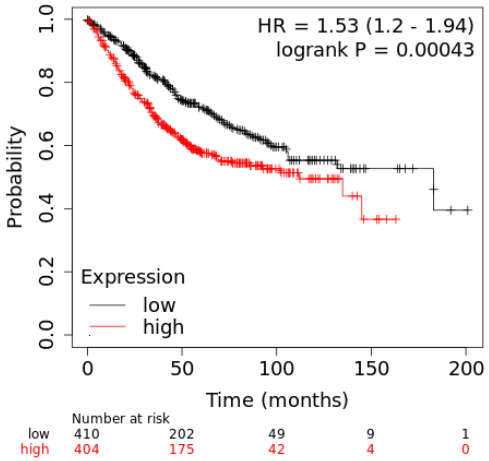
		RFS	OS			RFS	OS			RFS	OS
TGM6		0.00071	0.001	**TGFB2**		ns	ns	**TGFB2+TGM6**		0.0015	0.00043
	Female	ns	ns		Female	2.20E-06	ns		Female	0.042	0.021
	Male	ns	0.00098		Male	ns	ns		Male	0.00093	0.018
CMS	microsatellite unstable	ns	ns	**CMS**	microsatellite unstable	ns	ns	**CMS**	microsatellite unstable	ns	ns
	canonical	ns	ns		canonical	ns	ns		canonical	0.0075	ns
	metabolic	ns	ns		metabolic	ns	ns		metabolic	ns	ns
	mesenchyma	ns	ns		mesenchyma	ns	ns		mesenchyma	0.0052	1.40E-05
Mesenchymal	Female	ns	ns	**Mesenchyma**	Female	ns	ns	**mesenchyma**	Female	ns	0.0035
	Male	ns	ns		Male	ns	ns		Male	ns	0.0054

TGFB2 and TGM6 OS response is Mesenchymal specific

- Consensus Molecular Subtypes (CMS) of colorectal cancer.
  - **1. CMS1: Microsatellite Instability Immune (MSI Immune):** microsatellite instability (MSI-H). **Immune Activation**
  - **2. CMS2: Canonical: Epithelial:** CMS2 tumors are primarily epithelial, with high expression of WNT and MYC signaling pathway genes. **Chromosomal Instability**
  - **3. CMS3: Metabolic: Metabolic Dysregulation:** CMS3 tumor are distinguished by their metabolic signature. **Intermediat**
    Immune Features: some immune infiltration but not as pronounced as in CMS1.
  - **4. CMS4: Mesenchymal: Stromal Invasion:** significant stromal invasion, high content of cancer-associated fibroblasts and other stromal cells. This subtype is associated with a poor prognosis.

- The impact of combined TGFB2 and TGFM6 were synergistic and robust . The activity was specific to mesenchymal form of CRC

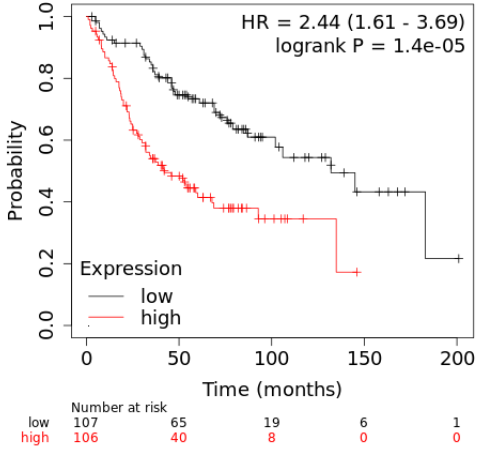
OS- All pts



Median survival

Low expression cohort (months)	High expression cohort (months)
183	112

OS- Mesenchymal



Median survival

Low expression cohort (months)	High expression cohort (months)
132	42

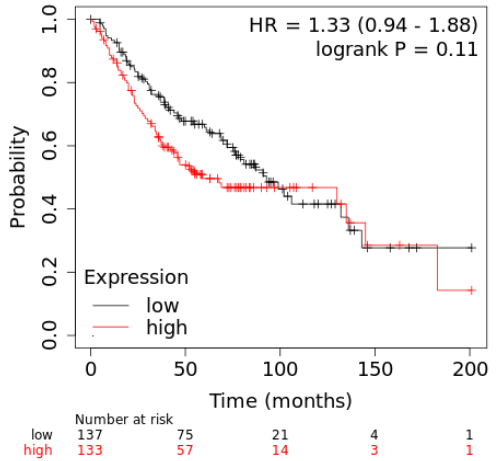
TGM6 has the highest impact on OS

- Different isoforms of TGM were examined and only TGM4, 5, and 6 were active with TGM6 being the most active.

	TGM5 (TG_X)	TGM7 (TG_Z)	EPB42 (band 4.2 protein)	TGM2 (TG_C)	TGM6 (TG_Y)	TGM3 (TG_E)	TGM4 (TG_P)	F13A1 (factor XIII a-subunit)	TGM1 (TG_K)
Chromosomal localization									
human	15q15.2	15q15.2	15q15.2 (27, 28, a)	20q11-12 (14,26, b)	20q11 (14, c)	20q11 (14, c)	3p21-22 (29, 30)	6p24-25 (25)	14q11.2 (18)
mouse	2, 67-69 cM	2, 67-69 cM	2, 67-69 cM (46, a)	2, 89-91 cM (47, a)		2, 74-78 cM			
Gene size									
human	~35kb	~26kb	~20kb (15)	~37kb (14, 26, b)	~45kb	~43kb (14)	~35kb (16)	~160kb (17)	~14kb (12, 18, 19)
mouse			~22kb (62)	~34kb (47)					
Number of exons									
human	13	13	13	13	13	13	13	15	15
mouse			13	13					

(a) this study
(b) GenBank™/EMBL Data Bank with accession number AL031651
(c) GenBank™/EMBL Data Bank with accession number AL031678

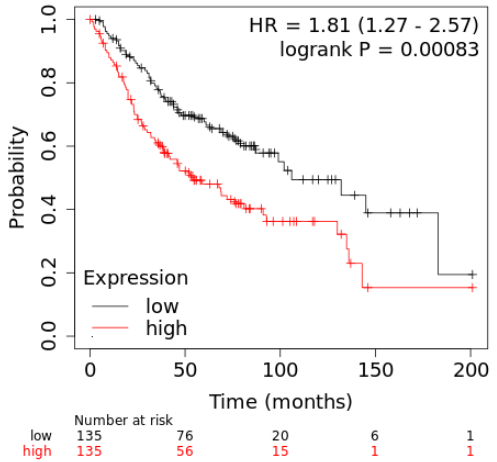
TGM1 (ns also for TGM2, TGM3, and TGM7)



Median survival

Low expression cohort (months)	High expression cohort (months)
92.77	59.07

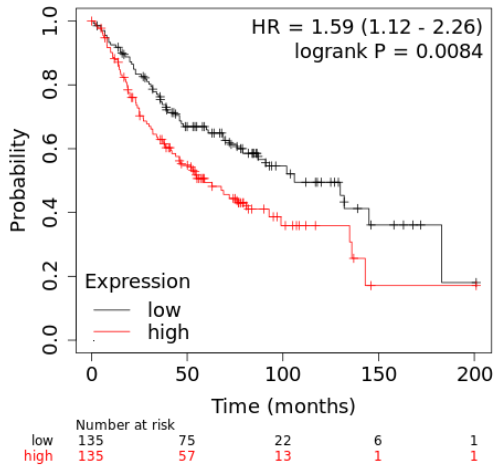
TGM4



Median survival

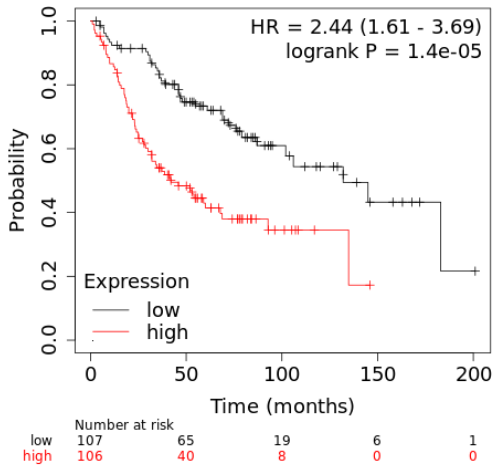
Low expression cohort (months)	High expression cohort (months)
106	54.04

TGM5



Median survival

TGM6



Median survival

Upcoming pipeline

High Intra-Tumor Transforming Growth Factor Beta 2 Level as a Predictor of Poor Treatment Outcomes in Pediatric Diffuse Intrinsic Pontine Glioma

by Fatih M. Uckun [1,2,*], Sanjive Qazi [1,2] and Vuong Trieu [2]

Transforming Growth Factor Beta 2 (TGFB2) and Interferon Gamma Receptor 2 (IFNGR2) mRNA Levels in the Brainstem Tumor Microenvironment (TME) Significantly Impact Overall Survival in Pediatric DMG Patients

by Sanjive Qazi [*], Zahra Talebi and Vuong Trieu

Transforming Growth Factor Beta 2 (TGFB2) mRNA Levels, in Conjunction with Interferon-Gamma Receptor Activation of Interferon Regulatory Factor 5 (IRF5) and Expression of CD276/B7-H3, Are Therapeutically Targetable Negative Prognostic Markers in Low-Grade Gliomas

by Vuong Trieu, Anthony E. Maida and Sanjive Qazi [*]

TGFB2 mRNA Levels Prognostically Interact with Interferon-Alpha Receptor Activation of IRF9 and IFI27, and an Immune Checkpoint LGALS9 to Impact Overall Survival in Pancreatic Ductal Adenocarcinoma

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