ONCOTELIC THERAPEUTICS

A TGF-beta Company

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Chief Clinical Officer – Translational Medicine
Oncotelic Therapeutics, Inc.

01/26/22

Management Team

- Vuong Trieu, PhD (CEO). Dr. Trieu, an expert in pharmaceutical development, currently serves as CEO/Chairman of Oncotelic Inc.. Previously he was President and CEO of Igdrasol- developer of 2nd generation Abraxane- Cynviloq. Igdrasol merged with Sorrento Therapeutics, he became CSO and Board Director. Cynviloq was acquired by NantPharma for 1.3B. He is one of the inventor of Abraxane- which was acquired by Celgene for 2.3B.
- Anthony E. Maida III, PhD, MA, MBA, Chief Clinical Officer – Translational Medicine Dr. Maida, an expert in immuno-oncology, served prior as Vice President, Clinical Research, Northwest Biotherapeutics, Inc. and General Manager, Oncology, World-wide at PharmaNet, Inc. Dr. Maida's focus is the conduct of clinical trials in immuno-oncology in various solid tumors. He is a member of AACR, ASCO, SNO, ACS and SITC. Dr. Maida has been in the development of various immunotherapies for over 30 years.
- Saran Saund (CBO). Mr. Saund is has been founder, CEO and GM at startups and public companies. His track record includes senior leadership roles at companies that were acquired by leaders such as Marvell (MRVL) and Qualcomm (QCOM). His startup Cybercash (CYCH) had a successful IPO on NASDAQ.
- Amit Shah (CFO). Mr. Shah has served as a senior financial officer for a number of life science companies, including Chief Financial Officer at Marina Biotech, Inc., a publicly traded biotechnology company (2017 to 2018)

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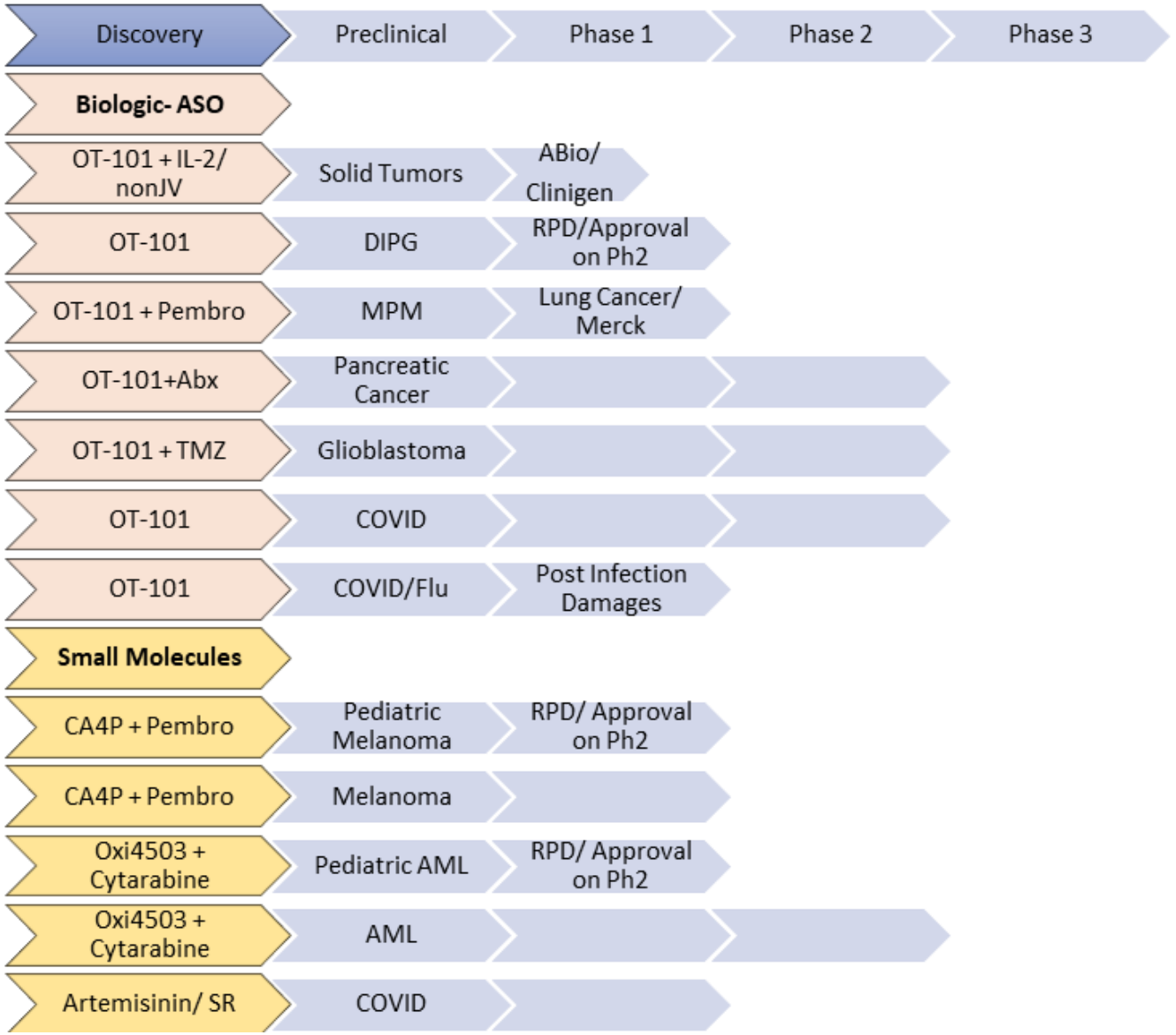
Pipeline (Oncology and Virology)



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OT-101/ Trabedersen

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A Brief Review of TGF-β2

- A pleiotropic and promiscuous immune modulator
- One of three (3) isomers, TGF-β1, TGF-β2 , TGF-β3
- A homodimeric cytokine 25kD that modulates, cell growth, differentiations, a potent immune suppressor, may act as a tumor promoter or tumor suppressor, induce EMT (epithelial to mesenchymal transition – the holy great of oncogenesis), can induce Foxp3 in precursor cell driving toward T regs, anti-viral properties, increase angiogenesis, profoundly impacts alveolar ion and ion and fluid transport by regulating the epithelial sodium channel (ENaC) activity thereby impairing alveolar fluid reabsorption particularly in ARDS resulting in pulmonary edema, as well as leading to remodeling and fibrosis,

Antisense 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	**1-5 yrs**
Manufacturing Cost	Low	High	**Low**
Amenable to Individual Therapy	No	No	**Yes**

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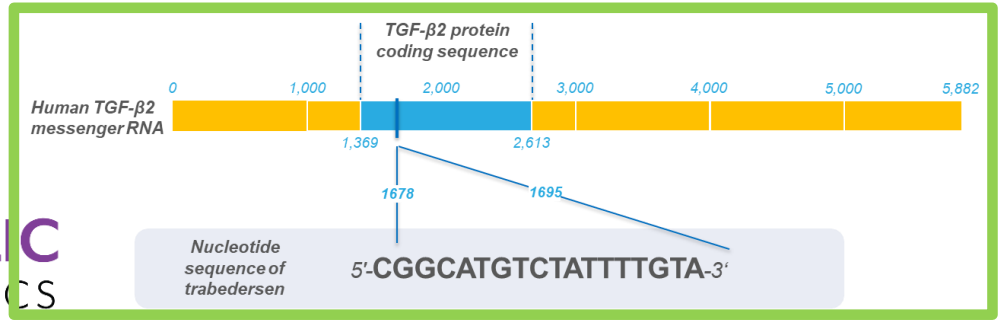
OT-101: Drug Product- TGF-β2 Antisense.

- Trabedersen (OT-101) is a single-stranded phosphorothioate antisense oligodeoxynucleotide (18-mer) targeting the human TGF-β2 messenger RNA
- Ready for registration trials--Over 200 patients treated across 6 clinical trials
- Strong Patent protection until 2037
- Orphan designation granted for three tumor indications in US & EU/ Rare Pediatric Designation in the US.
- Manufacturing process optimized and scaled up sufficient drug to treat over >5,000 patients
- **Clinical efficacy demonstrated in treatment failure patients- glioblastoma, pancreatic, melanoma**
- **Expected to improve tumor response to Keytruda and revenue to match that of Keytruda**
- The widespread interest in TGF-beta reflects the commercial opportunity for drugs that enable more people to respond to checkpoint inhibitors and evidence that the protein may be the key to unlocking those sales. In 2017, Roche shared bladder cancer data showing non-responders to its checkpoint inhibitor, Tecentriq, had high levels of TGF-beta. Roche followed up on that finding by linking the inhibition of TGF-beta in mice to increased Tecentriq efficacy. Since then data have been consistent that inhibition of TGF-beta would enhance immune checkpoint therapies



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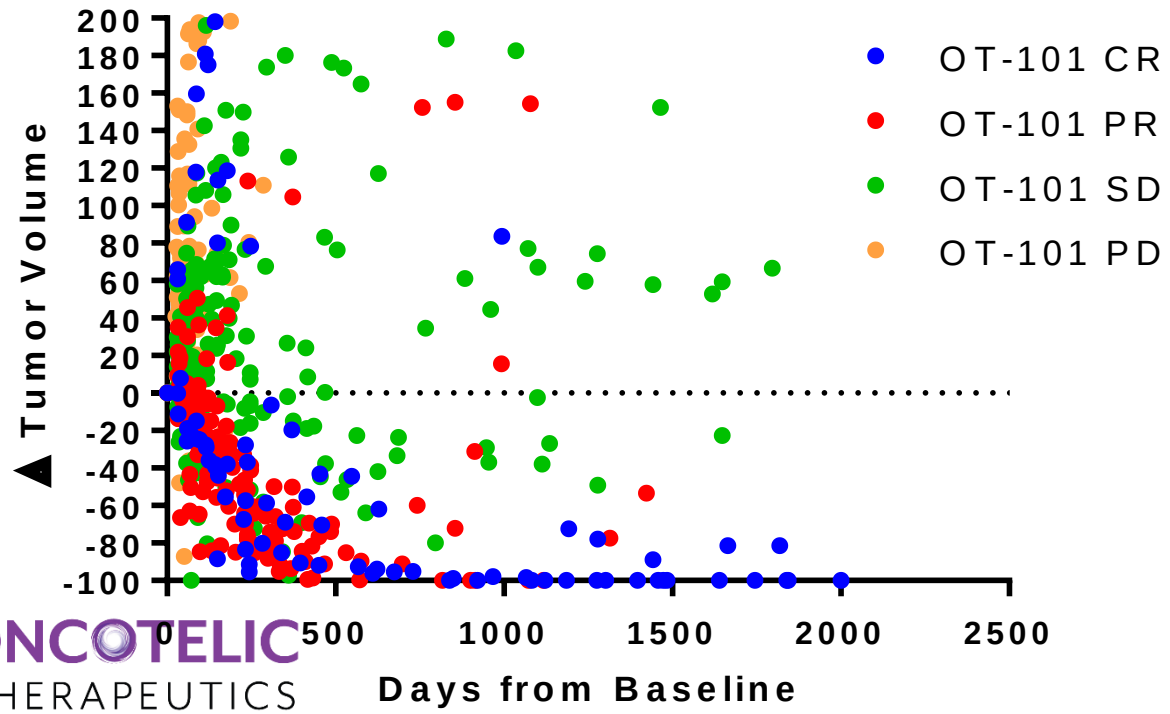
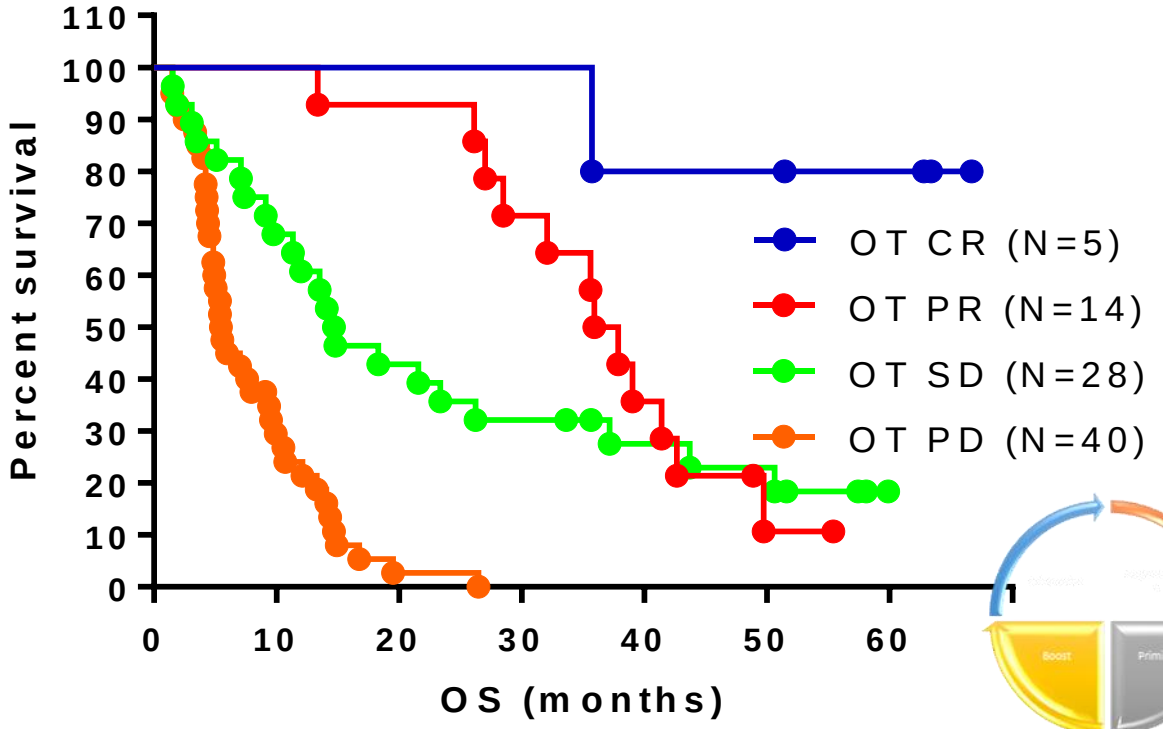
Clinical Efficacy: Glioblastoma

Treatment failure patients (recalcitrant to radiation, surgery, and chemo)

- 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.





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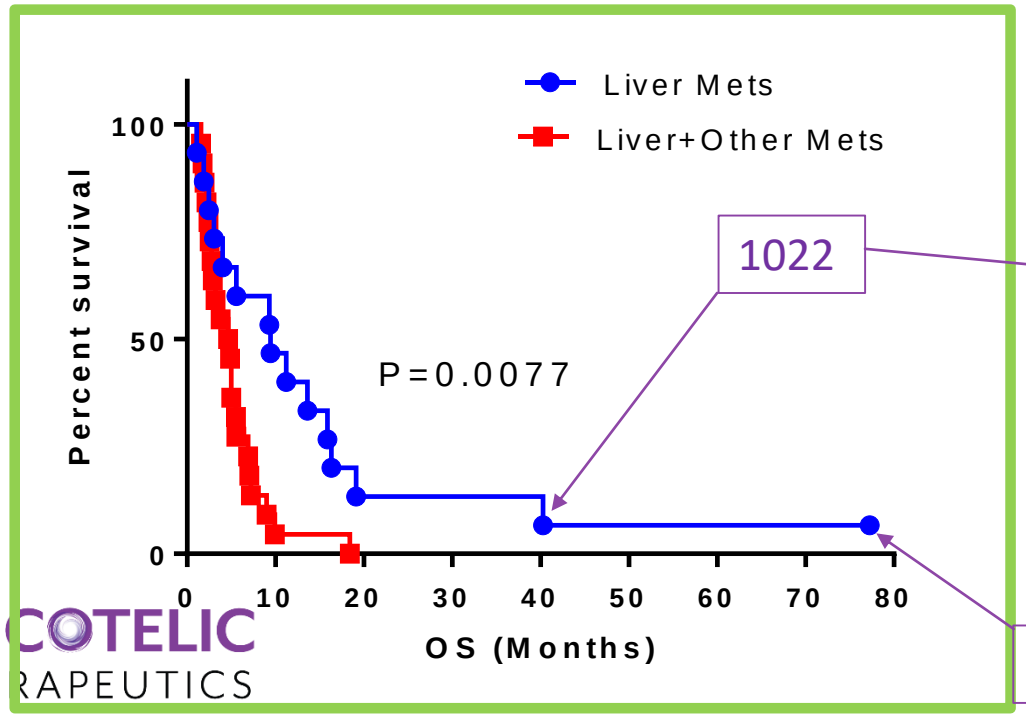
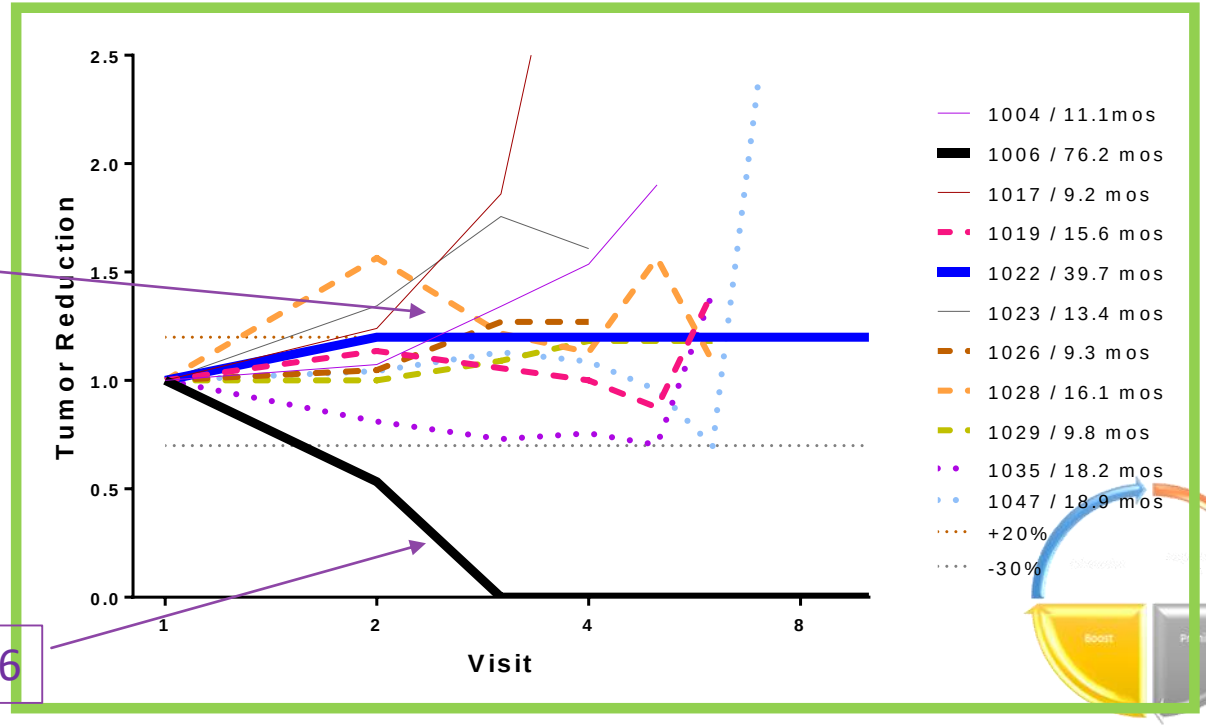
Clinical Efficacy: Pancreatic Cancer

Phase 2- treatment failure pts/ recalcitrant to Whipple and chemo

- **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)





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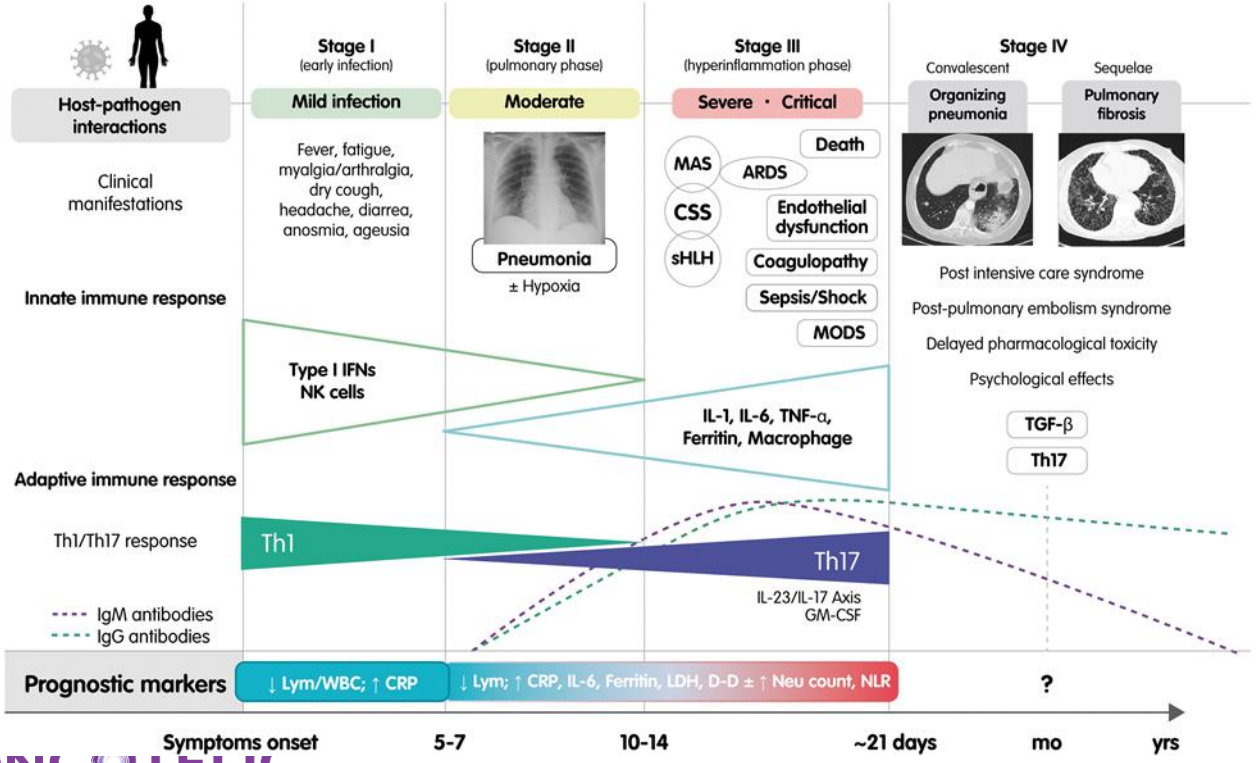
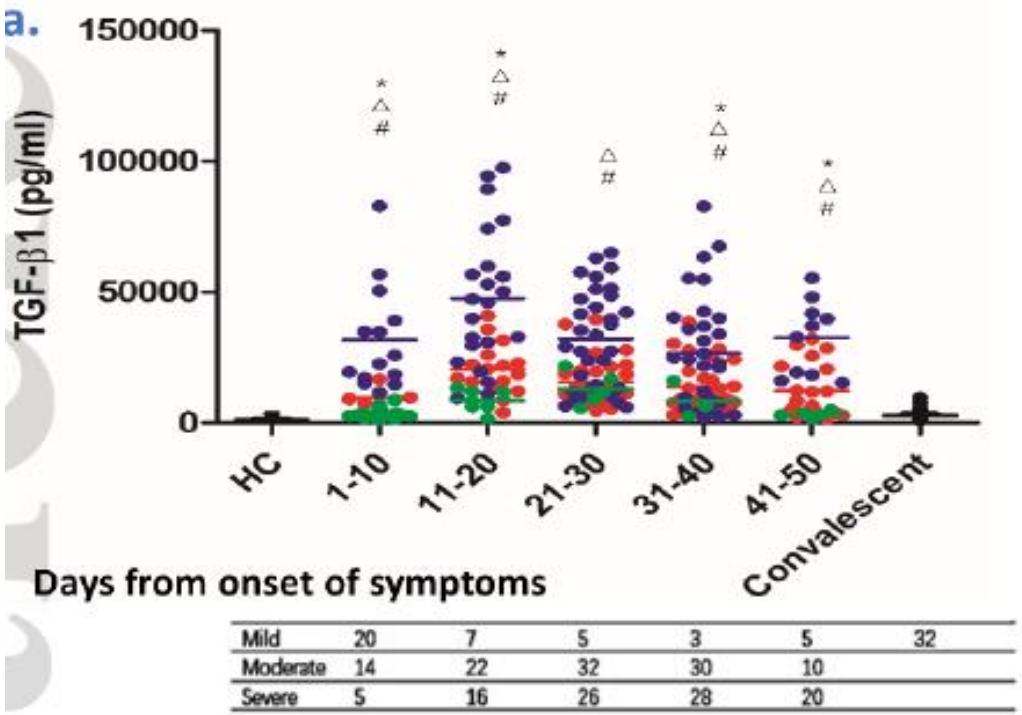
Clinical Efficacy: COVID

- Large surge in TGF-beta during active COVID infection
- An established role of TGF-beta in scarring and late stage post-COVID symptoms
- Strong in vitro activity against SARS-COV-2 on Vero cells
- OT-101 is in phase 2 clinical trial against COVID





Mild	20	7	5	3	5	32
Moderate	14	22	32	30	10	
Severe	5	16	26	28	20	

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A Double-Blind, Randomized, Placebo-Controlled, Multi-Center Study of OT-101 in Hospitalized COVID-19 Subjects

- Conducted in Peru and Argentina – 6 sites 3 in Peru and 3 in Argentina
- 20 Part 1 Patients and 12 Part 2 Patients, 2:1 Randomization
- Day 7 Mortality Rate of 4.5% vs 20% for Placebo for entire population in the trial
- Incidence of > 96% viral load knockdown
  - 89% vs OT-101 vs 67% for Placebo
- For those patients that expired MOS for OT-101 was 14 days vs 4 days on Placebo.
- The Company plans to continue the Phase II trial followed by a randomized Phare III clinical trial in the US, South America and potentially other countries.
- In terms of CRS, what did we need, no remarkable changes in circulating cytokine profiles including IL-6

* Cytokine elevation in sever and critical COVID-19: a rapid systematic review, meta analysis and comparison with other inflammatory, sydromes The Lancet, https//doi.org/10.1016/s2213-2600(20)30404-5

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Future Plans

- Phase II Clinical Trial in Metastatic Pleural Mesothelioma (MPM), a combination of OT-101 with a checkpoint inhibitor
- Phase II Clinical Trial in NSCLC, combination study
- Phase II Clinical Trial in a Basket Study, high grade gliomas (HGG), Tumors of the midline brain and diffuse intrinsic pontine glioma (DIPG) checkpoint inhibitor to be delivered IV and OT-101 delivered via convection enhanced delivery (CED)
- Phase II Clinical Trial in CRC, again a combination study
- Phase II Clinical Trial in Pancreatic Cancer, combination study.
- Phase II Clinical Trial in Melanoma, combination study
- It is planned that all studies will include pre and post therapy biopsies investigating changes in the tumor microenvironment (biomarkers) including T cell infiltration, cytokine expression, functionality, phenotypic changes, MDSCs, T regs, RNAseq, immunohistochemistry, M1 and M2 Ø looking for agnostic marker for wide use and approval

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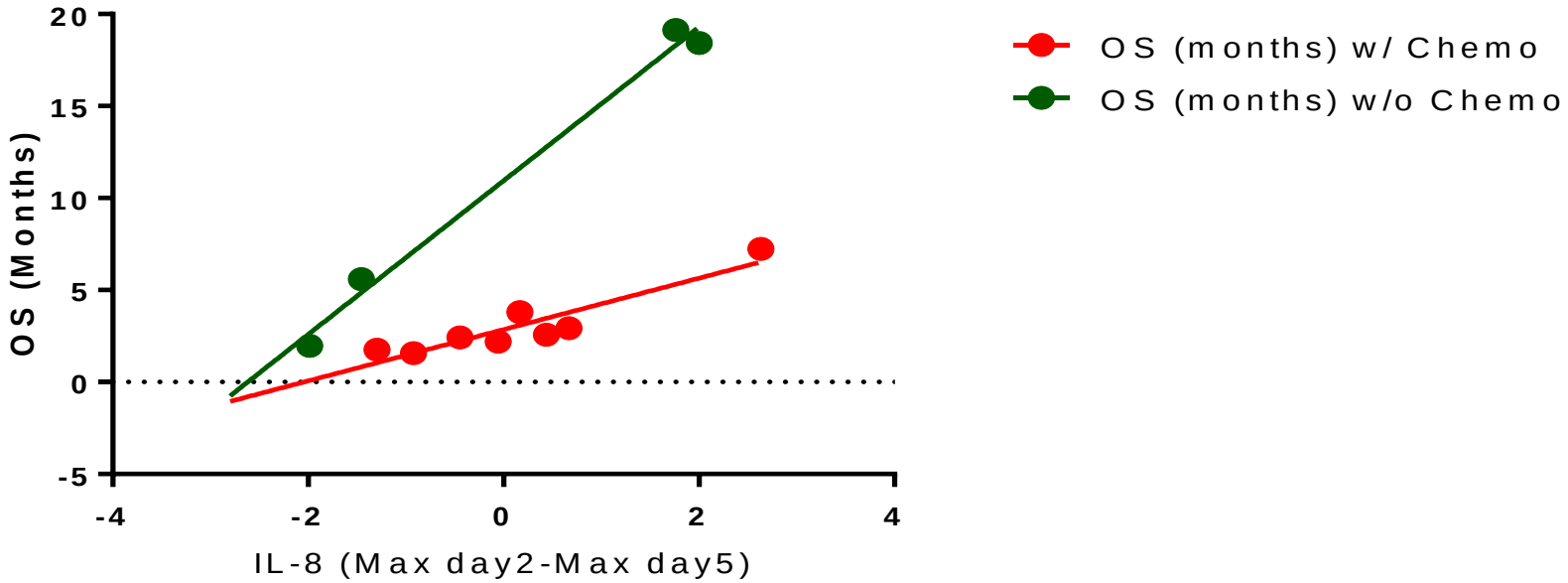
Rationale for Immunotherapy Combination

- Data supportive of improved OS with higher innate immune reservoir -> supplement with boost to innate immune reservoir (Cytokine -> IL2, Cell supplement -> NK or CART or ADCC
- Patients exhibited variable dynamics in IL-8 levels whereby increases were observed during cycles 1 (days 2, 5), 2 (days 1, 2, 5) and 3 (day 5). R^2 squares were 0.8522 and 0.9895 and p values were 0.0011 and 0.0053 for pts treated subsequently with chemo and without chemo, respectively.
- Patients 1035 and 1047 showed marked increases early in cycle 1 and exceptional OS.
- D'Cruz OJ, Qazi S, Hwang L, Ng K, Trieu V. Impact of targeting transforming growth factor β-2 with antisense OT-101 on the cytokine and chemokine profile in patients with advanced pancreatic cancer. Onco Targets Ther. 2018;11:2779-2796. Published 2018 May 14. doi:10.2147/OTT.S161905



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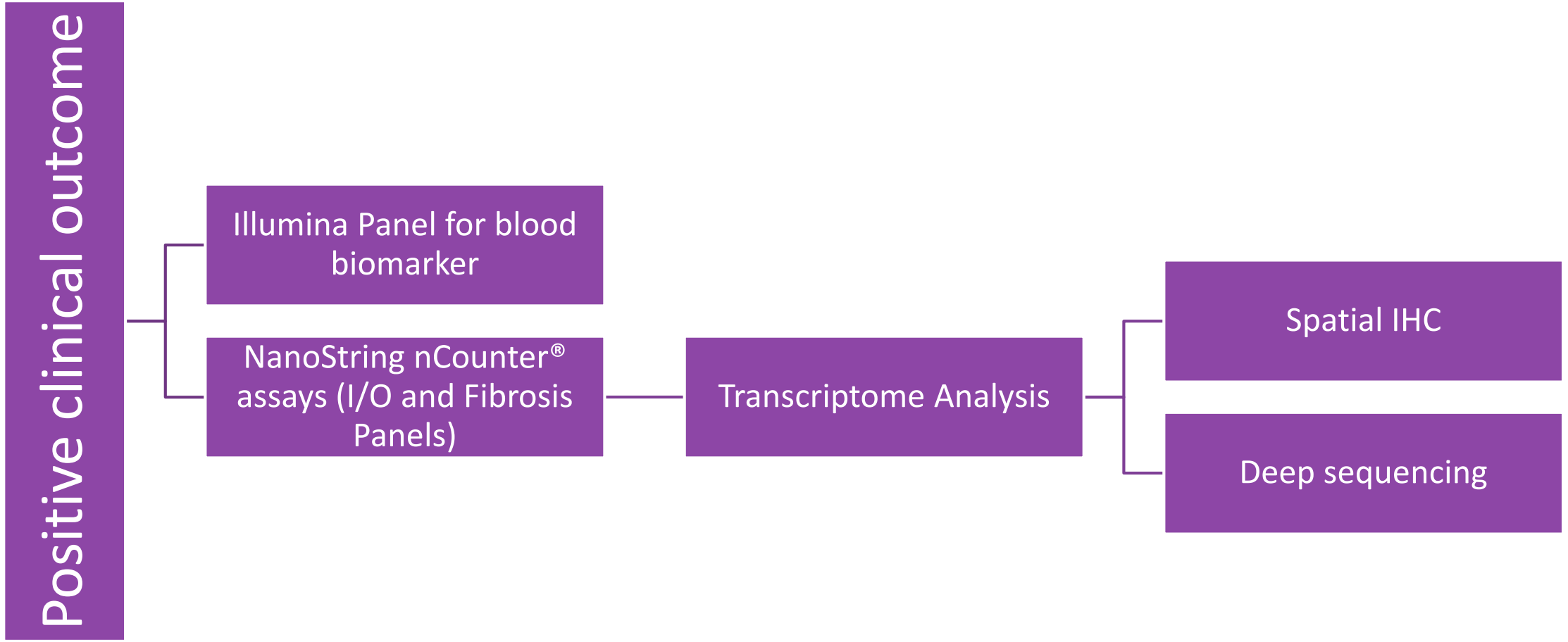
OT-101 Biomarker Program

- This is a combination of mesothelioma, lung, pancreatic, melanoma, DIPG, and GPM clinical trials in collaboration with Merck combining Keytruda with OT-101.
- Tumor biopsy previous to treatment and post treatment will be used to generate predictive biomarkers for tumor response as well as prognostic PD biomarkers.
- The objectives for the exploratory biomarker program are as follow:
- To determine whether TGF-β inhibition combined with PD-1 blockade will increase T cell infiltration, clonality and IFN-λ signatures in some tumors; and, the increased T cell infiltration, clonality (CD4, CD8 and Tregs) and IFN-λ signatures correlate with the reduced TBRS.
- To determine if pretreatment TBRS signature is predictive of improved efficacy per ORR, DOR, and 6-month and 12-month Overall Survival (OS), and progression free survival (PFS). Laboratory correlative analyses will determine whether treatment with OT-101 and pembrolizumab induces changes including the Tumor Micro Environment, TBRS, T cell infiltration and clonality, IFN-β signature and fibrosis score. Assays to be employed will include Multiplex IHC analysis along with Adaptive TCR ImmunoSeq Gene expression profiling (GEP) with RNA expression using NanoString nCounter® assays, including for changes in TGF-β (using the Tumor Signaling 360 panel).

Sequence of events



Positive finding on blood and Nanostring Panel

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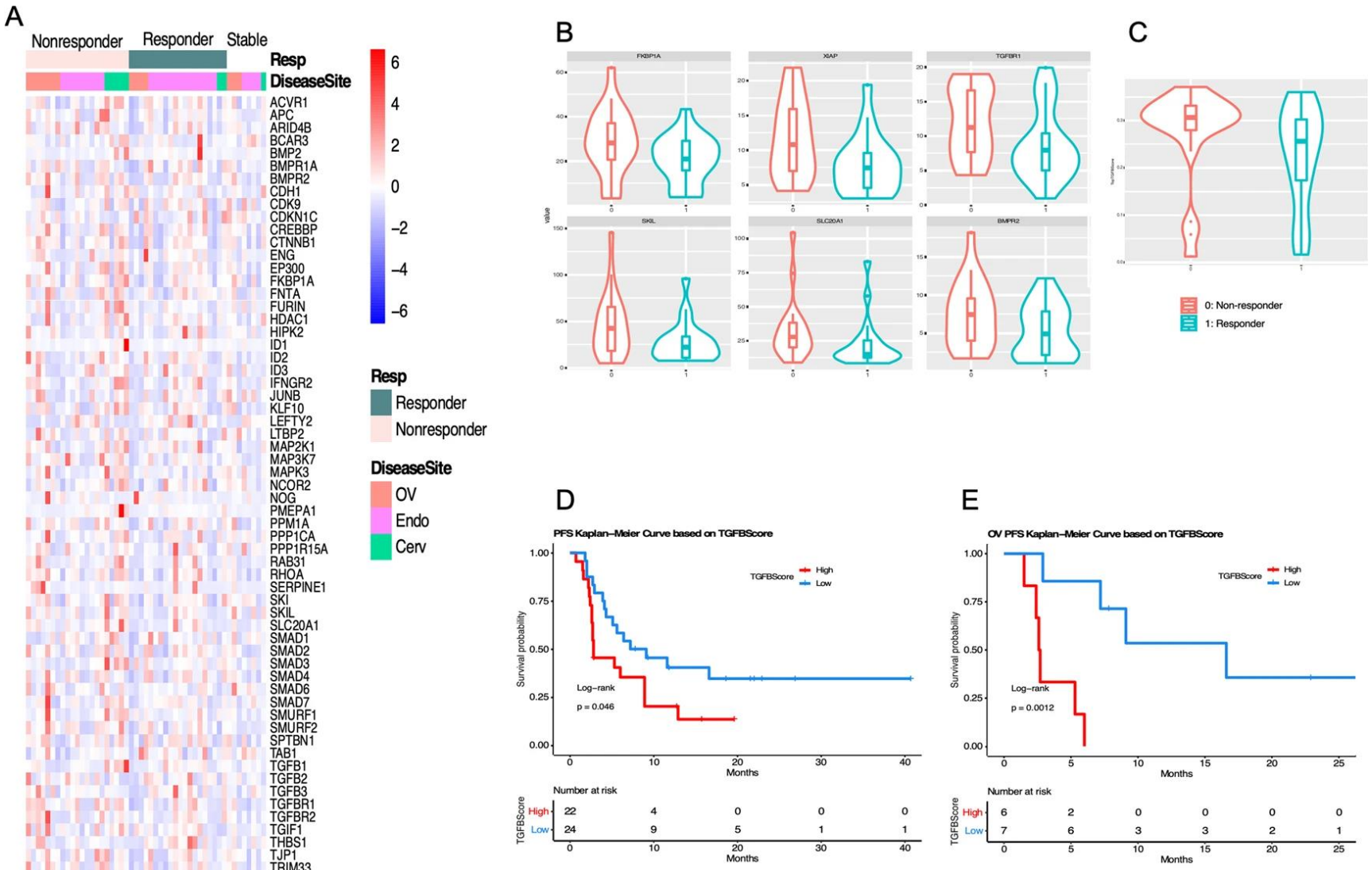
Ni, Y., Soliman, A., Joehlin-Price, A. et al. High TGF-β signature predicts immunotherapy resistance in gynecologic cancer patients treated with immune checkpoint inhibition. Precis. Onc. 5, 101 (2021).



A Heatmap of all 65 curated TGF-β pathway genes, sorted by responders and non-responders in each 3 disease types;

B Violin plot of top 6 individual genes (SLC20A1, XIAP, TGFBR1, BMPR2, FKBP1A, and SKIL) expression in TGF-β pathway between responders and non-responders;

C Violin plot of the TGF-β score generated using these 6 genes between responders and non-responders;

D Kaplan–Meier curves of PFS based on TGF-β score in the entire cohort;

E Kaplan–Meier curves of PFS based on TGF-β score in ovarian cancer patients. For panels D and E, the TGF-β score group “High” or “low” was defined by the median expression of the TGF-β score.