ONCOTELIC THERAPEUTICS

OT-101/ Trabedersen

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2/7/22

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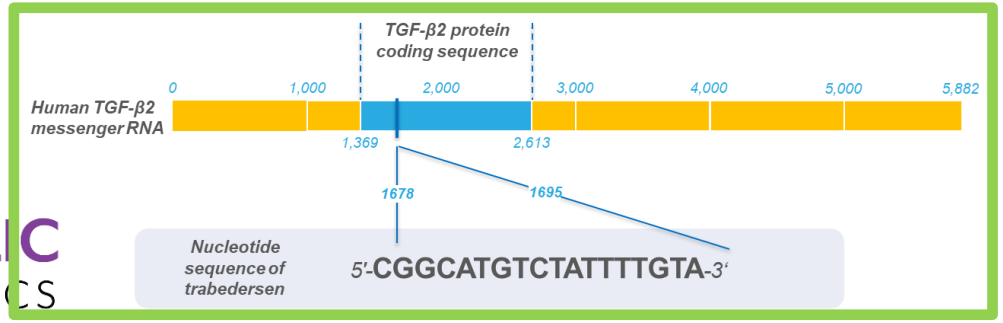
OT-101: Drug Product- TGF-β2 Antisense.

- 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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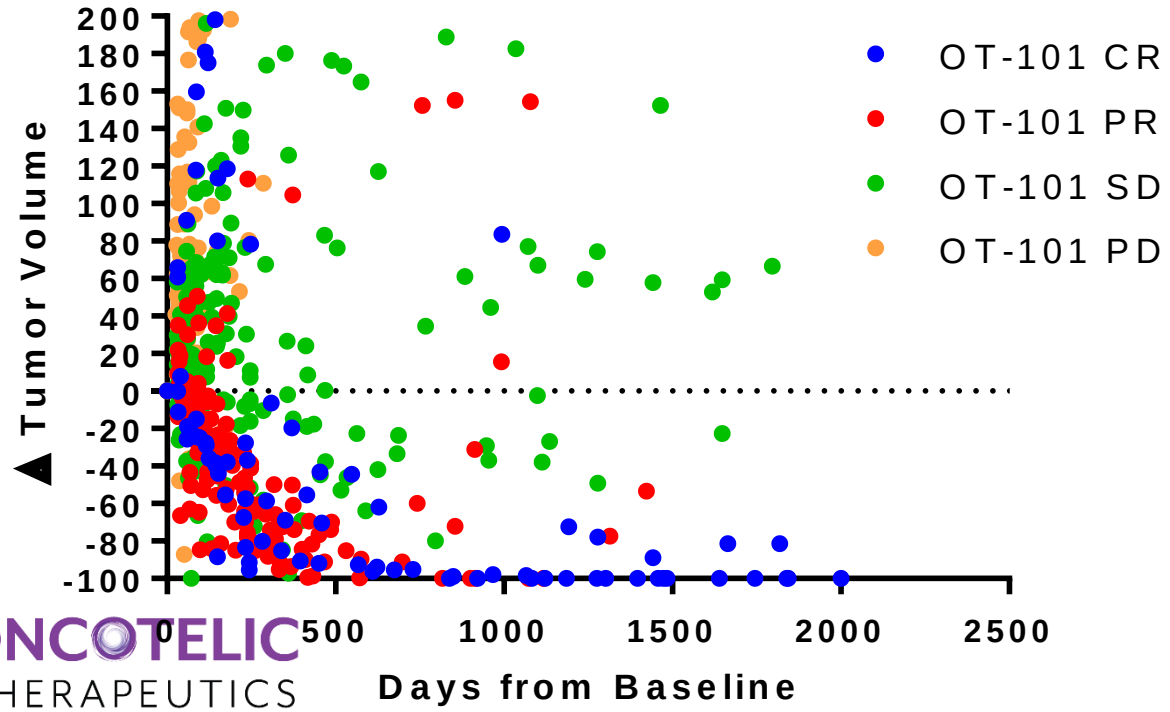
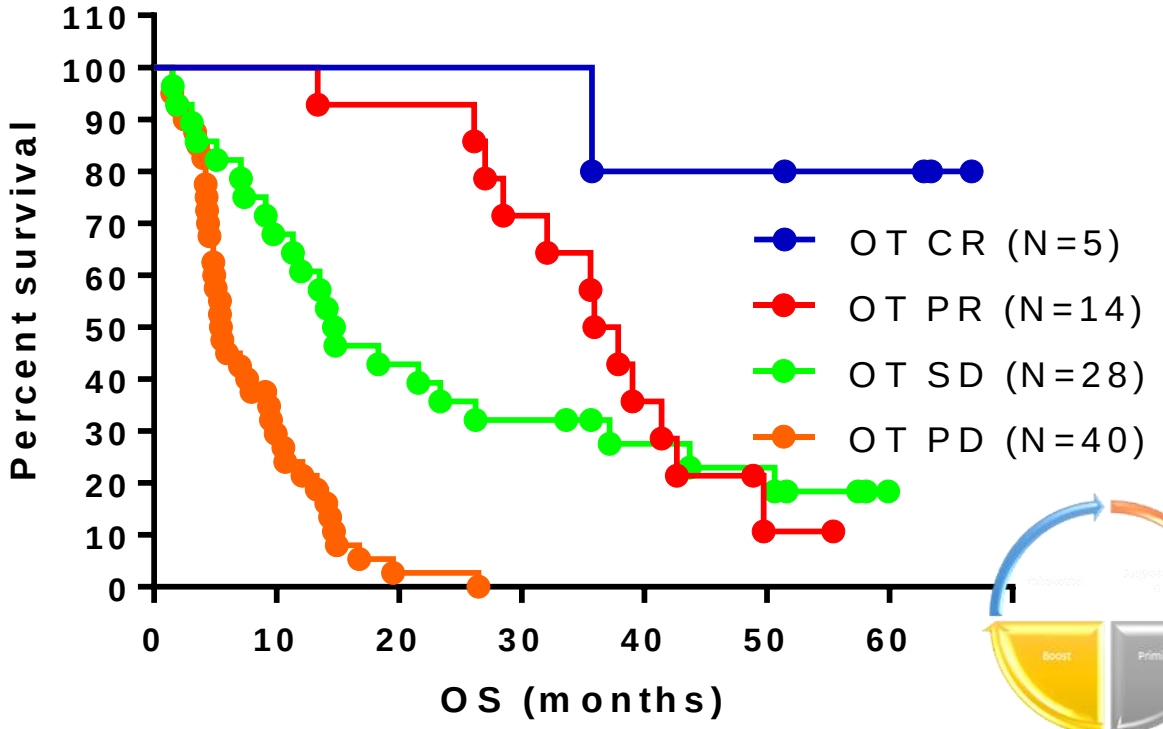
Clinical Efficacy: Glioblastoma

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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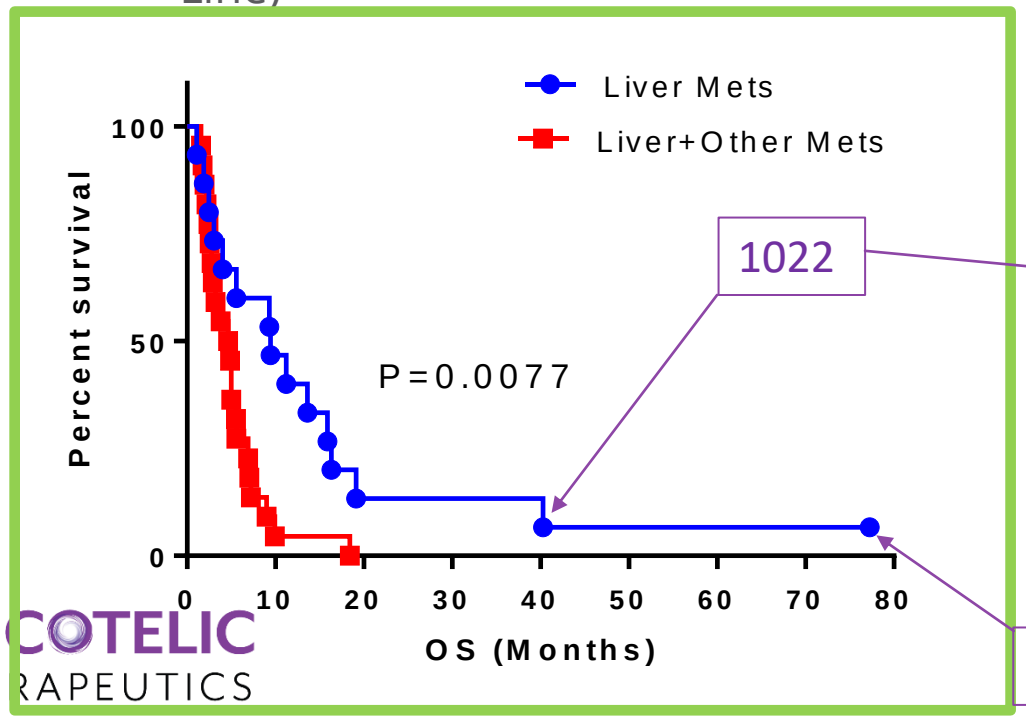
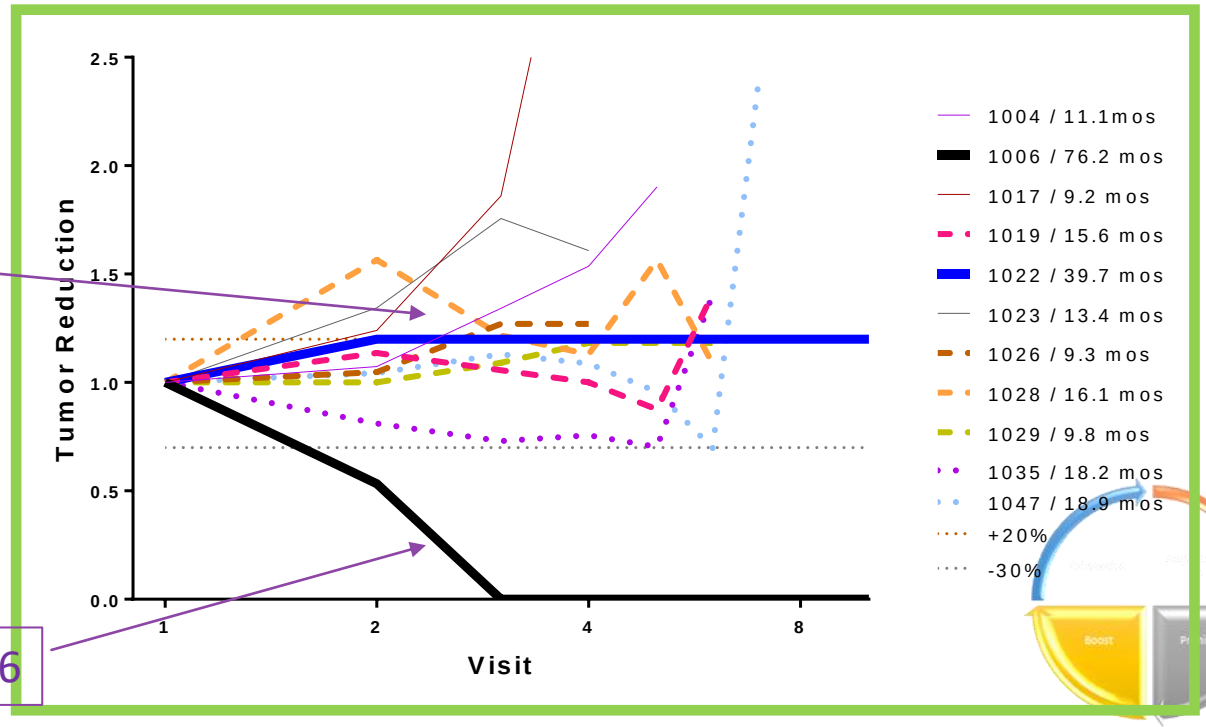
Clinical Efficacy: Pancreatic Cancer

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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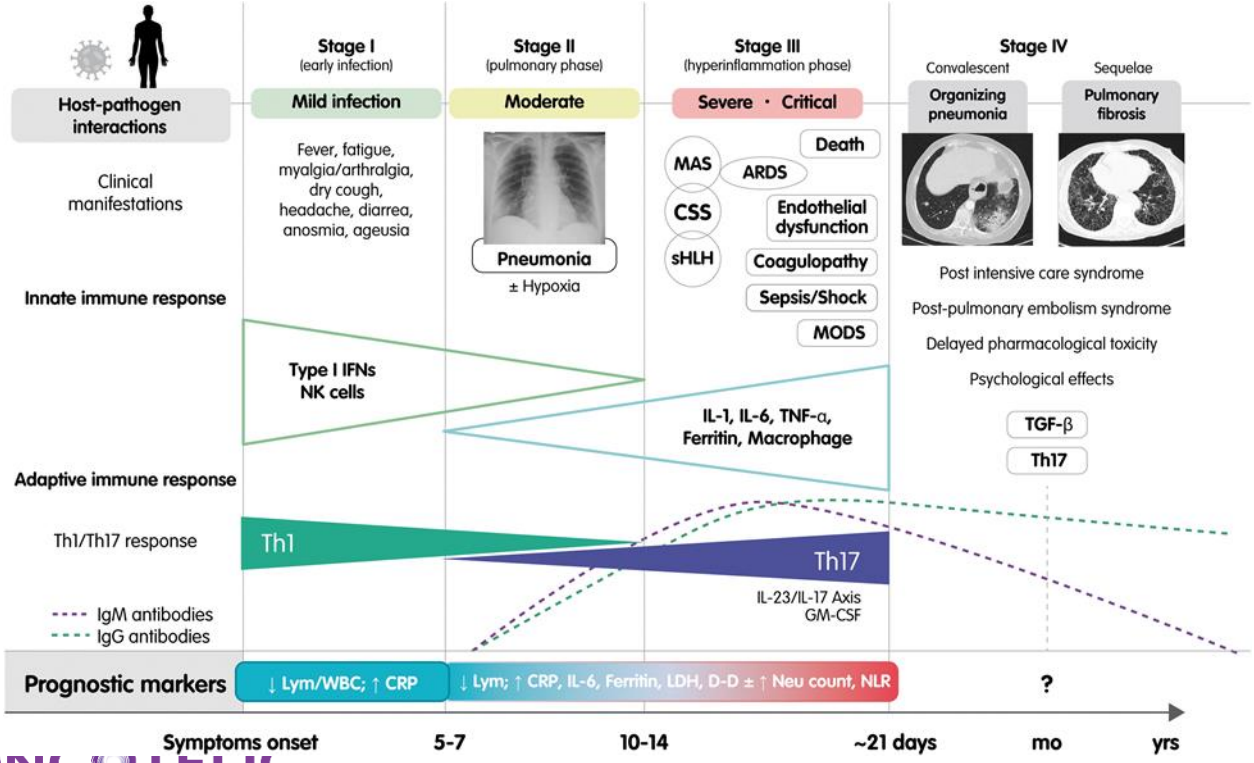
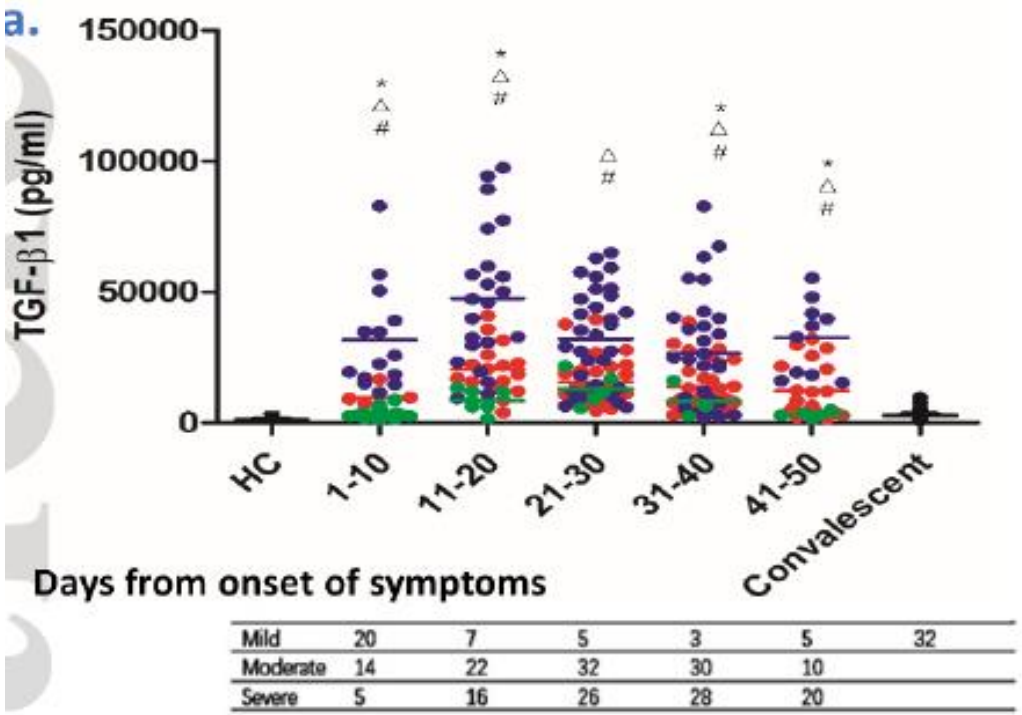
Clinical Efficacy: COVID

- 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
- Positive outcome for OT-101 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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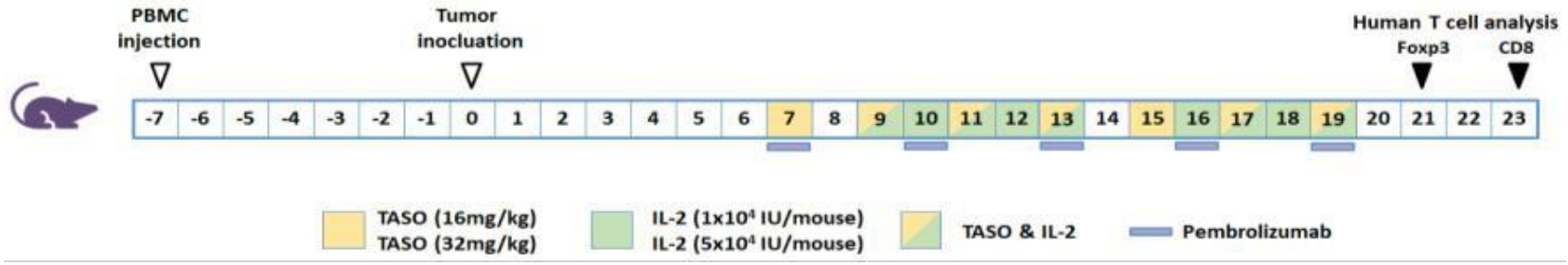
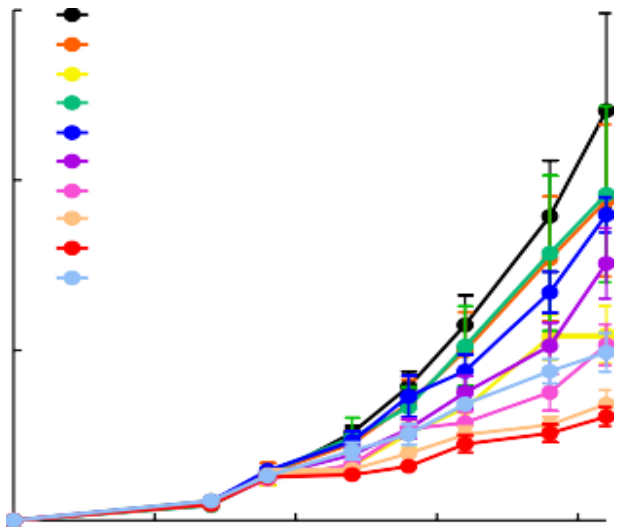
OT-101/IL-2 Efficacy In Vivo

- Combination of TASO and IL-2 treatment showed better tumor growth inhibition of melanoma cell line (A2058) than TASO alone, IL-2 alone and Pembrolizumab alone in humanized mouse model (NSG mouse)





Variables	Tumor growth Inhibition (%)	P-value
TASO 16mpk	21.9%	
TASO 32mpk	54.7%	
IL-2 1x10^4 IU	20.4%	
IL-2 5x10^4 IU	25.4%	
Keytruda	65.4%	
TASO 16mpk + IL-2 1x10^4 IU	37.3%	
TASO 16mpk + IL-2 5x10^4 IU	57.2%	
TASO 32mpk + IL-2 1x10^4 IU	71.6%	
TASO 32mpk + IL-2 5x10^4 IU	74.7%	

p=0.010
p=0.006
p=0.011
p=0.006
p=0.062
p=0.001

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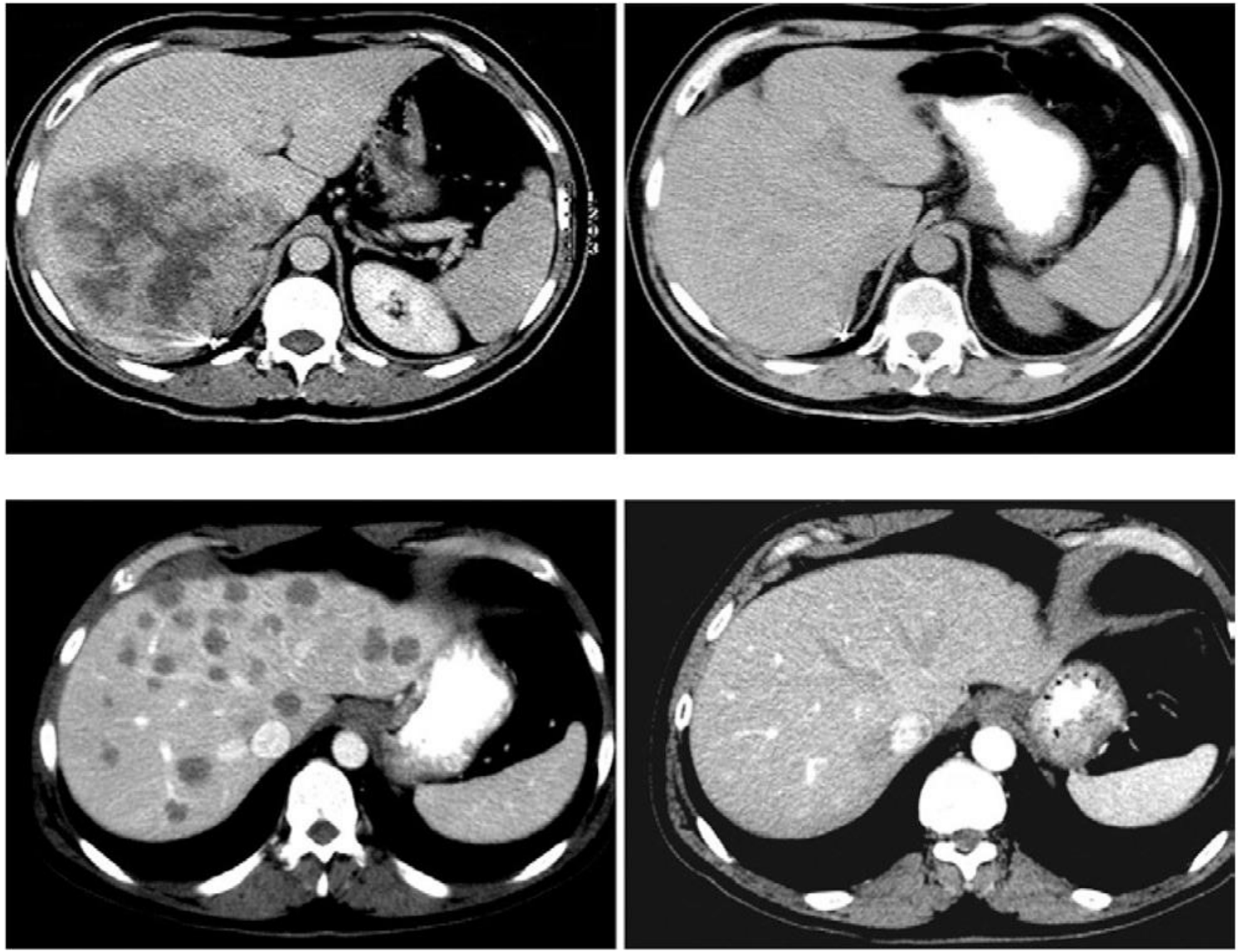
NCT04862767

- TASO-001 in Combination With Recombinant Interleukin-2(Aldesleukin) in Advanced or Metastatic Solid Tumor
- Multi-center, Open Label, Phase Ib Clinical Trial to Evaluate Safety, Tolerance and Efficacy of TASO(TGF-β2 Targeting Anti-sense Oligonucleotide)-001 in Combination With Recombinant Interleukin-2 in Advanced or Metastatic Solid Tumor
- To evaluate safety, tolerance and efficacy of TASO(TGF-β2 targeting anti-sense oligonucleotide)-001 in combination with recombinant interleukin-2(Aldesleukin) in advanced or metastatic solid tumor and to find appropriate dose for phase 2 clinical trial.
- This clinical trial is conducted by dividing into two cohorts according to the dose of the test drug, starting with Cohort 1, and confirming whether DLT occurs until 14 days after the 2nd cycle of the test drug administration and proceed with Cohort 2 after discussion by DMC. Recruitment of each cohort is applied with a 3+3 design.
- Safety was confirmed at 140 mg/m2 of OT-101 and IL-2
- Expansion into phase 2 and higher dose of 190 mg/m2

IL-2 single agent activity – To be improved on by OT-101

- Upper panel, Fifty-six– year-old male with metastatic renal cell cancer to the liver and subcarinal lymph nodes was treated with high-dose bolus IL-2 in January 1994. Patient underwent a complete regression of all disease and remains disease-free 20 y later. Upper middle panel, Fifty-four– year-old male with metastatic melanoma to the lungs and liver was treated with autologous TILs plus IL-2 following a lymphodepleting regimen in December 2003. The patient underwent a complete regression of all disease and remains disease-free .10 y later.
- J Immunol 2014; 192:5451-5458



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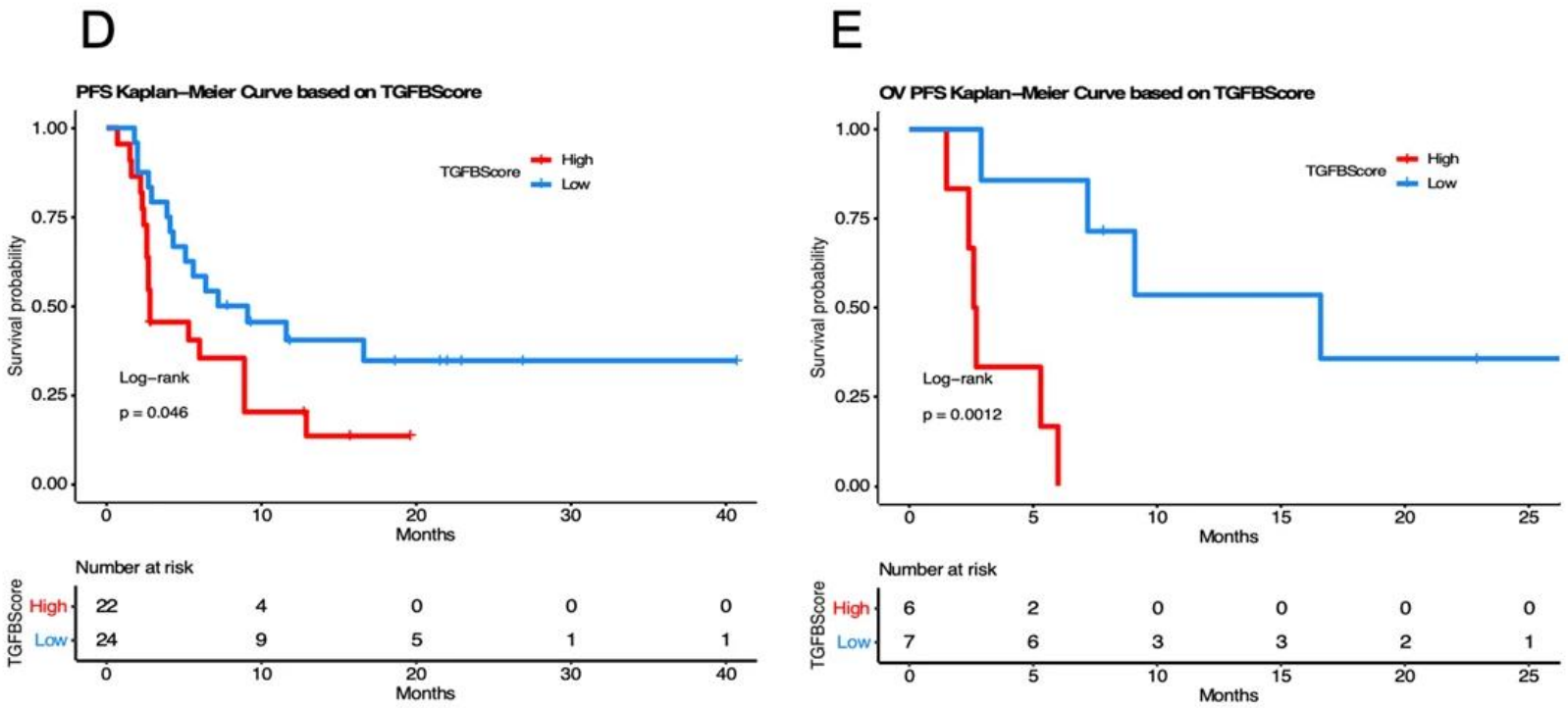
OT-101 Biomarker Program

- 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).

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).



Low TGF-beta signature is predictive out improved outcome to immunotherapy

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.

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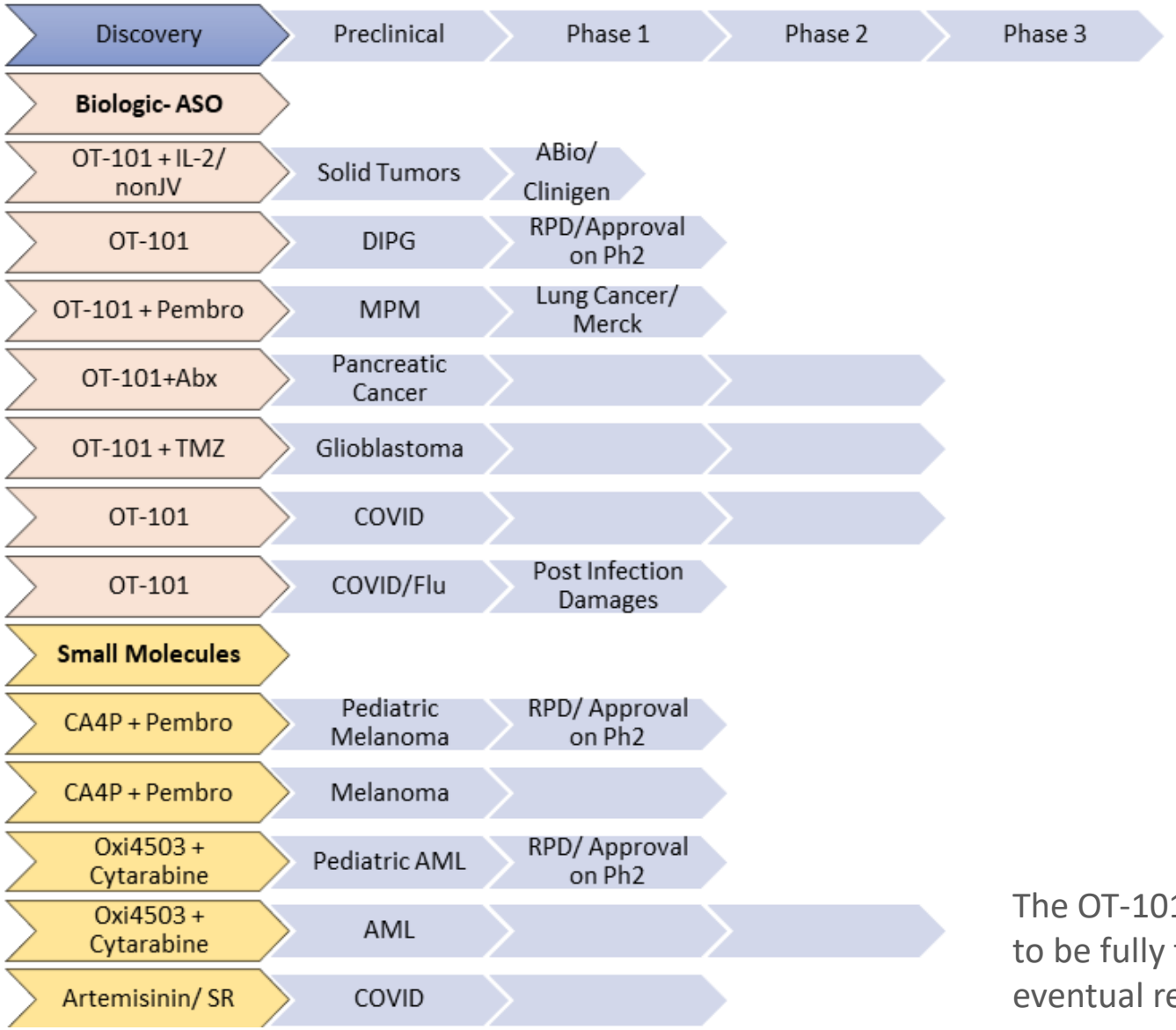
Keytruda Agnostic Approval

- On June 16, 2020, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- The FDA also approved the FoundationOneCDx assay (Foundation Medicine, Inc.) as a companion diagnostic for pembrolizumab.
- Efficacy was investigated in a prospectively-planned retrospective analysis of 10 cohorts of patients with various previously treated unresectable or metastatic TMB-H solid tumors enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067). Patients received pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression.
- A total of 102 patients (13%) had tumors identified as TMB-H, defined as TMB ≥10 mut/Mb. The ORR for these patients was 29% (95% CI: 21,39), with a 4% complete response rate and 25% partial response rate. The median DoR was not reached, with 57% of patients having response durations ≥12 months and 50% of patients having response durations ≥24 months.
- We are planning to follow the same regulatory pathway for OT-101/Pembro

Pipeline (Oncology and Virology)



The OT-101 program is on track to be fully funded by JV for eventual re-IPO.

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