Clinical Immune Monitoring and Biomarker Data of Tavo Monotherapy Compared to Tavo with Pembrolizumab in Metastatic Melanoma Supports the Rationale for Combination Therapy

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Disclosure

I have the following potential conflict(s) of interest to report.

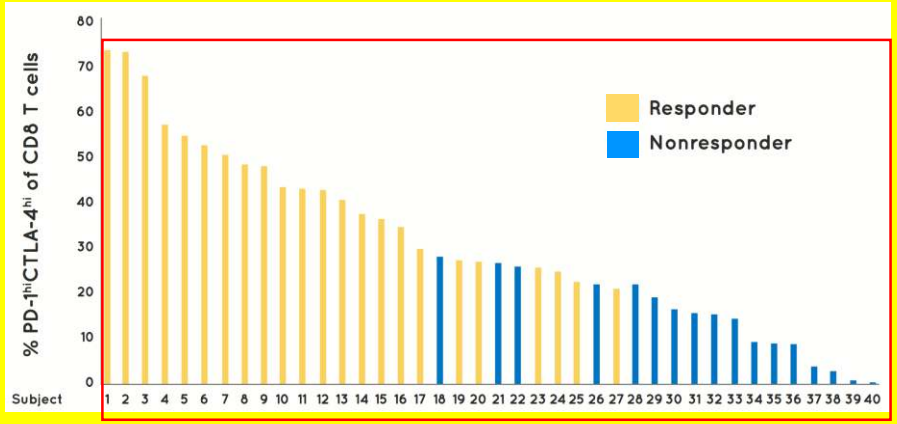
- I participate in research funded by:
    - Acerta
    - AstraZeneca
    - Bristol Myers Squibb
    - Dynavax
    - Genentech
    - Incyte
    - Medimmune
    - Merck
    - Novartis
    - OncoSec
- I serve as an unpaid advisor to OncoSec Medical Incorporated

Both clinical trials are in patients with metastatic melanoma with accessible lesions

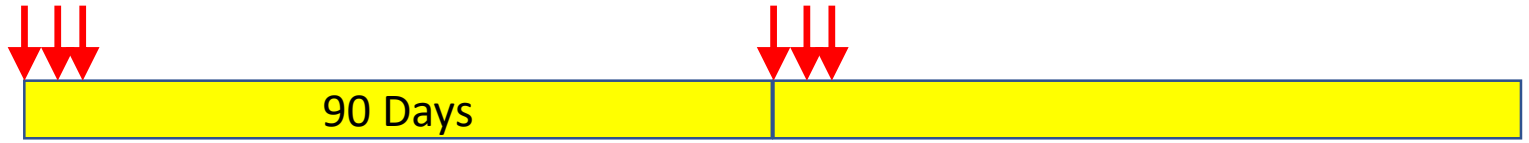
	OMS-I100	OMS-I102
Phase	2	2
Centers	Multi	Multi
Therapy	IT-tavo-EP	IT-tavo-EP / pembrolizumab
	IT-tavo-EP D1, 5, 8 or D1, 8, 15 Q6w or q90d	IT-tavo-EP D1, 5, 8 q6w pembrolizumab 200 mg IV q3 weeks
Patients	Metastatic melanoma	Metastatic melanoma predicted to be PD-1 non responders
Efficacy Endpoint	ORR by modified skin RECIST	ORR by RECIST v1.1

Clinical Trial Designs

No selection for PD-1^{hi}CTLA-4^{hi}

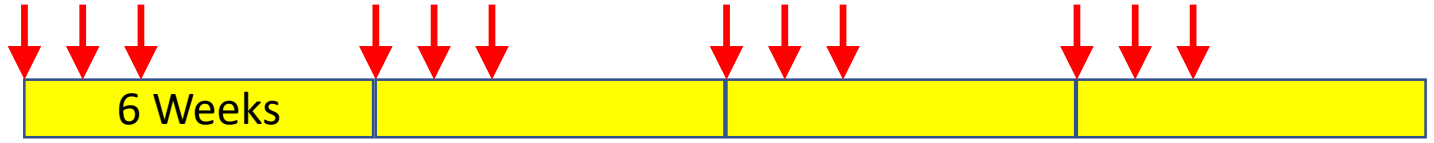


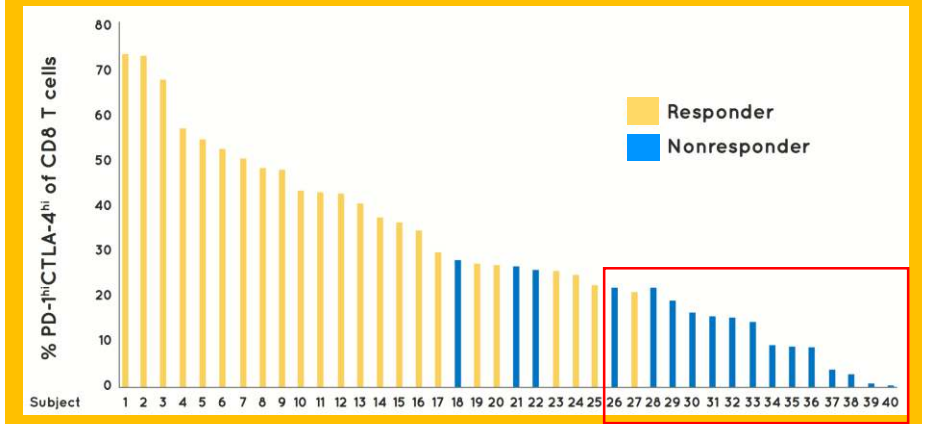
IT-tavo-EP
D 1, 5, 8



IT-tavo-EP
D 1, 8, 15

OMS-I100

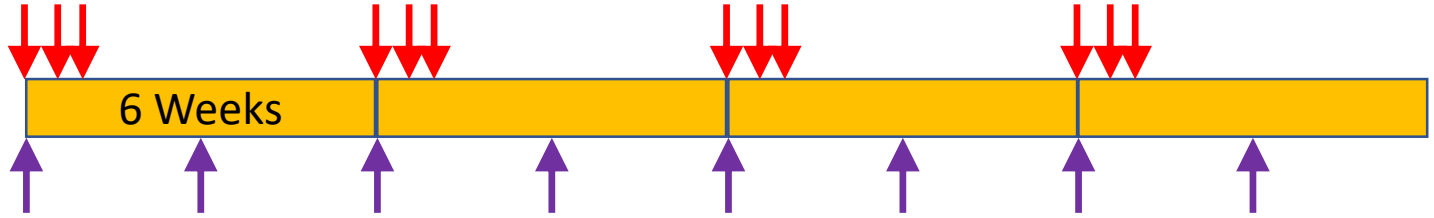




Selection for PD-1^{hi}CTLA-4^{hi}

IT-tavo-EP
D 1, 5, 8

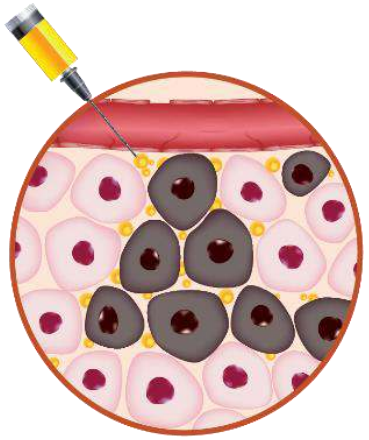
OMS-I102



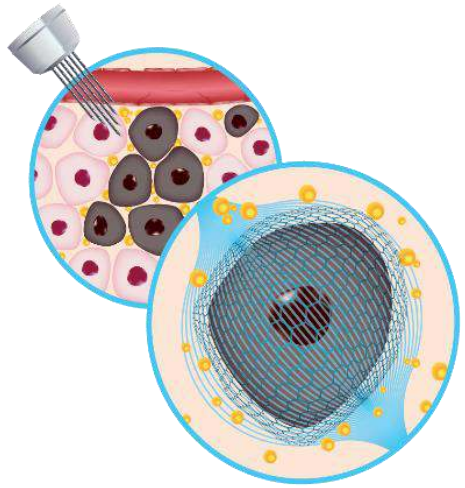
Pembrolizumab
D1, 22

tavokinogene telseplasmid **(tavo; pIL-12)** delivery by electroporation

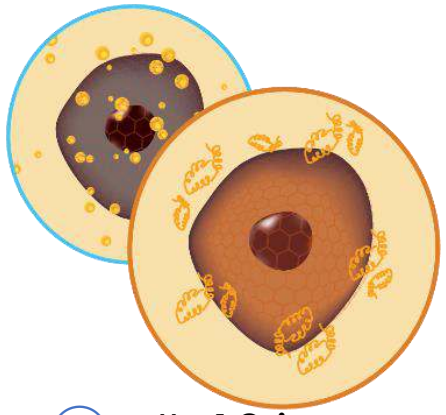
- Interleukin-12 (IL-12) is a potent, well-characterized pro-inflammatory cytokine
- Intratumoral delivery of IL-12 stimulates a safe but powerful immune response



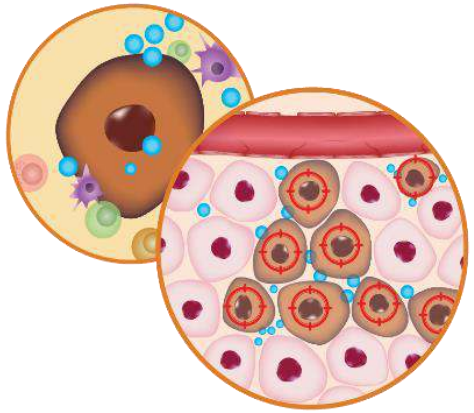
① Injection of tavokinogene telseplasmid **(tavo)**



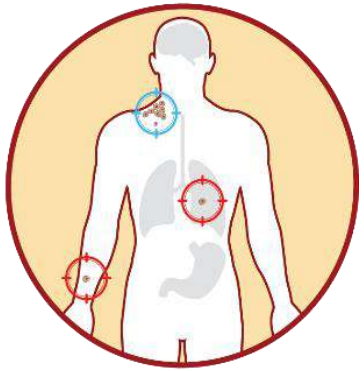
② Intratumoral electroporation delivers tavo into the cells



③ IL-12 is expressed and secreted



④ Local inflammation and T cell education



⑤ Systemic anti-tumor immune response

Patient demographics were similar between the trials

	OMS-I100 tavo monotherapy	OMS-I102 tavo + pembro combination
Age (years)		
N / mean (SD)	N=51/ 66.7 (11/2)	N=23 / 65.5 (12.2)
Median, min max	65.0, 44, 89	67, 39, 91
Sex - Male / Female	33 (64.7%) / 18 (35.3%)	13 (56.5%) / 10 (43.5%)
Stage at enrollment		
Stage III b and IIIc	29 (56.8 %)	14 (60.9%)
Stage IV M1a and M1b	19 (36.3%)	4 (17.4%)
Stage M 1c	3 (5.9%)	5 (21.7%)
Prior checkpoint inhibitors		
αPD-1	8	10
αCTLA-4	16	7
BRAF		
Mutant	17 (33.3%)	7 (30.4%)
Unknown, not tested	34 (66.7%)	16 (59.6%)

Less than 10% Treatment Emergent Serious AE reported to date in monotherapy or in combination

Preferred Term	OMS-I100 tavo monotherapy N=51	OMS-I102 tavo + pembro combination N=23
Patients reporting any TESAE	**5 (9.8%)**	**2 (8.7%)**
Coronary Artery Disorder		
Non ST- elevation myocardial infarction	0	1 (4.3%)
Infections and infestations		
Cellulitis	1 (2.0%)*	1 (4.3%)*
Musculoskeletal and connective tissue disorder		
Rhabdomyolysis	1 (2.0%)	0
Nervous System Disorder		
Cerebrovascular accident	1 (2.0%)	0
Dizziness	1 (2.0%)	0
Respiratory, thoracic, and mediastinal disorder		
Pulmonary embolism	1 (2.0%)	0

*possibly related

Clinical relevant responses

BORR	OMS-I100 Tavo D 1,5,8 @90d monotherapy N=26	OMS-I100 Tavo D 1,8,15 @ 6 weeks monotherapy N=20	OMS-I102# Tavo + pembro Combination *in predicted αPD-1 non responders* N=22
BORR (CR + PR)*	**9 (34.6%)**	**5 (25%)**	**11 (50%)**
DCR (CR + PR +SD)*	18 (69.2%)	13 (65.0%)	13 (59.0%)
CR	5 (19.2%)	0	9 (41.0%)
PR	4 (15.4%)	5 (25.0%)	2 (9.0%)
SD	9 (34.6%)	8 (40.0%)	2 (9.0%)
PD	8 (30.8%)	7 (35.0%)	9 (41.0%)

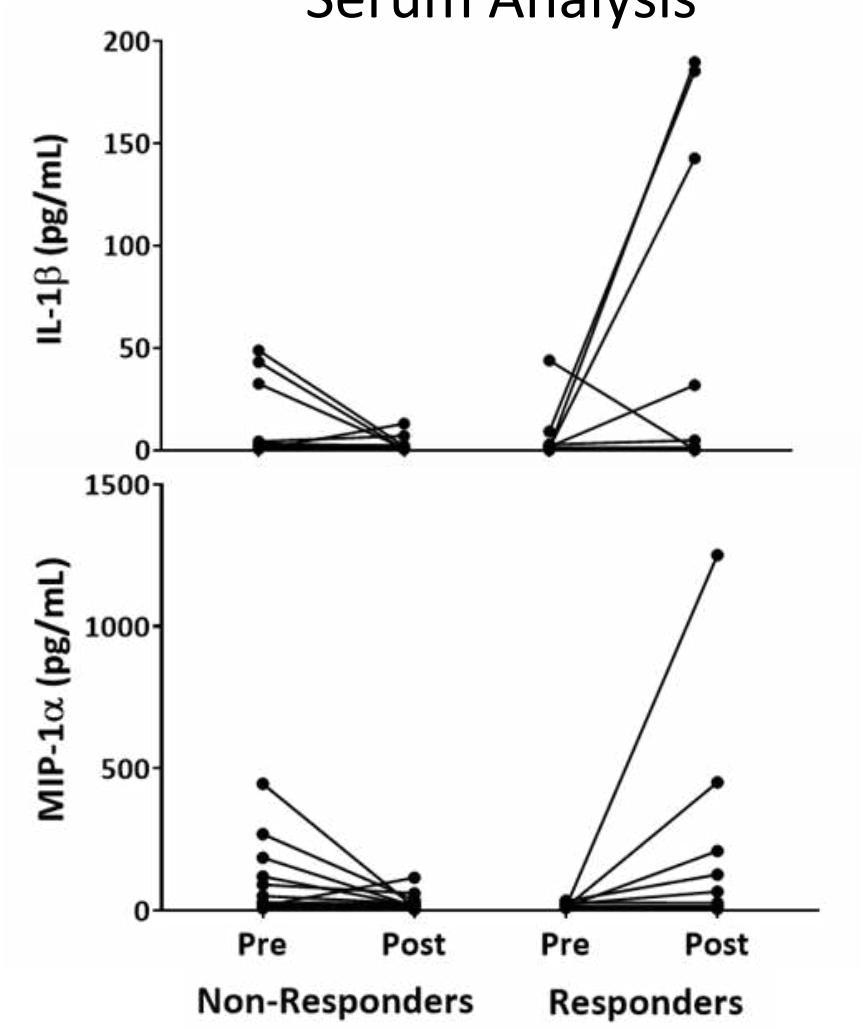
OMS-I102 patients were selected based on biomarker data, thus the PISCES /Keynote 695 trial to address the patient populations

*OMS-I100 was modified skin RECIST and OMS-I102 RECIST with one pseudo progression. RECISTv1.1 BORR was 42.9%

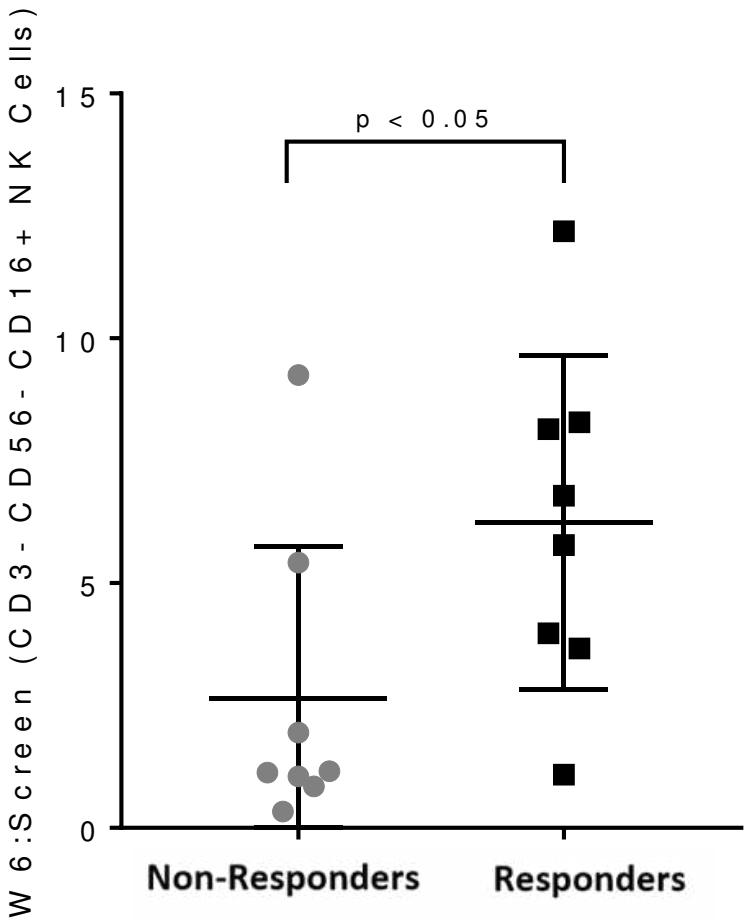
What is the mechanism of the immune responses observed?

Upregulation of innate immune mediators in the periphery of responding patients after monotherapy

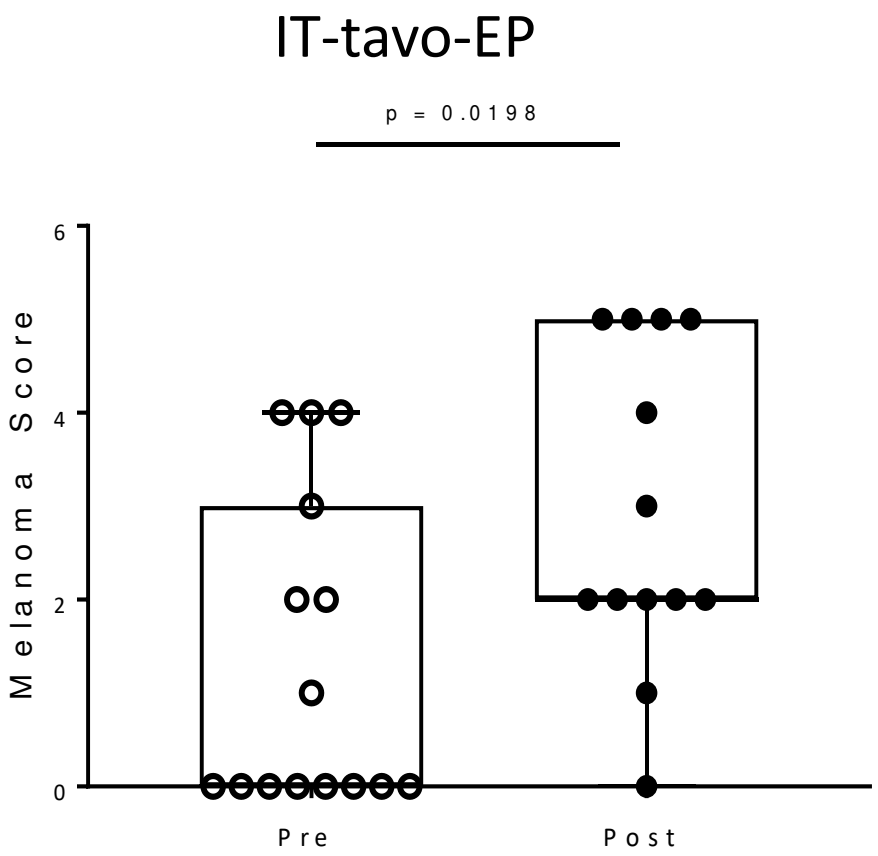
Serum Analysis

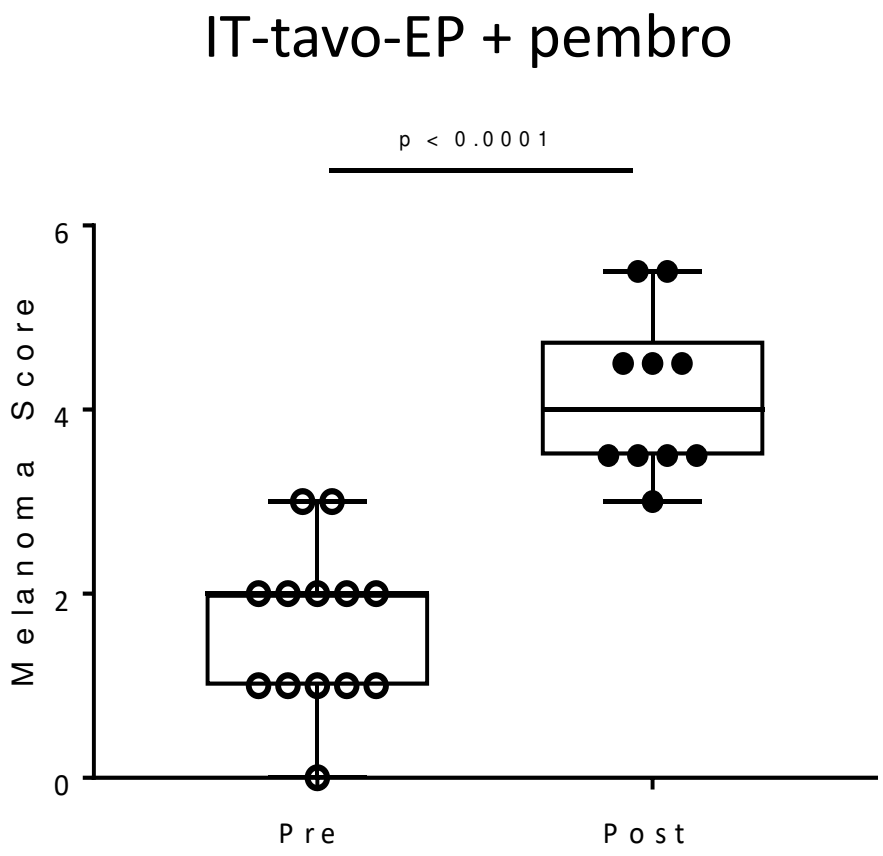


PBMC – Flow Analysis

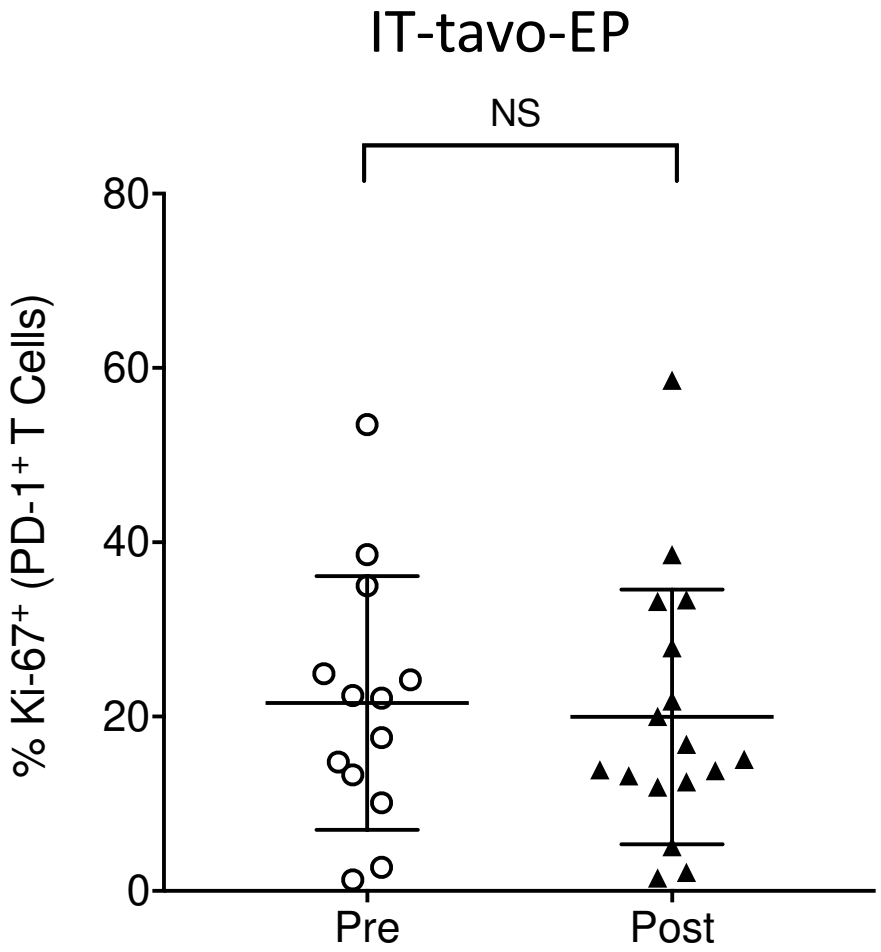


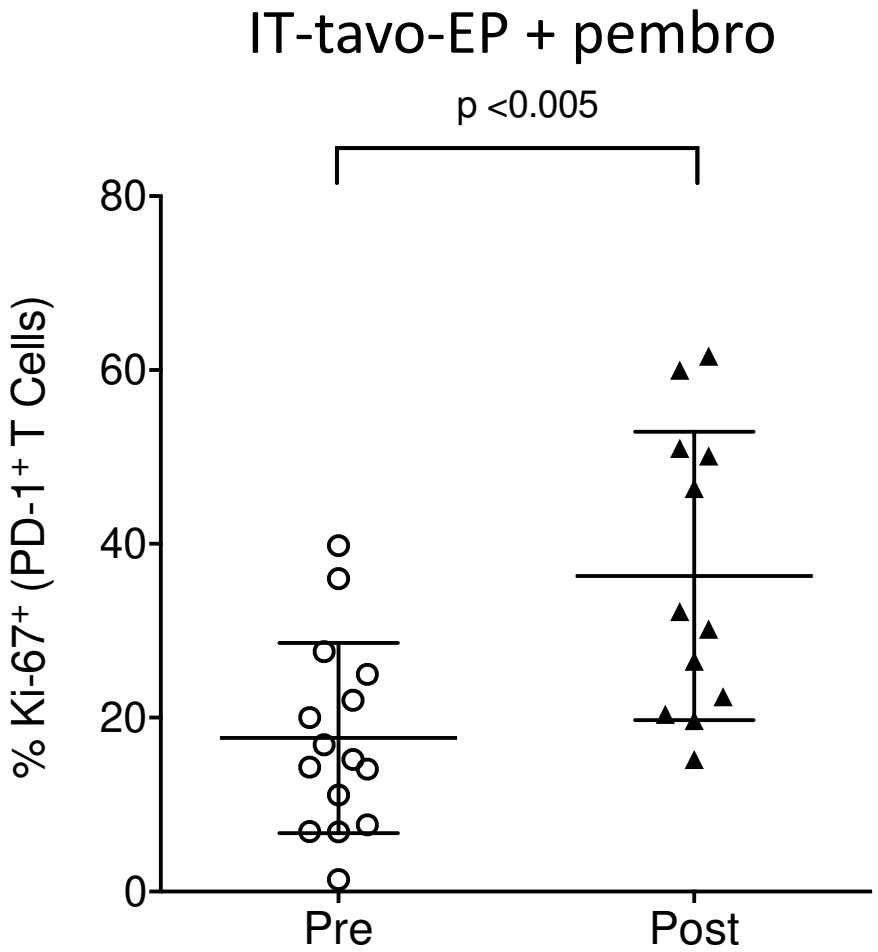
Intratumoral tavo triggers adaptive resistance which is enhanced with anti-PD-1 combination



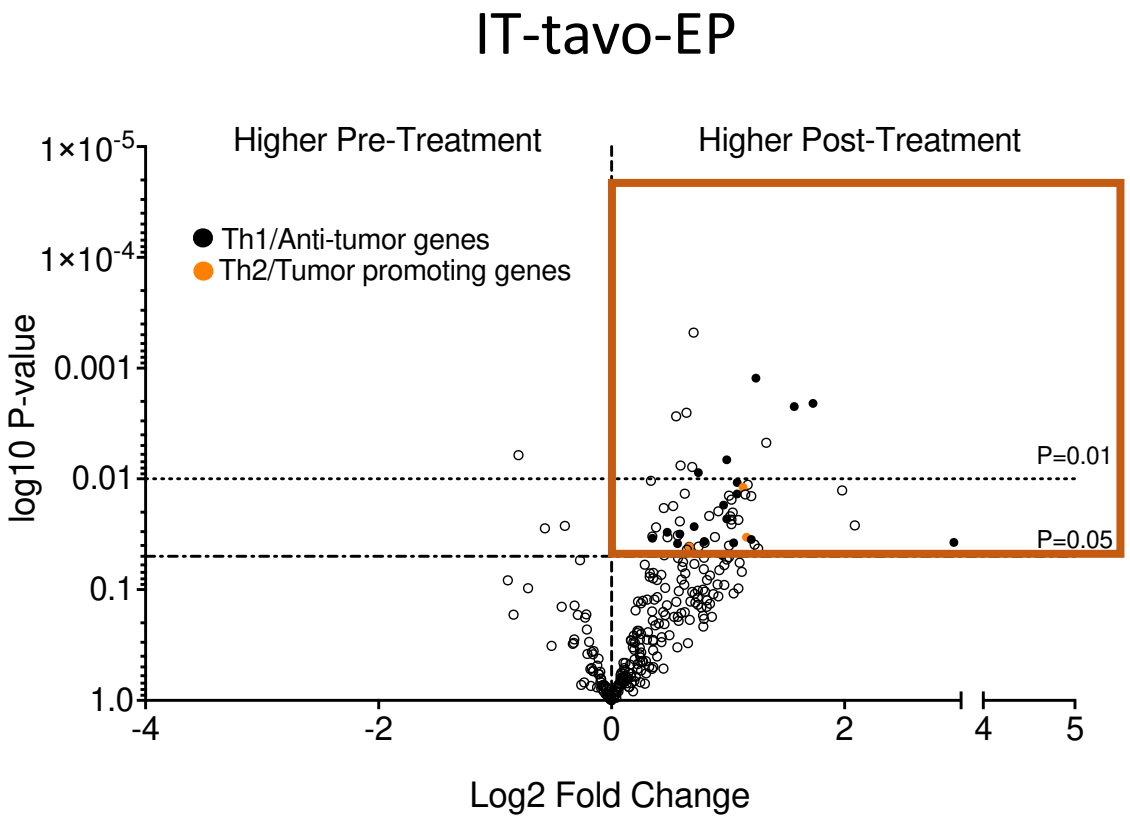


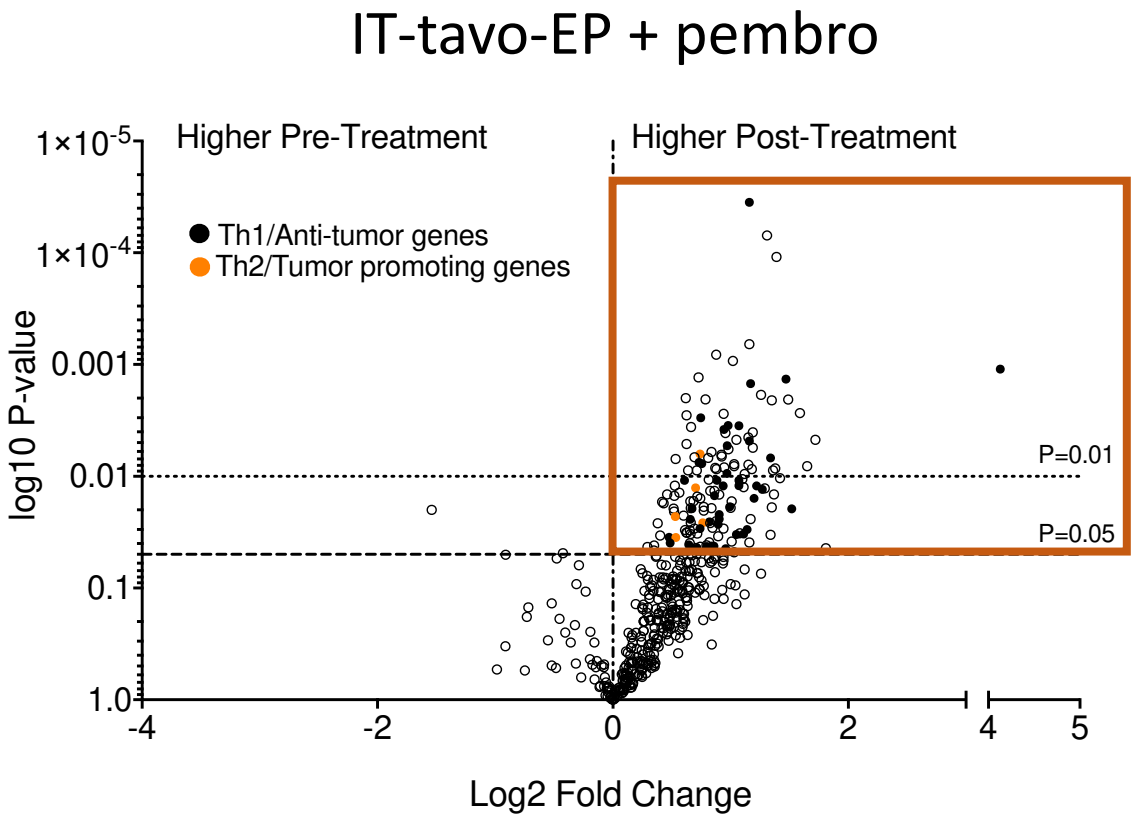
Significant increase of proliferating “partially exhausted” CD8+ T cells with combination therapy



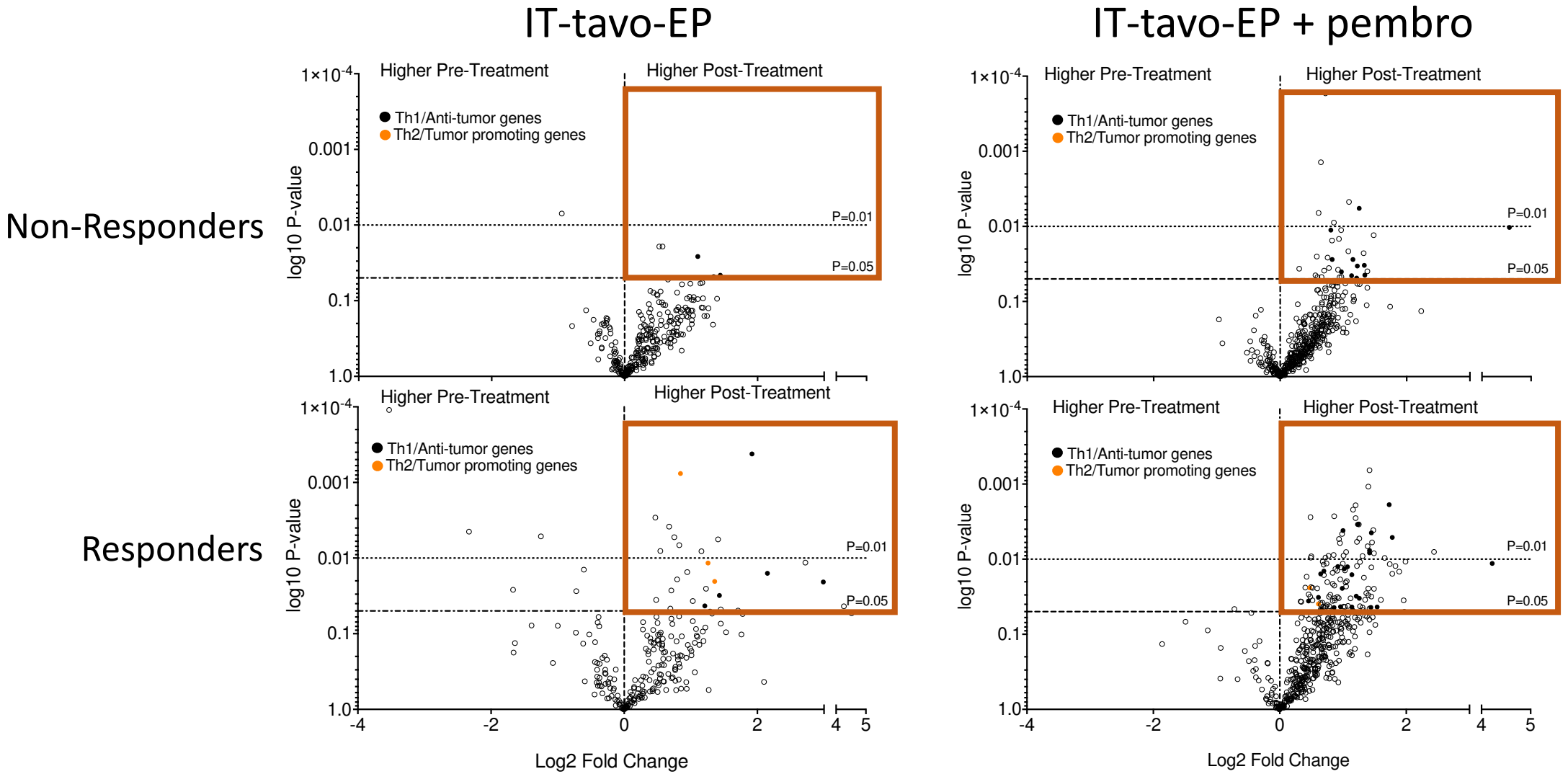


Combination increases post-treatment intratumoral expression of NanoString immune-based gene set

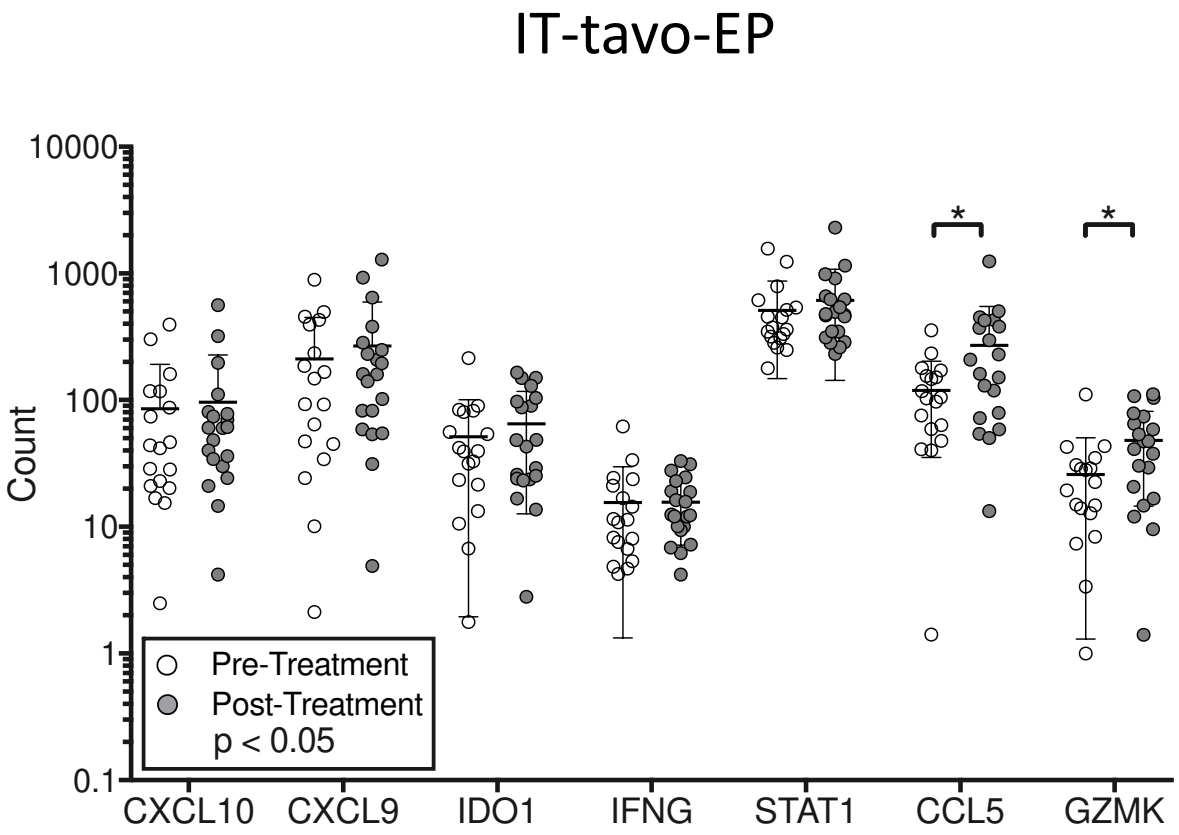


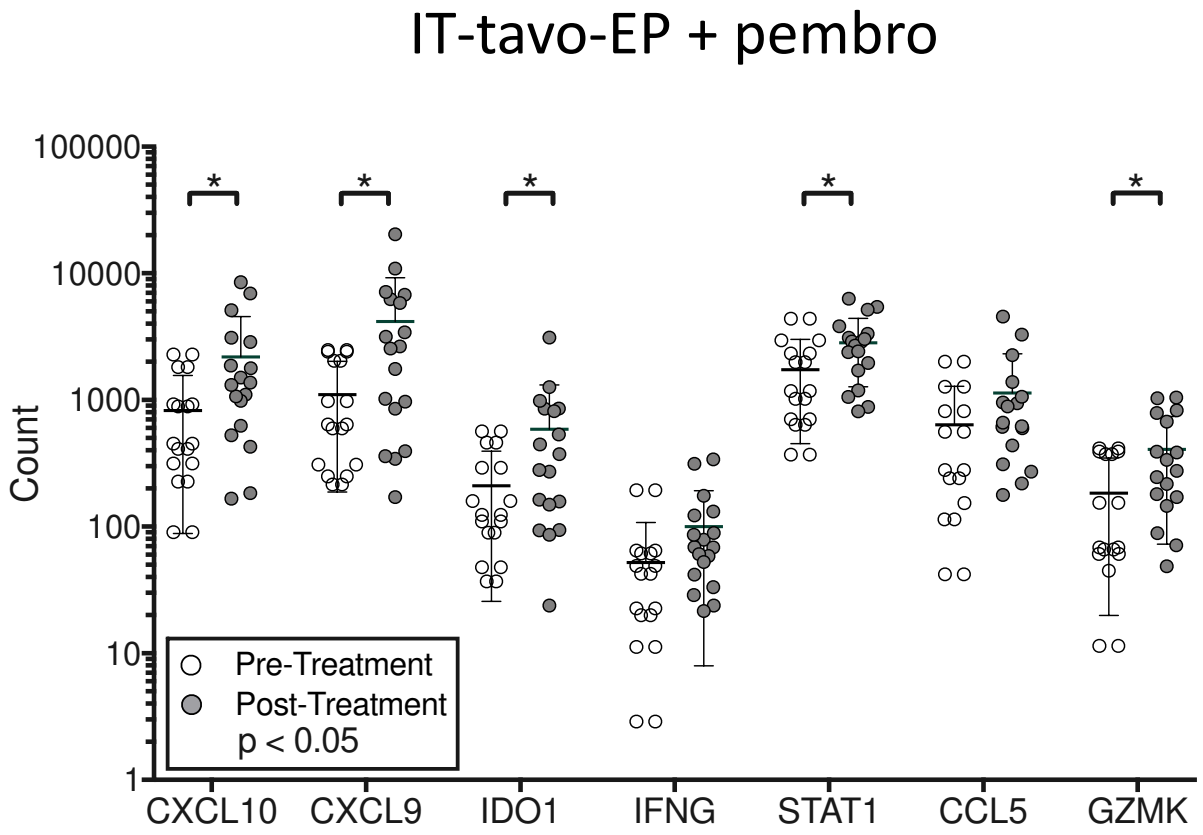


Treatment-related increased Th1/anti-tumor-related gene expression pronounced in responders



Combination therapy significantly increases IFN-γ responsive genes in the tumor microenvironment





Conclusions

- Clinically
  - IT-tavo-EP is well tolerated (<10% SAE) alone and in combination with pembrolizumab
  - BORR 25-34.6% with IT-tavo-EP alone
  - Clinically meaningful response rate in predicted non-responders to αPD-1 was 50% with IT-tavo-EP + pembrolizumab
- Immunologically
  - Systemic innate responses with IT-tavo-EP but combination drives the frequency of peCTL
  - Increase of adaptive resistance with IT-tavo-EP is augmented with combination therapy
  - Increased intratumoral Th1/IFN-γ gene expression is augmented with combination therapy

IT-tavo-EP promotes innate and adaptive cellular responses, triggering adaptive resistance and a partially exhausted immune response that pembrolizumab is able to reinvigorate leading to increased efficacy

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