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Intratumoral CD40 Agonist Sotigalimab (APX005M) with Pembrolizumab Induces Broad Innate and Adaptive Immune Activation in Local and Distant Tumors in Metastatic Melanoma

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Presenter Disclosure Information

Salah-Eddine Bentebibel

I have no financial relationships to disclose.

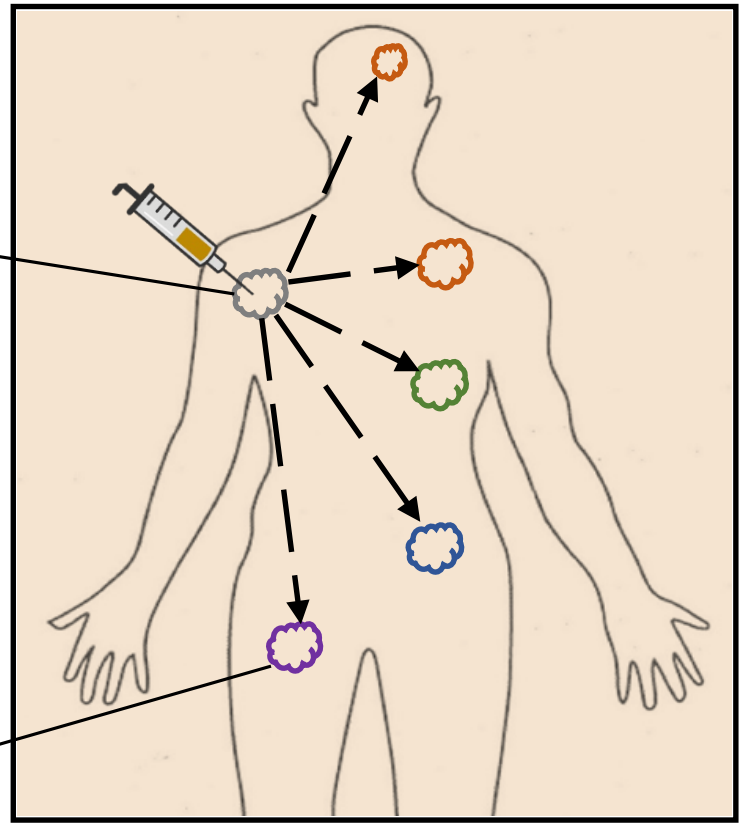
In Situ Priming of Intratumoral Immunity (Vaccine Effect)

Local Priming

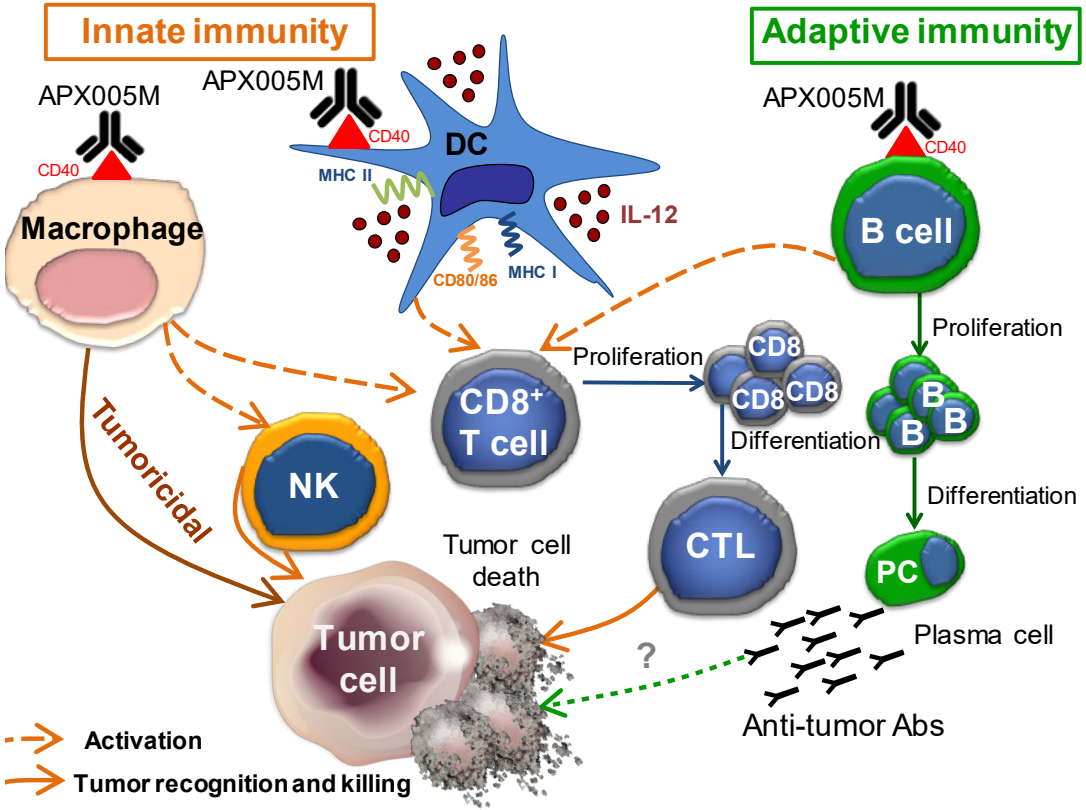
Intra-tumoral injection of immunostimulatory agents to trigger tumor-specific immunity

Distant Effects

Systemic anti-tumor immunity against non-injected tumor sites



Sotigalimab (APX005M) : Harnessing the CD40 Pathway to Activate Innate and Adaptive Immunity



- The use of immune-checkpoint inhibitors (CPI) is an important modality for the treatment of metastatic melanoma
- New combinations are needed to improve benefit-risk profiles
- Sotigalimab is a humanized IgG1 mAb against human CD40
- Sotigalimab binds the ligand binding domain of CD40

Objectives of our Study

- Assess the safety and tolerability of the combination of sotigalimab and pembrolizumab.
- Define the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D).
- Assess objective response rate (ORR) based on RECIST 1.1.
- Measure biomarkers in blood and tumor samples.

Dose-Escalation and Recommended Phase 2 Dose Expansion

Phase 1 (N=14)

CPI Treatment-Naïve

- Histologically or cytologically confirmed cutaneous or mucosal melanoma
- Measurable, unresectable stage III or IV disease.
- Measurable disease per RECIST 1.1
- ECOG 0 or 1
- Adequate organ function
- Fresh biopsy and archival tissue

I.V. Pembro 2 mg/kg + I.T. Sotigalimab 10mg

I.V. Pembro 2 mg/kg + I.T. Sotigalimab 3 mg

I.V. Pembro 2 mg/kg + I.T. Sotigalimab 1 mg

I.V. Pembro 2 mg/kg + I.T. Sotigalimab 0.5 mg

I.V. Pembro 2 mg/kg + I.T. Sotigalimab 0.1 mg

Pembro 2 mg/kg + Sotigalimab 10 mg

Recommended Phase 2 Dose (RP2D)

Phase 2 (N= ~20) underway

As of December 30, 2021, 30 patients were enrolled. Patients received sotigalimab every 3 weeks for a total of 4 injections

Patient Demographics and Disease Characteristics

Characteristic	Total n (%) (N=30)
Sex	
Male	26 (87%)
Female	4 (13%)
Age (years)	
Median (Range)	65 (32-81)
ECOG Performance Status	
0	17 (57%)
1	13 (43%)

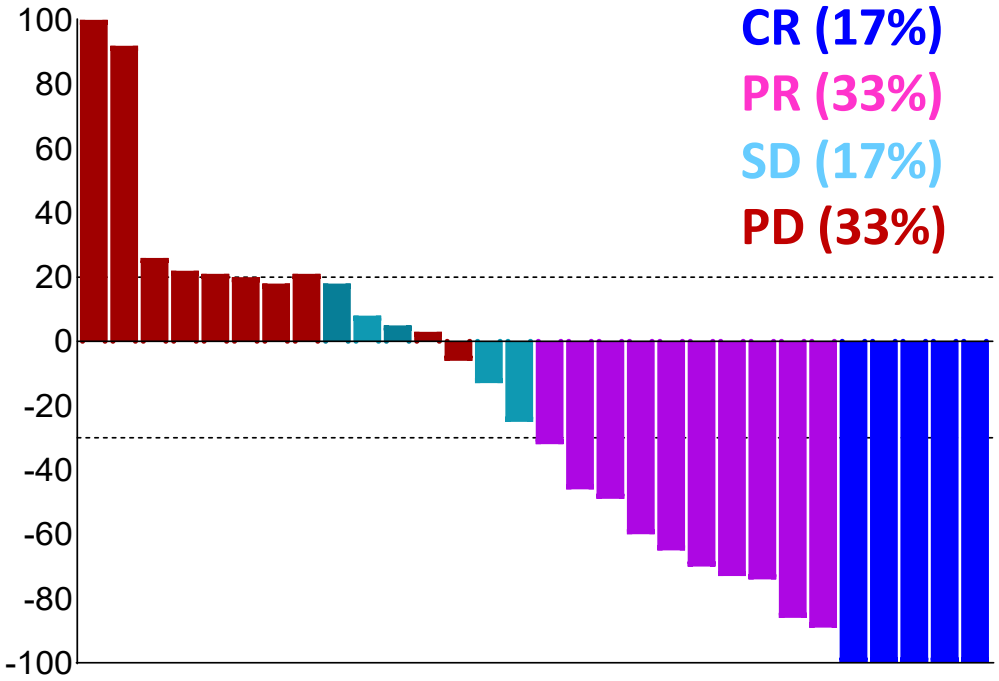
Characteristic	(N=30)	%
BRAF status		
Positive	10	38
Negative	18	54
Unknown	2	8
LDH at baseline		
< ULN	14	47
> ULN	7	23
×2 ULN	9	30
PD-L1 status		
Positive	8	26
Negative	11	37
Unknown	11	37
Stage		
III	7	23
IV M1a or M1b	17	57
IV M1c	6	20

PD-L1 positivity with immunohistochemistry defined by ≥ 1% of tumor cells

Safety and Tolerability

- The combination of sotigalimab with pembrolizumab is well tolerated.
- No study discontinuations or death due to treatment-related adverse events (TRAEs).
- Most common TRAEs were injection-site reactions; 6 patients (20%) experienced grade-3 immune-related adverse events.
- The combination therapy did not induce dose limiting toxicity at any dose level of sotigalimab.

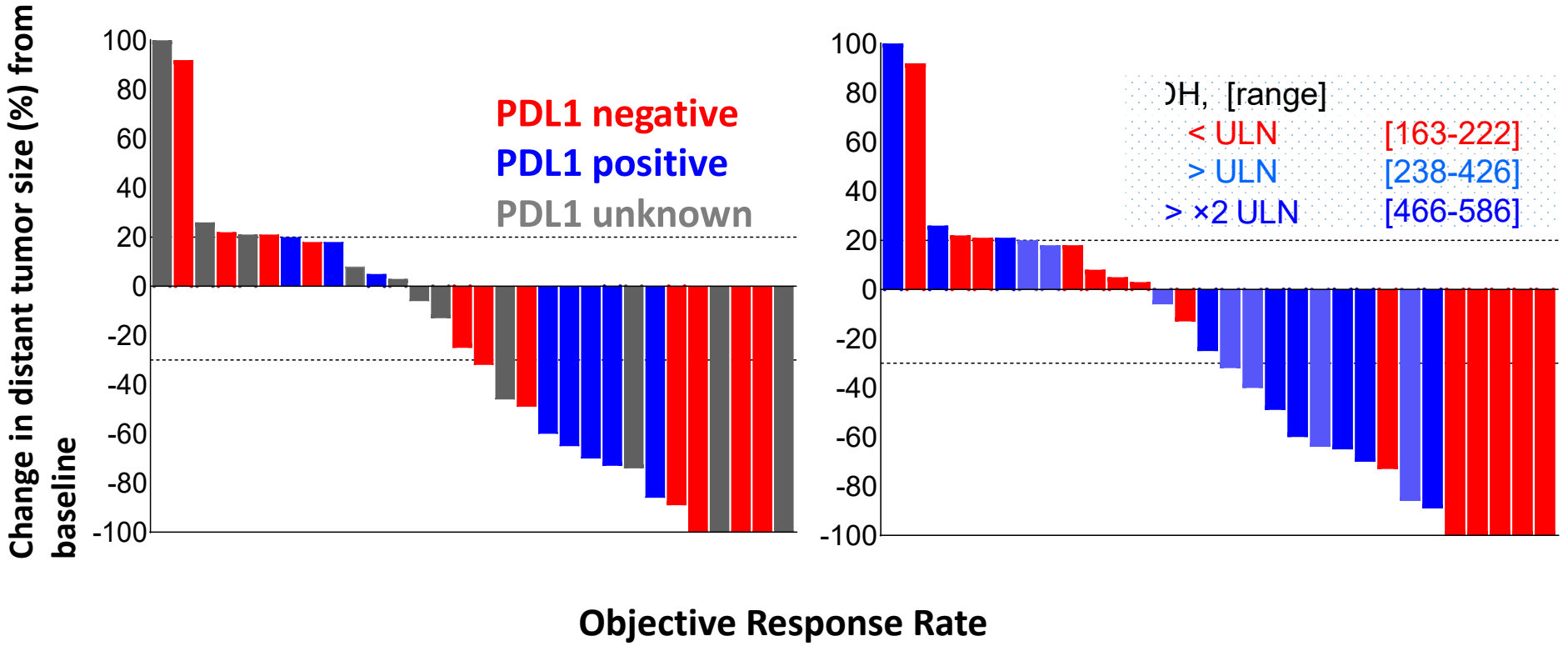
Best Overall Response by RECIST 1.1 as of December 30, 2021



Patients	(N=30)
Total Evaluable	**30**
ORR (CR+PR)	**15 (50%)**
CR	5 (17%)
PR	10 (33%)
SD	5 (17%)
DCR (CR+PR+SD)	**20 (67%)**
PD	10 (33%)

Response rate at the RP2D (10 mg= 12/22 (55%)

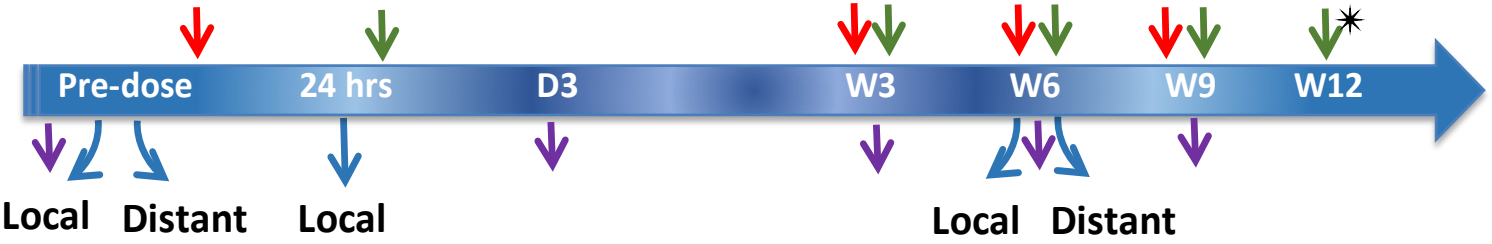
Clinical Responses were Observed in Both PD-L1 Negative Tumors and Patients with Elevated LDH

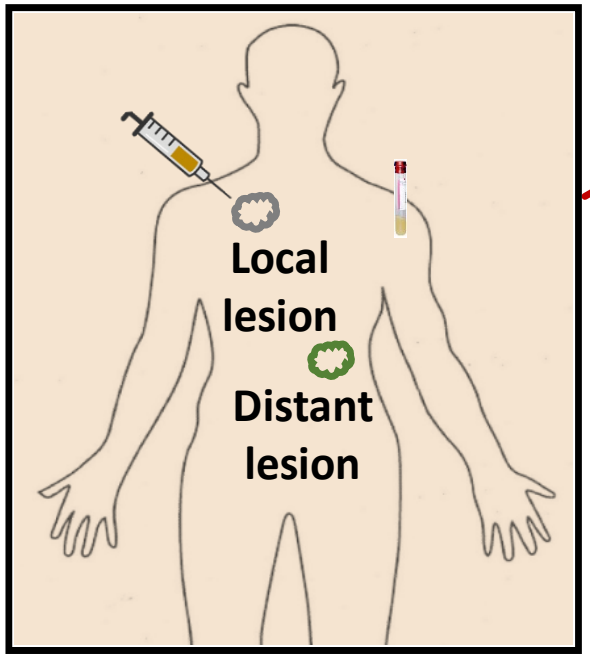


Strategy for Biomarker Analysis

Sotigalimab

Pembrolizumab





Tumor core needle biopsy

NanoString gene expression assay

TCR repertoire analysis using immunoSEQ

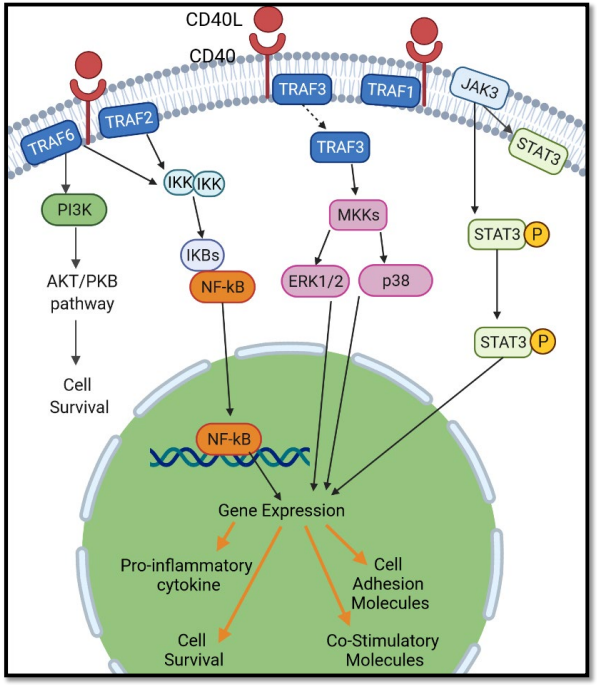
Collection of tumor biopsy Collection of PBMCs

Local = Injected lesion, Distant = Un-injected lesion

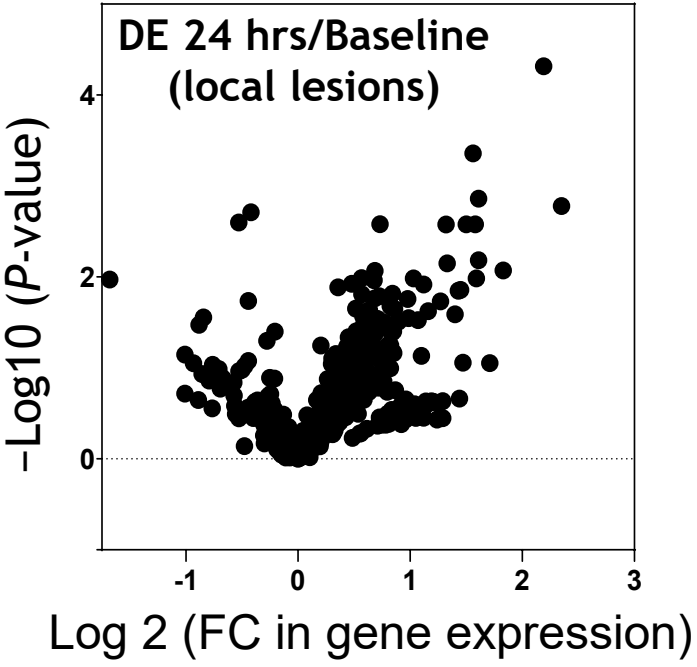
Pembrolizumab administration continues q 3wks

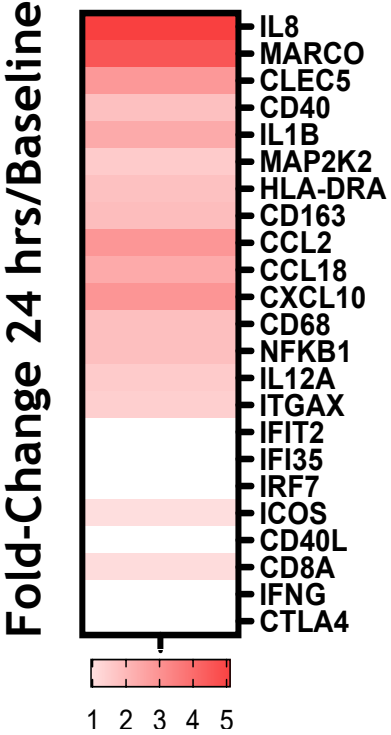
Sotigalimab Engaged CD40 Activation and Up-regulation of Genes Associated with Antigen Presenting Cells (APCs)

CD40 Signaling Pathway



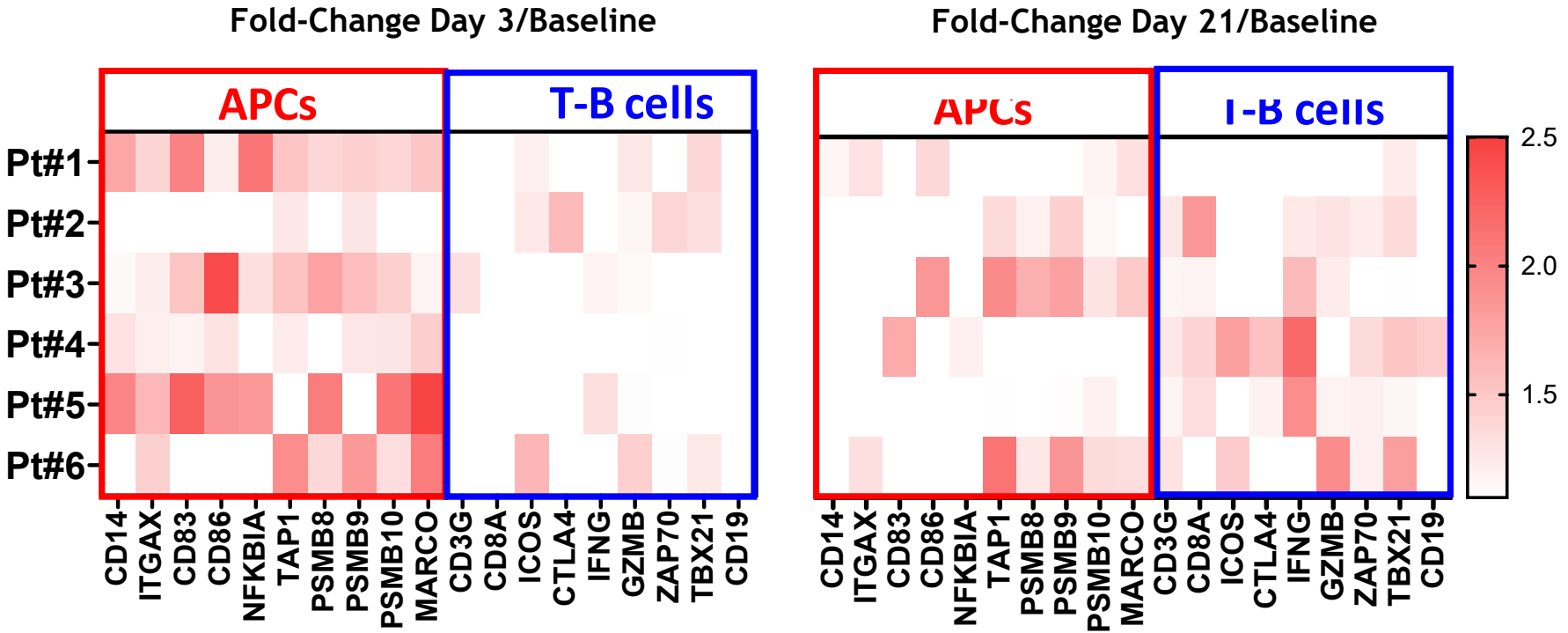
(NanoString Gene Expression)





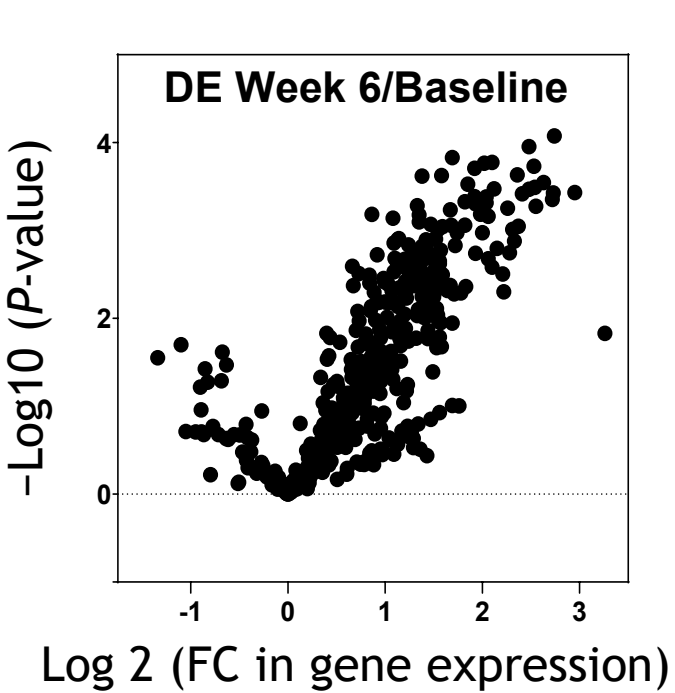
Early Up-regulation of Genes Associated with APCs Followed by Genes Associated with T Cell Activation

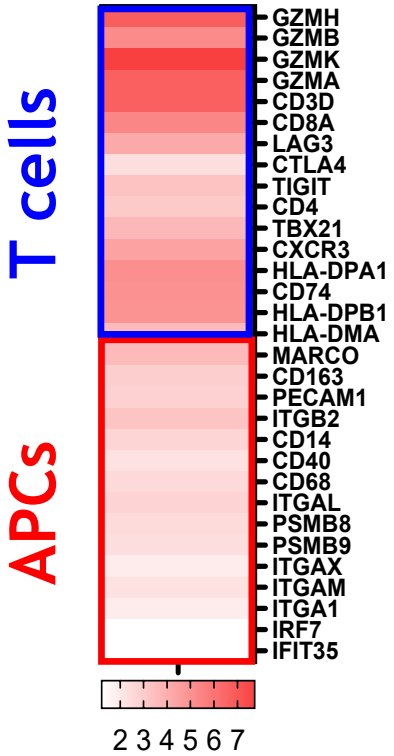
(NanoString gene expression in blood samples)



Sotigalimab with Pembrolizumab Induced the Up-regulation of Genes Associated with APCs and T cells

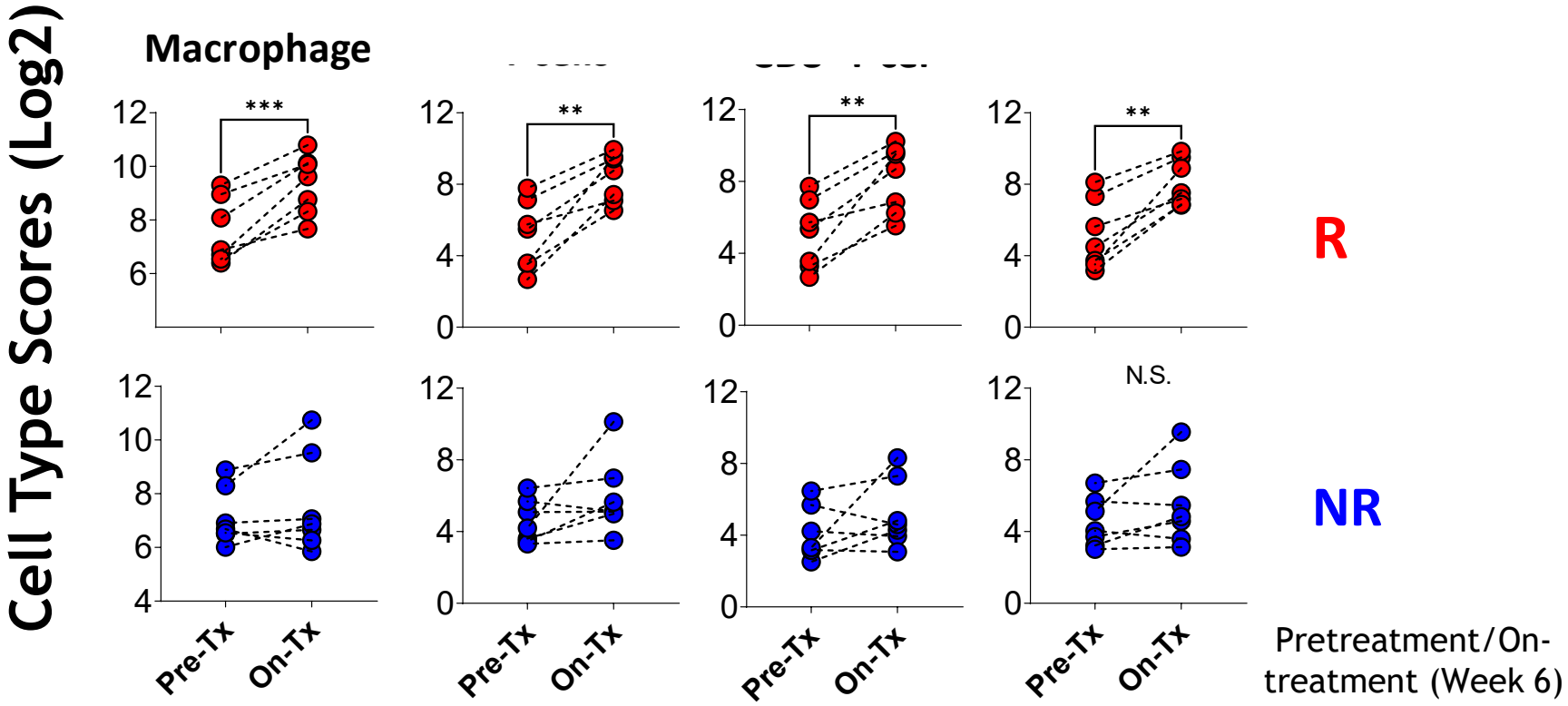
(NanoString Gene Expression) Local Lesions



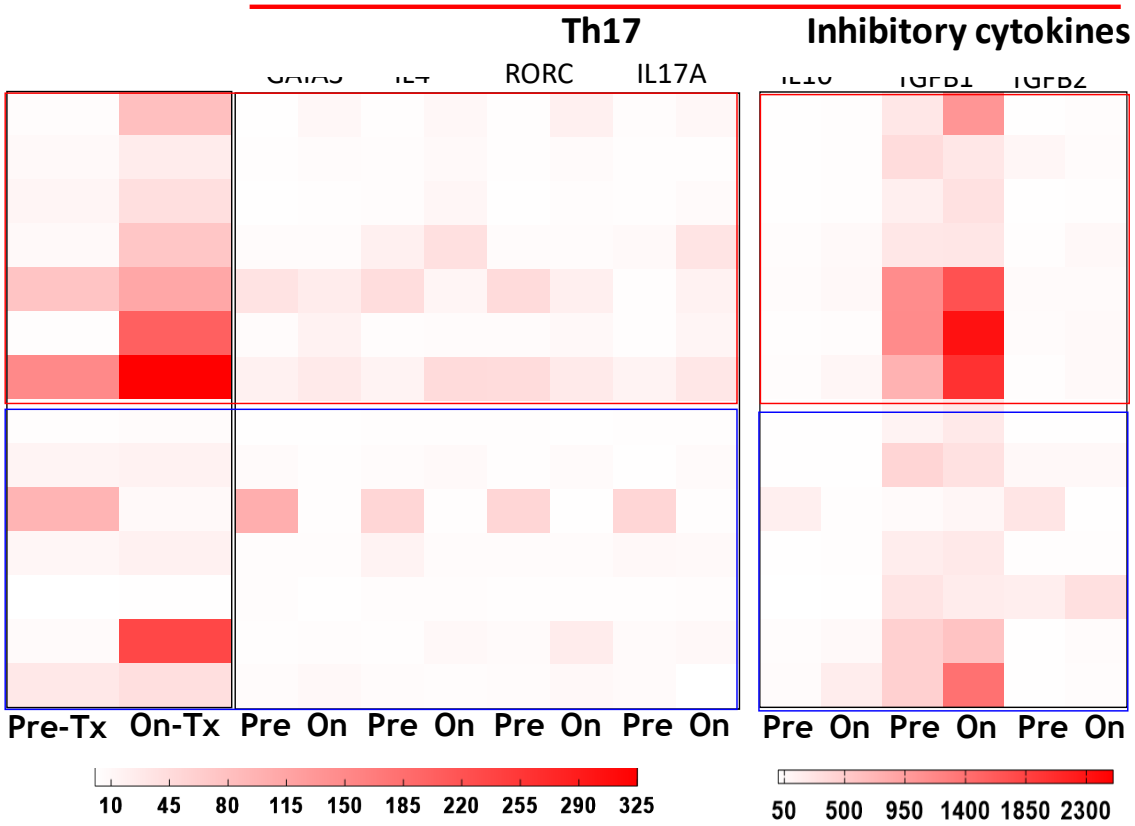


On-treatment Increase in Macrophage, T cells, CD8+ T and Cytotoxic Gene Signatures in Responding Patients

(NanoString Gene Expression) Local Lesions



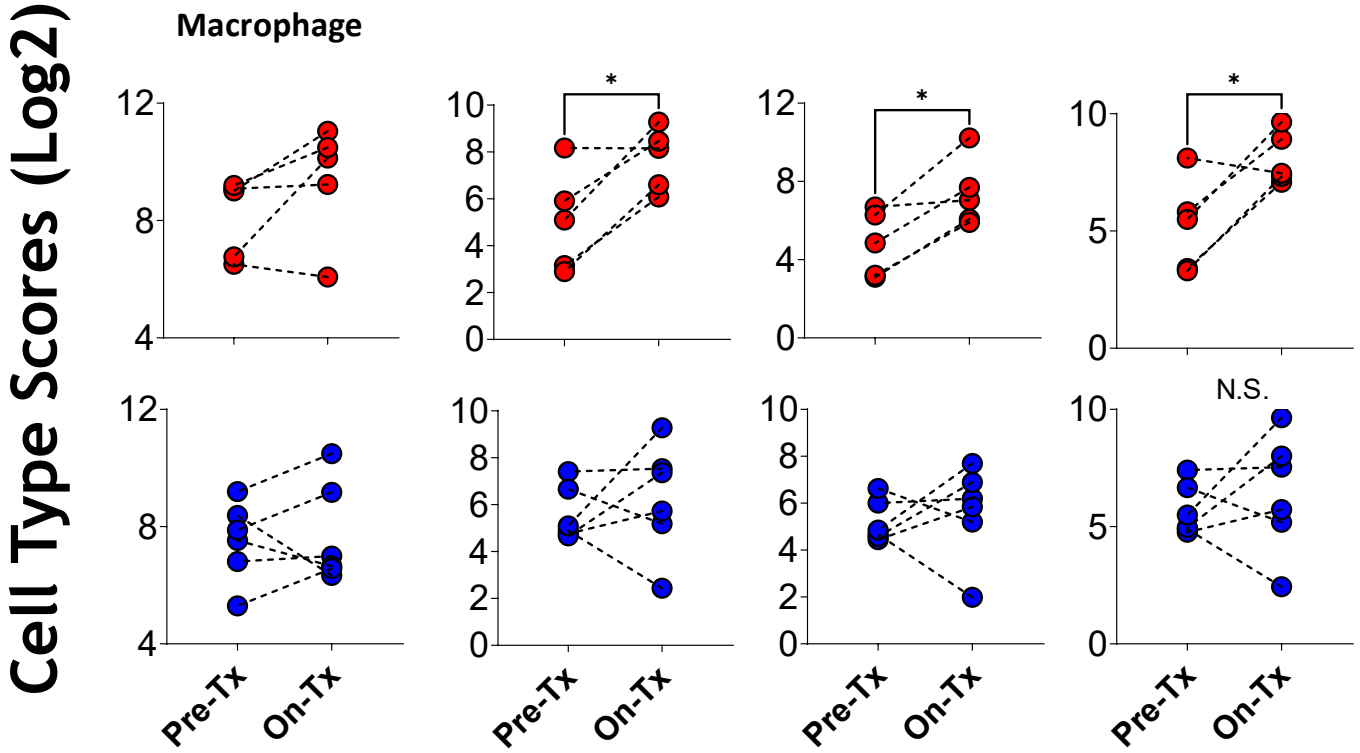
On-treatment Increase in Th1 Gene Signature and TGF-B1 in Responding Patients



Pretreatment/On-treatment (Week 6)

On-treatment Increase in T cells, CD8+ T and Cytotoxic Gene Signatures in Responding Patients

(NanoString Gene Expression) Distant Lesions

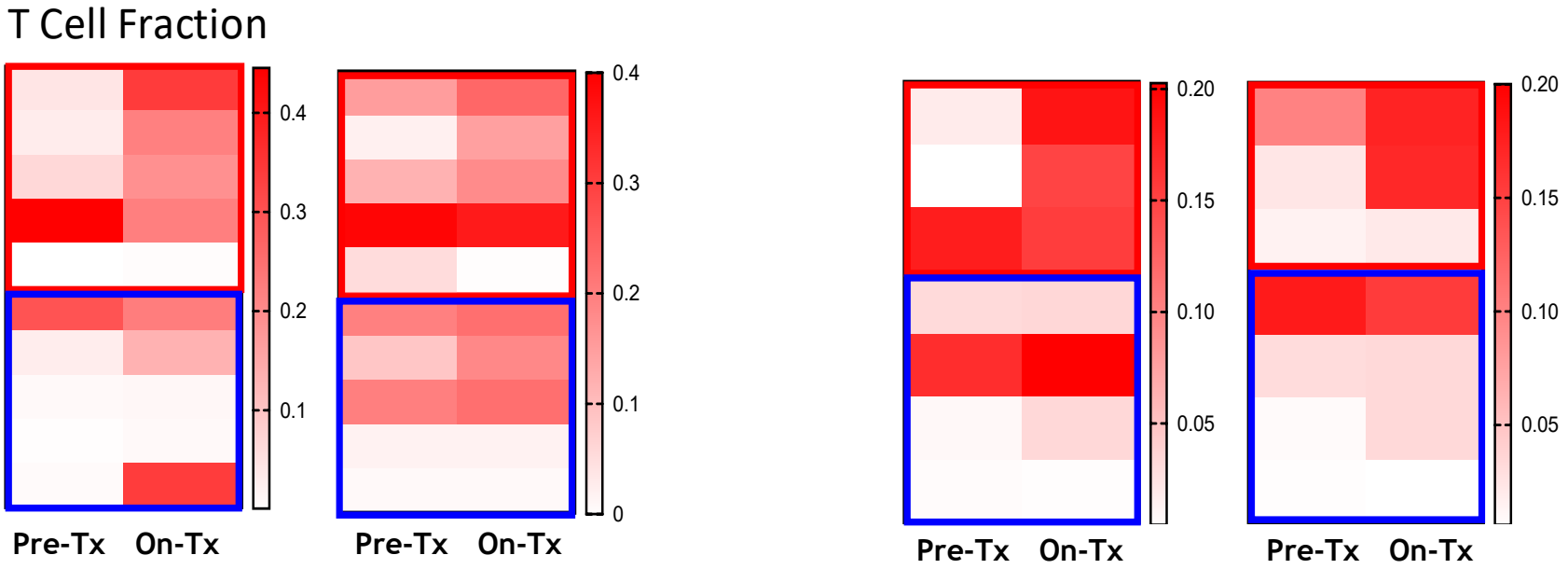


The Combination Treatment Can Lead to an Increase in T cell Infiltration and Clonality

(TCR Sequencing in Tumor Samples)

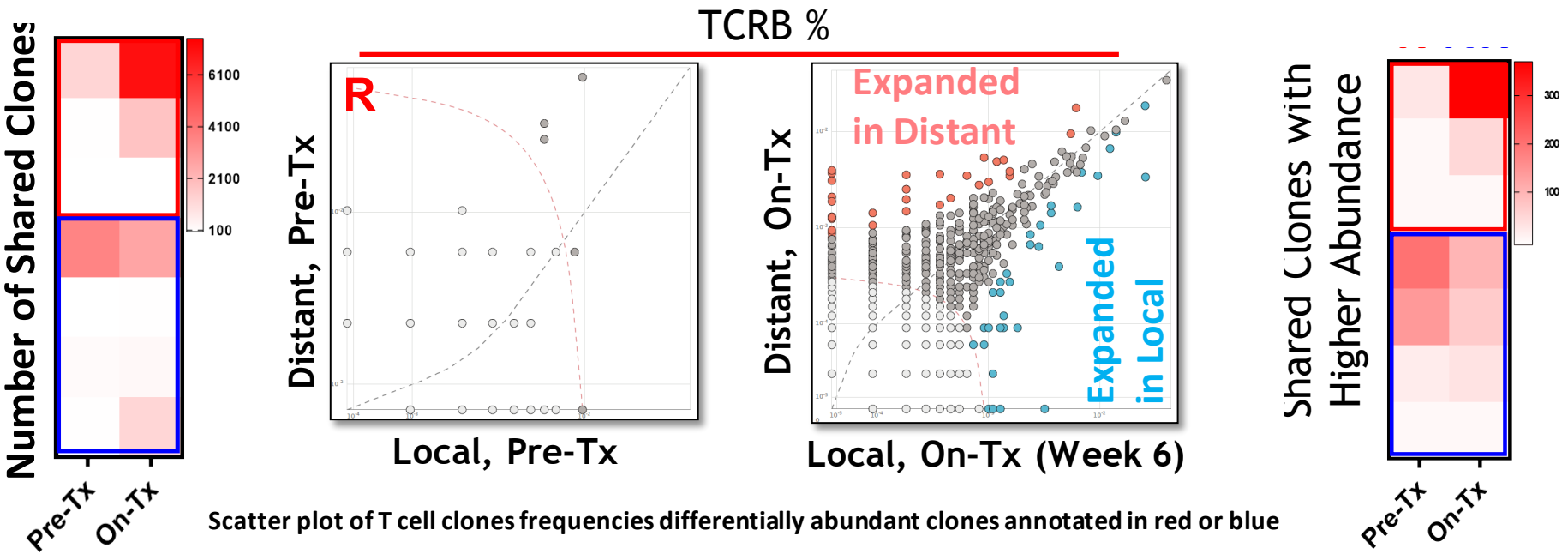
Local Lesions

Distant Lesions



The Combination Treatment Can Lead to an Expansion of New Clones Shared between Local and Distal Lesions

Assessment of Shared Clones between Local and Distant Lesions by TCR Sequencing



Scatter plot of T cell clones frequencies differentially abundant clones annotated in red or blue

Conclusions

- Sotigalimab in combination with pembrolizumab is well tolerated.
- Sotigalimab in combination with pembrolizumab showed encouraging anti-tumor activity.
- Biomarker analysis demonstrates that combination therapy can induce broad innate and adaptive immune activation in both local and distant lesions.

Acknowledgments

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