SITC 2022

NOVEMBER 8-12 BOSTON MASSACHUSETTS

The Society for Immunotherapy of Cancer 37th Annual Meeting and Pre-Conference Programs

THE LEADING CANCER IMMUNOTHERAPY AND TUMOR IMMUNOLOGY CONFERENCE

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Intratumoral Sotigalimab with Pembrolizumab Activates Antigen-presenting cells and Induces Local and Distant Anti-tumor Responses in First-line Metastatic Melanoma: Results of a Phase I/II Study

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Presenter Disclosure Information

Salah-Eddine Bentebibel

I have no financial relationships to disclose.

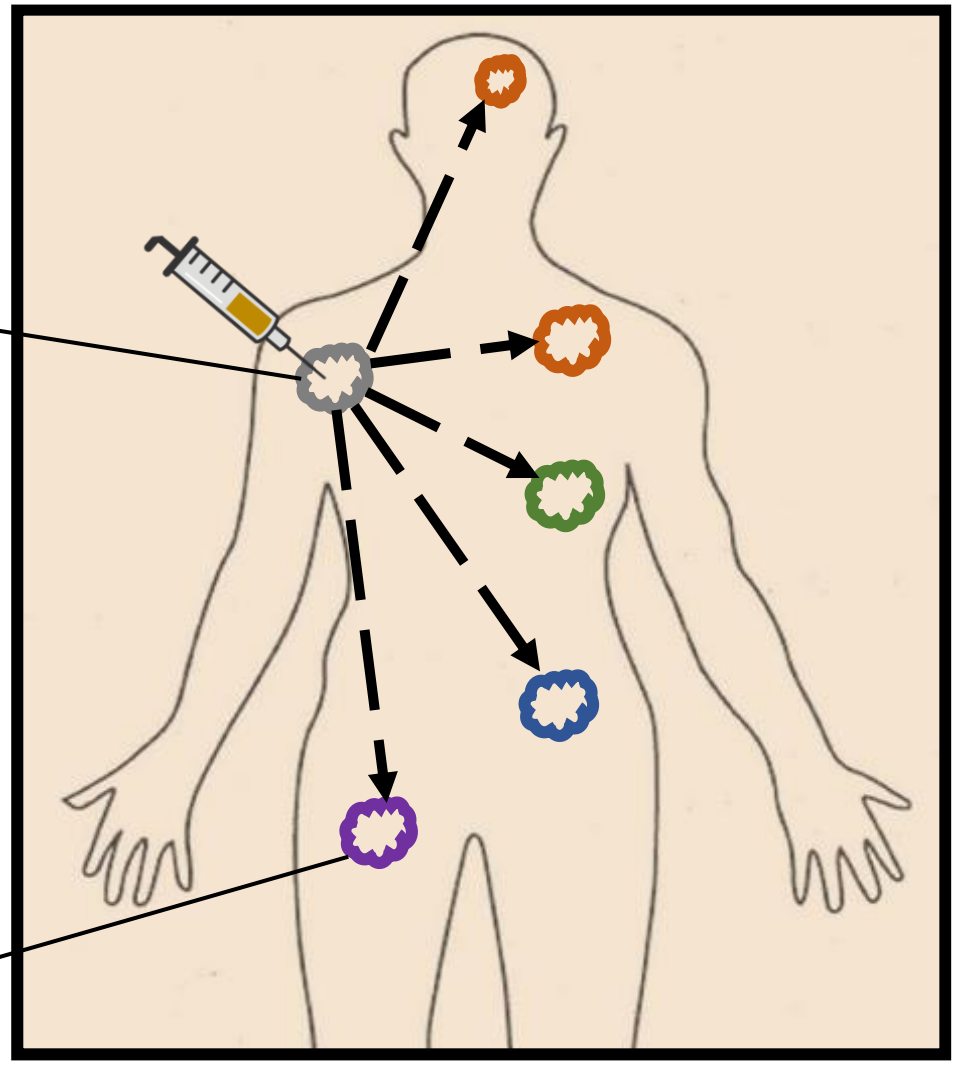
In Situ Priming of Intratumoral Immunity (Vaccine Effect)

Local Priming

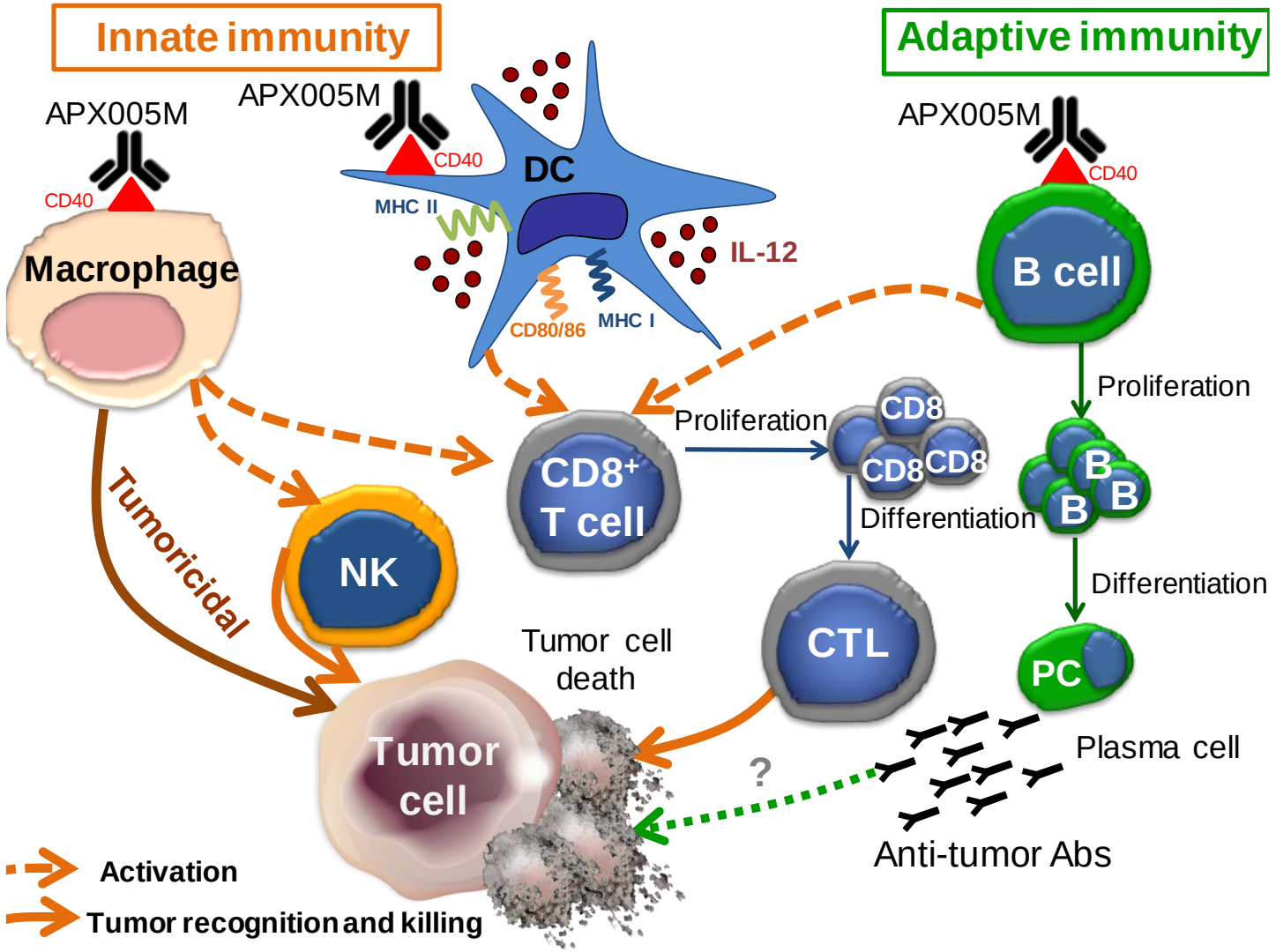
Intra-tumoral injection of immunostimulatory agents to trigger tumor-specific immunity

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 Trial of Intratumoral Sotigalimab + Pembrolizumab

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=18)

As of October 28, 2022, 32 patients were enrolled. Patients received sotigalimab every 3 weeks for a total of 4 injections

Patient Demographics and Disease Characteristics

Characteristic	Total n (%) (N=32)
Sex	
Male	27 (84%)
Female	5 (16%)
Age (years)	
Median (Range)	64.5 (32-81)
ECOG Performance Status	
0	18 (56%)
1	14 (44%)

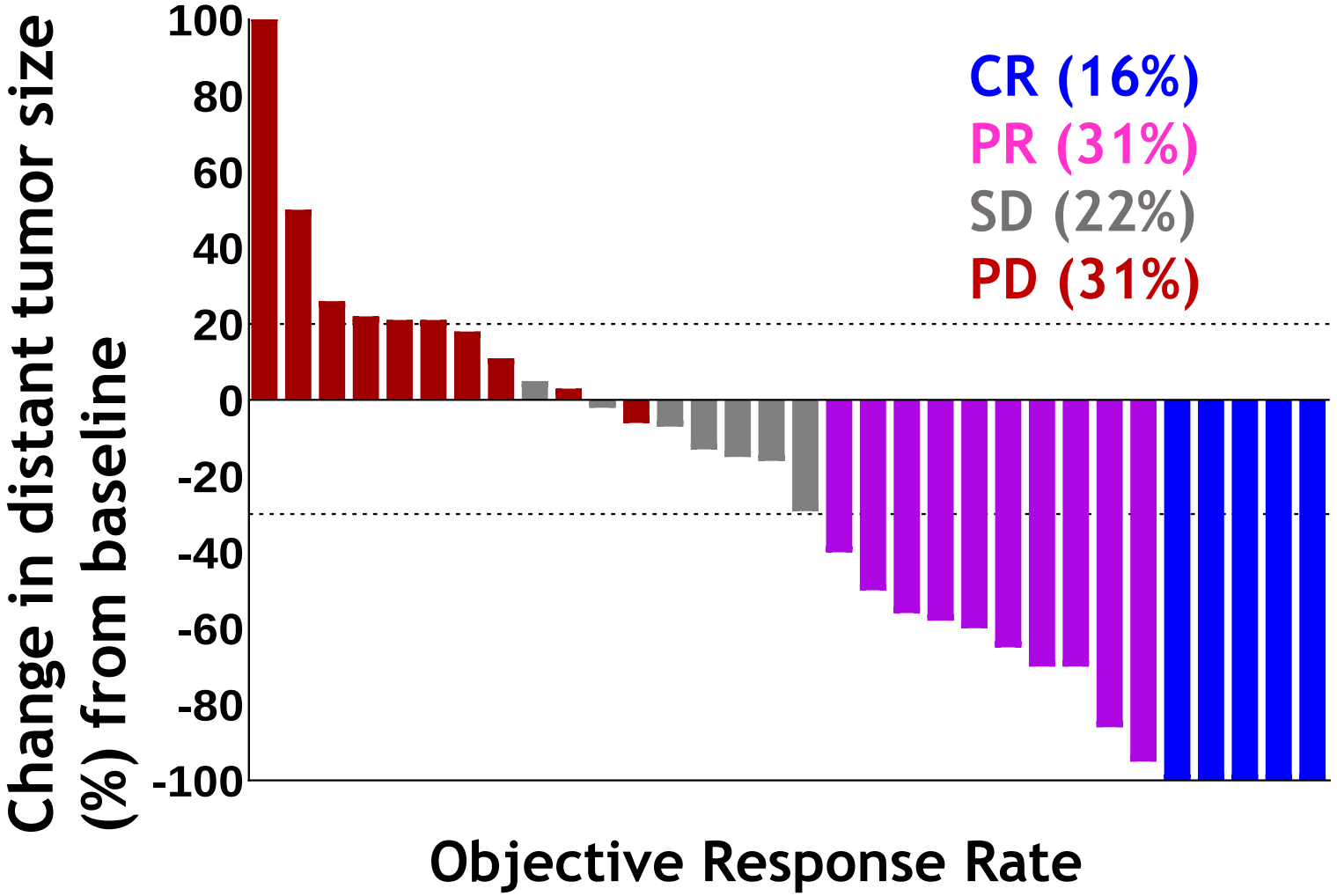
Characteristic	(N=32)	%
BRAF status		
Positive	11	34
Negative	19	59
Unknown	2	7
LDH at baseline		
< ULN	16	50
> ULN	7	22
×2 ULN	9	28
PD-L1 status		
Positive	8	25
Negative	11	34
Unknown	13	41
Stage		
III	8	25
IV M1a or M1b	17	53
IV M1c	7	22

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; six patients (18%) experienced grade-3 immune-related adverse events.
- The combination therapy did not induce dose limiting toxicity at any dose level of sotigalimab.
- No immunosuppressive therapy needed.

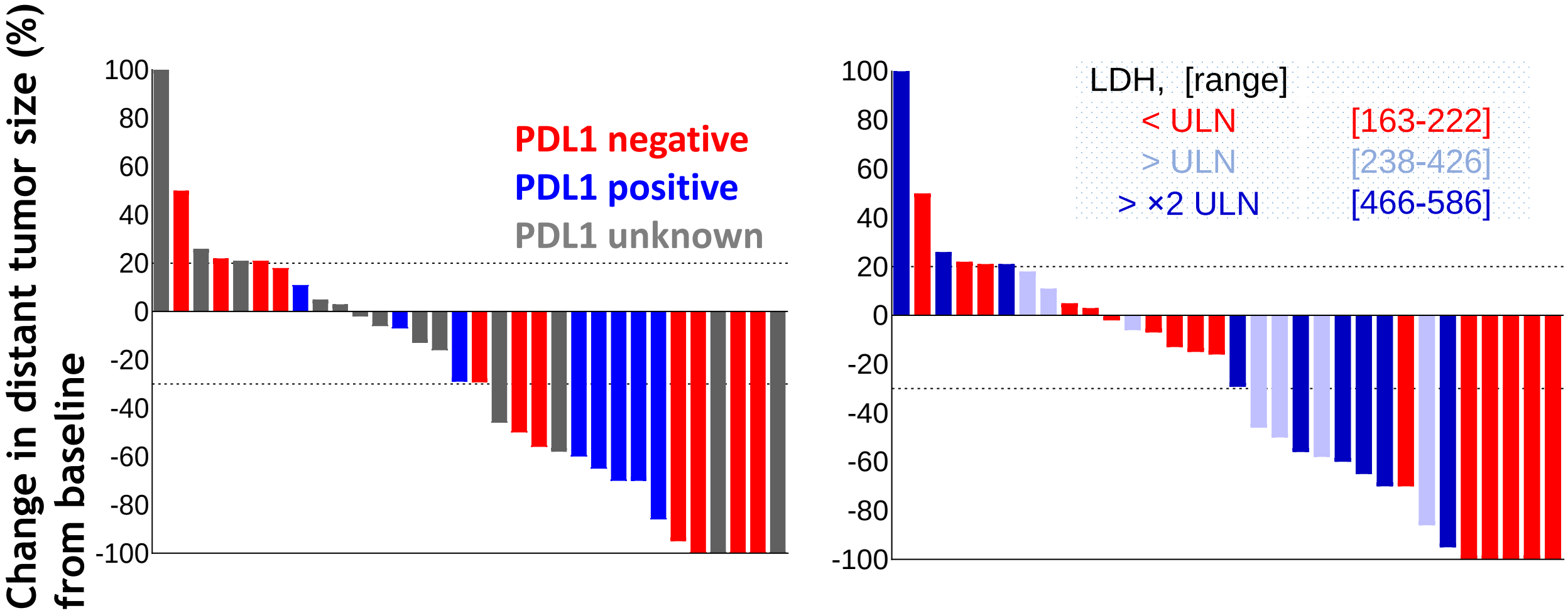
Best Overall Response by RECIST 1.1 as of October 28, 2022



Patients	(N=32)
Total Evaluable	**32**
ORR (CR+PR)	**15 (47%)**
CR	5 (16%)
PR	10 (31%)
SD	7 (22%)
DCR (CR+PR+SD)	**22 (69%)**
PD	10 (31%)

Response rate at the RP2D (10 mg= 12/24 (50%)) assisted by QIAC

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

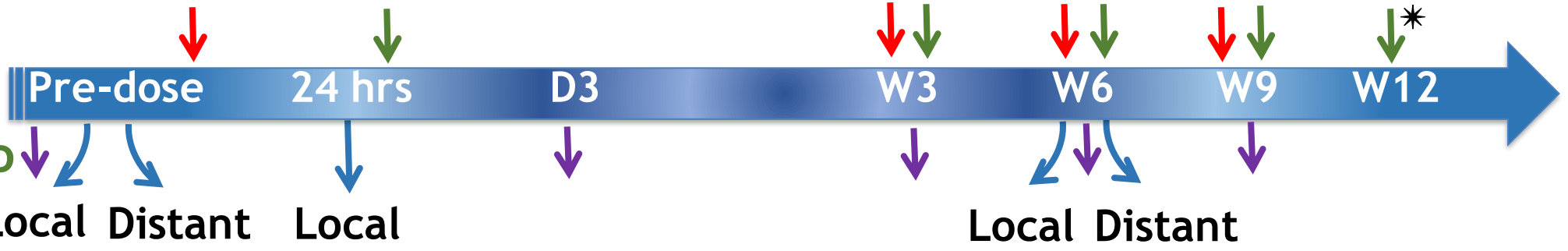


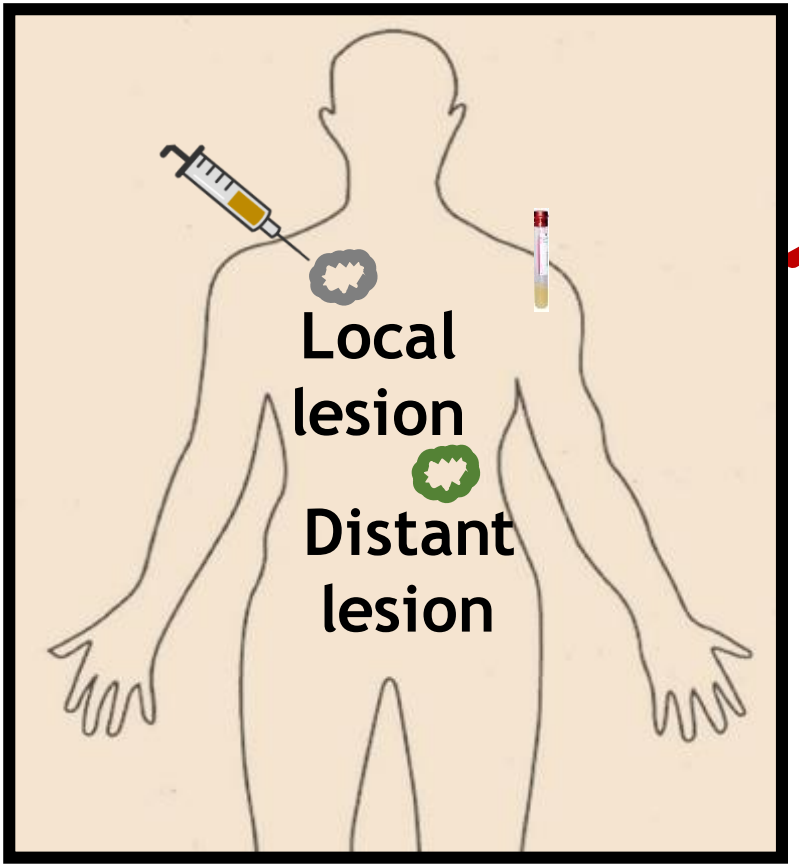
Objective Response Rate

Strategy for Biomarker Analysis

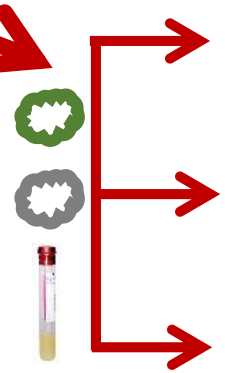
Sotigalimab

Pembrolizumab





Tumor core needle biopsy



NanoString gene expression assay

Opal multiplex immunofluorescence (mIF) and imaging mass cytometry (IMC)

TCR repertoire analysis using immunoSEQ

Collection of tumor biopsy Collection of PBMCs

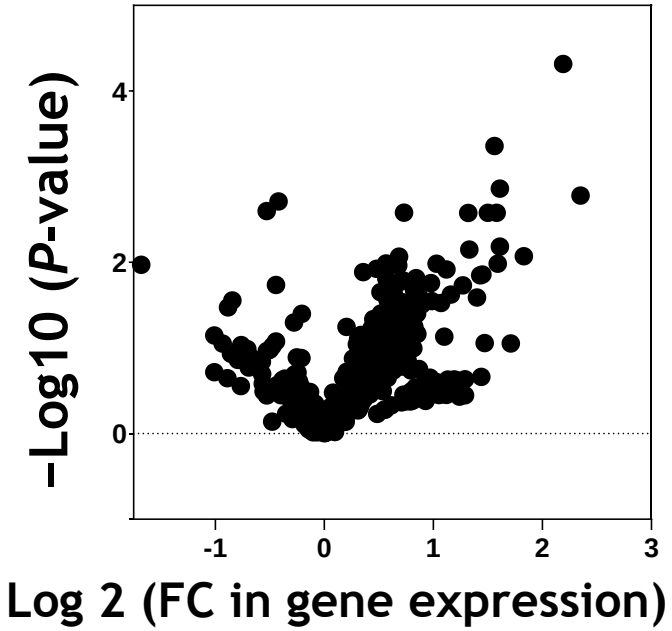
Local = Injected lesion, Distant = Un-injected lesion

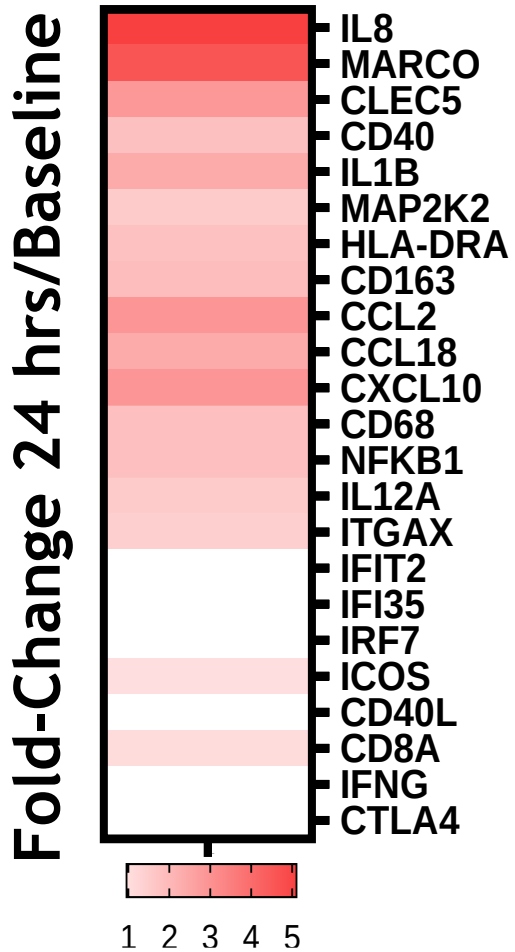
✳ Pembrolizumab administration continues q 3wks

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

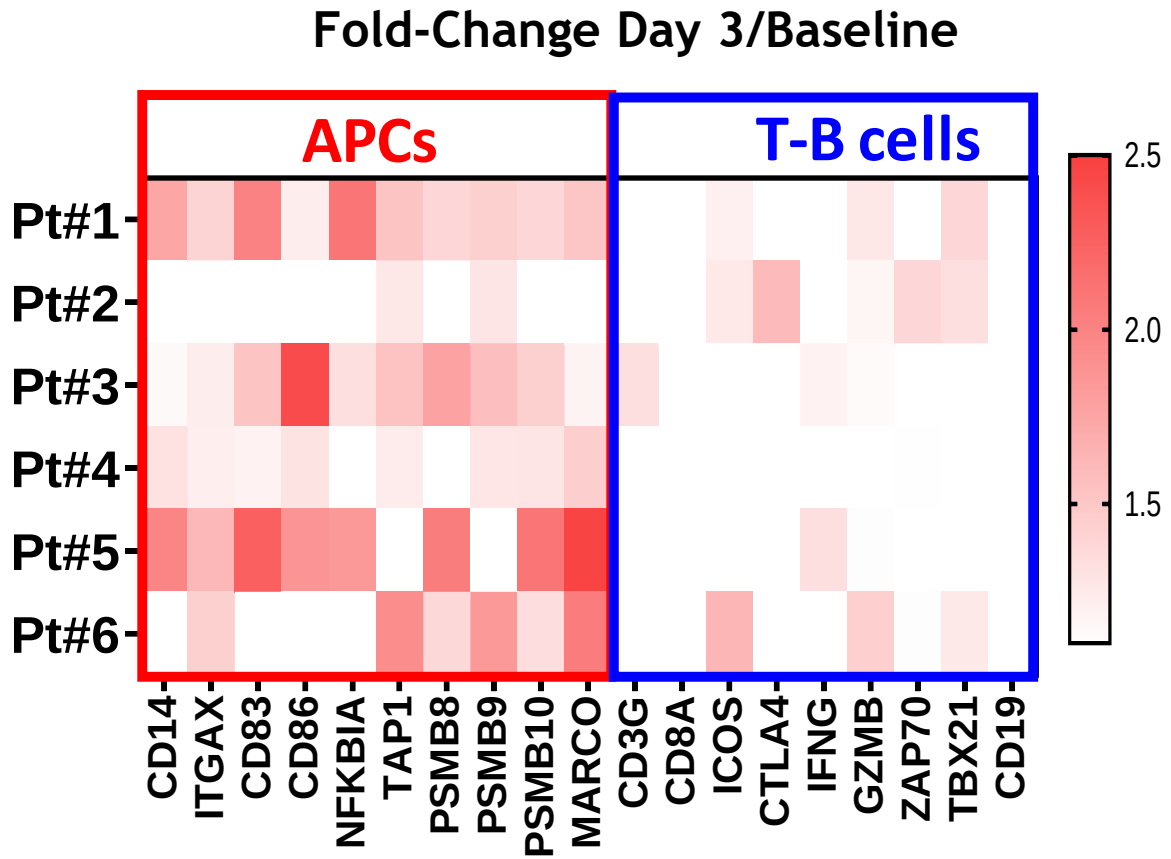
(NanoString Gene Expression)

DE 24 hrs/Baseline (local lesions)



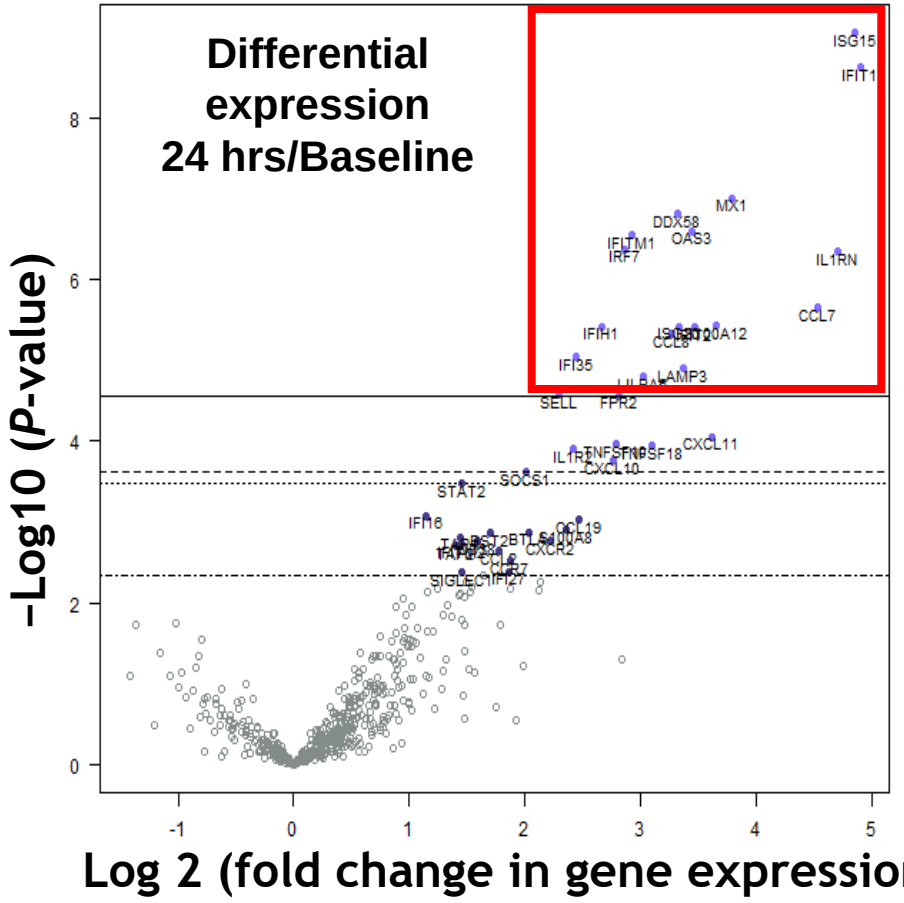


Blood



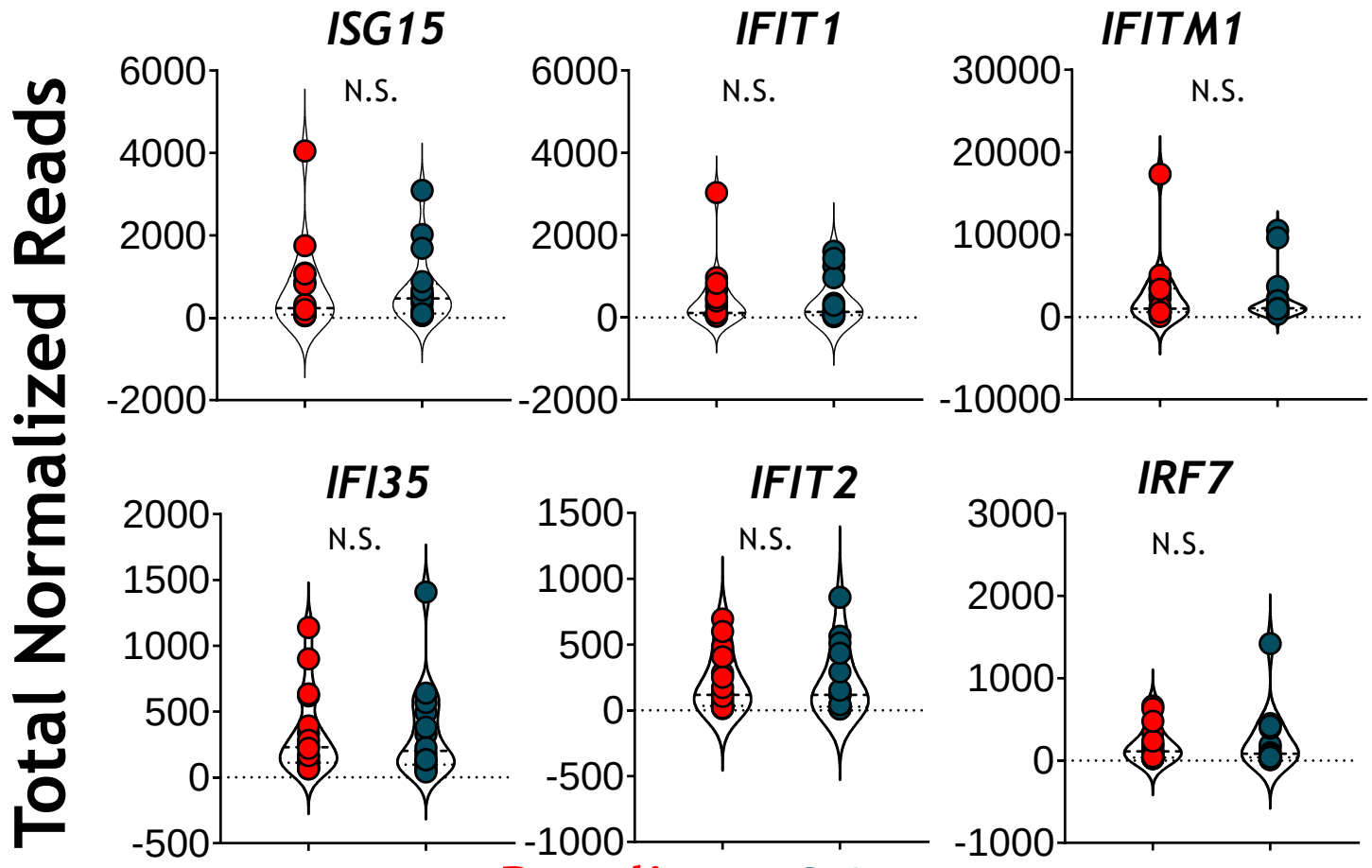
Sotigalimab Administration Leads to Activation Profile Distinct from TLR9 agonist

IFNα gene signature after i.t TLR9 agonist (IMO-2125)



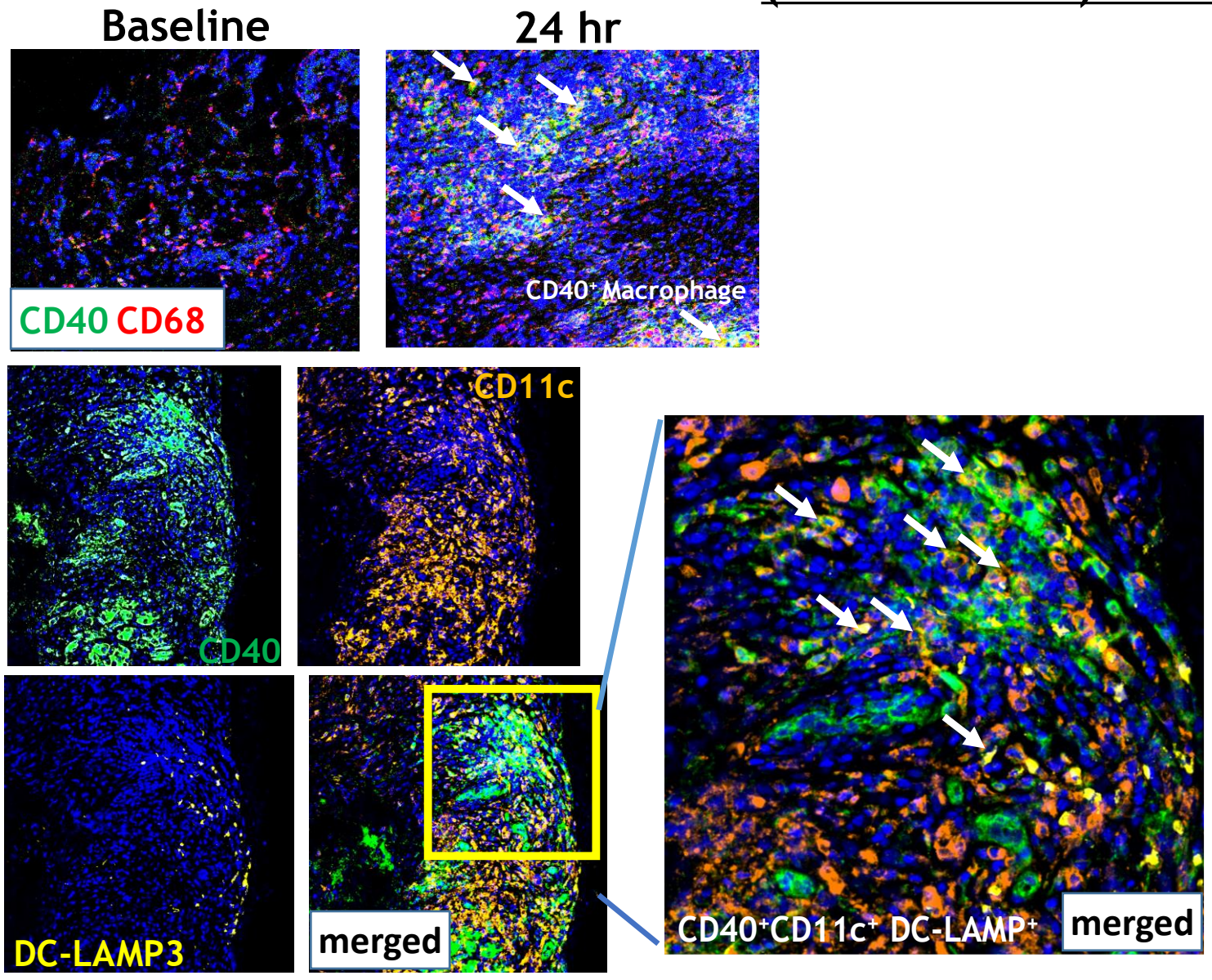
Haymaker, Diab et al., Cancer Discovery 2021

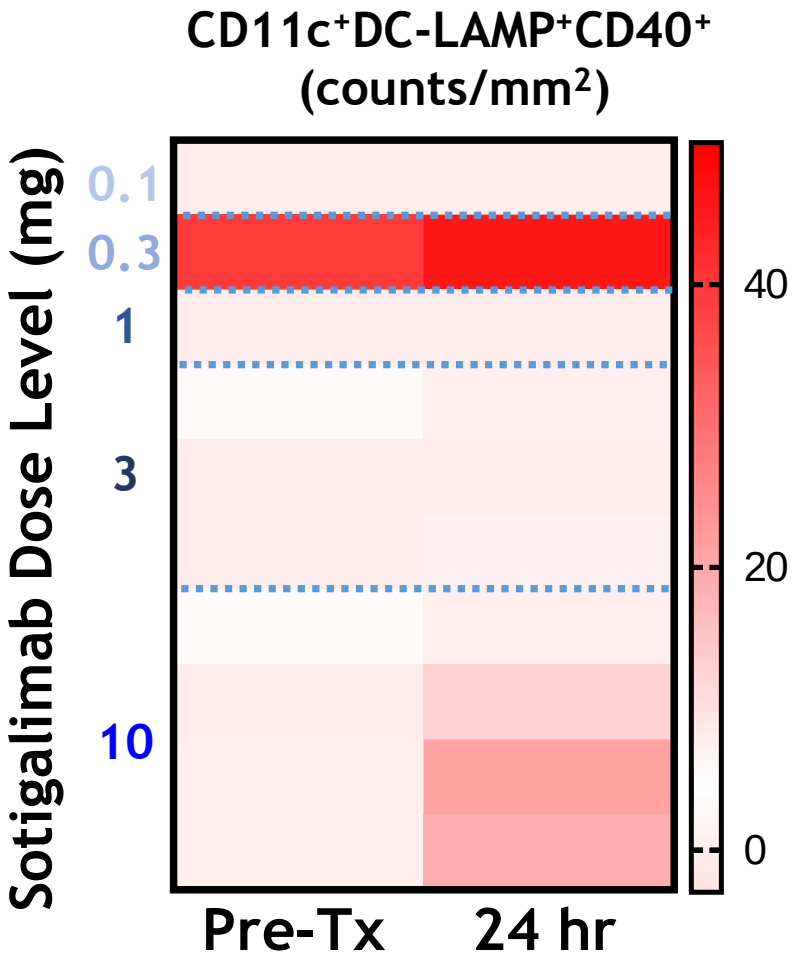
IFNα gene signature after i.t CD40 agonist (Sotigalimab)



Sotigalimab induced Rapid DC and Macrophage Activation

(mIF and IMC) Local Lesions



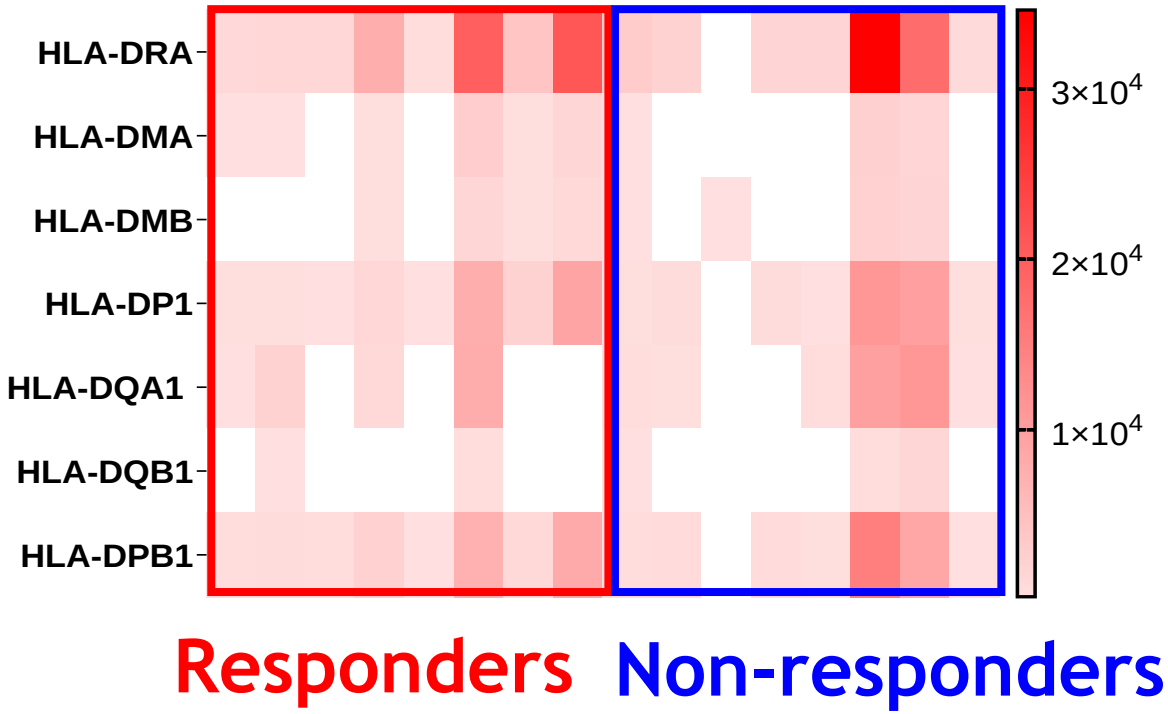


The Clinical Response to the Combination Therapy Does not Require Pre-existing IFN-γ Mediated Immune Activation at Baseline

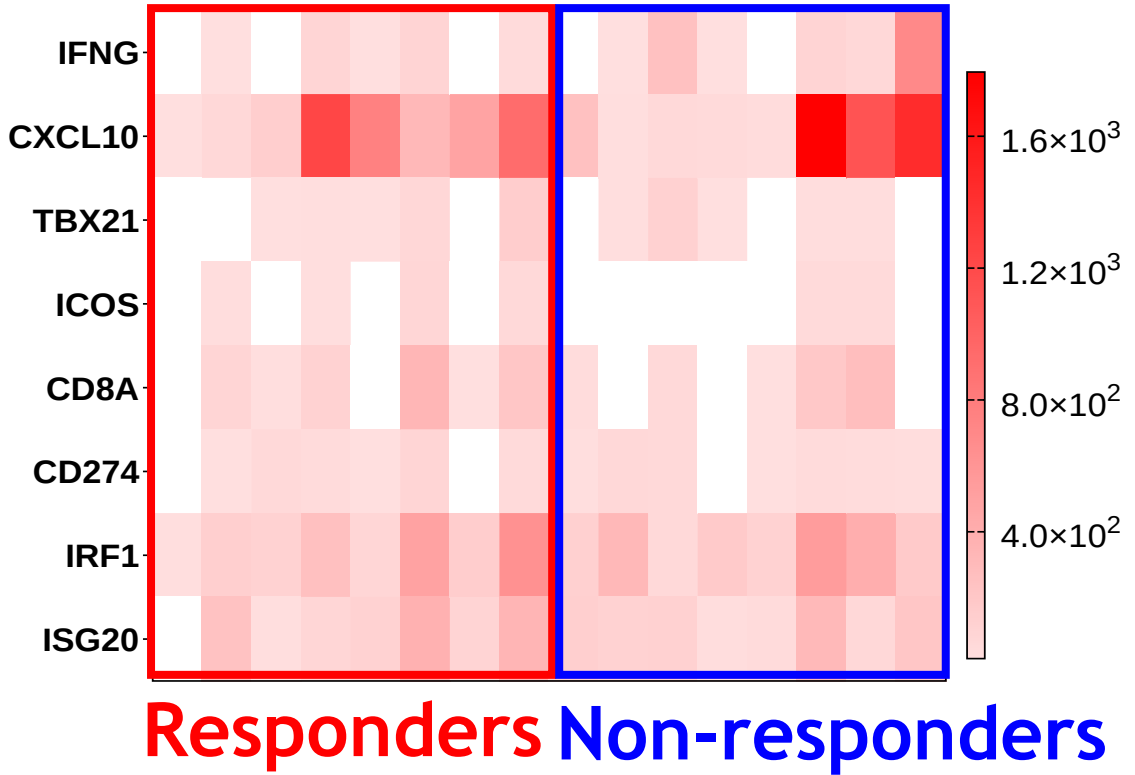
- The clinical response to anti-PD1 is associated with Pre-existing IFN-g Mediated Immune Activation (*Rodig, Science Translational Medicine 2018 Ayers, J. Clin. Invest 2017, Gide, Cancer Cell 2019, Grasso, Cancer Cell 2020)*

(NanoString Gene Expression) Local lesions

MHC class II expression at baseline



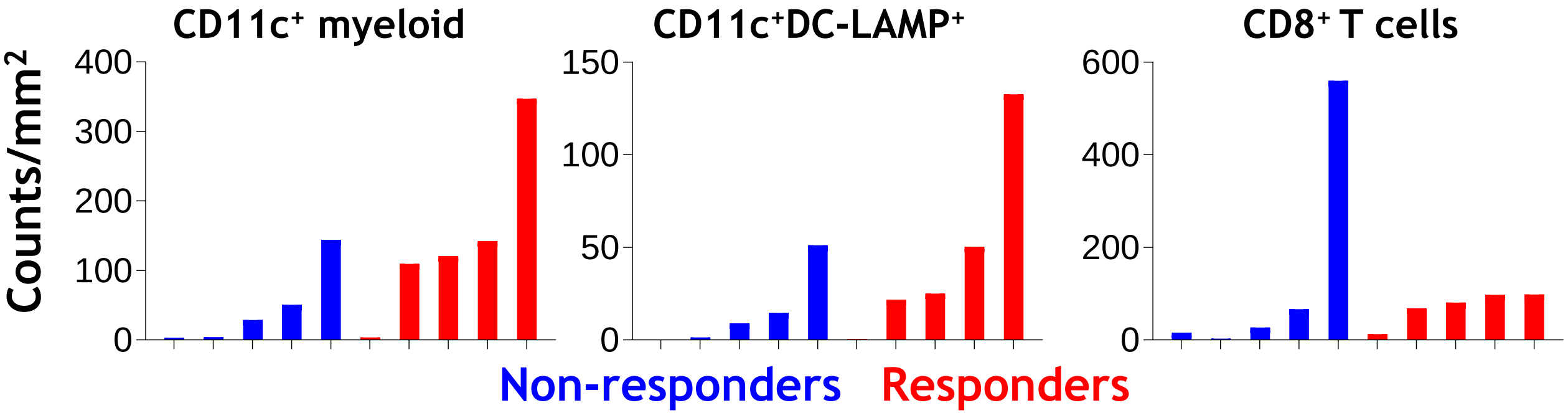
IFN-γ Mediated Immune Activation at Baseline



Responding Patients Appear to Have Higher Pre-existing CD11c$^+$ Myeloid cells and CD11c$^+$DC-LAMP$^+$ DC

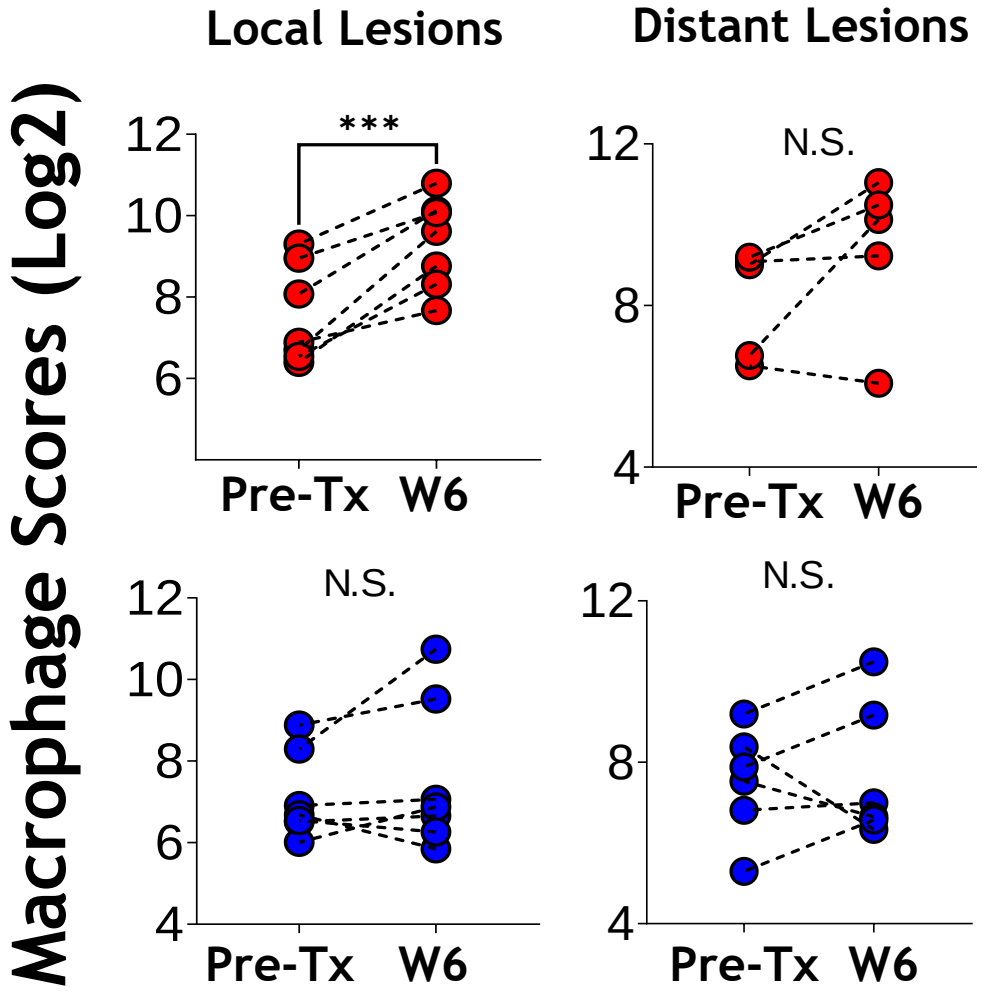
(mIF) Local Lesions at Baseline

CD11c$^+$ myeloid (SOX10$^-$CD8$^-$CD11C$^+$)
CD11c$^+$DC-LAMP$^+$ (Sox10$^-$CD8$^-$CD11c$^+$DC-LAMP$^+$)
CD8$^+$ (SOX10$^-$CD8$^+$)

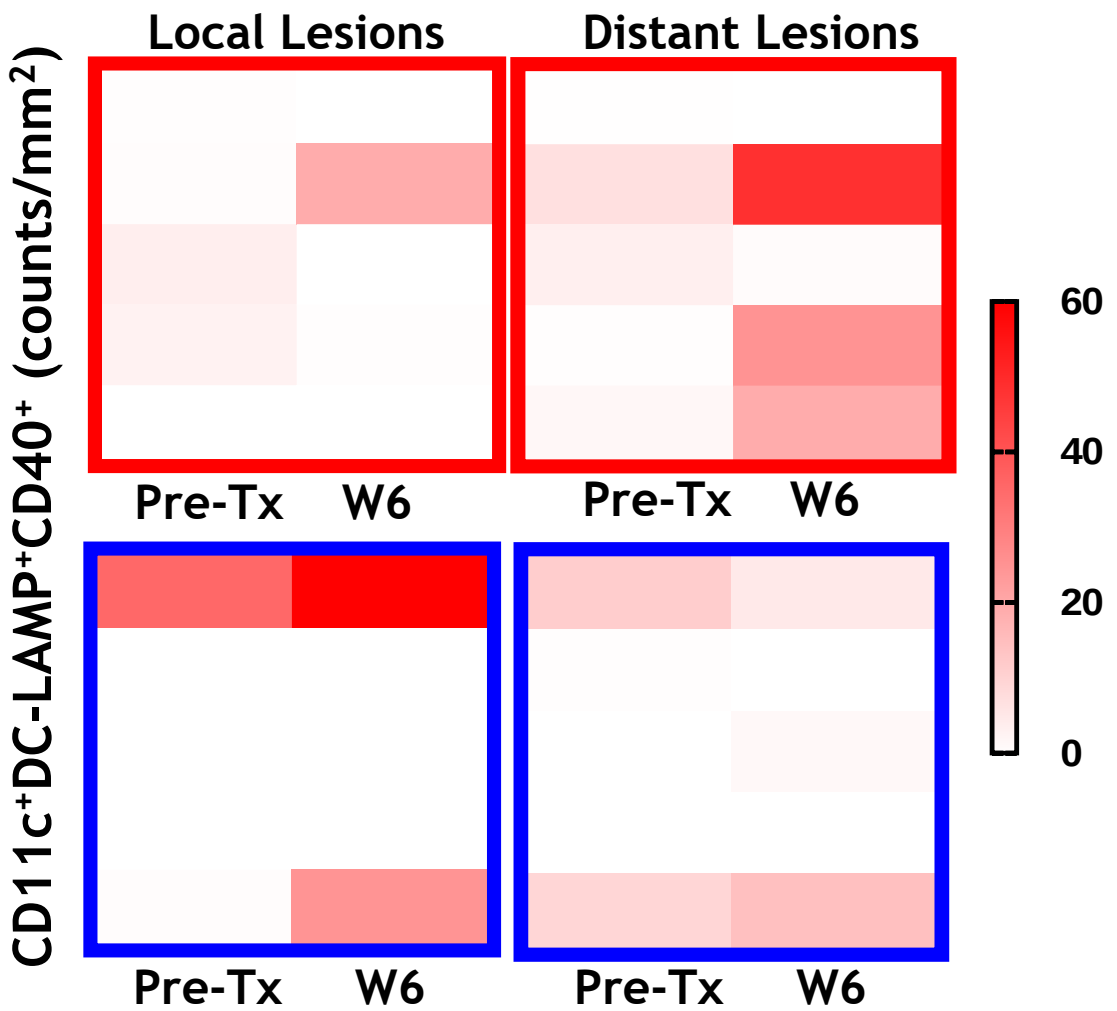


The Combination Treatment Activated DC and Increases Macrophage Signature in Local and Distant Tumors

(NanoString Gene Expression)

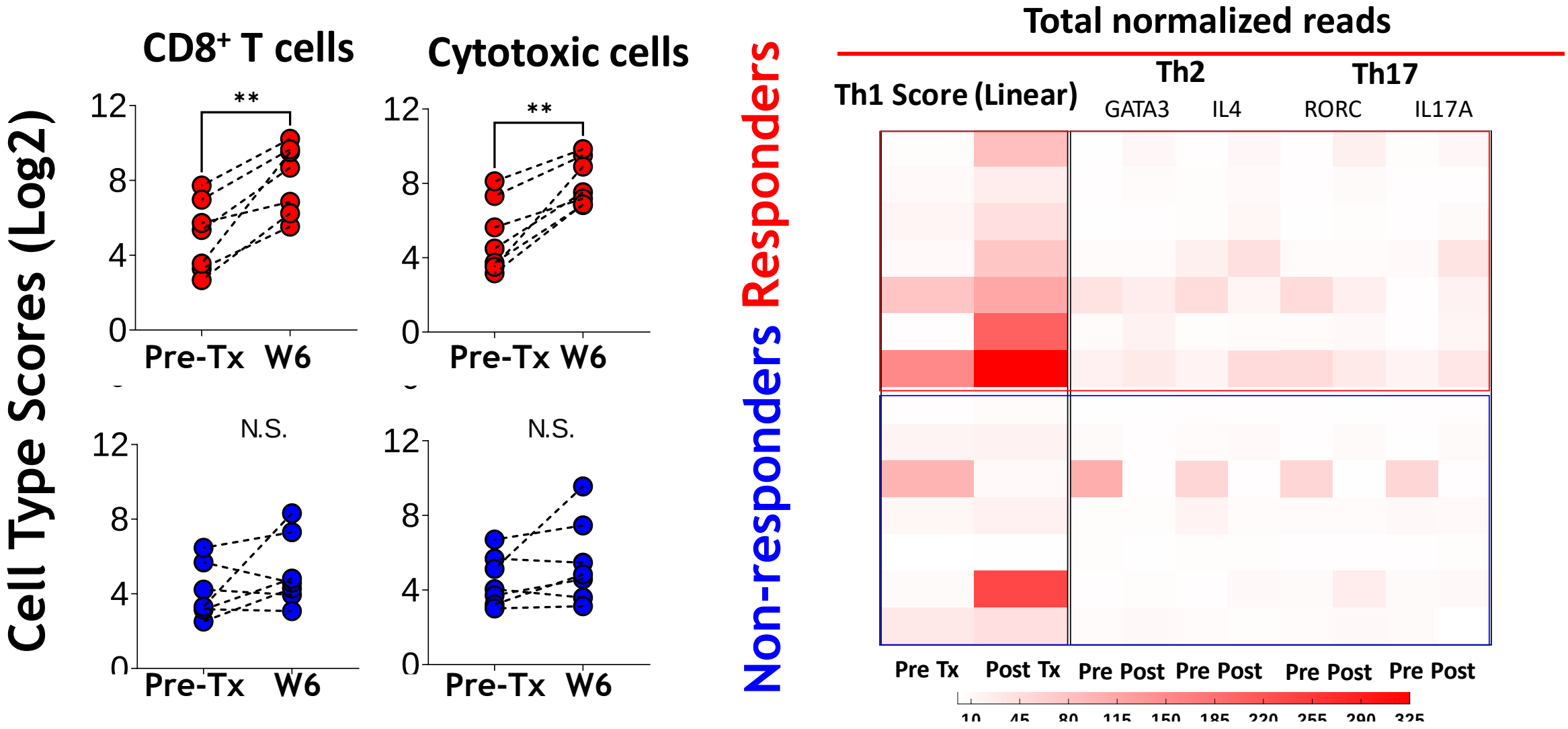


(mIF)



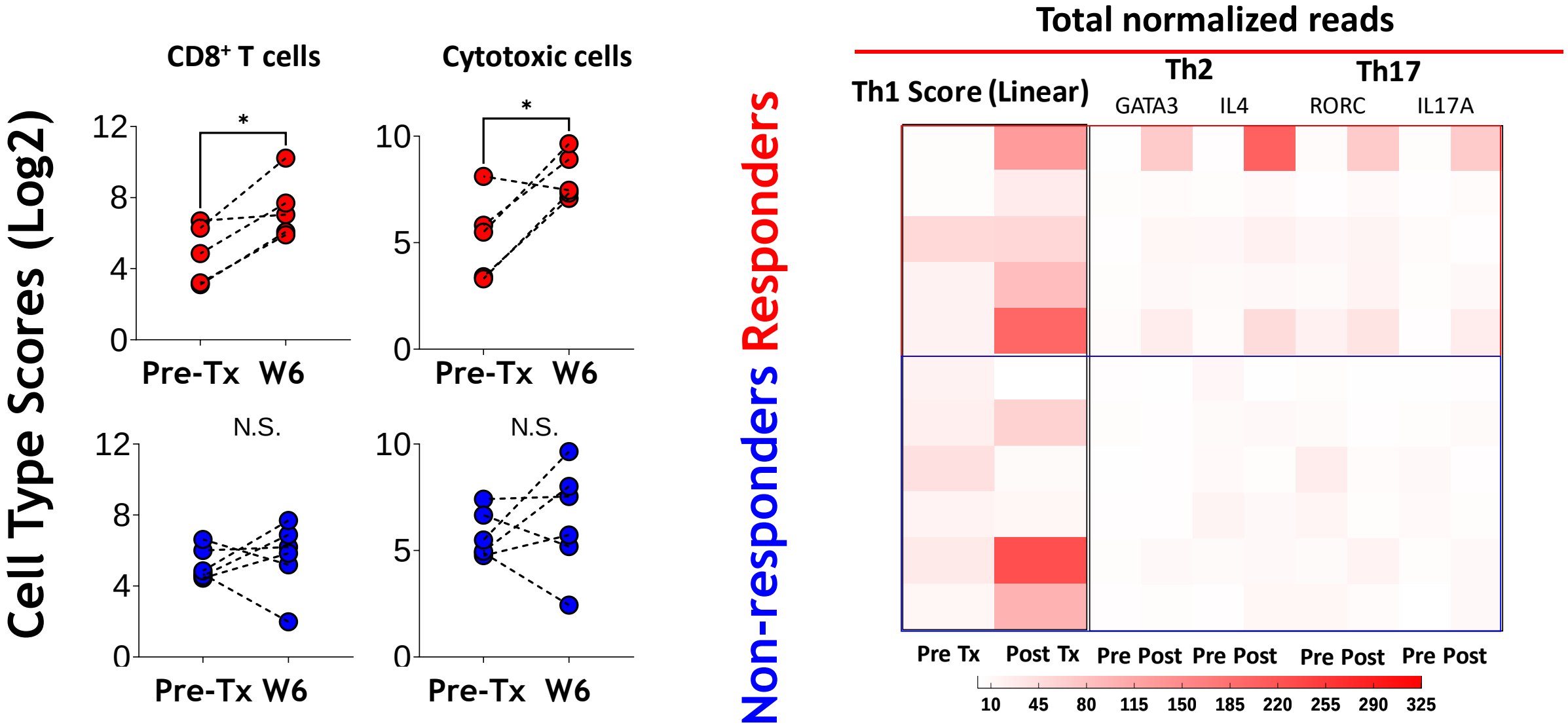
On-treatment Increase in CD8+ T, Cytotoxic and Th1 Scores in Tumor Observed in Responding Patients

(NanoString Gene Expression) Local Lesions

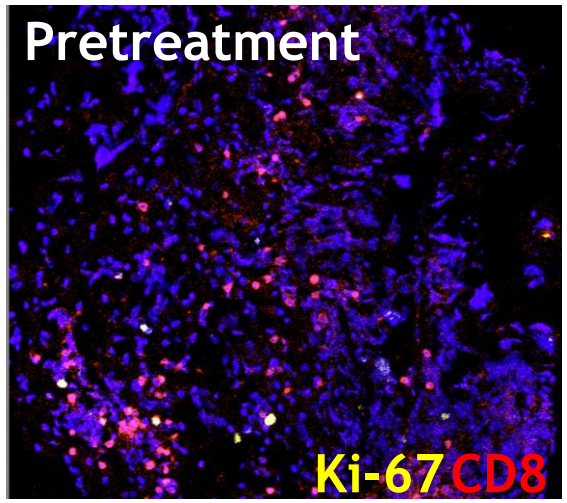


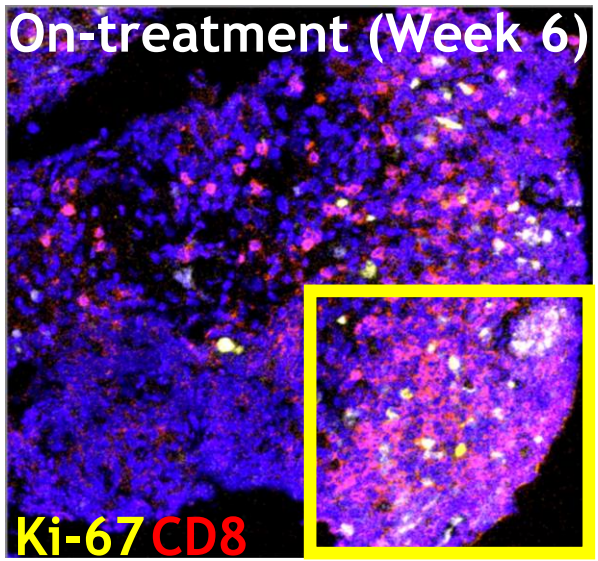
On-treatment Increase in CD8+ T, Cytotoxic and Th1 Scores in Tumor Observed in Responding Patients

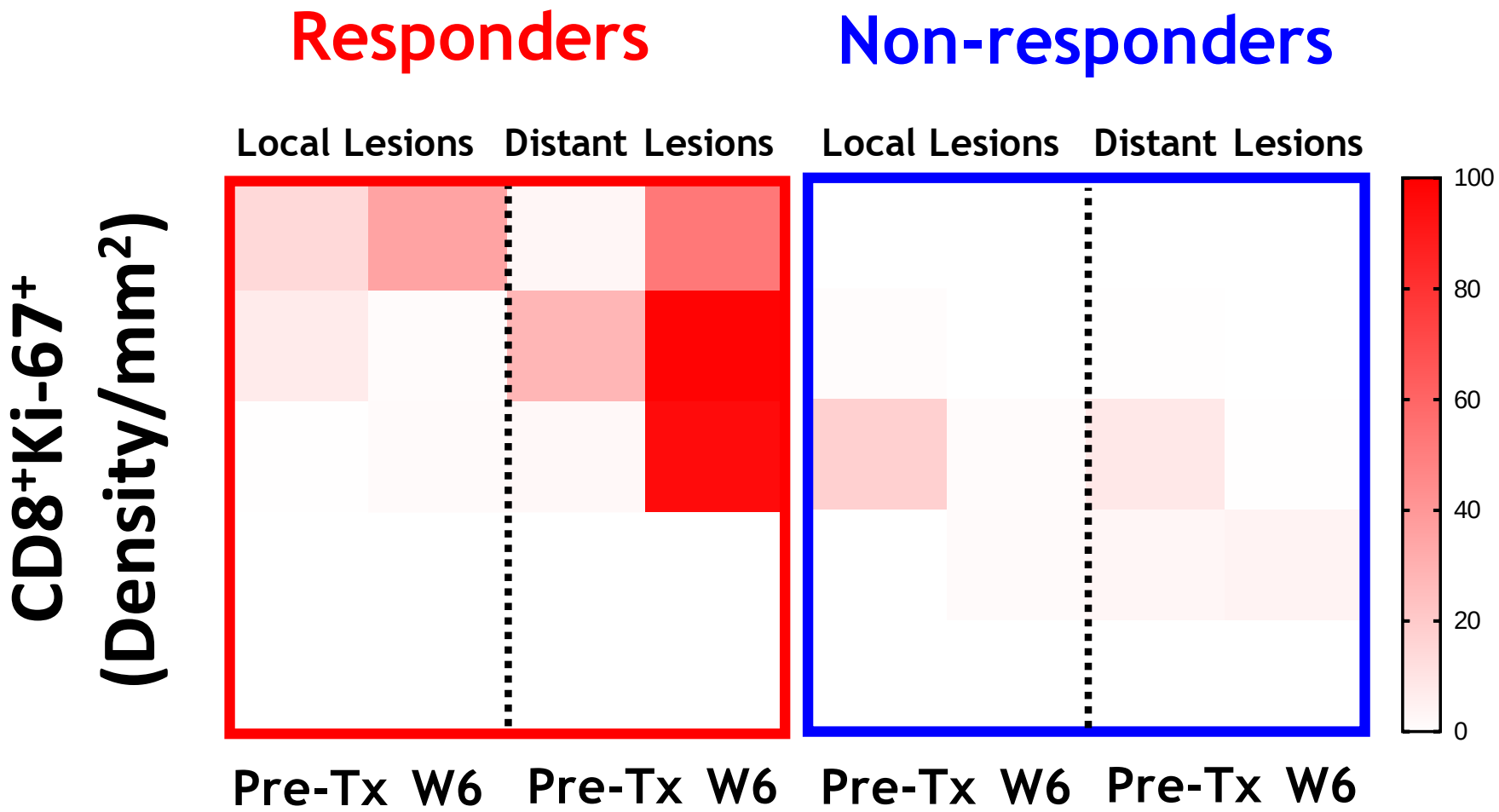
(NanoString Gene Expression) Distant Lesions



The Combination Treatment Can Lead to an Increase in CD8⁺ T cell proliferation in Responding Patients



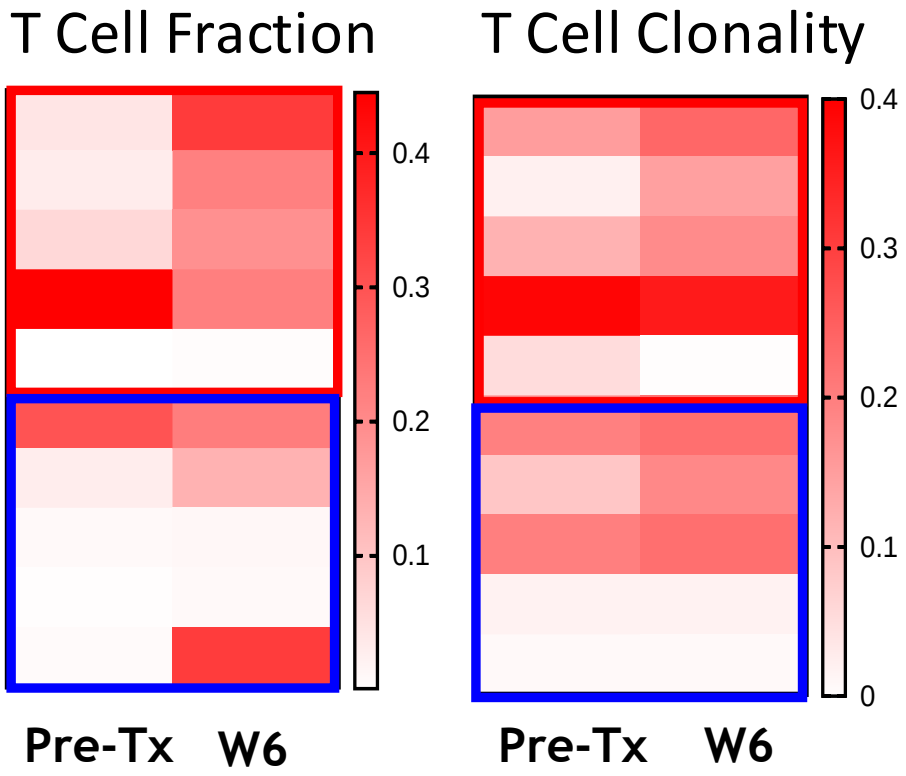




The Combination Treatment Can Lead to an Increase in T cell Infiltration and Clonality

(TCR Sequencing in Tumor Samples)

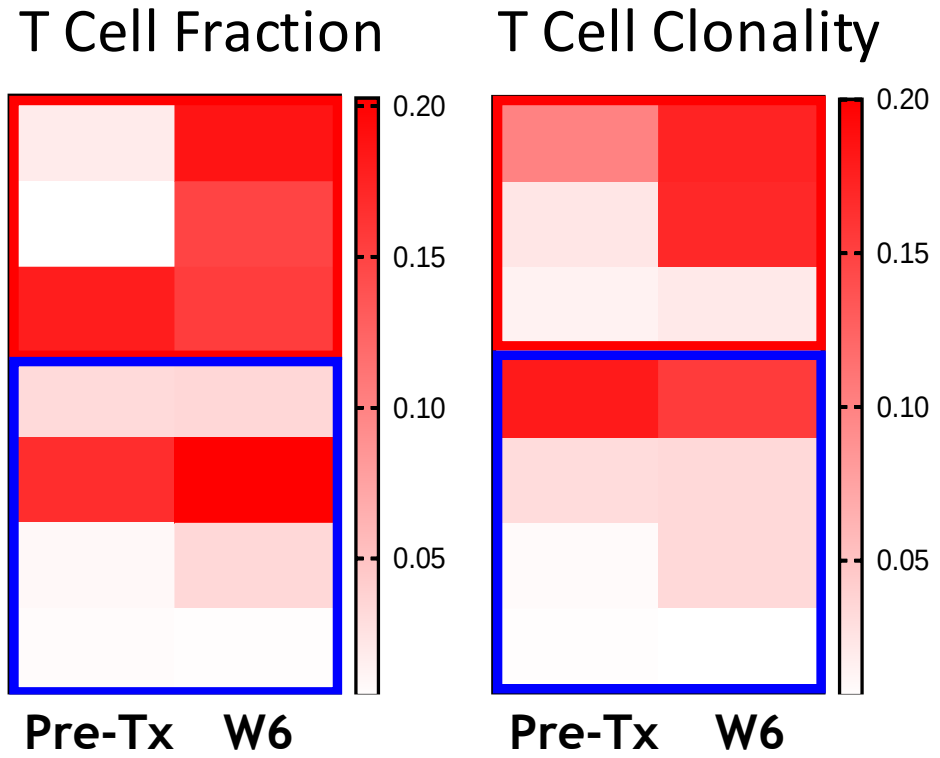
Local Lesions



Responders

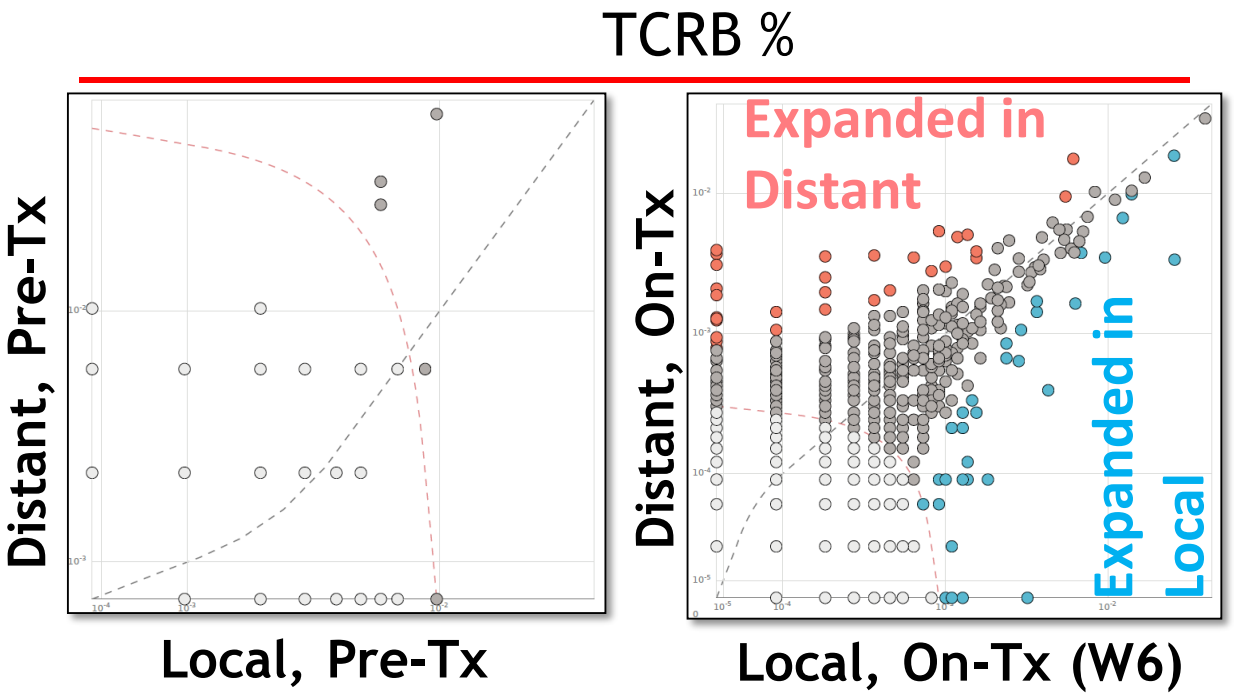
Non-responders

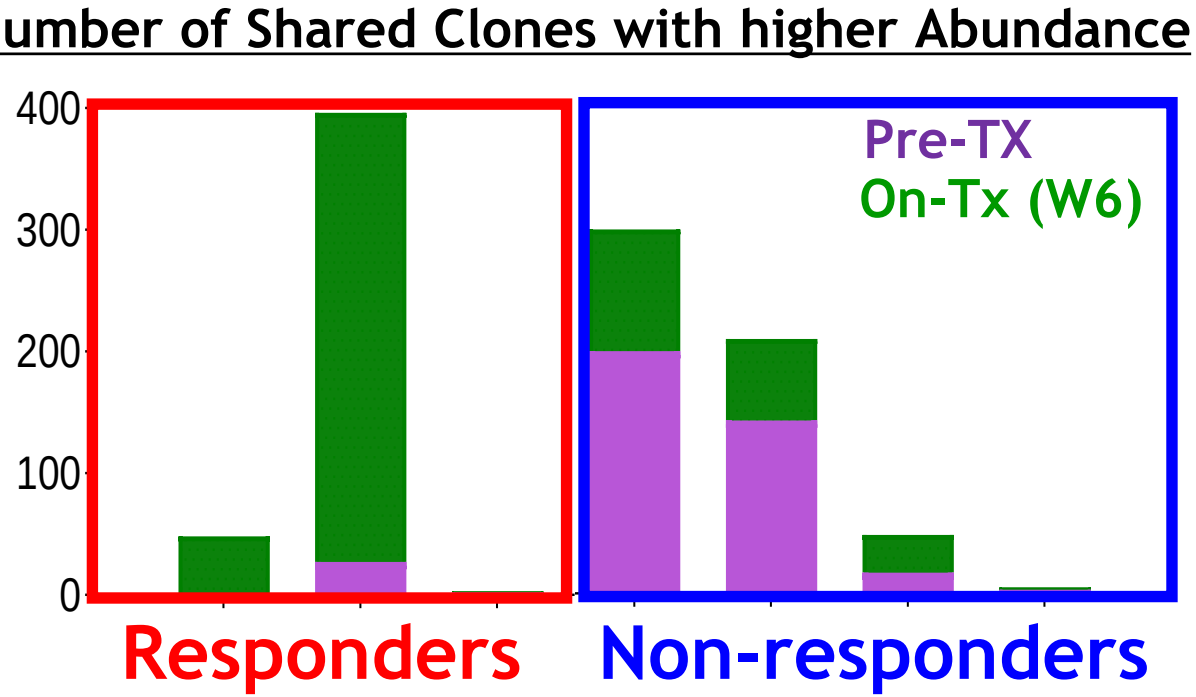
Distant Lesions



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





Lessons and Take Home Messages

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

A special thank you is extended to the patients and their families

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