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Society for Immunotherapy of Cancer

SITC
2017

TLR9 agonist harnesses innate immunity to drive tumor-infiltrating T-cell expansion in distant lesions in a phase 1/2 study of intratumoral IMO-2125+ipilimumab in anti-PD1 refractory melanoma patients

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THE UNIVERSITY OF TEXAS
MDAnderson
~~Cancer~~ Center

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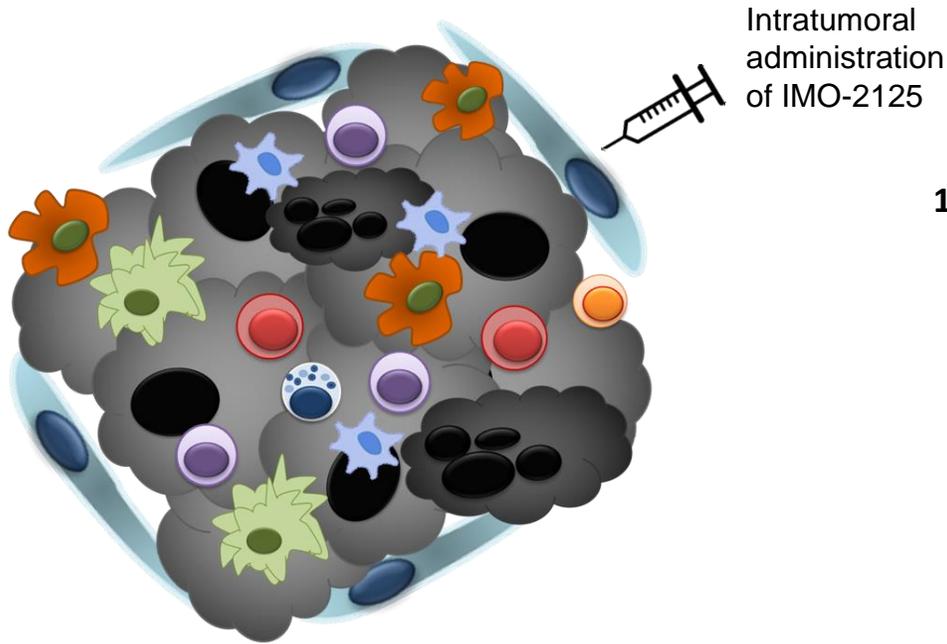
Presenter Disclosure Information

Cara Haymaker

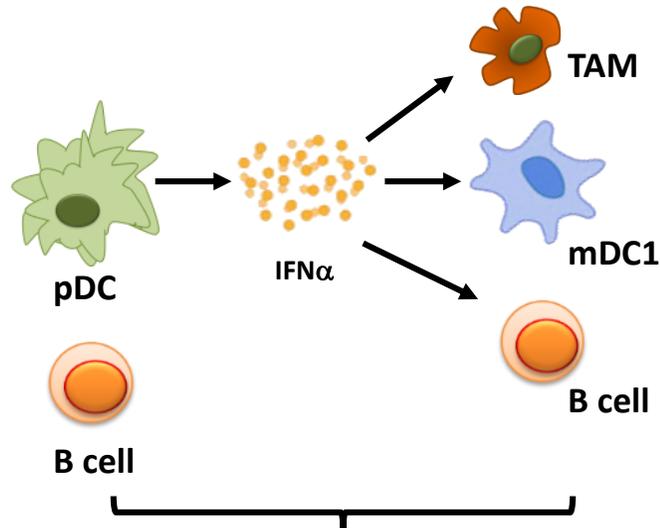
The following relationships exist related to this presentation:

No Relationships to Disclose

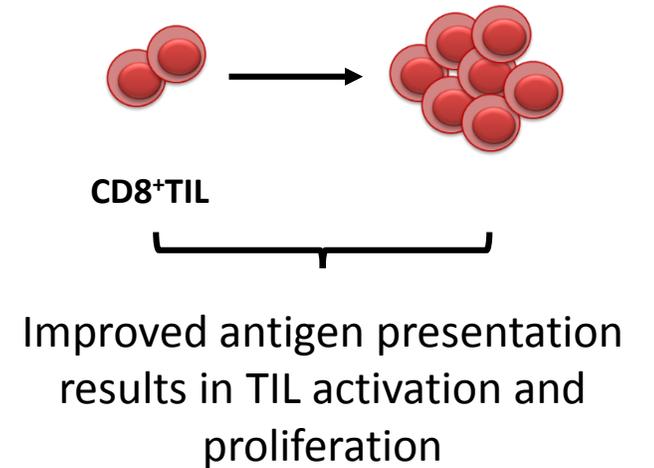
Modulation of the tumor microenvironment by intratumoral administration of the TLR9 agonist IMO-2125



1. TLR9 induction of IFN α and APC maturation



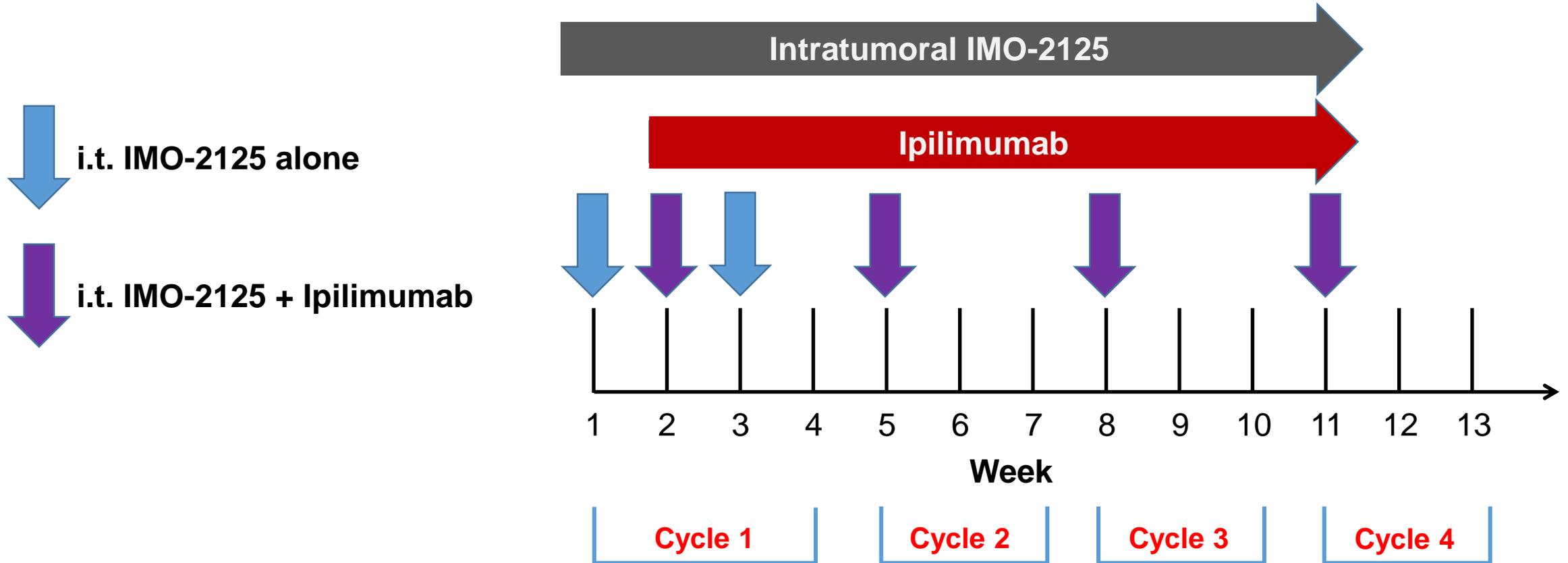
2. TIL Activation and Proliferation



	pDC		CD8 ⁺ TIL
	mDC1		Tumor cell
	TAM		CD4 ⁺ TIL
	TAF		NK
			B cell

Activation of APCs to improve T-cell priming

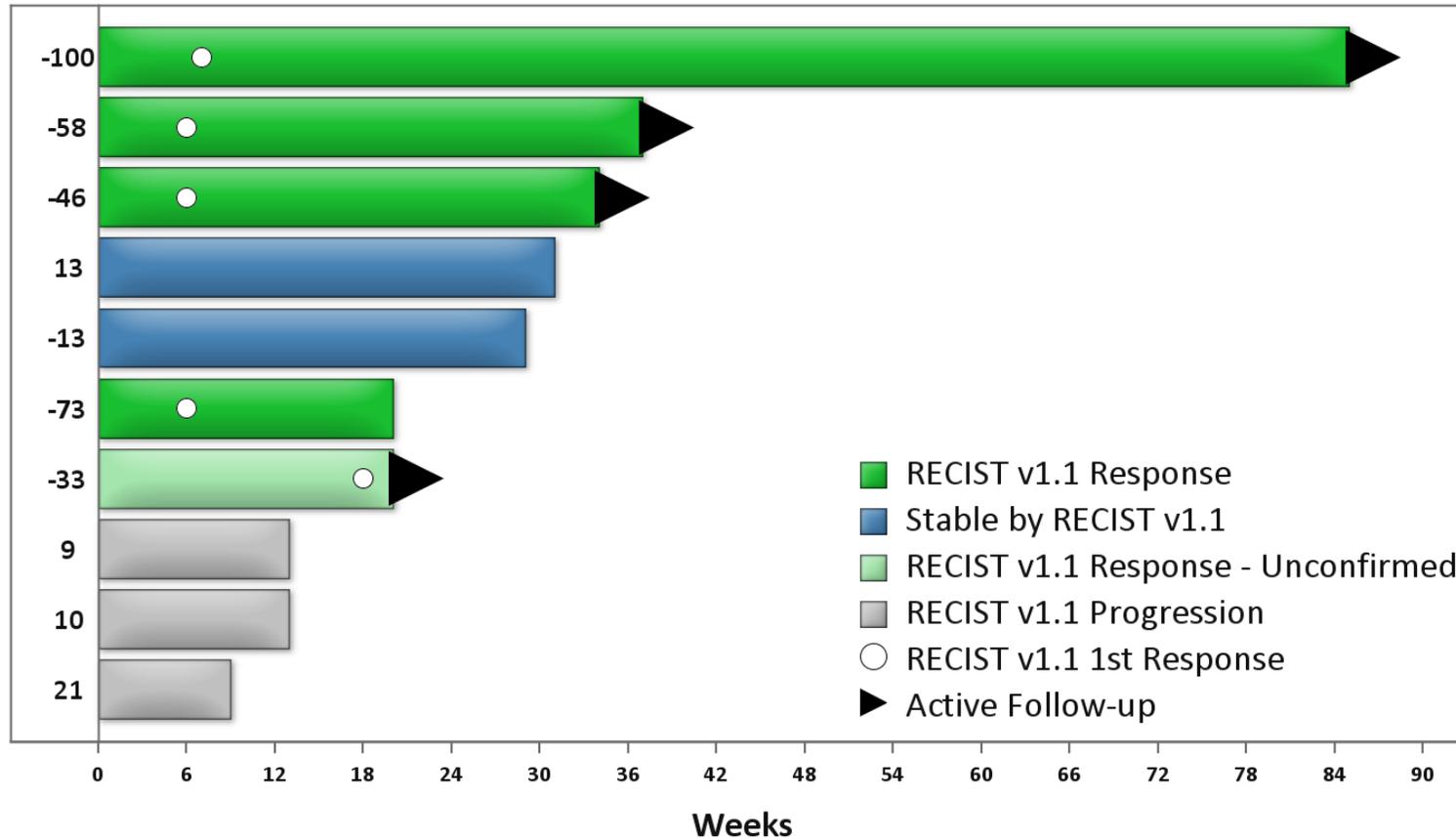
Trial Design (NCT02644967)



Dose-finding phase : IMO-2125 + Ipilimumab

- ❖ 18 subjects treated with IMO-2125 doses from 4 – 32 mg (with standard ipilimumab)
 - Patient population was refractory to PD-1 inhibitors and had a high frequency of visceral metastases (M1c; 72%)
 - Patients were injected in a single focus of tumor; deep visceral injections were permitted
- ❖ Safety:
 - No DLT, treatment-related deaths or discontinuations from therapy
 - Immune-related AE were similar to ipilimumab monotherapy
 - RP2D selected as IMO-2125 8 mg with standard ipilimumab
- ❖ Efficacy (RP2D population):
 - 5/10 patients had either confirmed (4) or unconfirmed (1) RECIST response (**BOR = 50%**), including 1 durable CR (> 1 year)
 - Another 2 subjects had durable SD (>6 mos)
 - Clinical benefit rate = 67%
 - 1 additional durable PR (> 1 year) at the 4 mg IMO-2125 dose level

Early response data to IMO-2125 + Ipilimumab



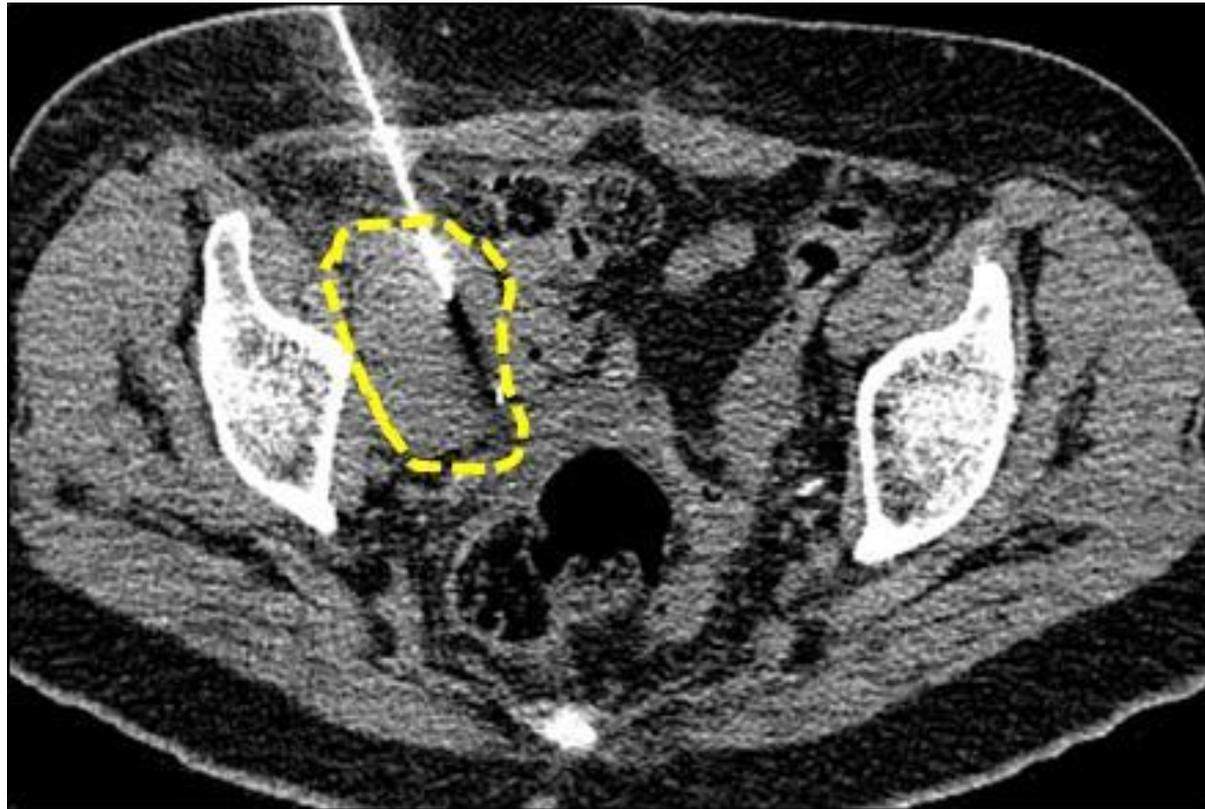
Time on study ends at RECIST v1.1 PD (including death & start of new anti-cancer therapy) or study withdrawal for any reason.

Subjects treated with IMO-2125 8mg + Ipilimumab with at least 1 post-baseline disease evaluation.

Data cut-off date: 03NOV2017

Produced on 06NOV2017

Image-guided intratumoral injection of deep lesions with IMO-2125



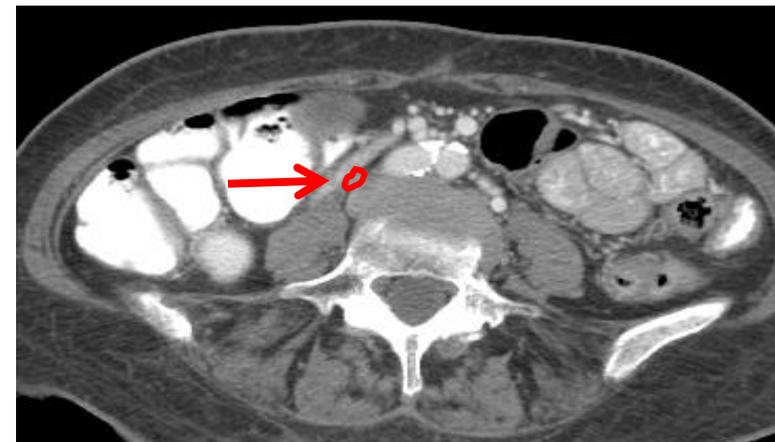
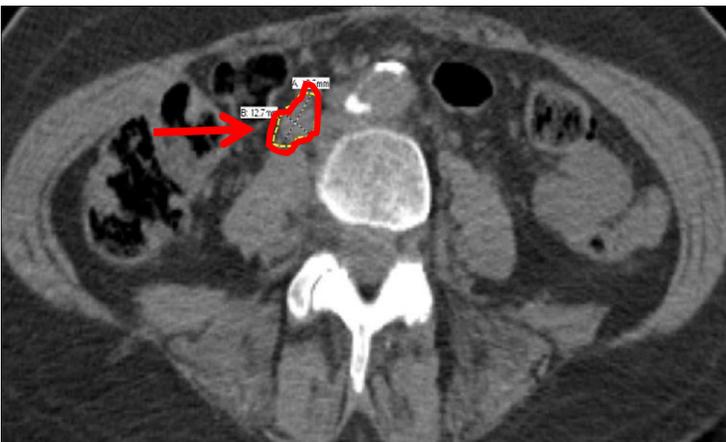
CT guided Intratumoral injection of deep inguinal soft tissue mass

Tumor Imaging of Patient with a Partial Response: Ipilimumab + i.t. IMO-2125 (8mg)

Pre-Therapy



Post-Therapy



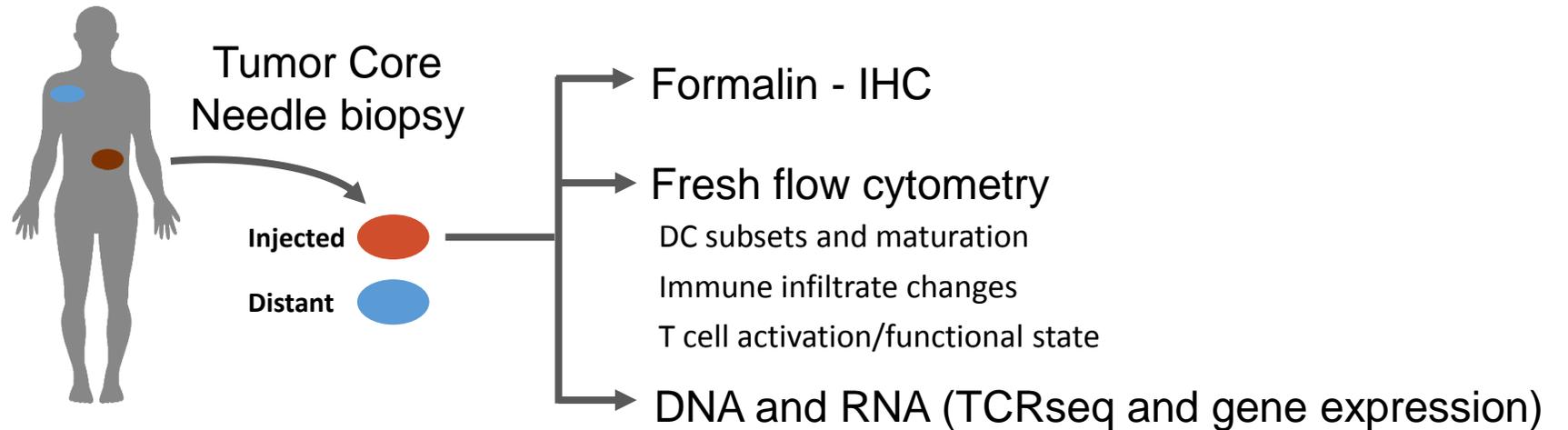
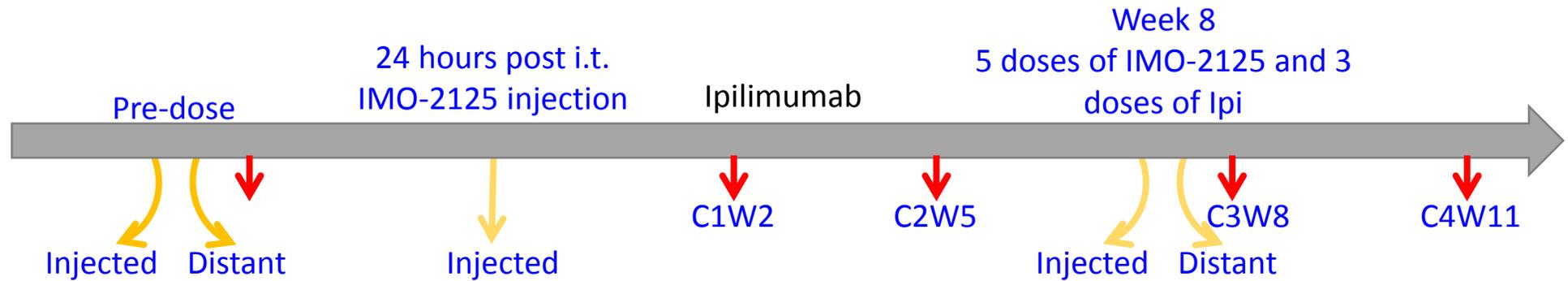
Injected Lesion 

Distant Lesion 

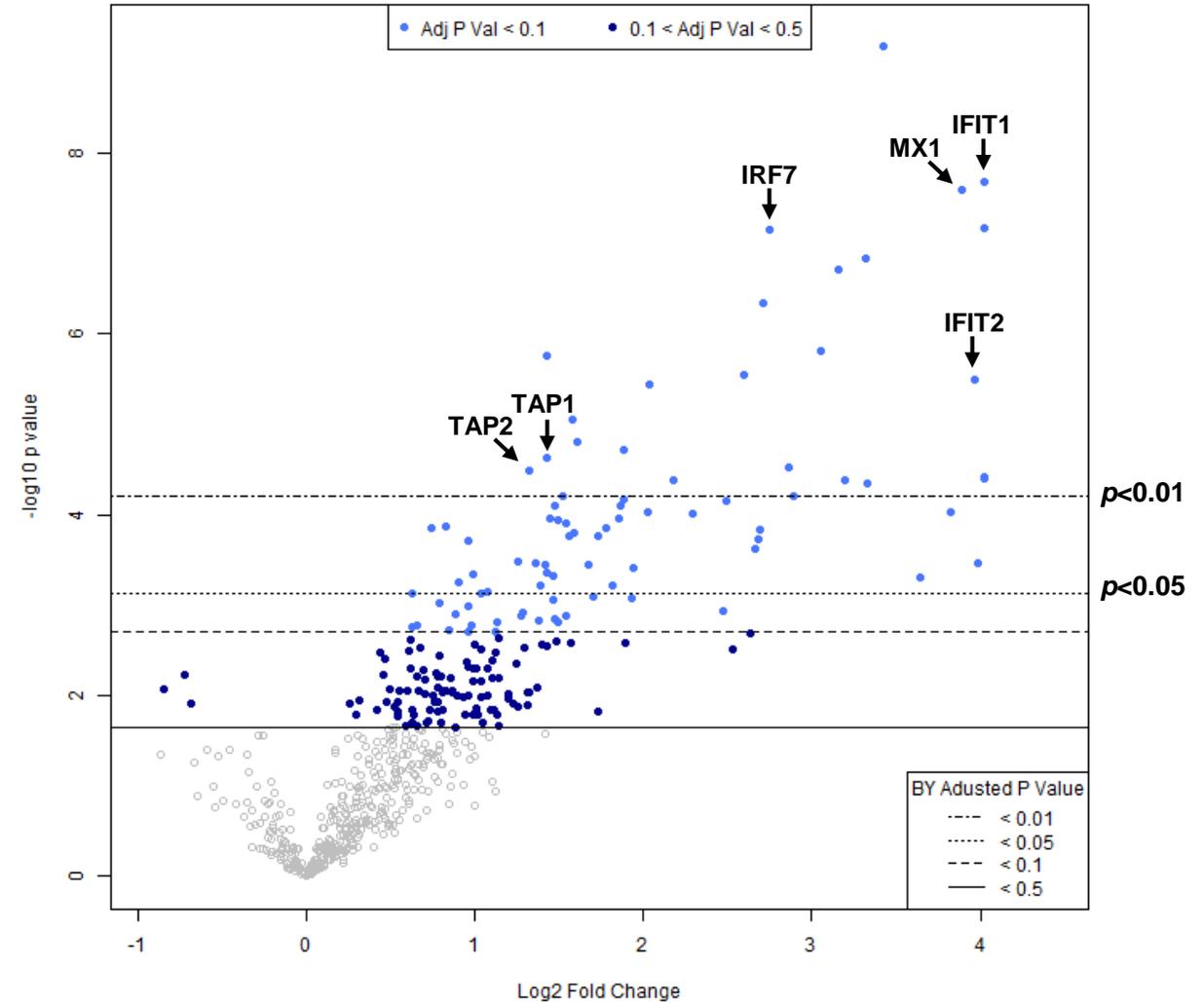
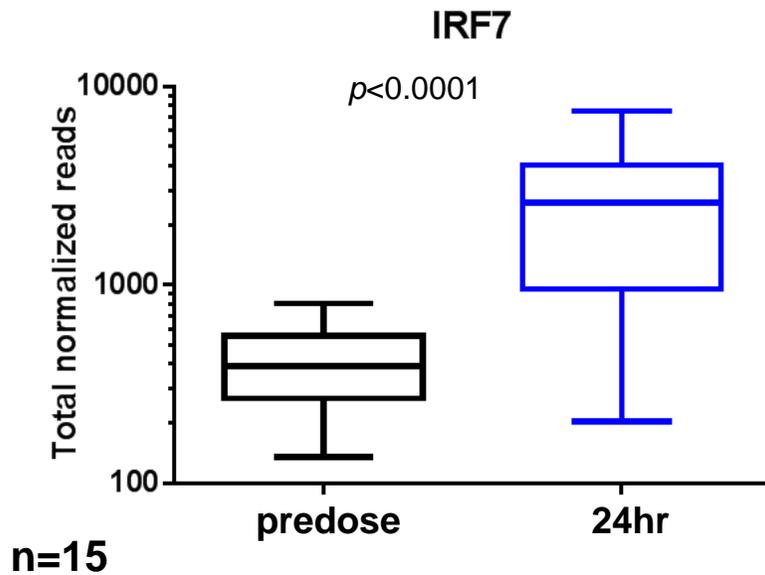
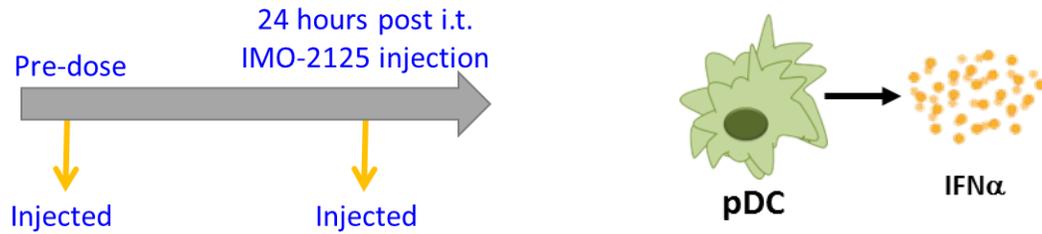
Immune response monitoring to correlate with mechanism of action

Injected = Injected lesion
Distant = Un-injected Lesion

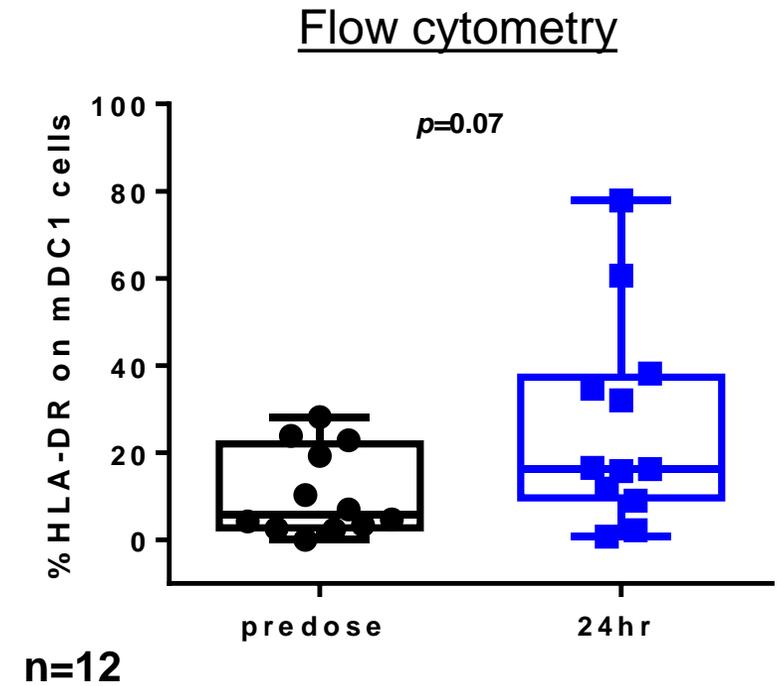
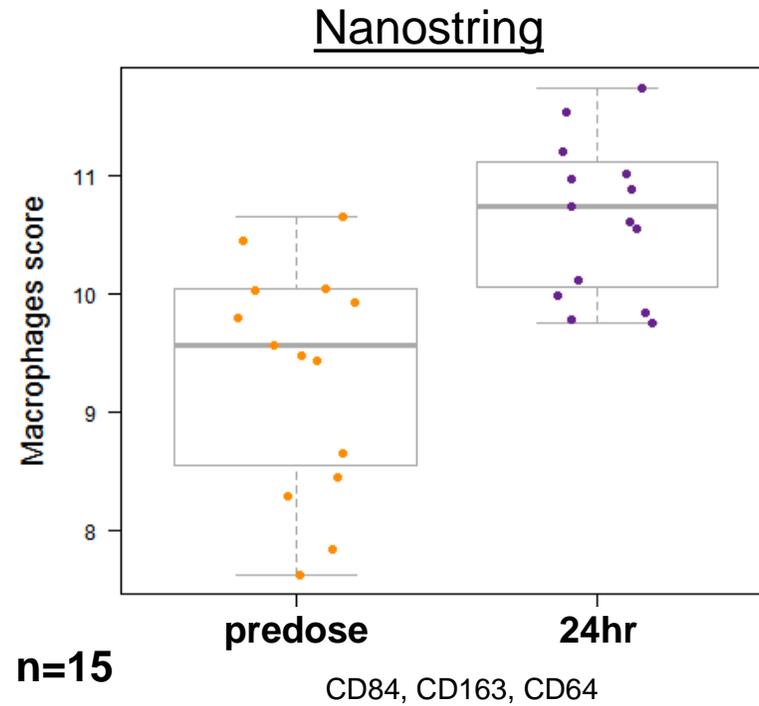
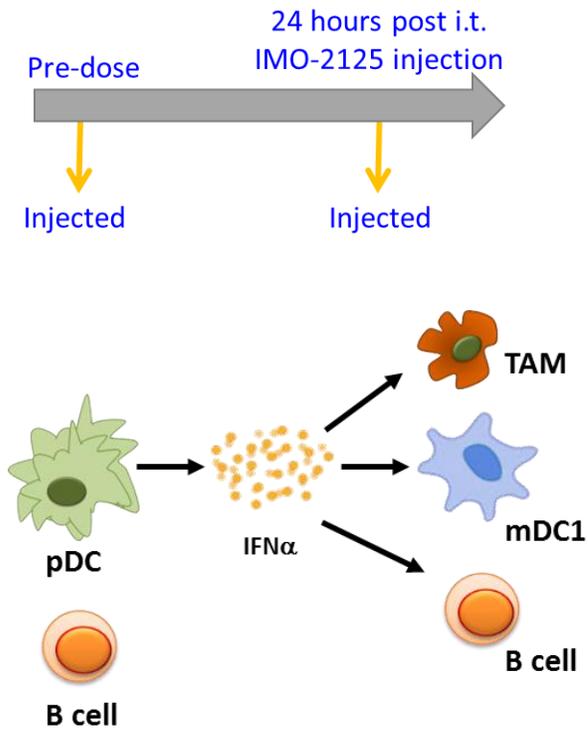
↓ = collection of biopsy
↓ = collection of PBMCs



Induction of IFN α -response gene signature after i.t. IMO-2125

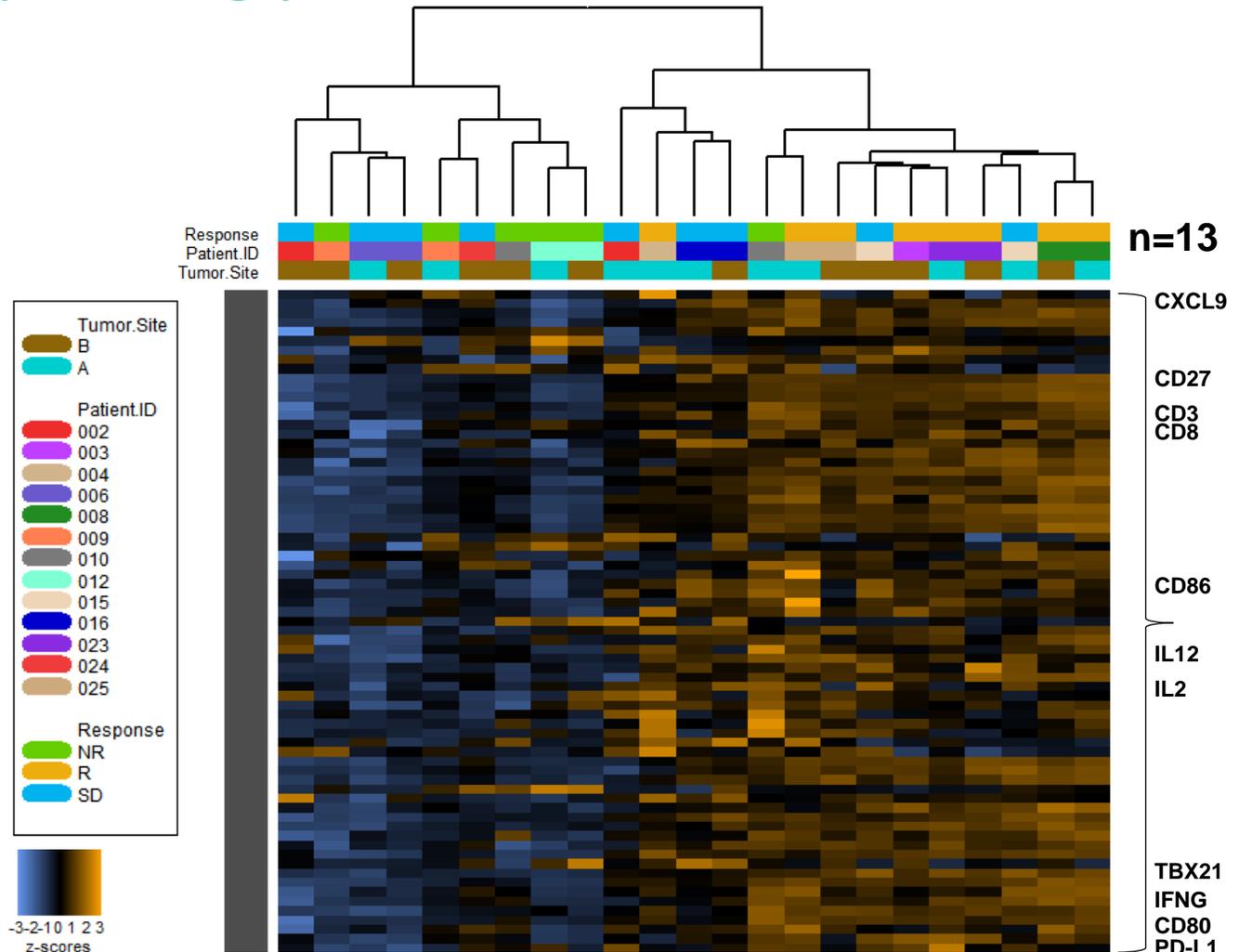
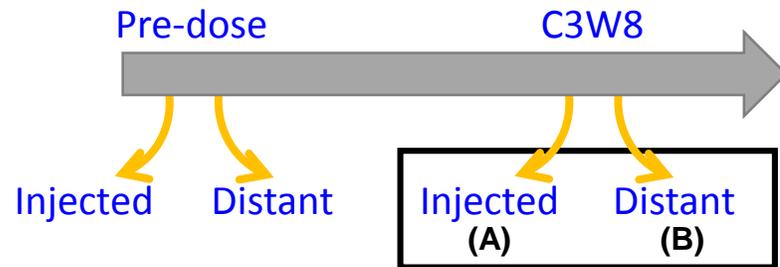


Rapid mDC1 maturation and macrophage influx induced by IMO-2125 in the tumor



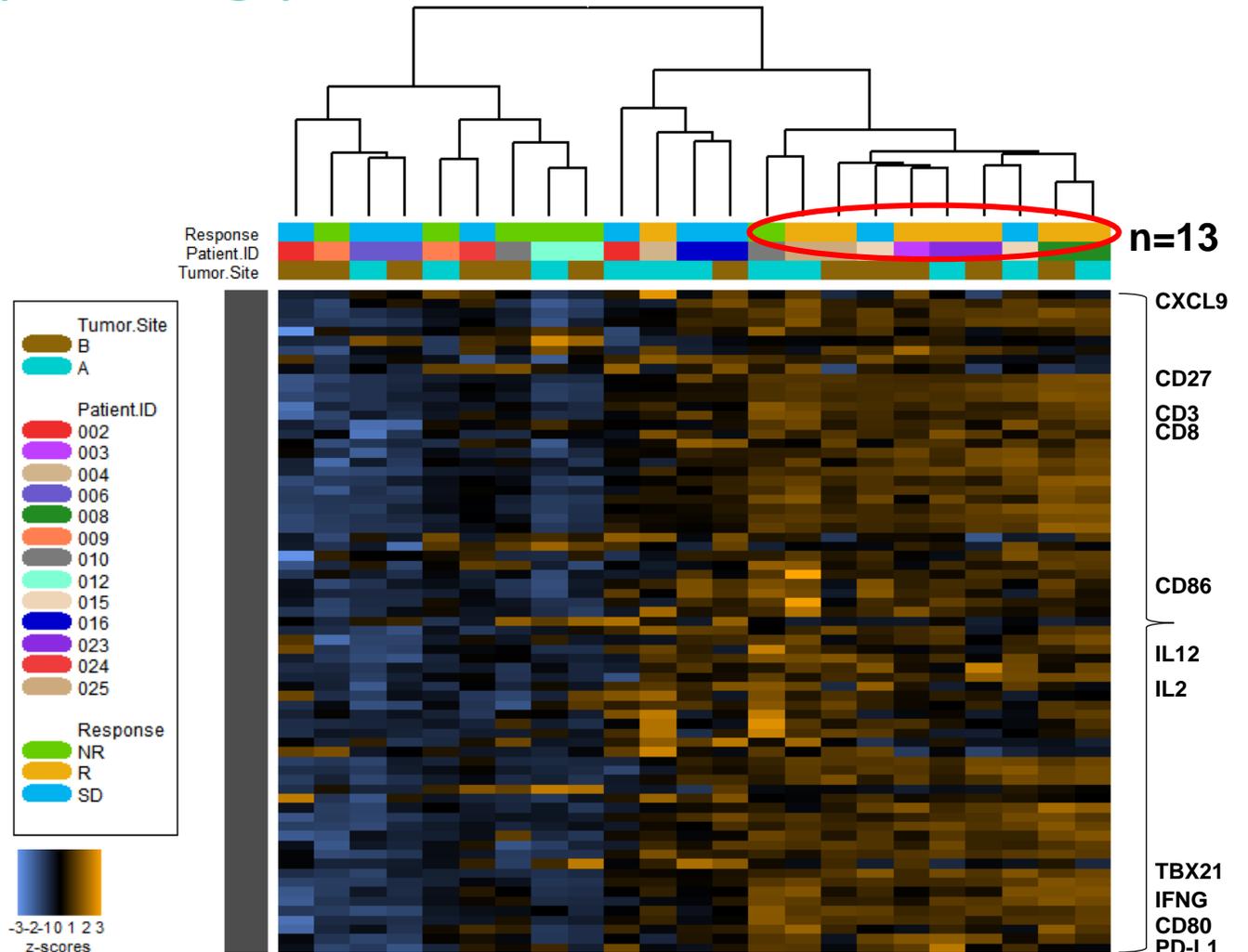
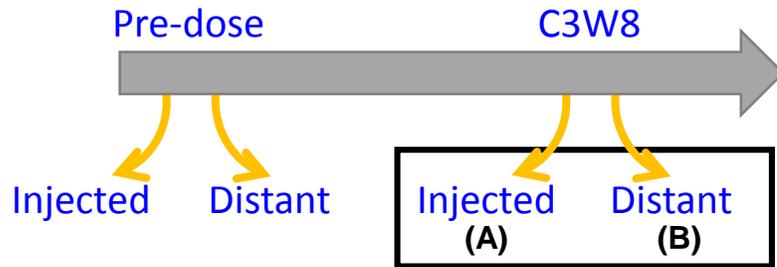
Combination therapy induces CD8⁺ TIL activation early on-treatment in responding patients

Activation at C3W8 by Nanostring

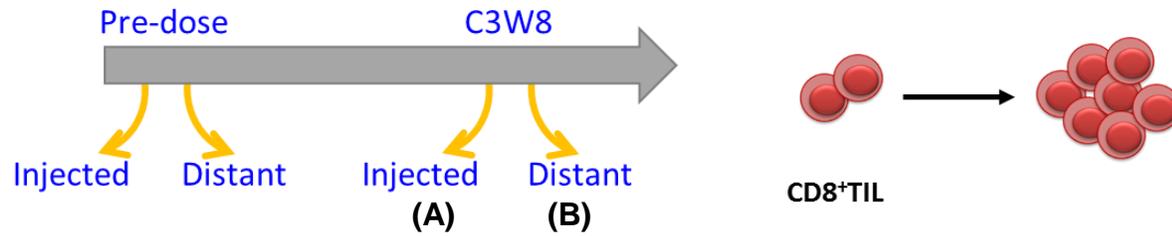


Combination therapy induces CD8⁺ TIL activation early on-treatment in responding patients

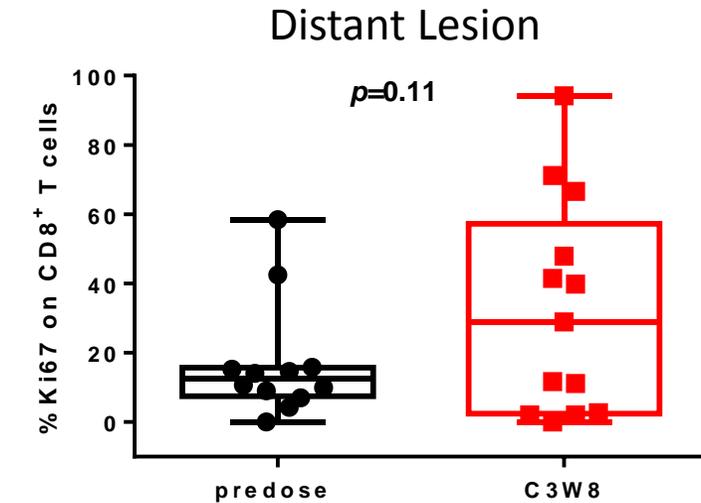
Activation at C3W8 by Nanostring



Combination therapy induces CD8⁺ TIL proliferation and CTL function

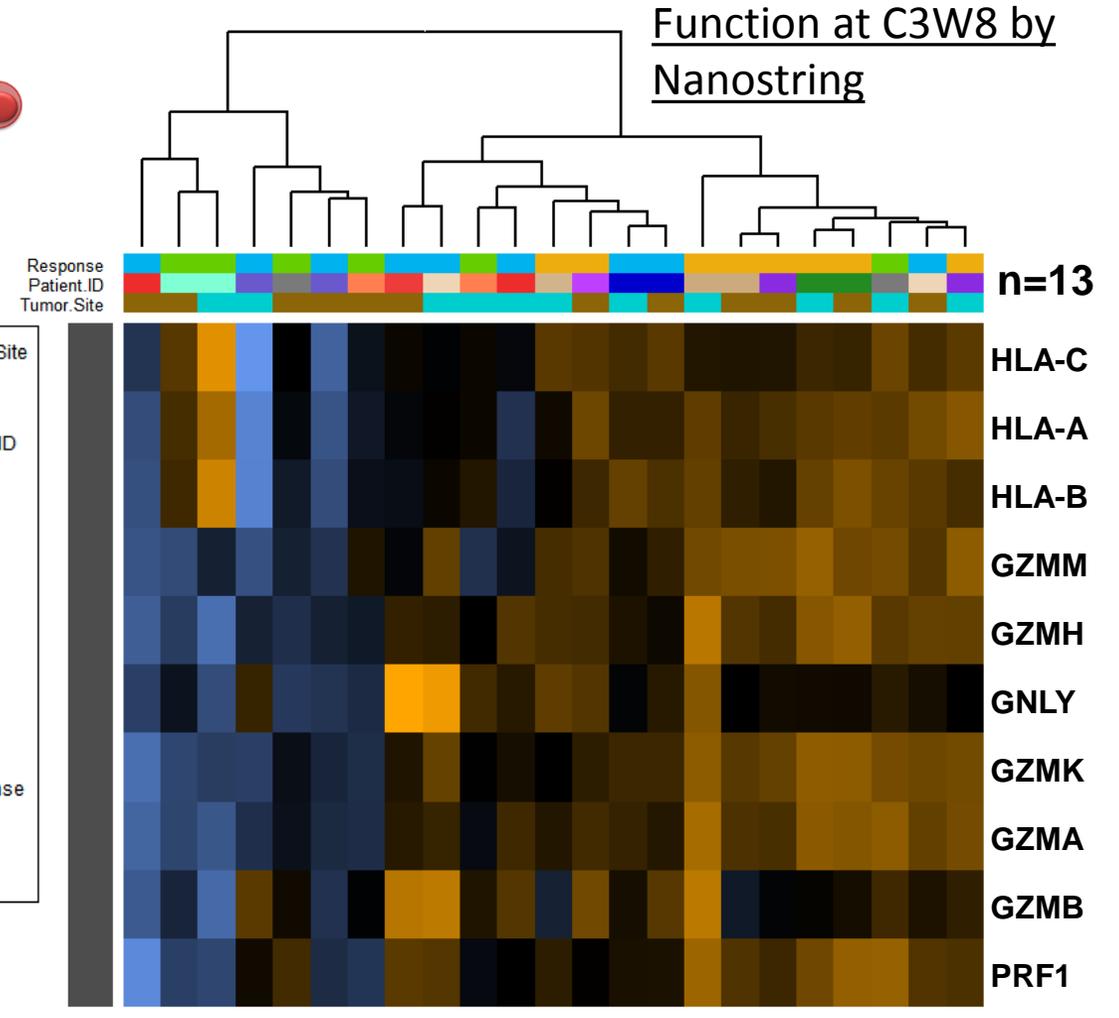
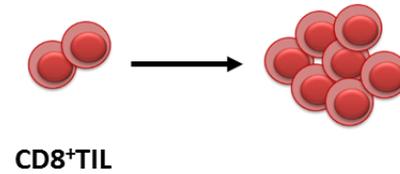
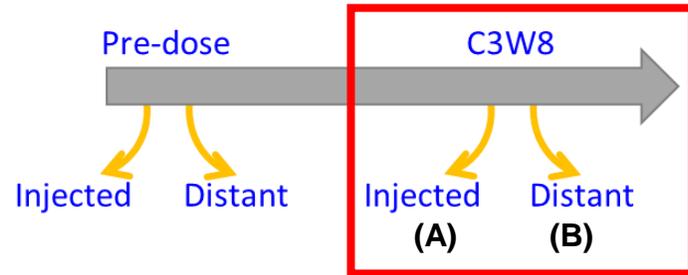


Proliferation by flow cytometry

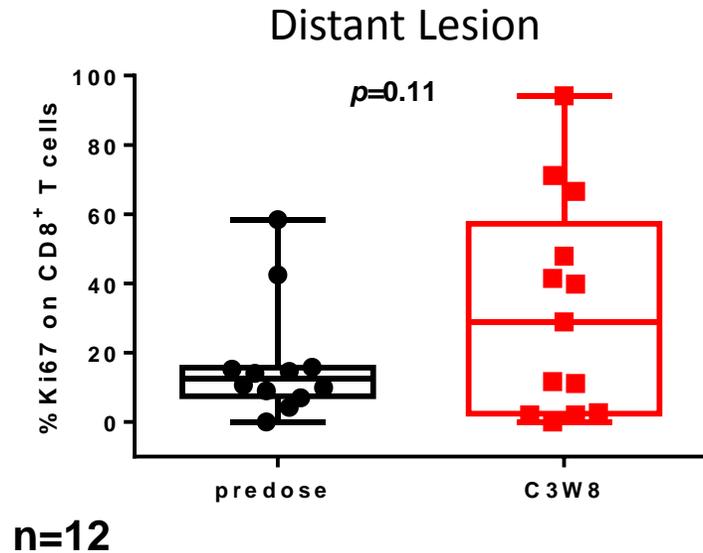


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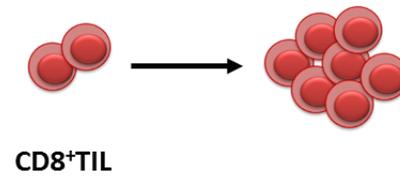
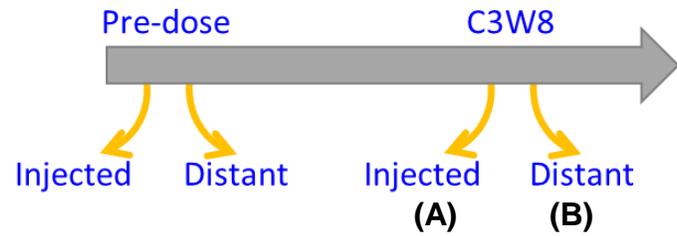
Combination therapy induces CD8⁺ TIL proliferation and CTL function



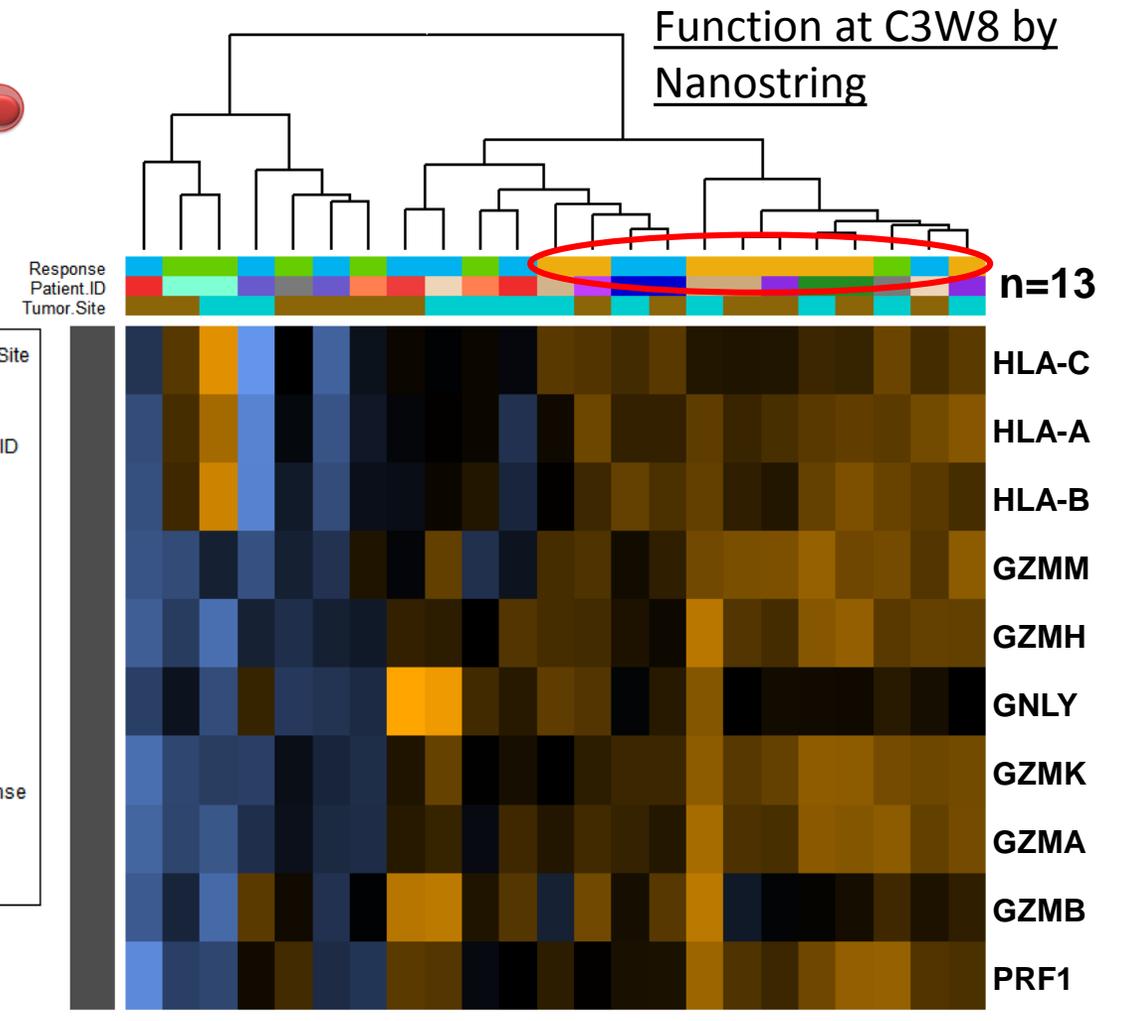
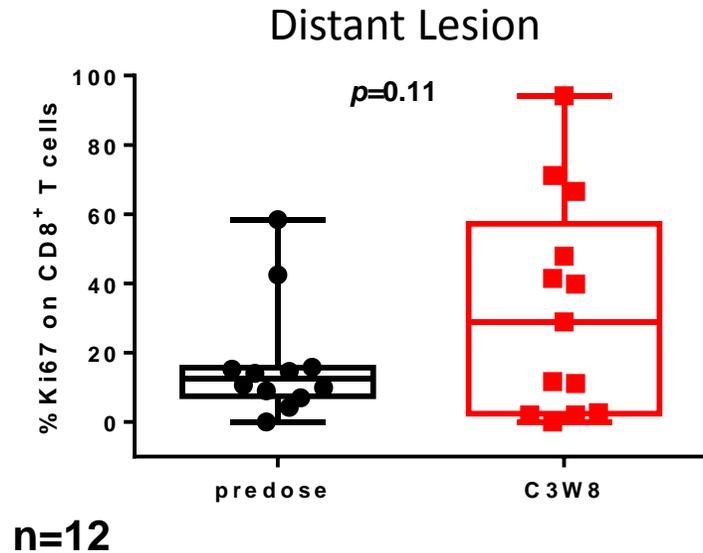
Proliferation by flow cytometry



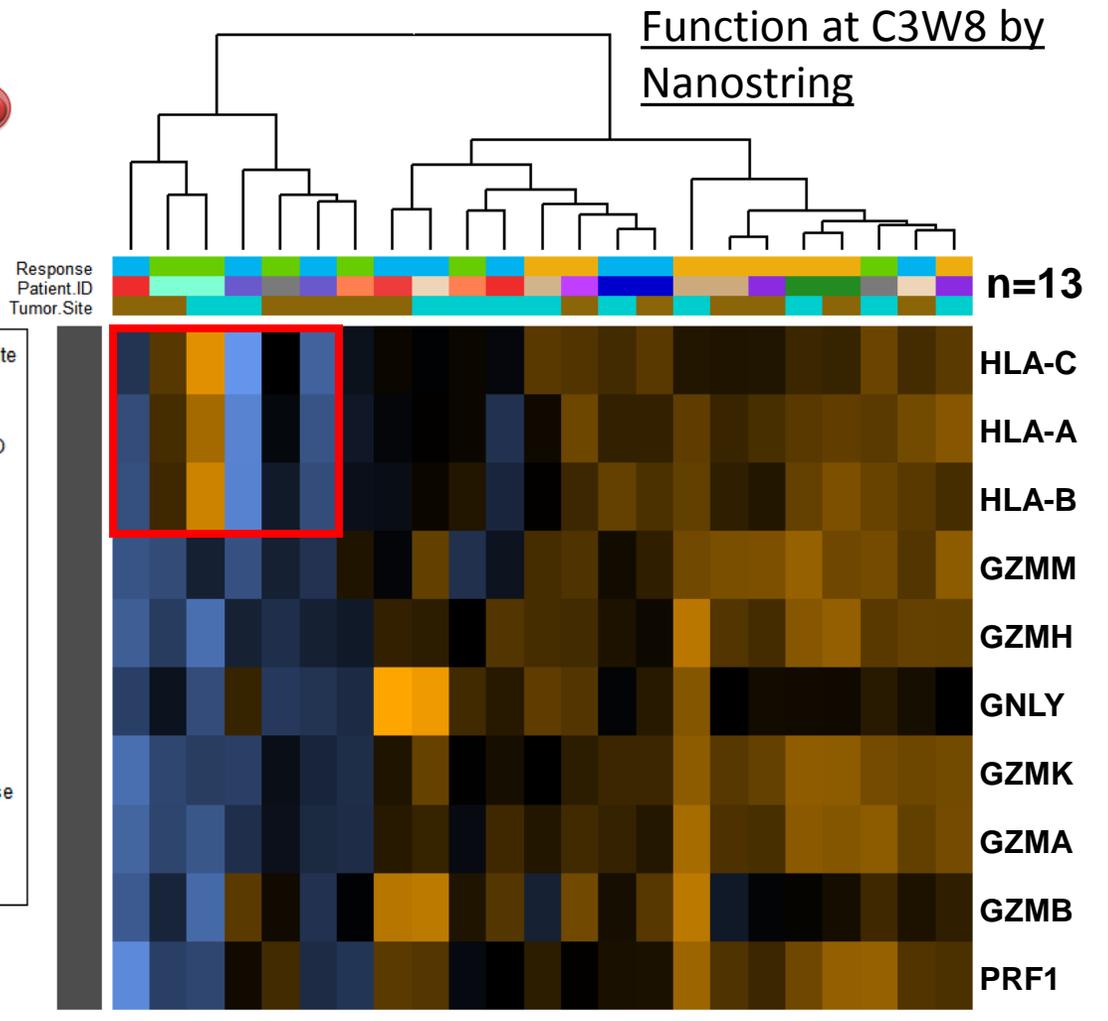
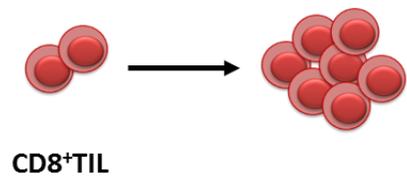
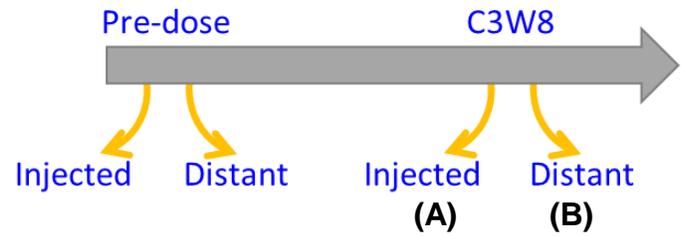
Combination therapy induces CD8⁺ TIL proliferation and CTL function



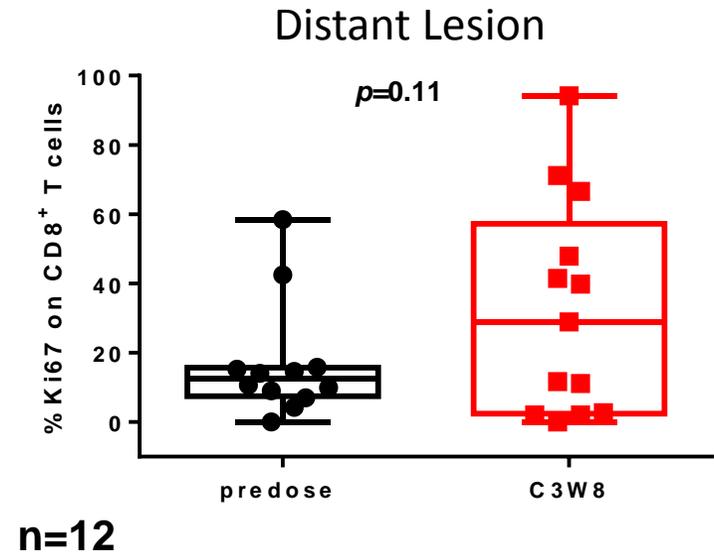
Proliferation by flow cytometry



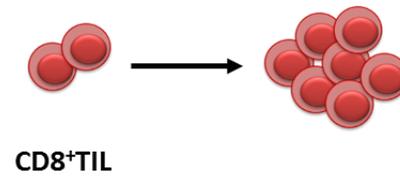
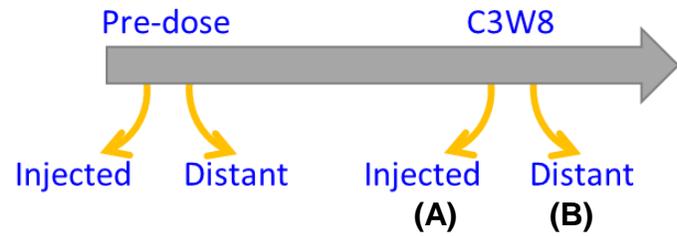
Combination therapy induces CD8⁺ TIL proliferation and CTL function



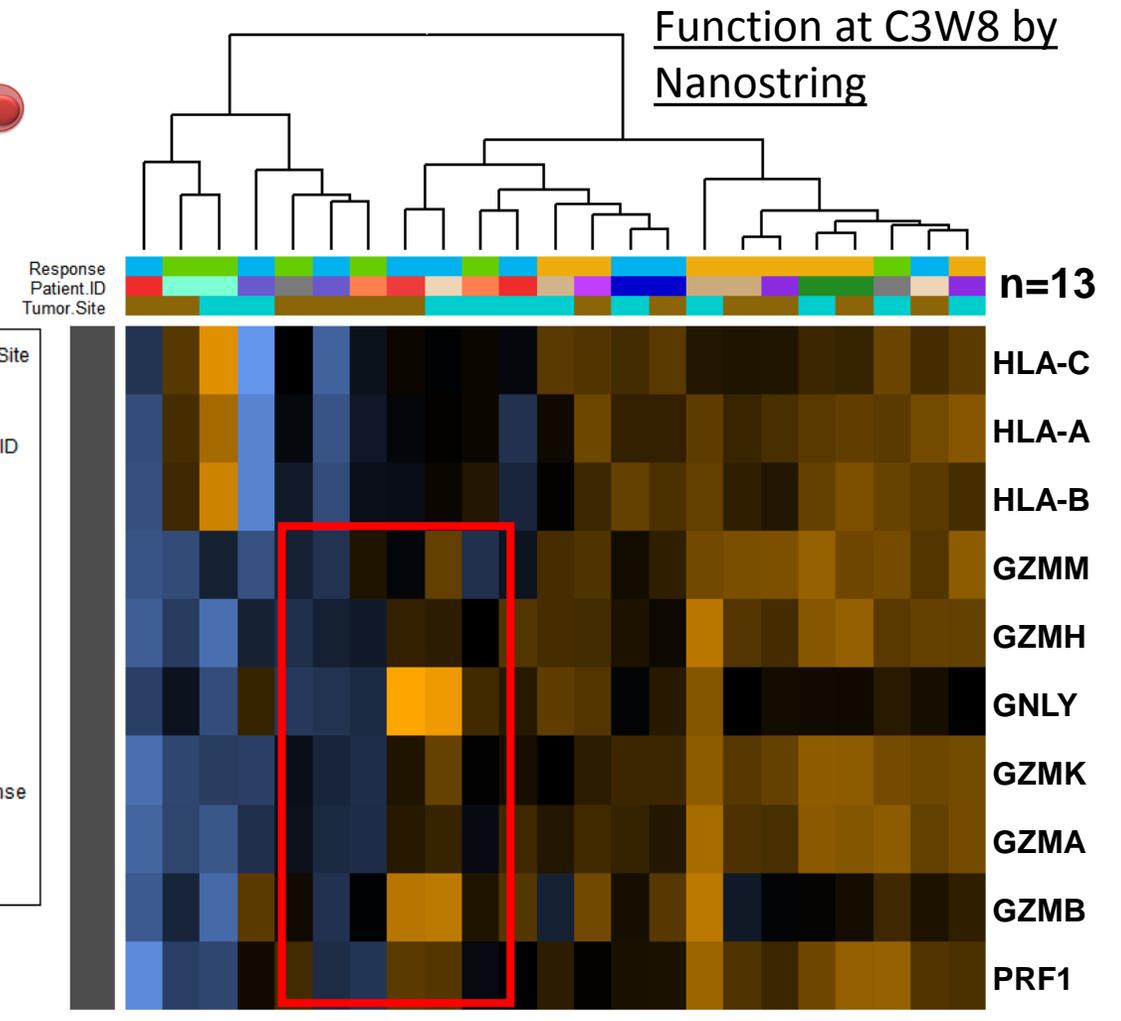
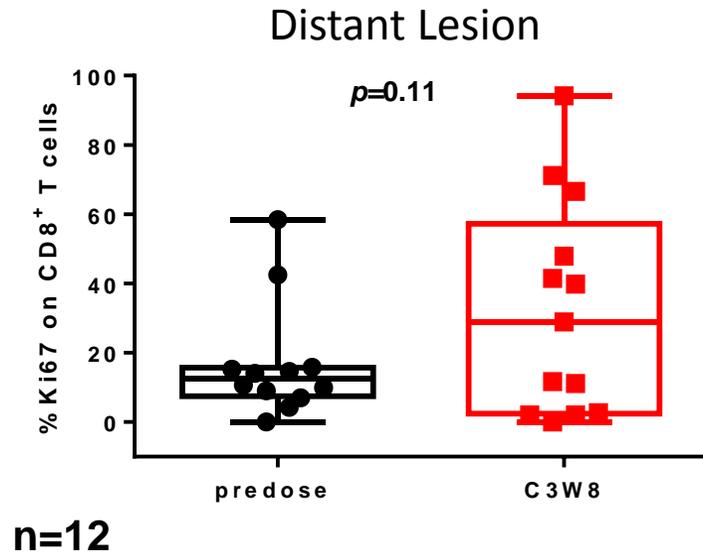
Proliferation by flow cytometry



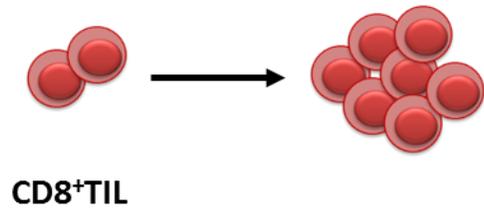
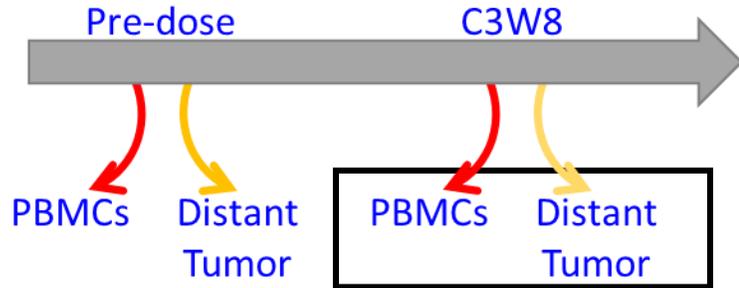
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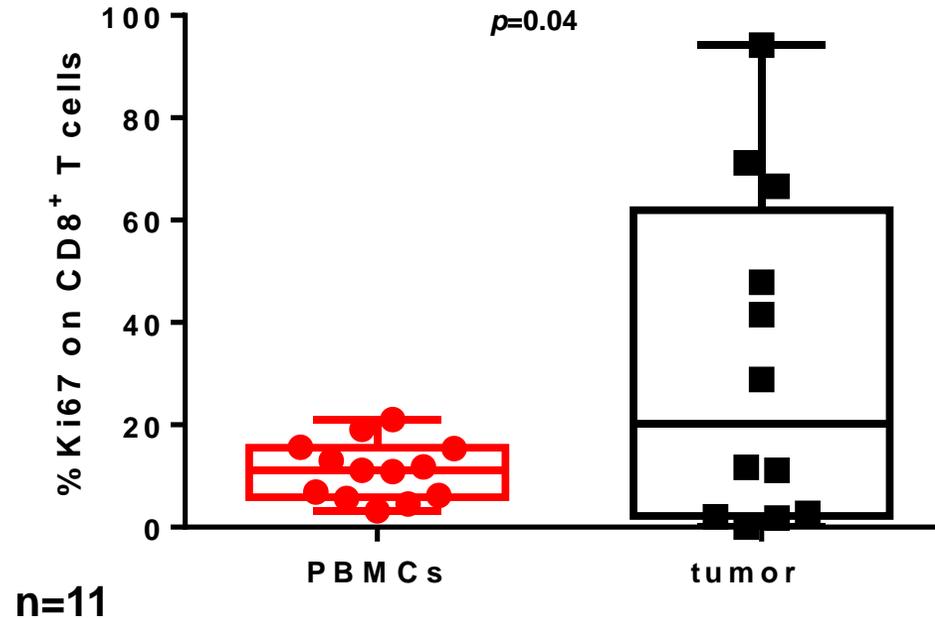
Proliferation by flow cytometry



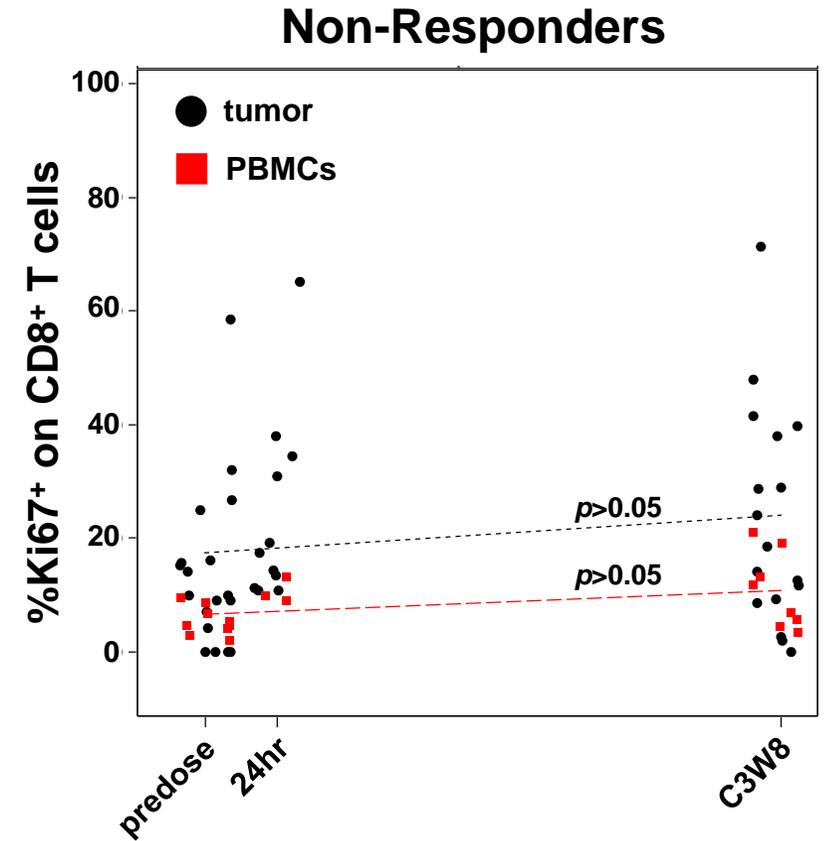
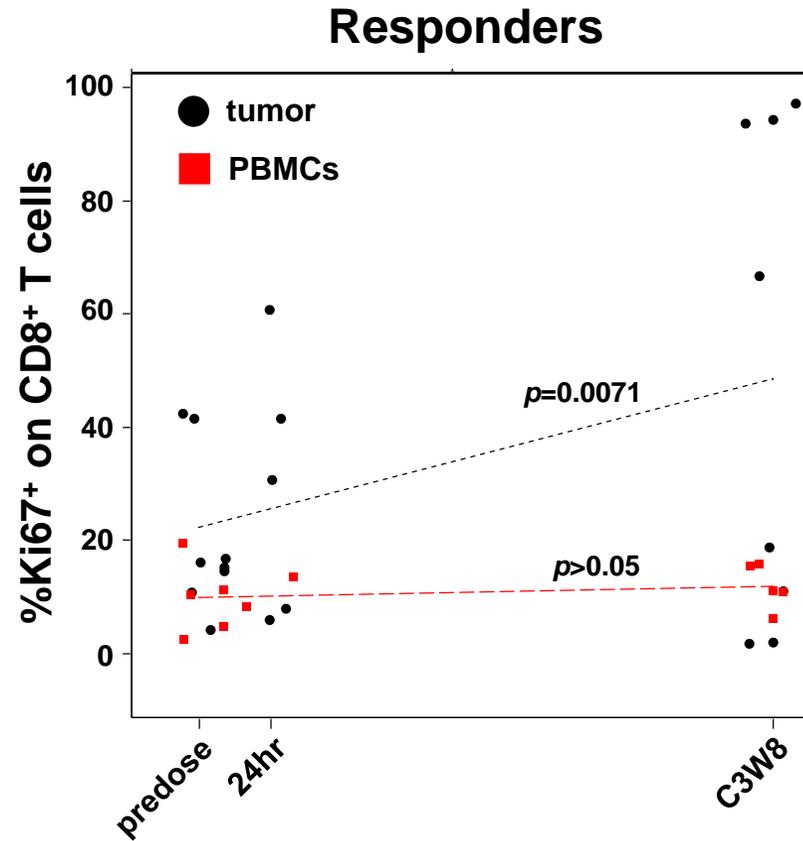
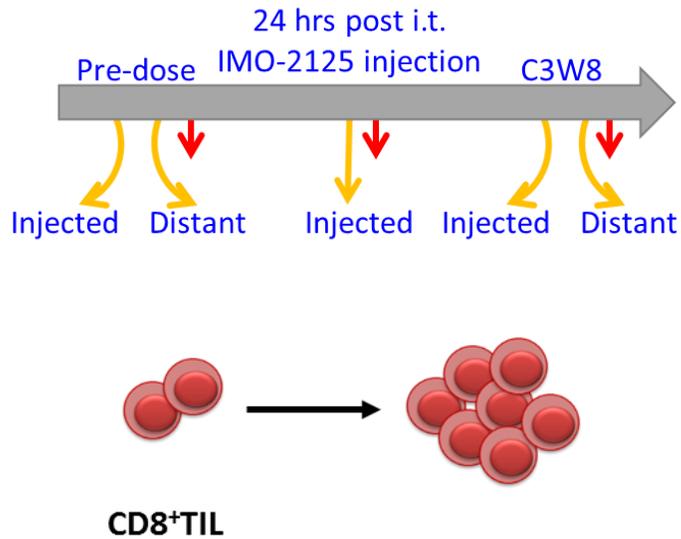
Preferential CD8⁺ T-cell proliferation at the distant lesion



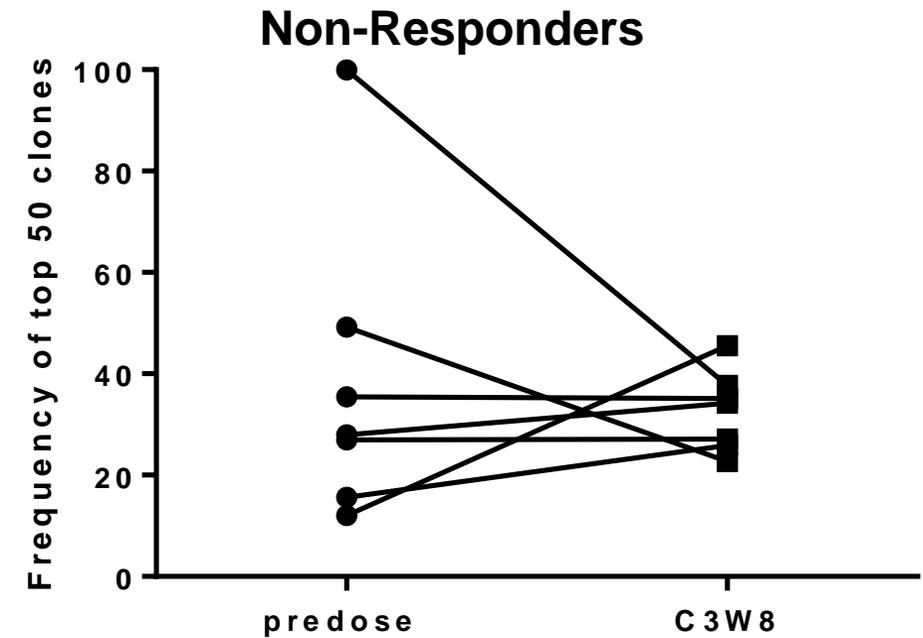
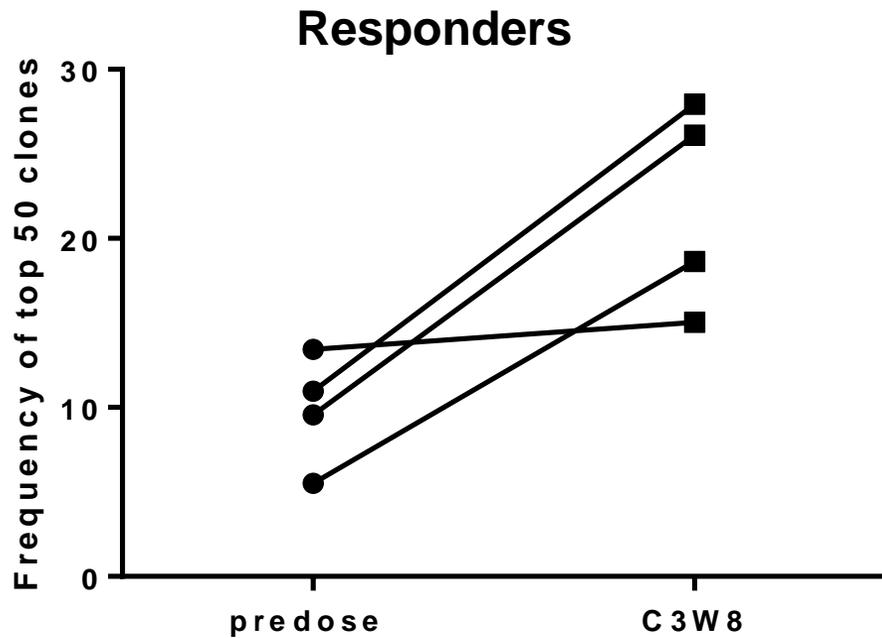
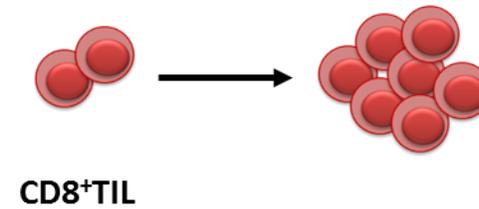
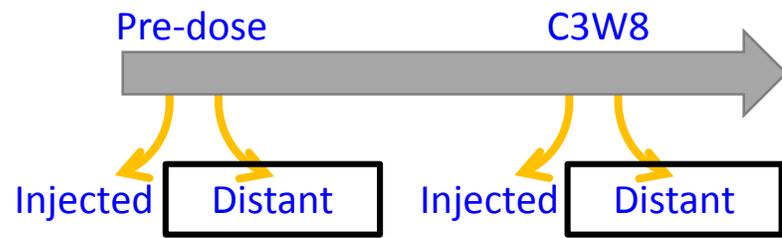
Time point: C3W8



Selective increase in CD8⁺ T-cell proliferation in the tumors of responding patients



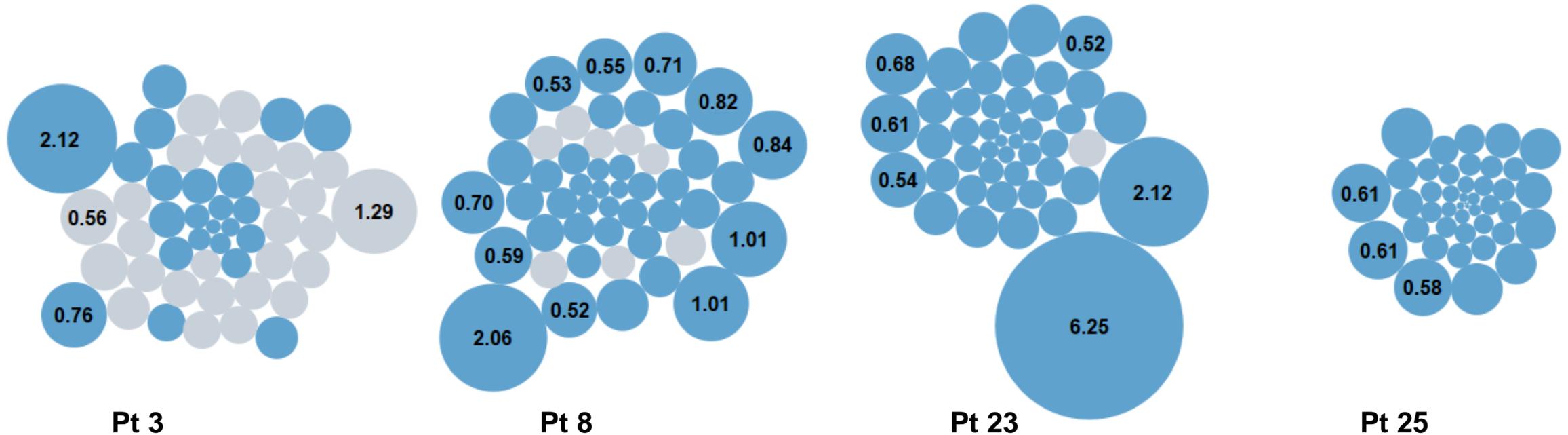
Expansion of top 50 T-cell clones in the distant lesion of responding patients



Expanding clones in the distant lesion are shared with the injected lesion

Top 50 clones in the distant lesion at C3W8 of responding patients

Clone shared between lesions No
 Yes



Number = clonal specific change in frequency (C3W8 – predose)
 Circle size reflects the frequency of the clone relative to the other clones present

Lessons and Take Home Messages

- Key points

- IMO-2125 induces a strong type 1 interferon gene signature, macrophage influx and robust DC maturation post injection independent of ipilimumab
- Combination therapy induces CD8⁺ T cell proliferation and activation that is preferential to the tumor
- Major T-cell clones expanding on therapy in responding patients are shared between local and distant lesions indicating that priming/reactivation is to a shared antigen

- Potential impact on the field

- Combining intra-tumoral DC activation to enhance T-cell priming with checkpoint blockade may be key in IO refractory patient population
- A local tumor can be used as an *in situ* vaccine through activation of local APCs and injection of one lesion results in regression of distant lesions that may not be easily accessible

- Lessons learned

- On-treatment biopsy timing is critical!!

Acknowledgements

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