



# SITC 2017

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& Convention Center



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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**Cancer Center**  
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# Presenter Disclosure Information

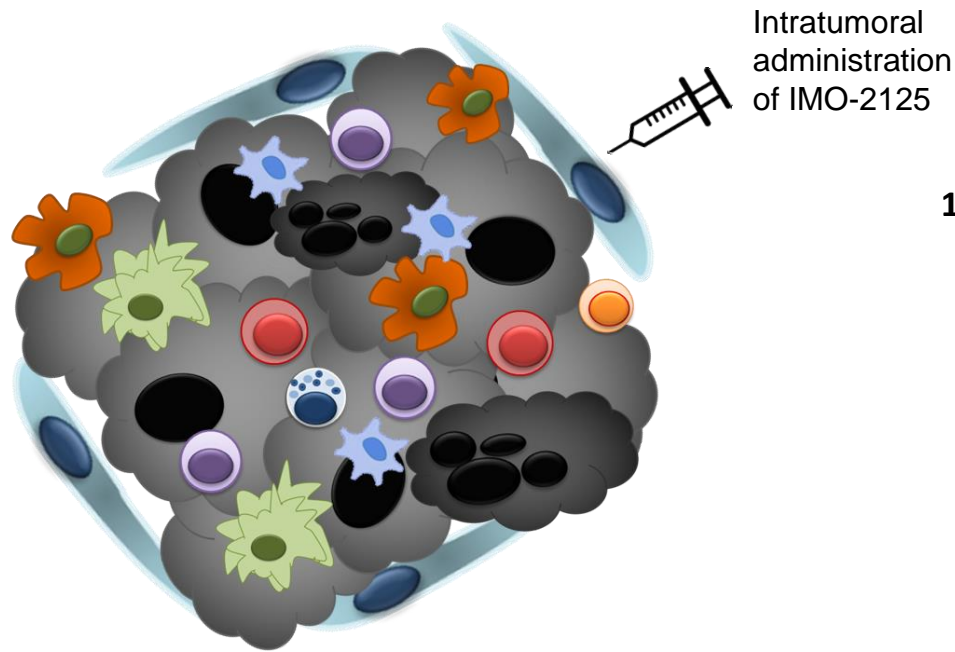
*Cara Haymaker*

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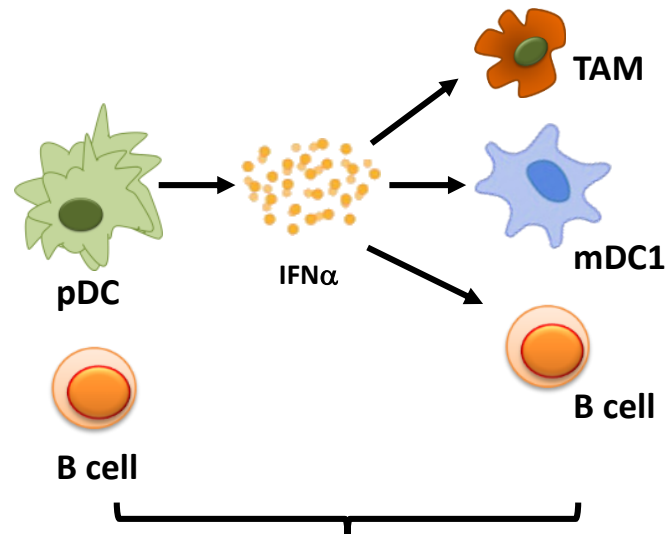
*No Relationships to Disclose*



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

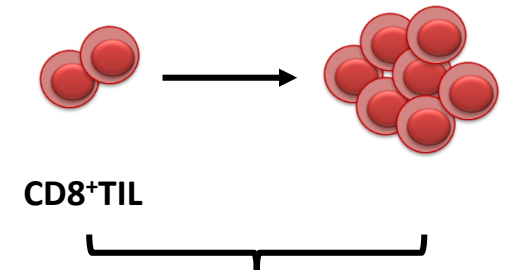


## 1. TLR9 induction of IFN $\alpha$ and APC maturation

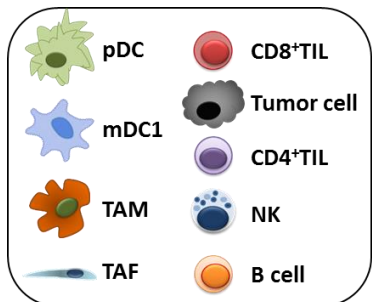


Activation of APCs to improve T-cell priming

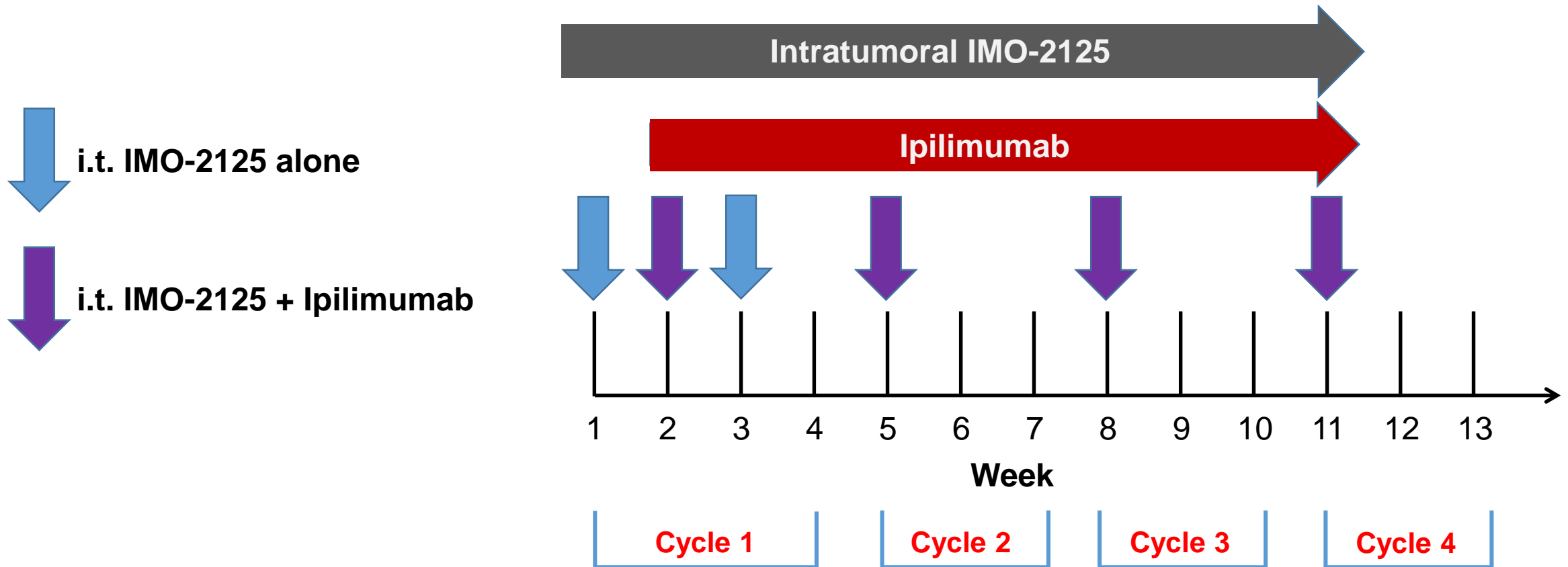
## 2. TIL Activation and Proliferation



Improved antigen presentation results in TIL activation and proliferation



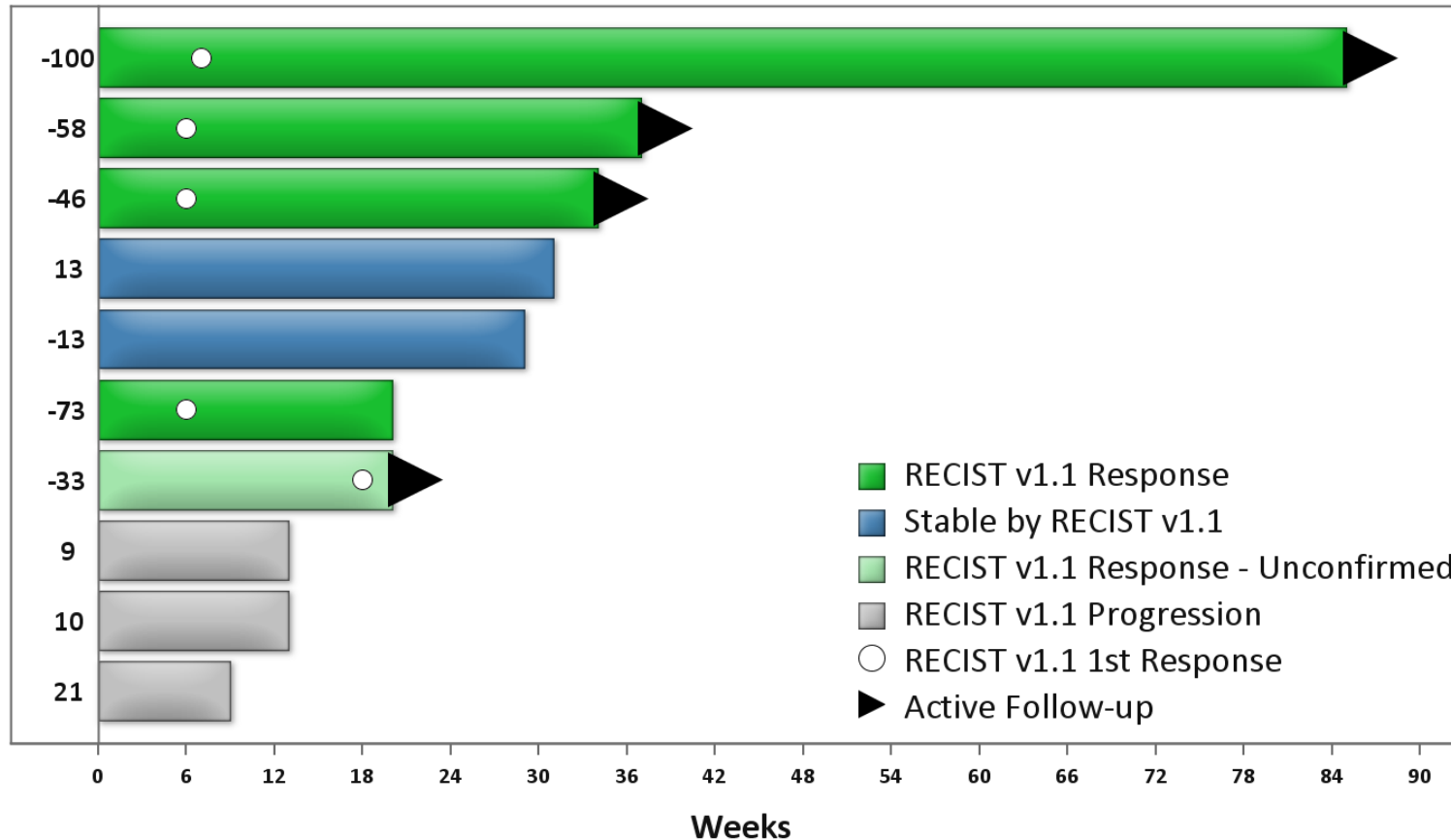
## Trial Design (NCT02644967)



## 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



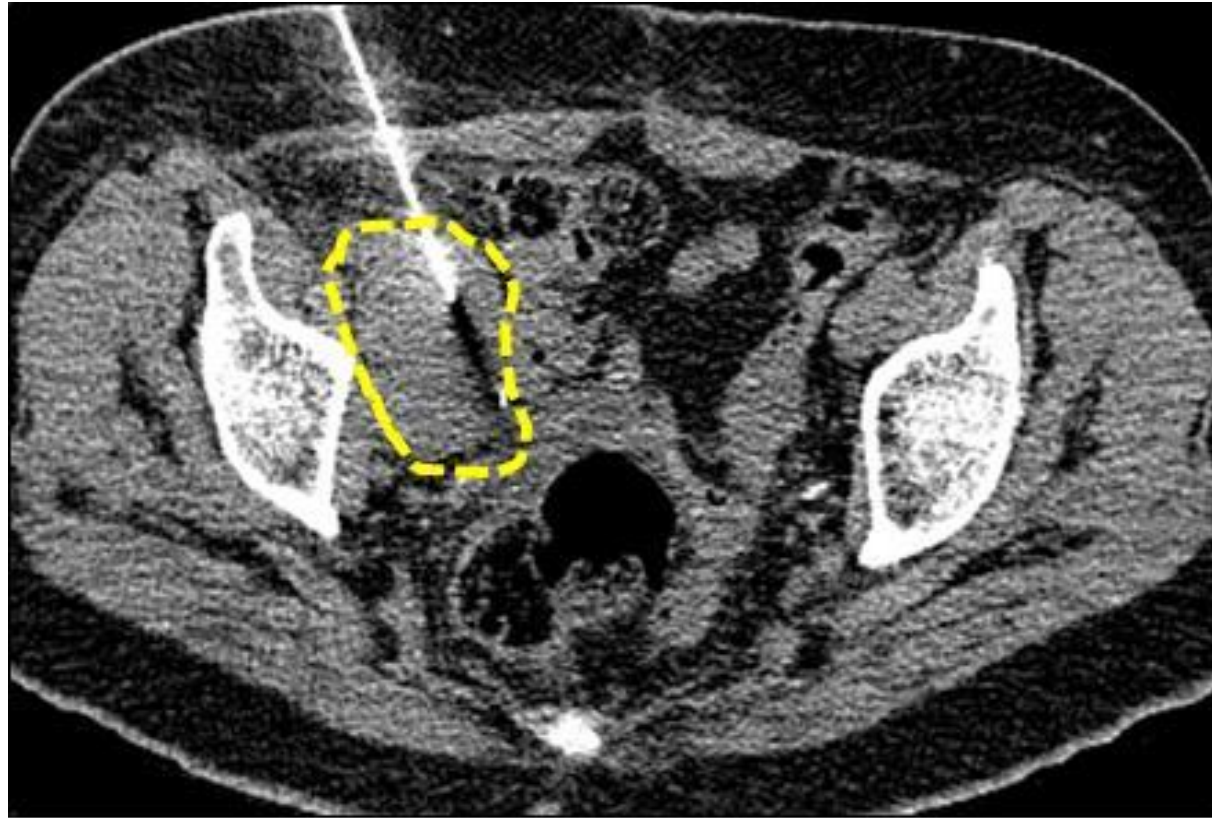
Time on study ends at RECIST v1.1 PD (including death & start of new anti-cancer therapy) or study withdrawal for any reason.

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

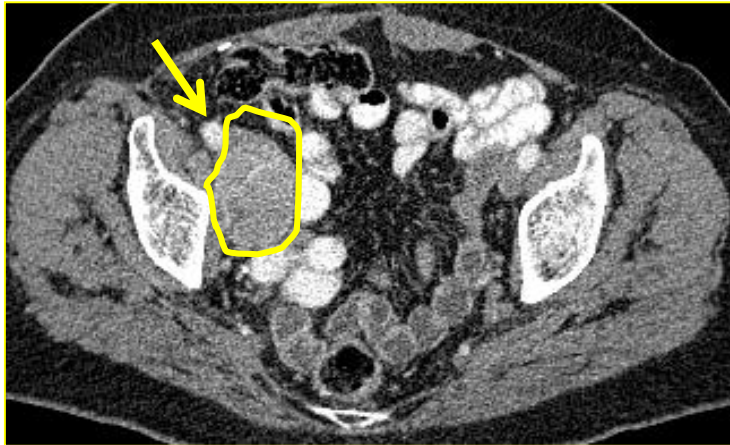


CT guided Intratumoral injection of deep inguinal soft tissue mass

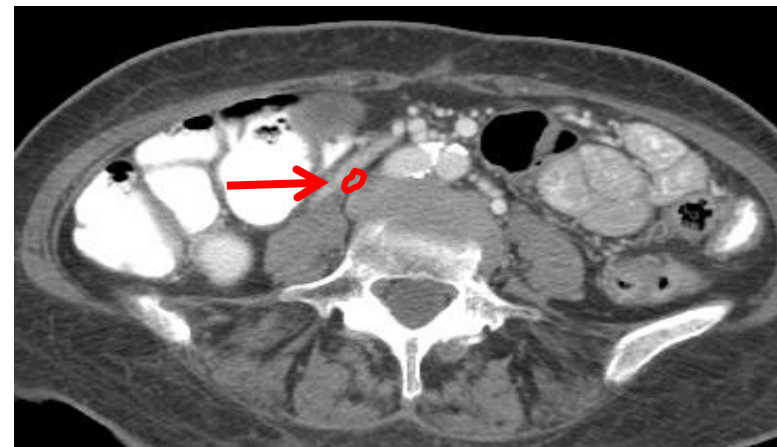
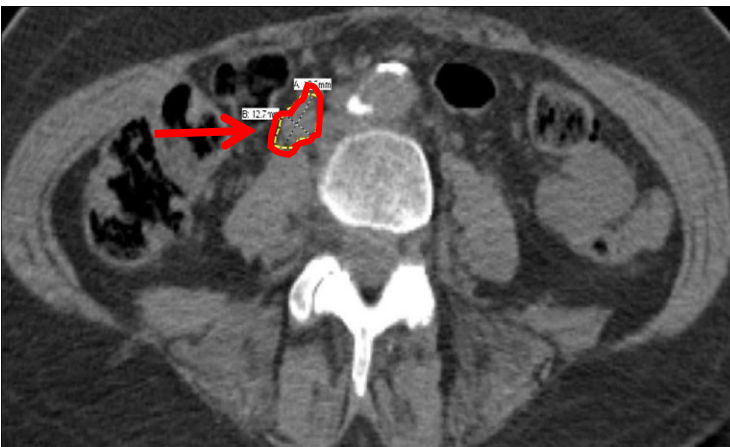


# Tumor Imaging of Patient with a Partial Response: Ipilimumab + i.t. IMO-2125 (8mg)

**Pre-Therapy**



**Post-Therapy**



Injected Lesion 

Distant Lesion 

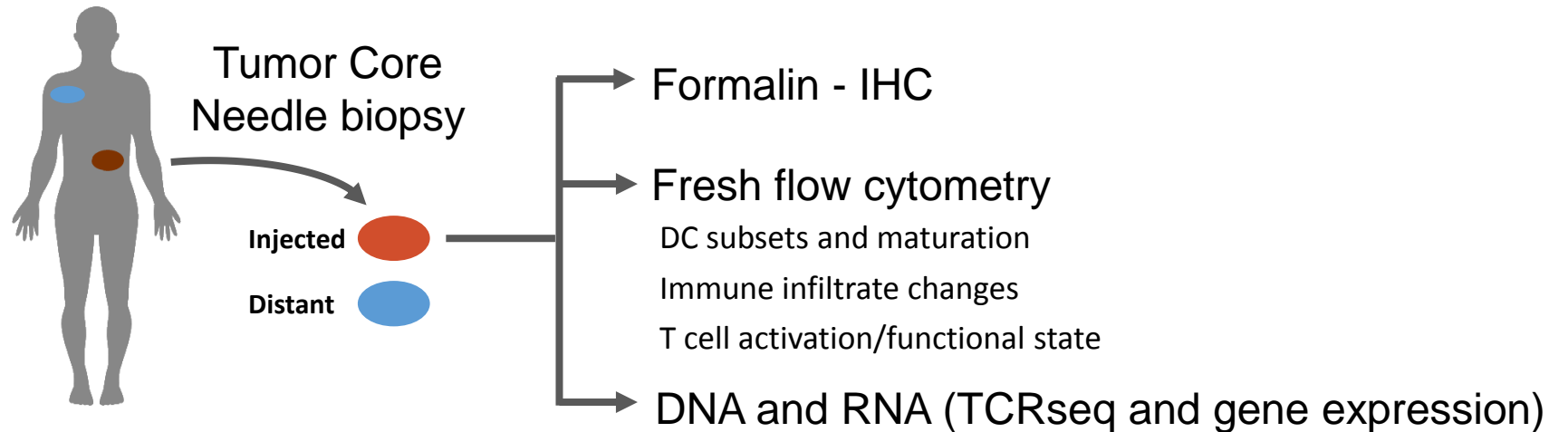
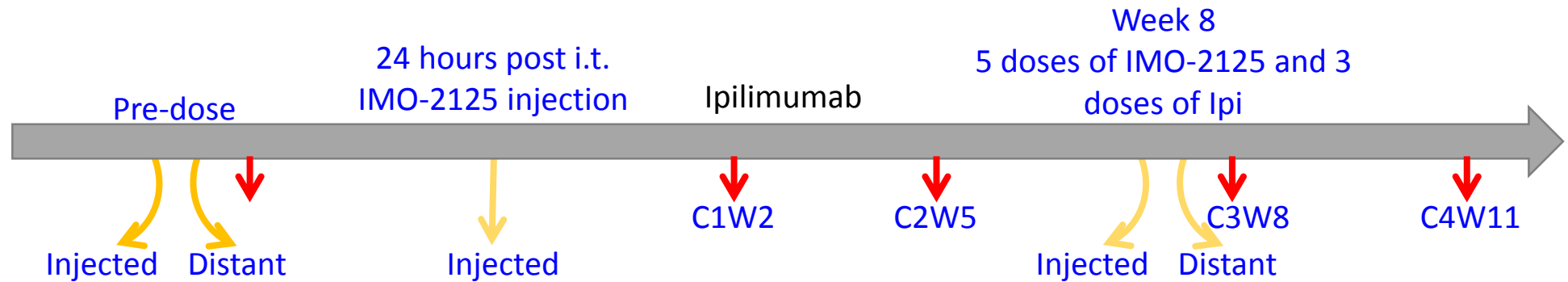
# Immune response monitoring to correlate with mechanism of action

Injected = Injected lesion

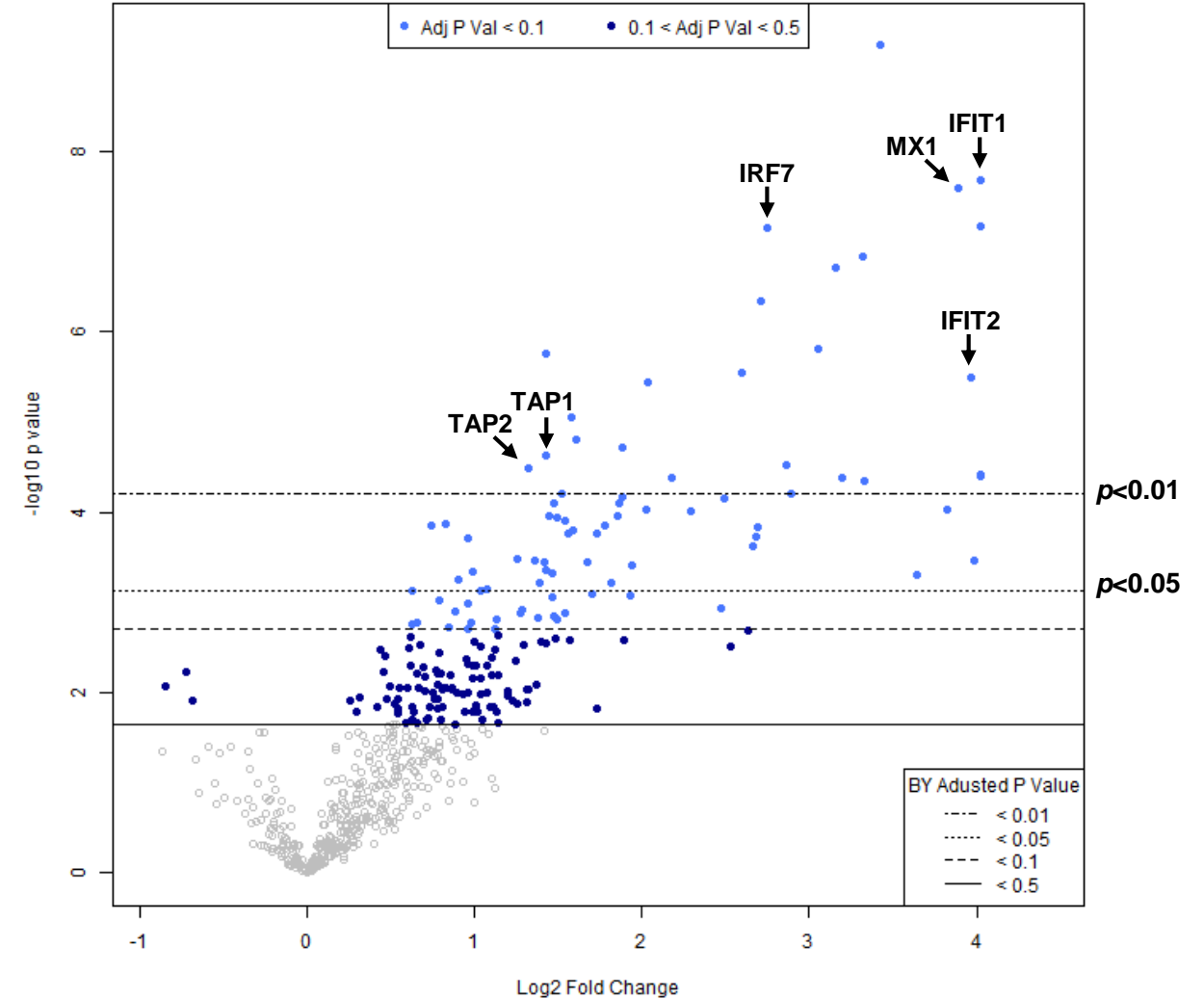
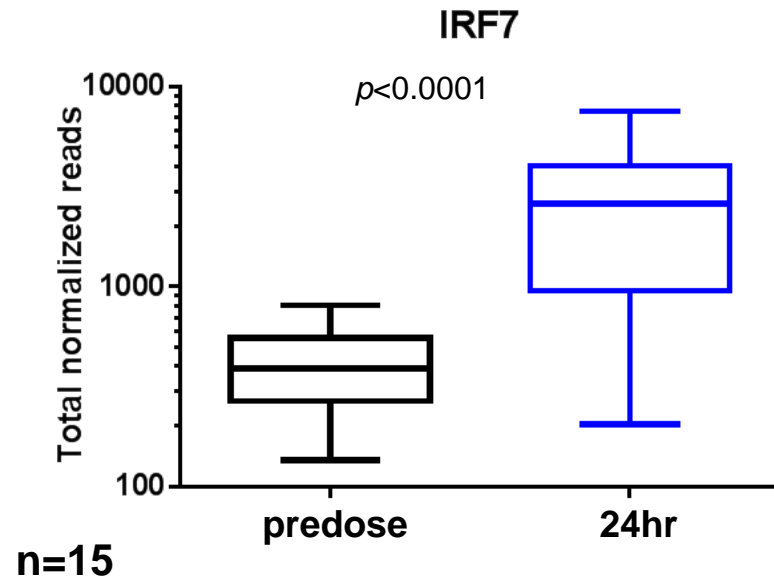
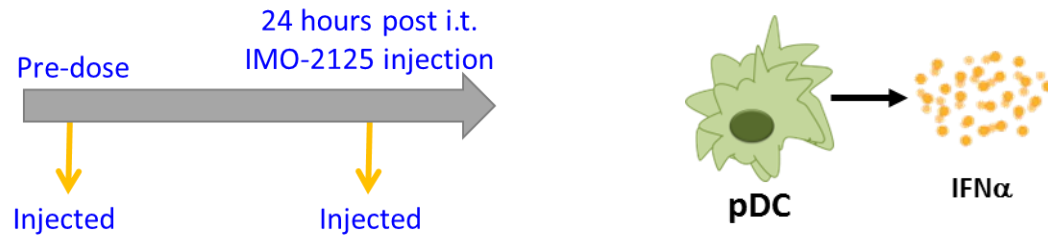
Distant = Un-injected Lesion

↓ = collection of biopsy

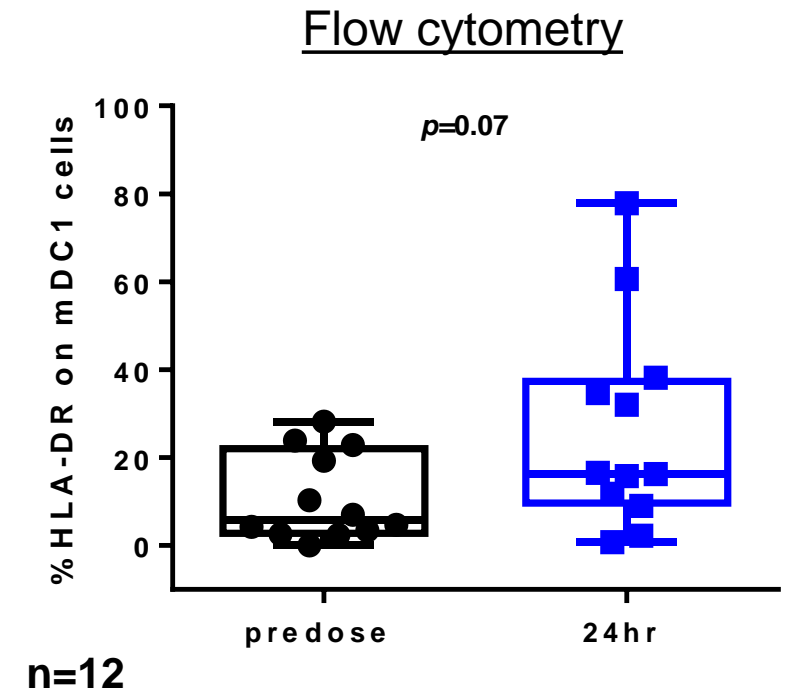
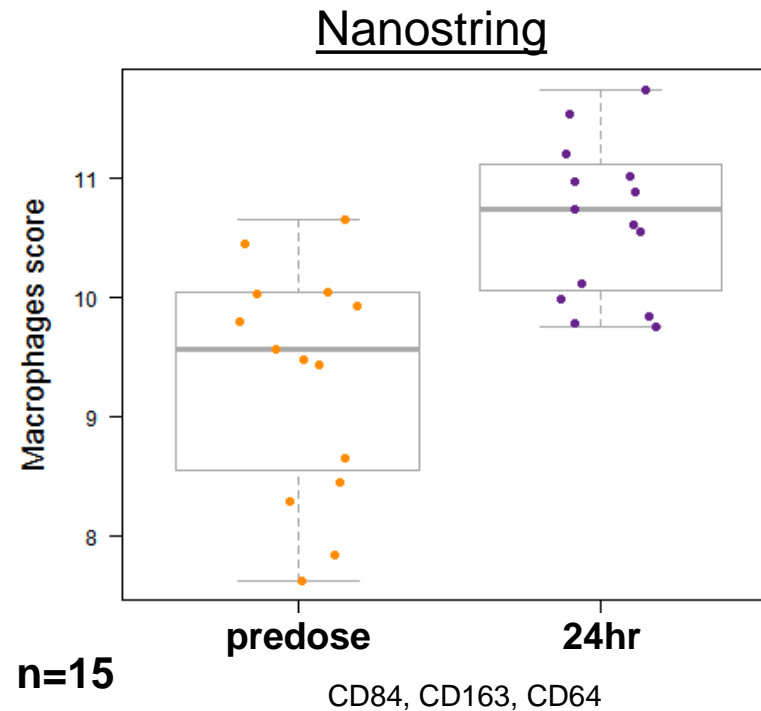
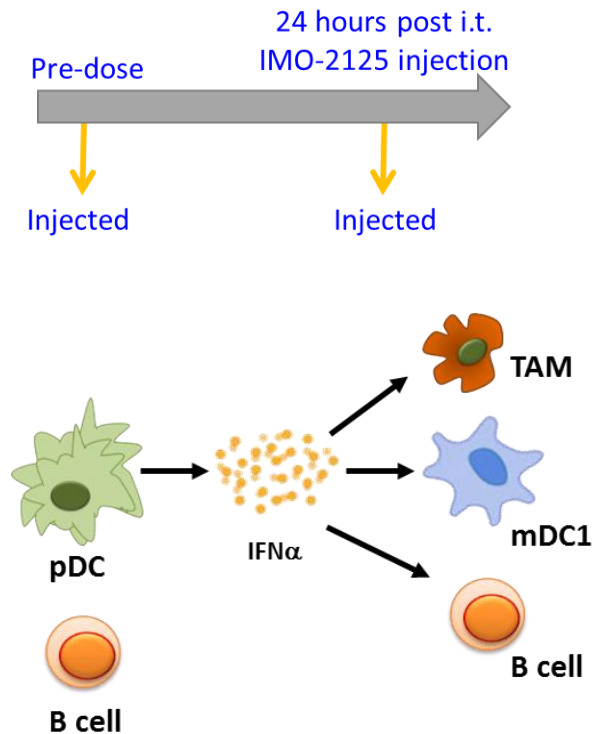
↓ = collection of PBMCs



# Induction of IFN $\alpha$ -response gene signature after i.t. IMO-2125



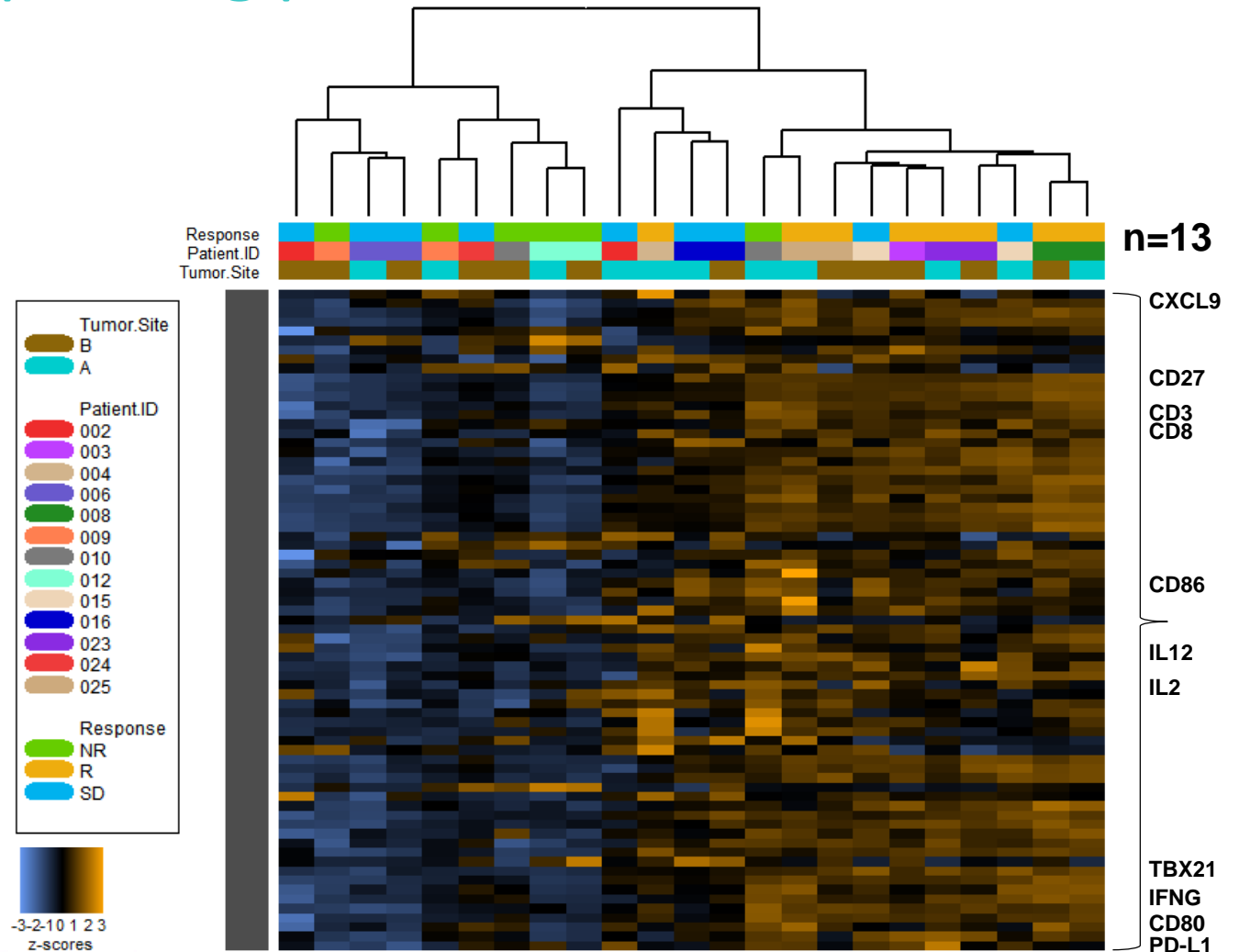
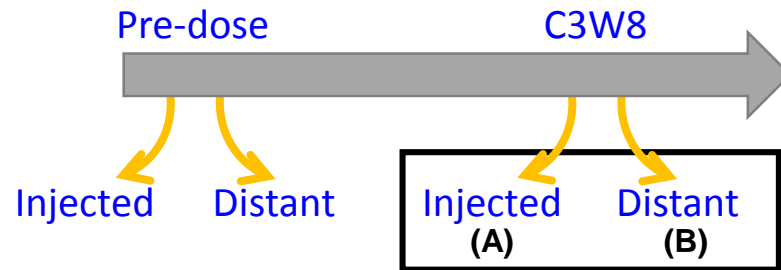
# Rapid mDC1 maturation and macrophage influx induced by IMO-2125 in the tumor





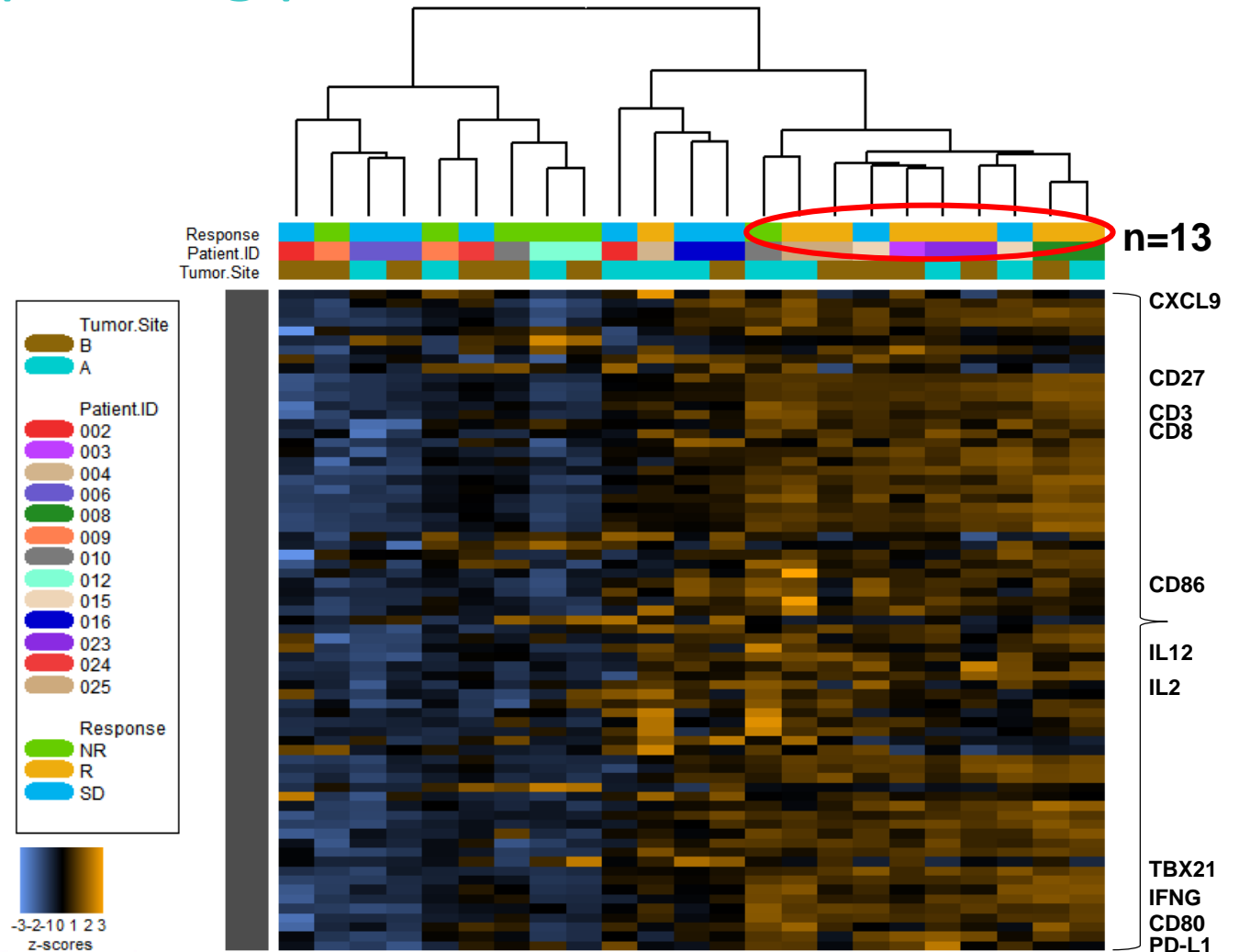
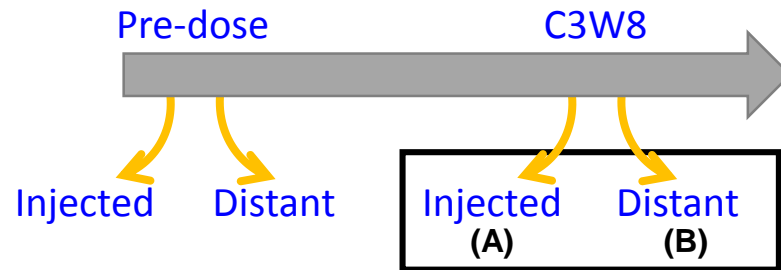
# Combination therapy induces CD8<sup>+</sup> TIL activation early on-treatment in responding patients

Activation at C3W8 by Nanostring

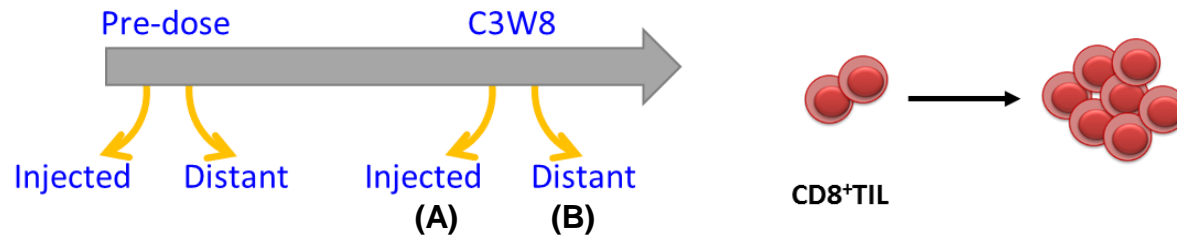


# Combination therapy induces CD8<sup>+</sup> TIL activation early on-treatment in responding patients

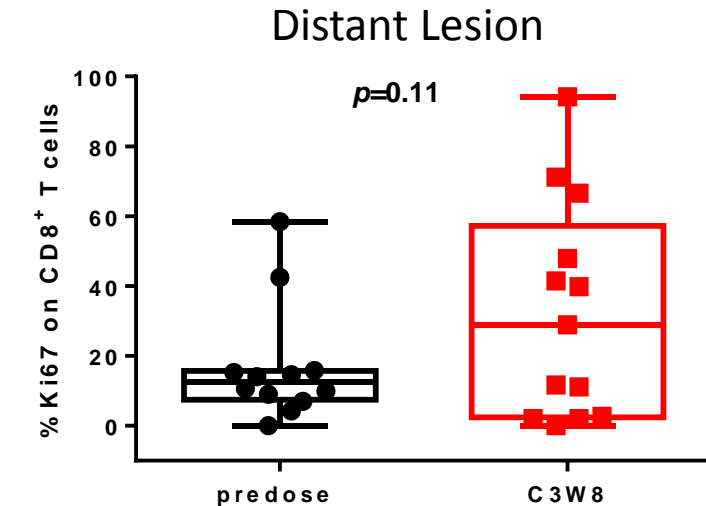
Activation at C3W8 by Nanostring



# Combination therapy induces CD8<sup>+</sup> TIL proliferation and CTL function

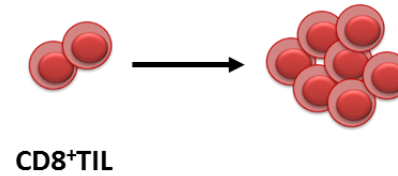
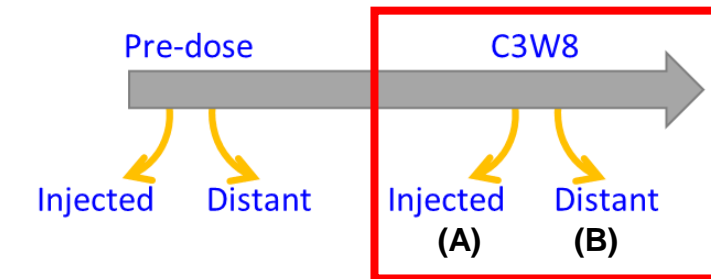


Proliferation by flow cytometry

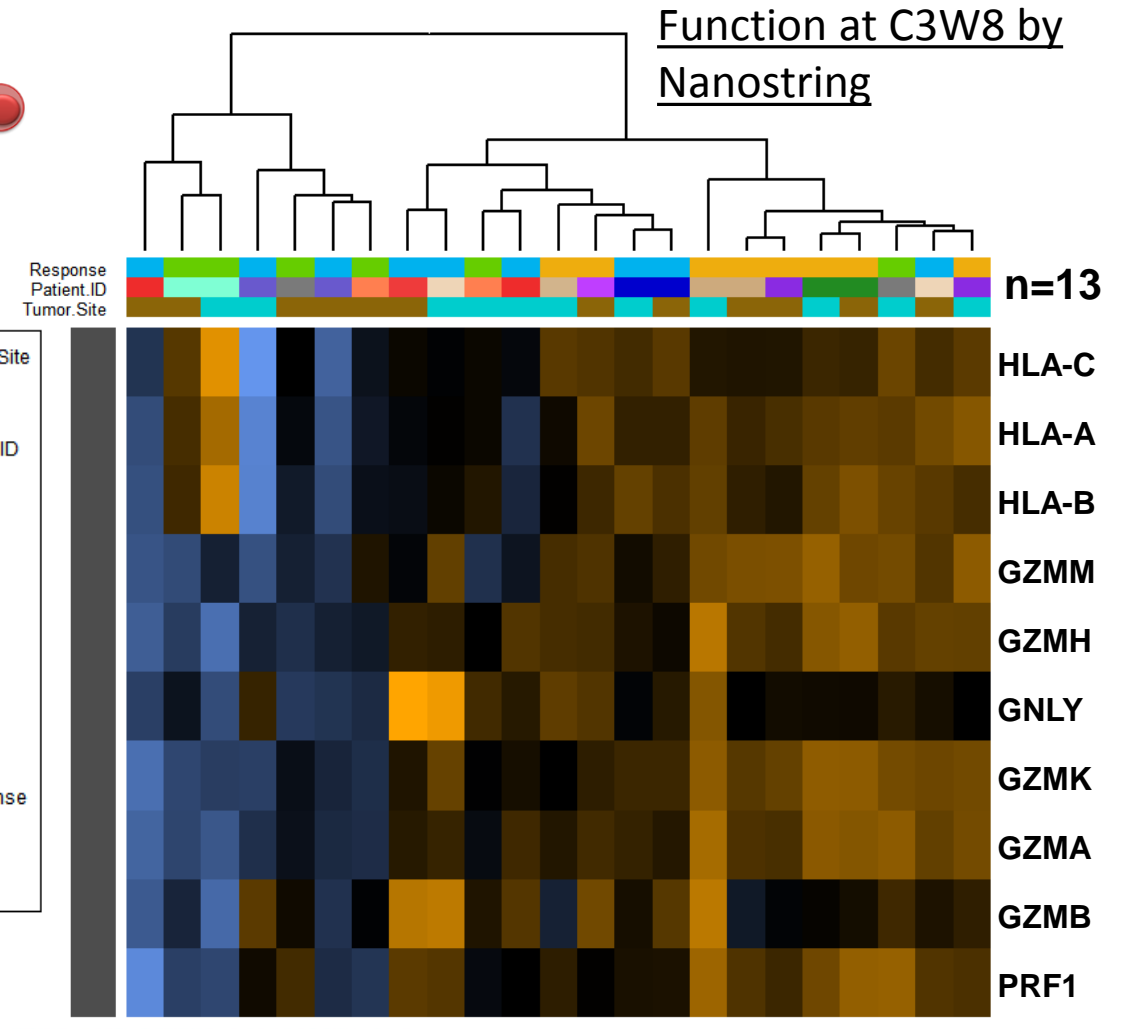
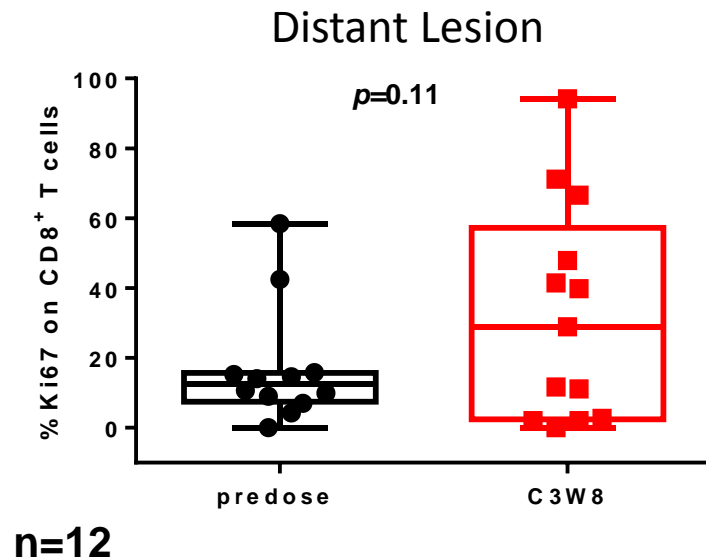


n=12

# Combination therapy induces CD8<sup>+</sup> TIL proliferation and CTL function

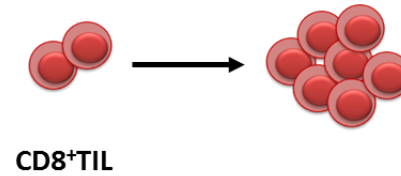
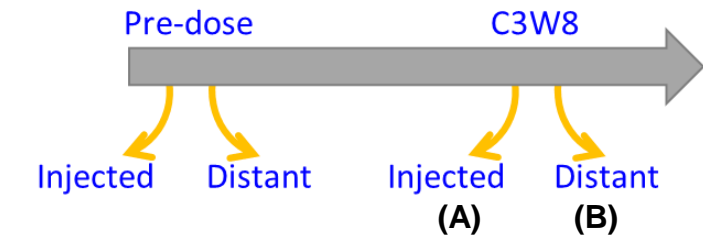


## Proliferation by flow cytometry

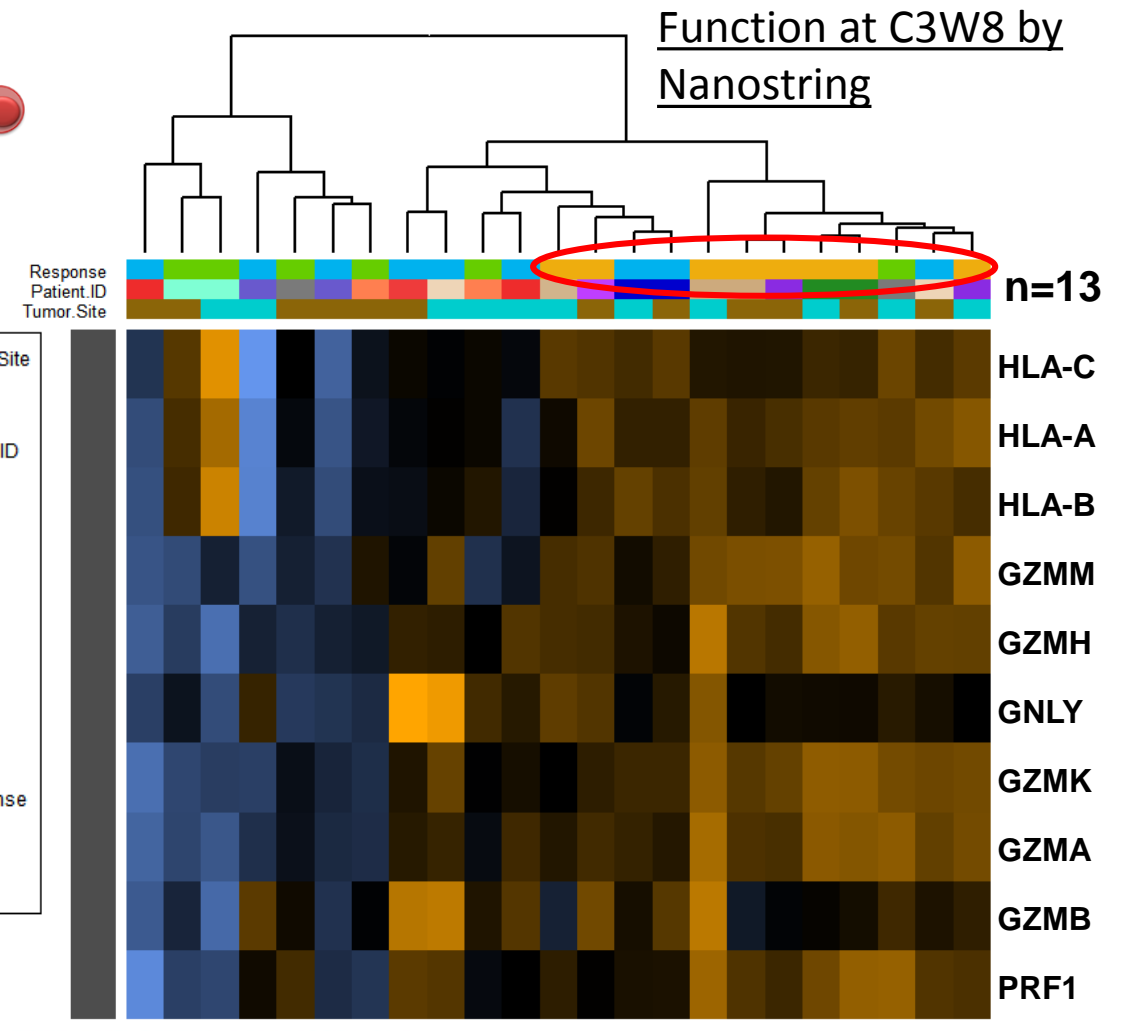
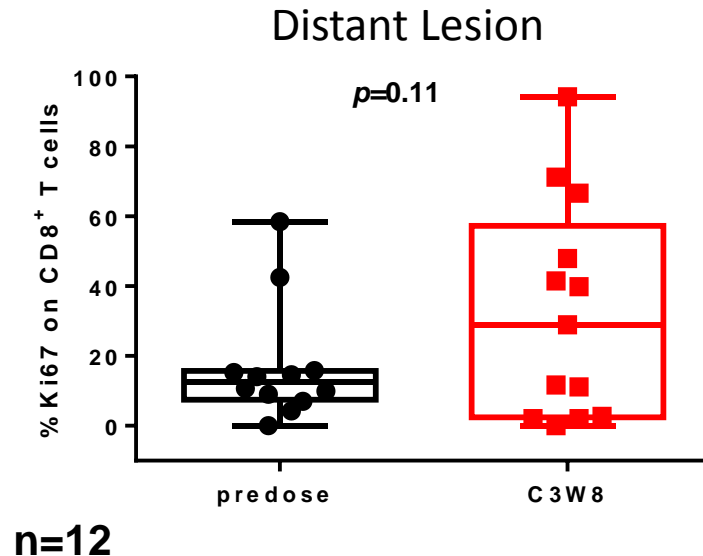




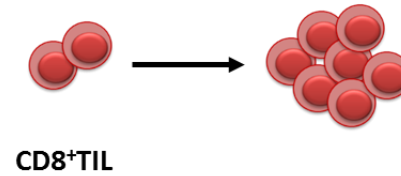
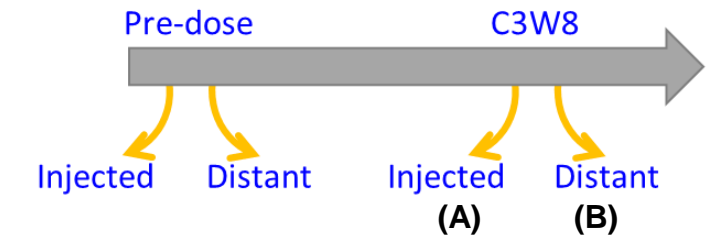
# Combination therapy induces CD8<sup>+</sup> TIL proliferation and CTL function



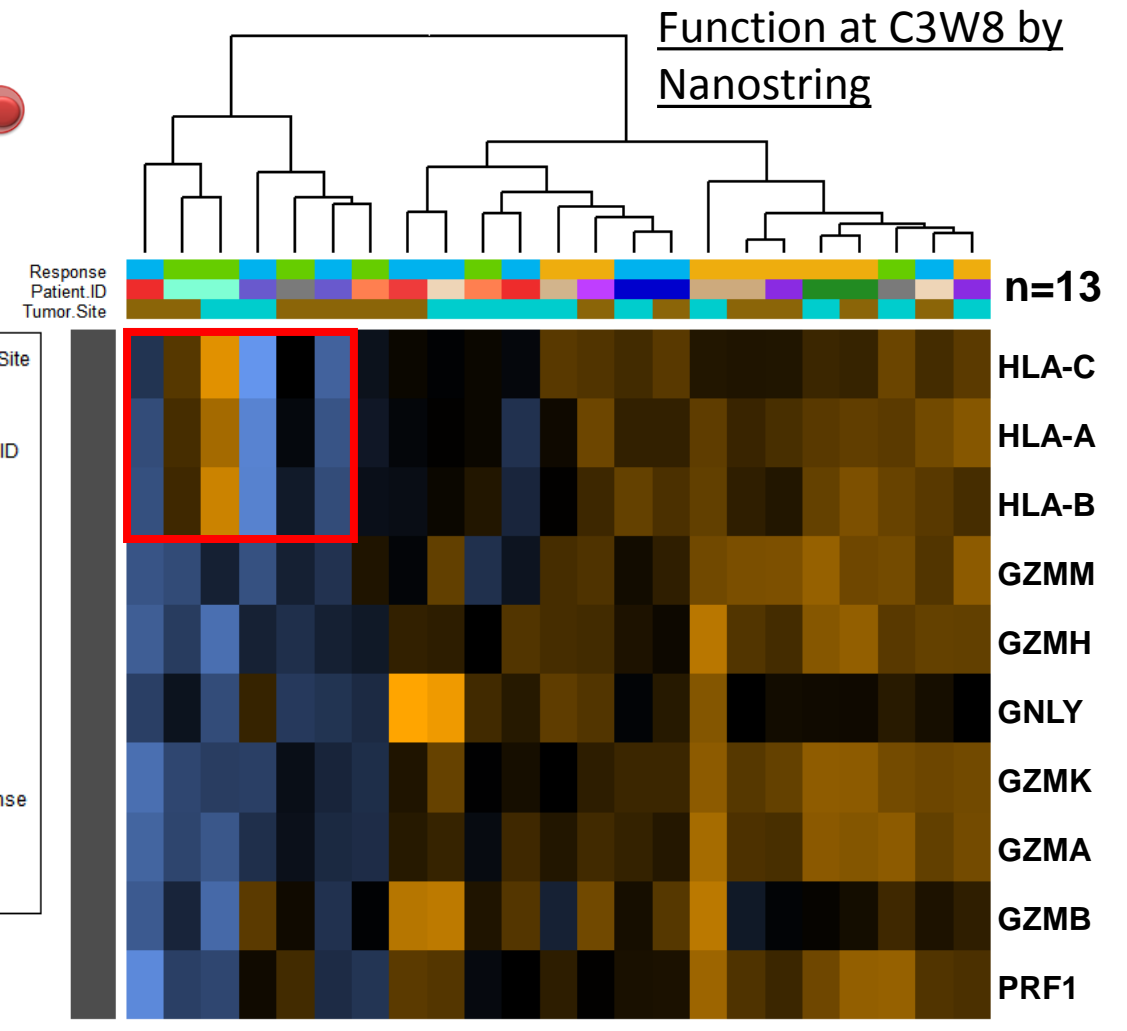
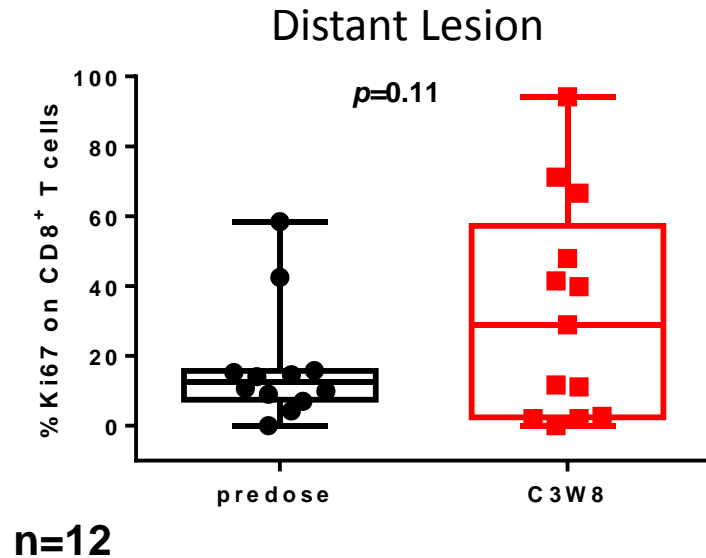
## Proliferation by flow cytometry



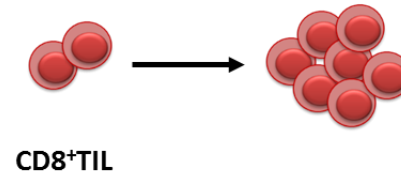
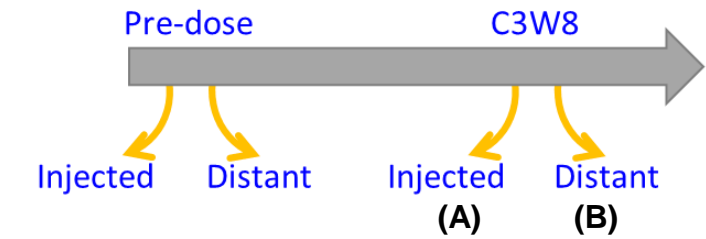
# Combination therapy induces CD8<sup>+</sup> TIL proliferation and CTL function



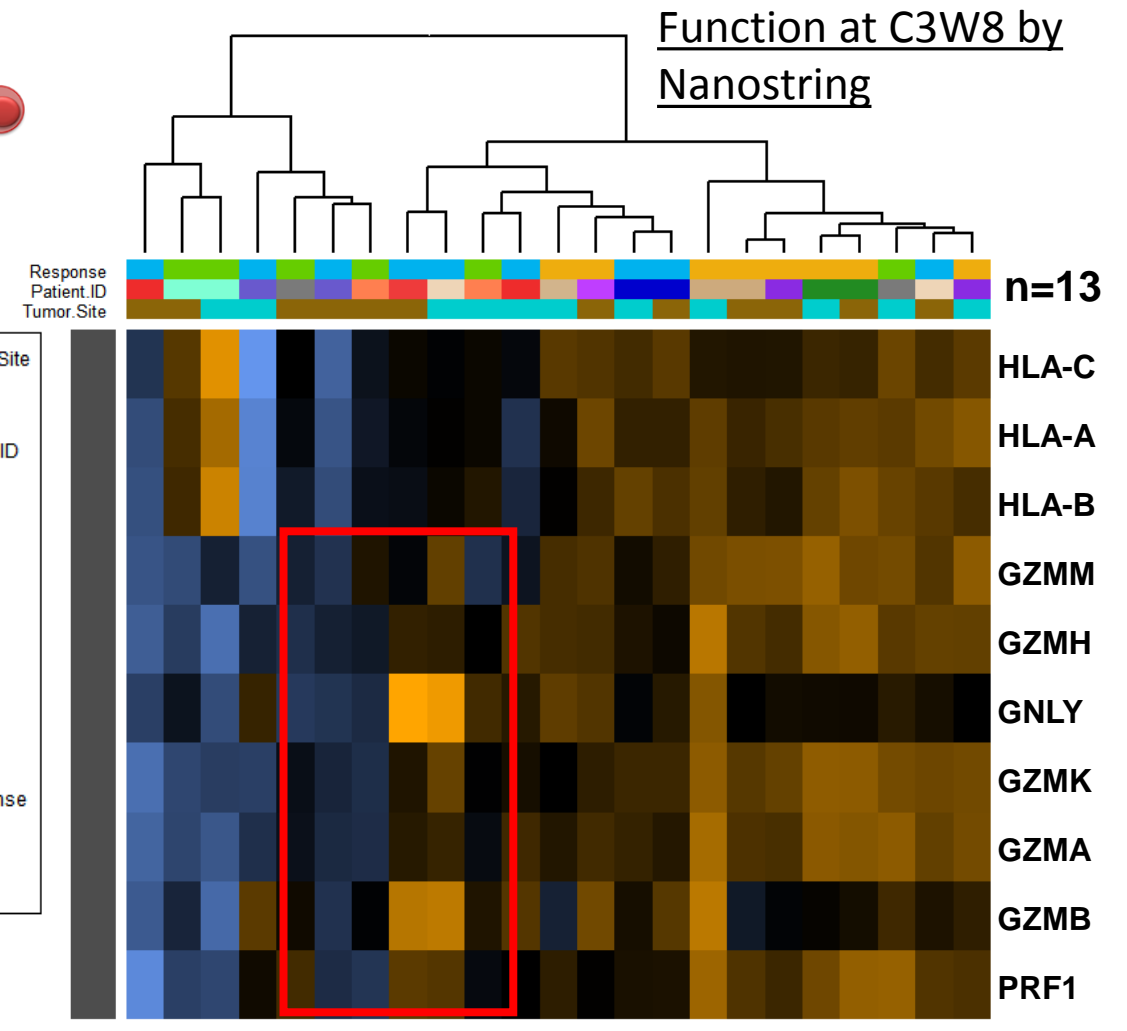
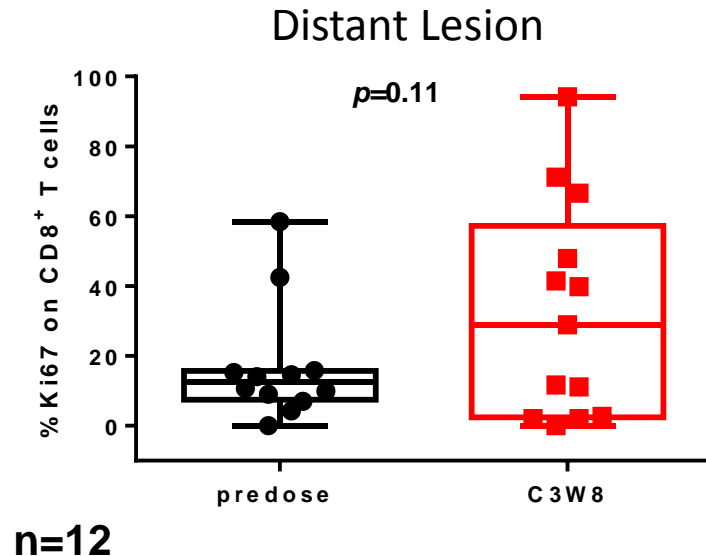
## Proliferation by flow cytometry



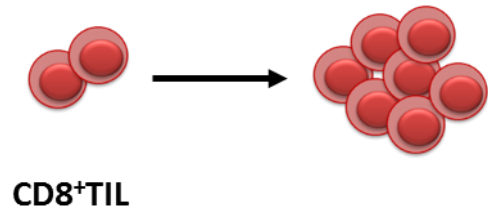
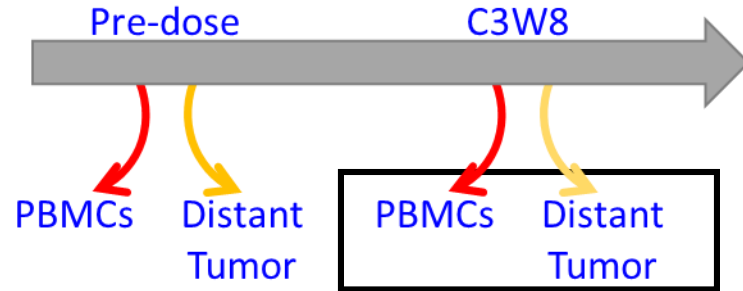
# Combination therapy induces CD8<sup>+</sup> TIL proliferation and CTL function



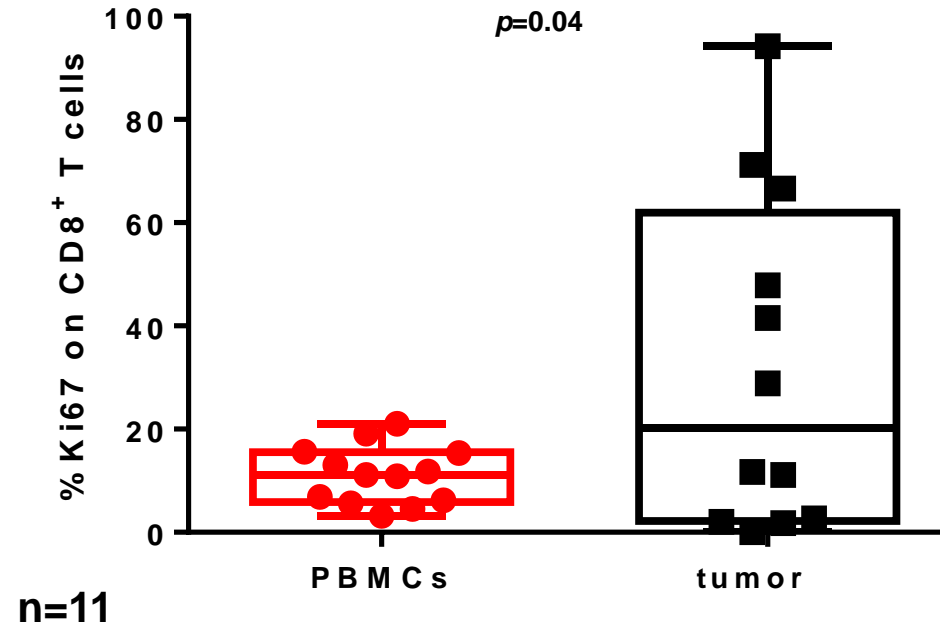
## Proliferation by flow cytometry



## Preferential CD8<sup>+</sup> T-cell proliferation at the distant lesion

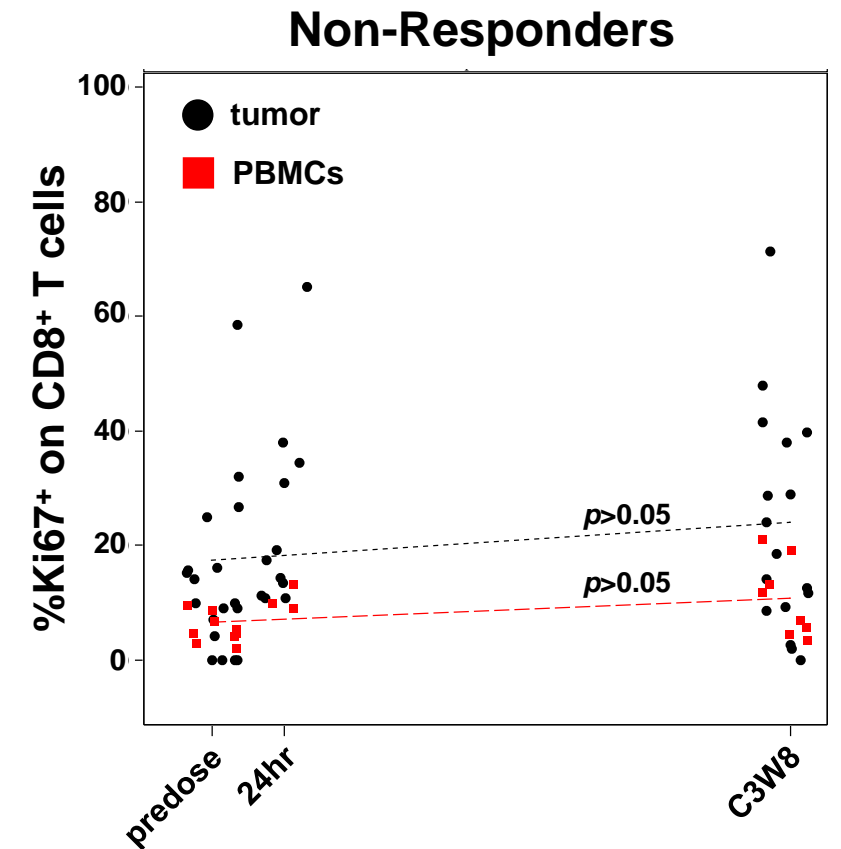
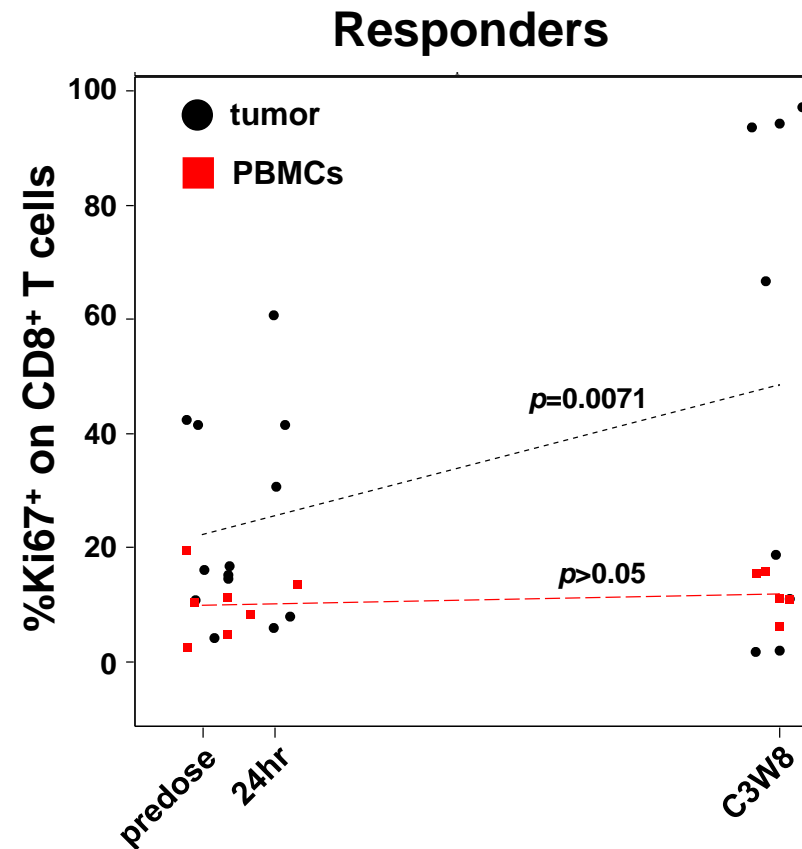
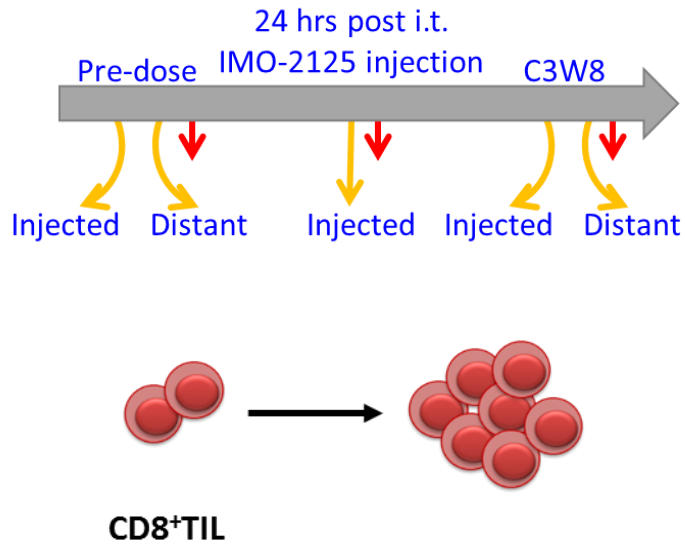


Time point: C3W8

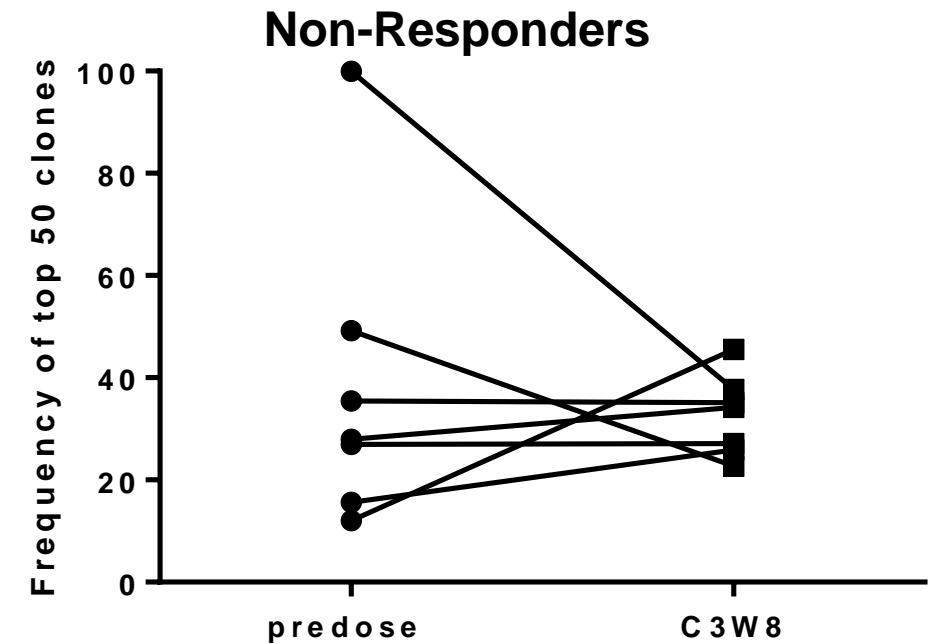
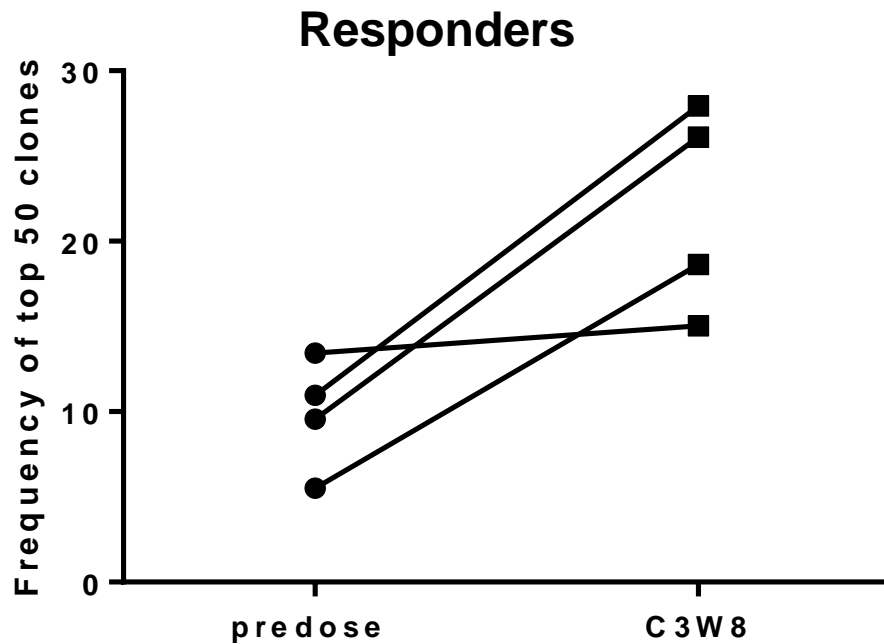
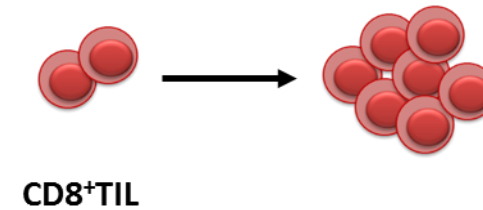
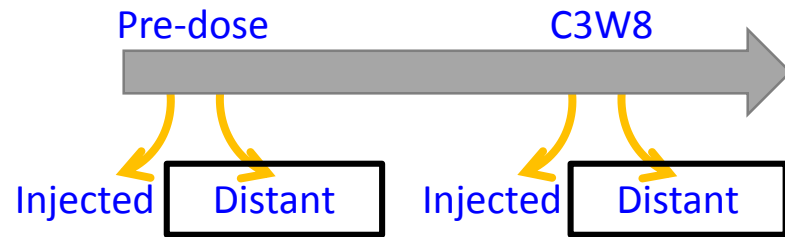




# Selective increase in CD8<sup>+</sup> T-cell proliferation in the tumors of responding patients



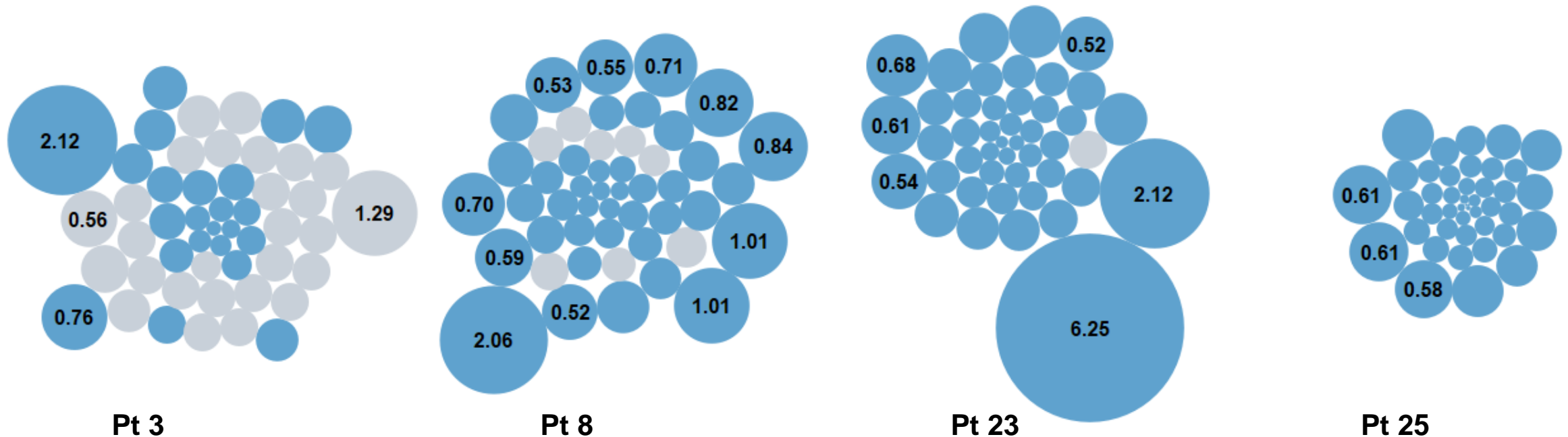
# Expansion of top 50 T-cell clones in the distant lesion of responding patients



# 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<sup>+</sup> 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

### **MDACC**

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Oncology Clinicians and  
Staff**

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**Poster #018**

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