



# SITC 2018

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Walter E. Washington  
Convention Center



Society for Immunotherapy of Cancer

# Peripheral T cell dynamics in resectable NSCLC patients treated with neoadjuvant PD-1 blockade

**Jiajia Zhang**, Zhicheng Ji, Margueritta El Asmar, Justina X. Caushi, Valsamo Anagnostou, Tricia R. Cottrell, Hok Yee Chan, Perna Suri, Haidan Guo, Kristen A. Marrone, Jarushka Naidoo, Taha Merghoub, Jamie E. Chaft, Matthew D. Hellmann, Janis M. Taube, Julie R. Brahmer, Victor Velculescu, Ni Zhao, Patrick M. Forde, Drew M. Pardoll, Hongkai Ji, **Kellie N. Smith**



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# No disclosures

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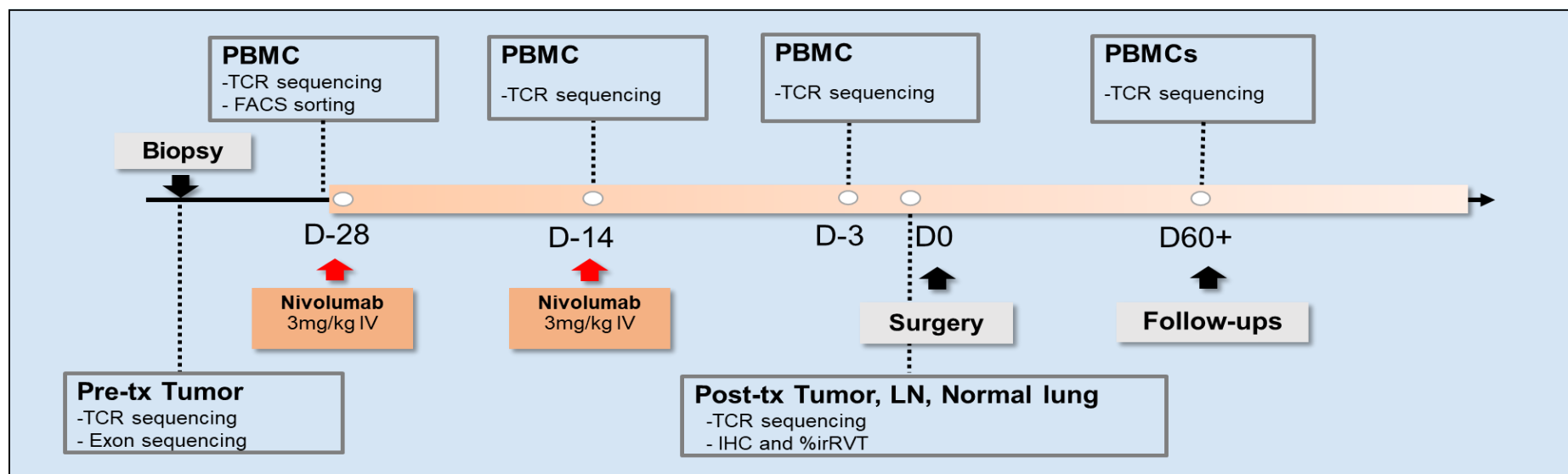
## Backgrounds & aims

- Phase 2 clinical trial to test feasibility and safety of neoadjuvant PD-1 blockade in resectable NSCLC (NCT02259621)
- Neoantigen-specific T-cell clones detected in patient with CR
- Little known about the systematic effect of neoadjuvant PD-1 blockade on anti-tumor T cell repertoire and correlation with clinical outcomes
- Objective: systematically model the mobility of TCR after checkpoint blockade in NSCLC patients receiving neoadjuvant anti-PD-1

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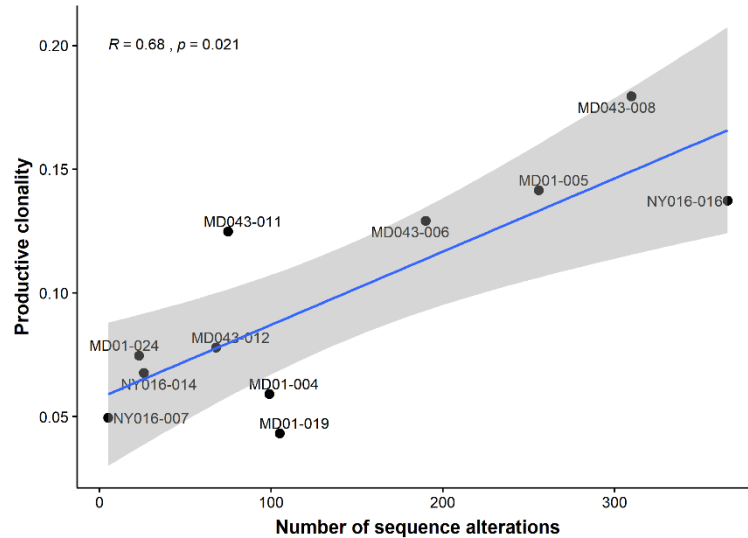
### Study design:





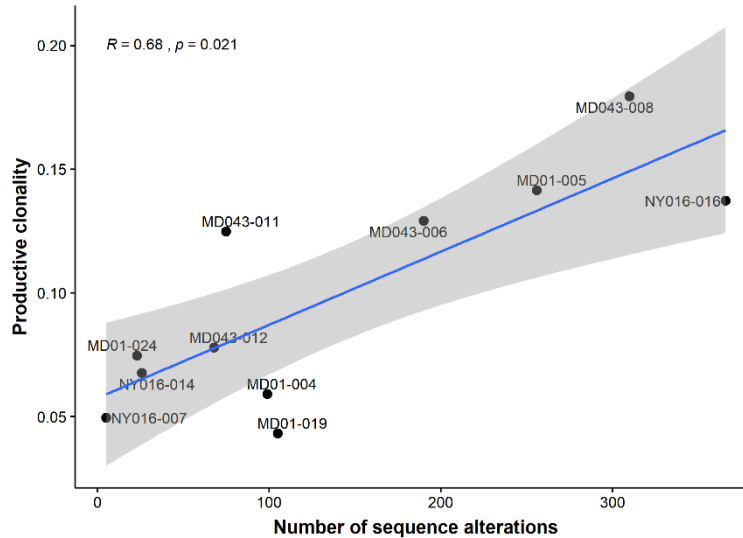
# TIL clonality positively associates with TMB, and inversely with % residual tumor

## Clonality vs TMB

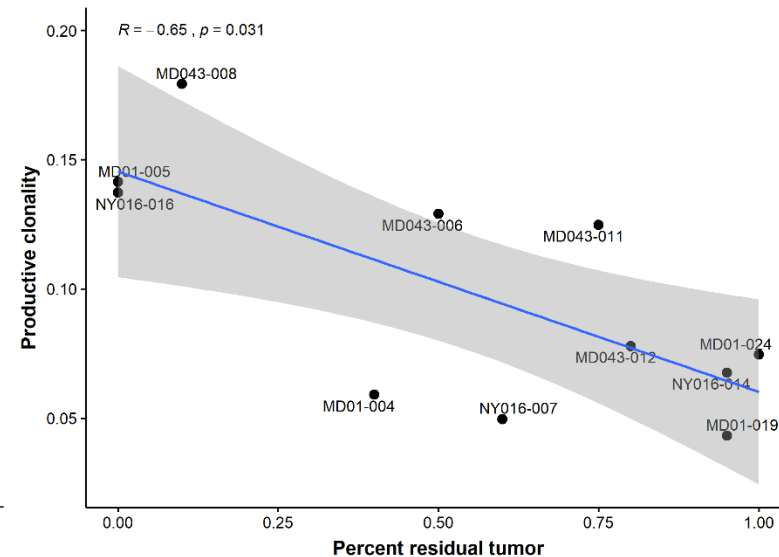


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Clonality vs TMB

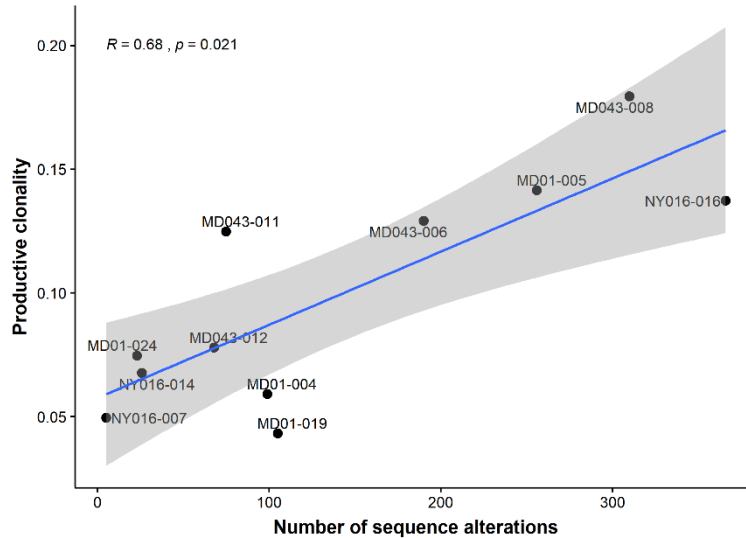


Clonality vs % residual tumor

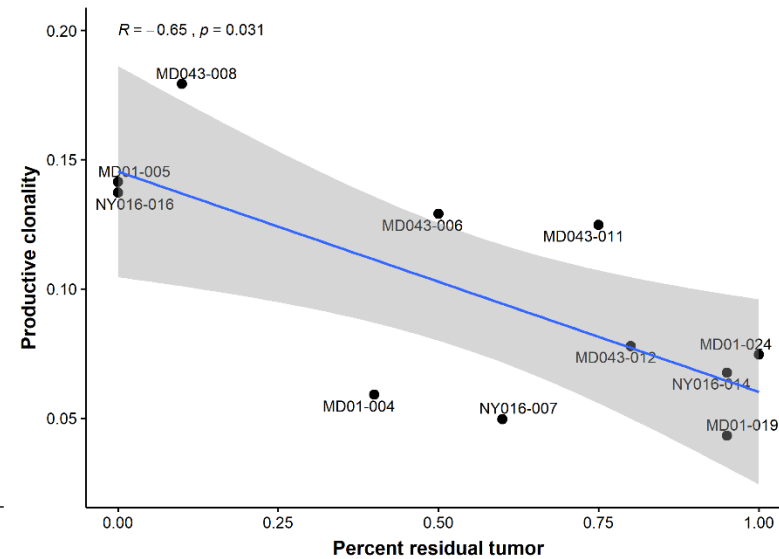


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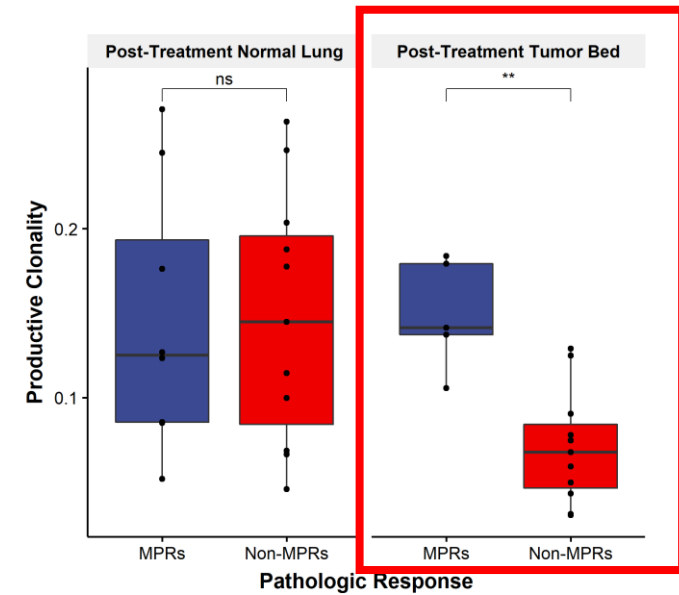
Clonality vs TMB



Clonality vs % residual tumor



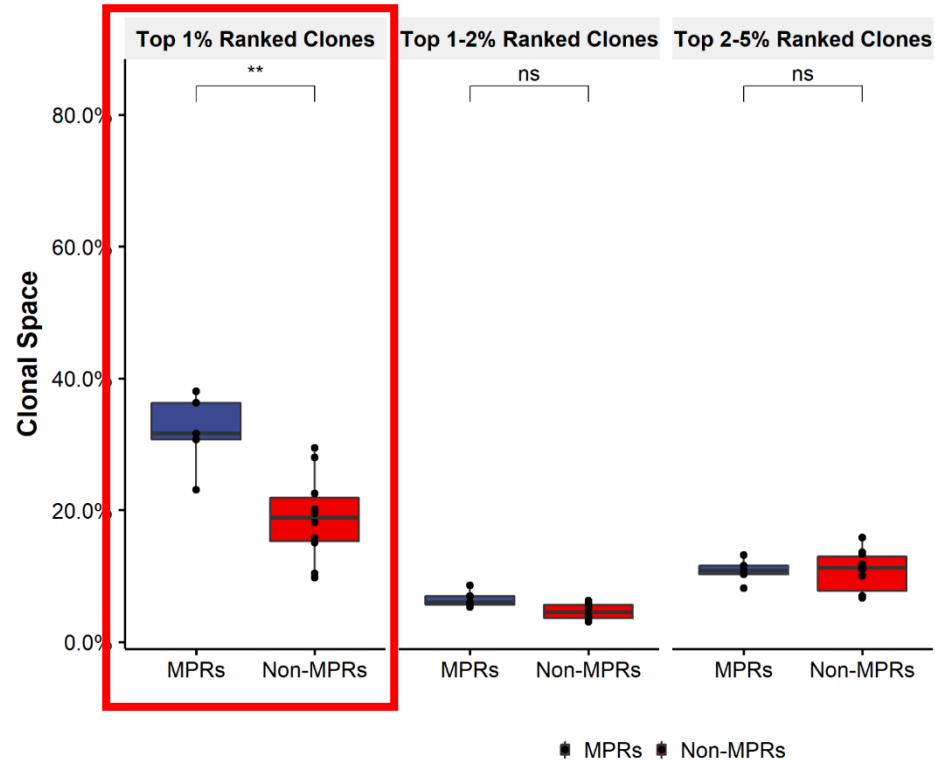
Clonality in normal lung/tumor





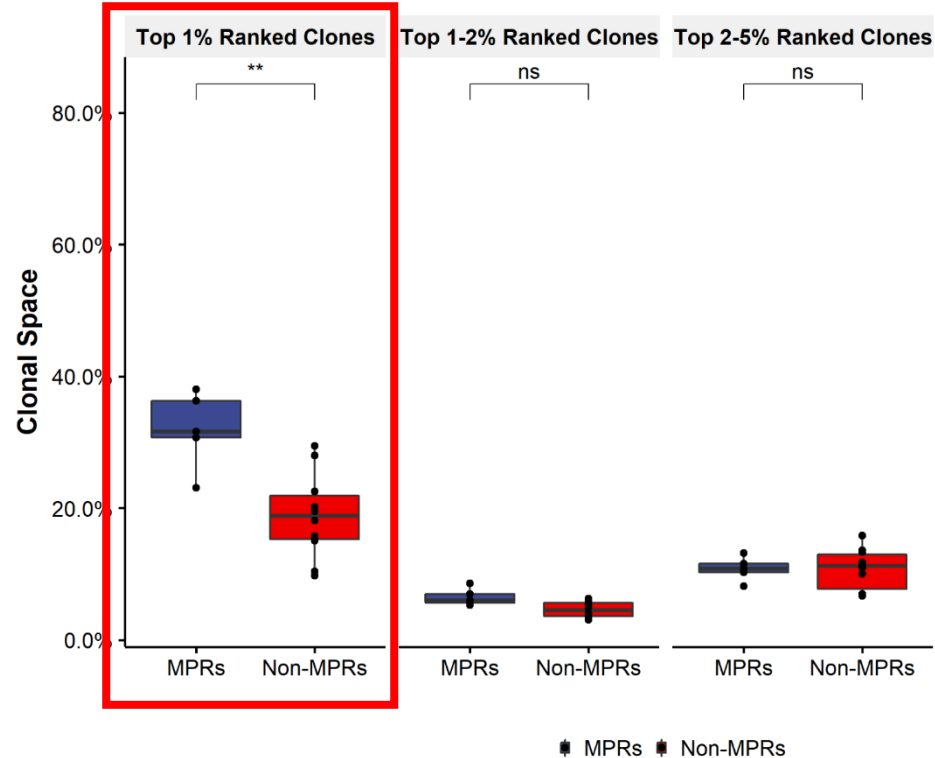
# Top 1% ranked clones orchestrate anti-tumor response in tumor bed and are highly co-presented in the periphery

## Tumor bed: MPR vs non-MPR

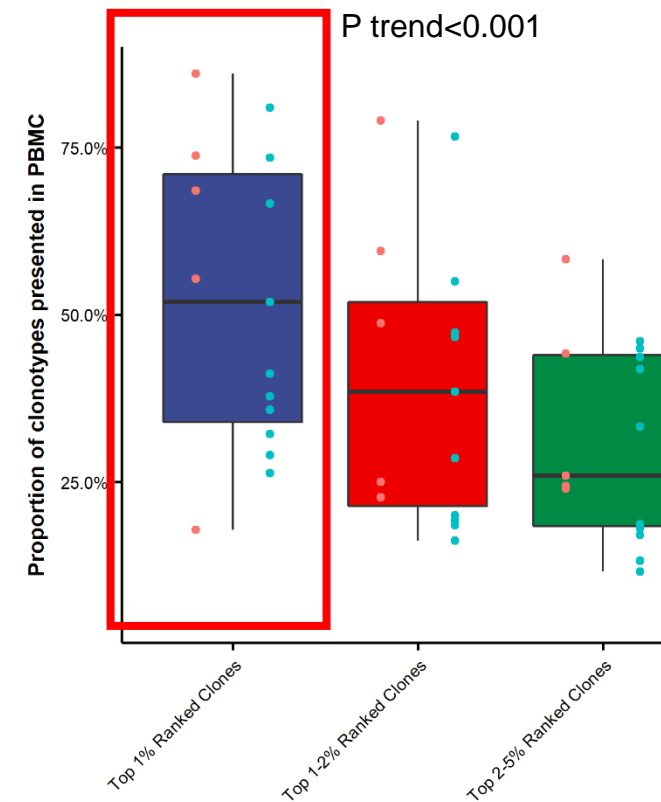


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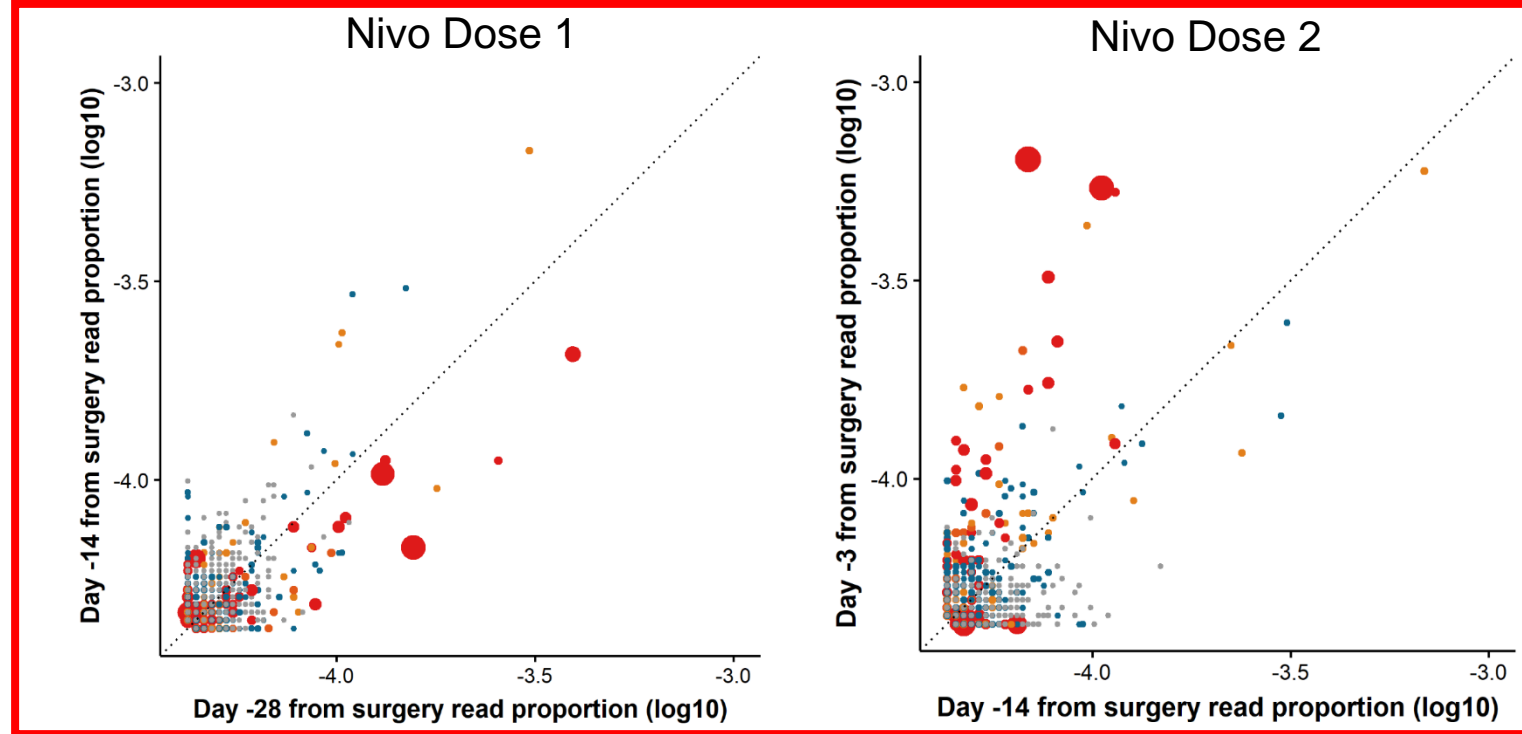


## Baseline PBMC presentation

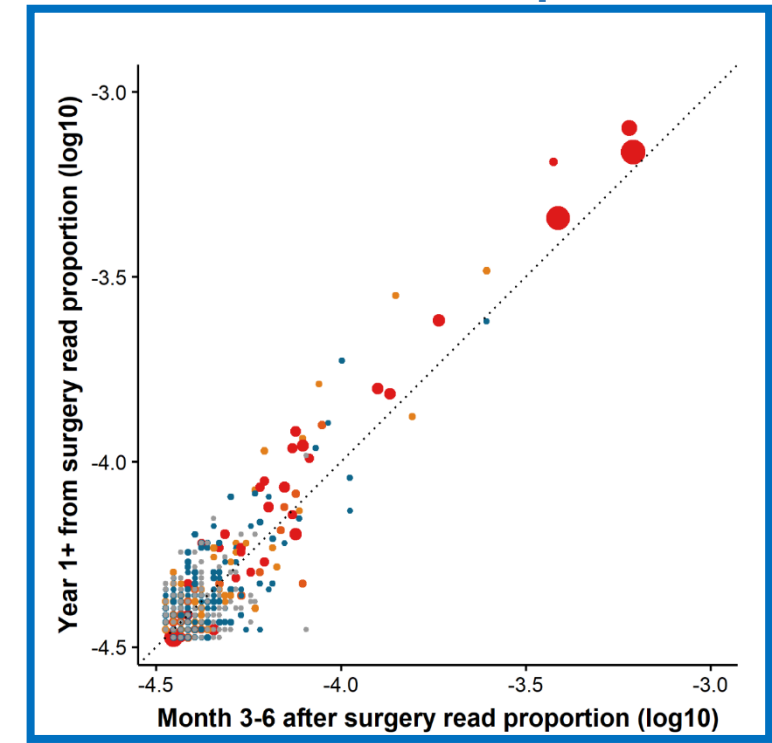


# Significant and systematic reshaping of tumor associated TCR repertoire in the periphery (pt with MPR)

1 month from treatment initiation



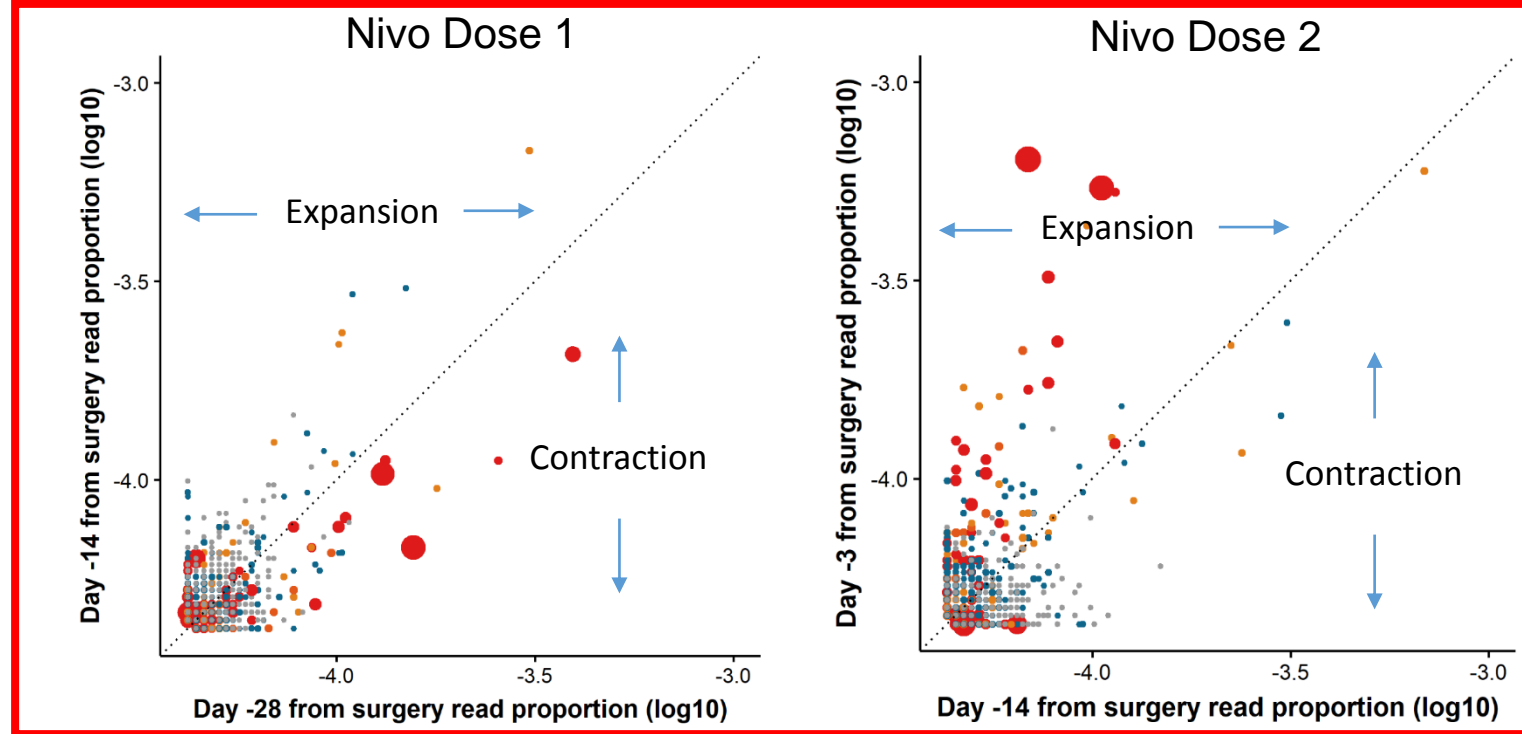
6 m+ follow-ups



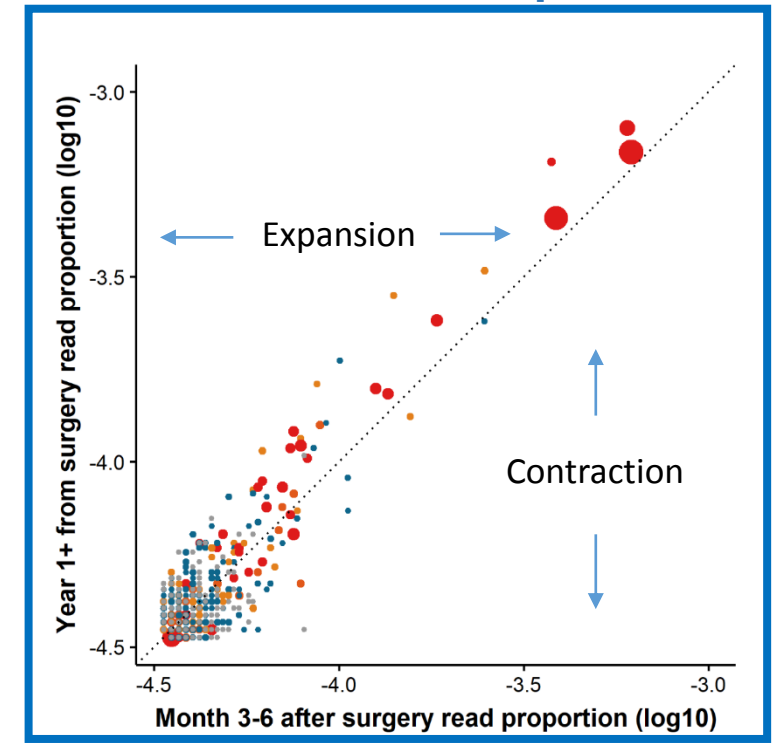
● Top 1% tumor clones    ● Top 1-5% tumor clones    ● > 5% tumor clones    ● PBMC only clones

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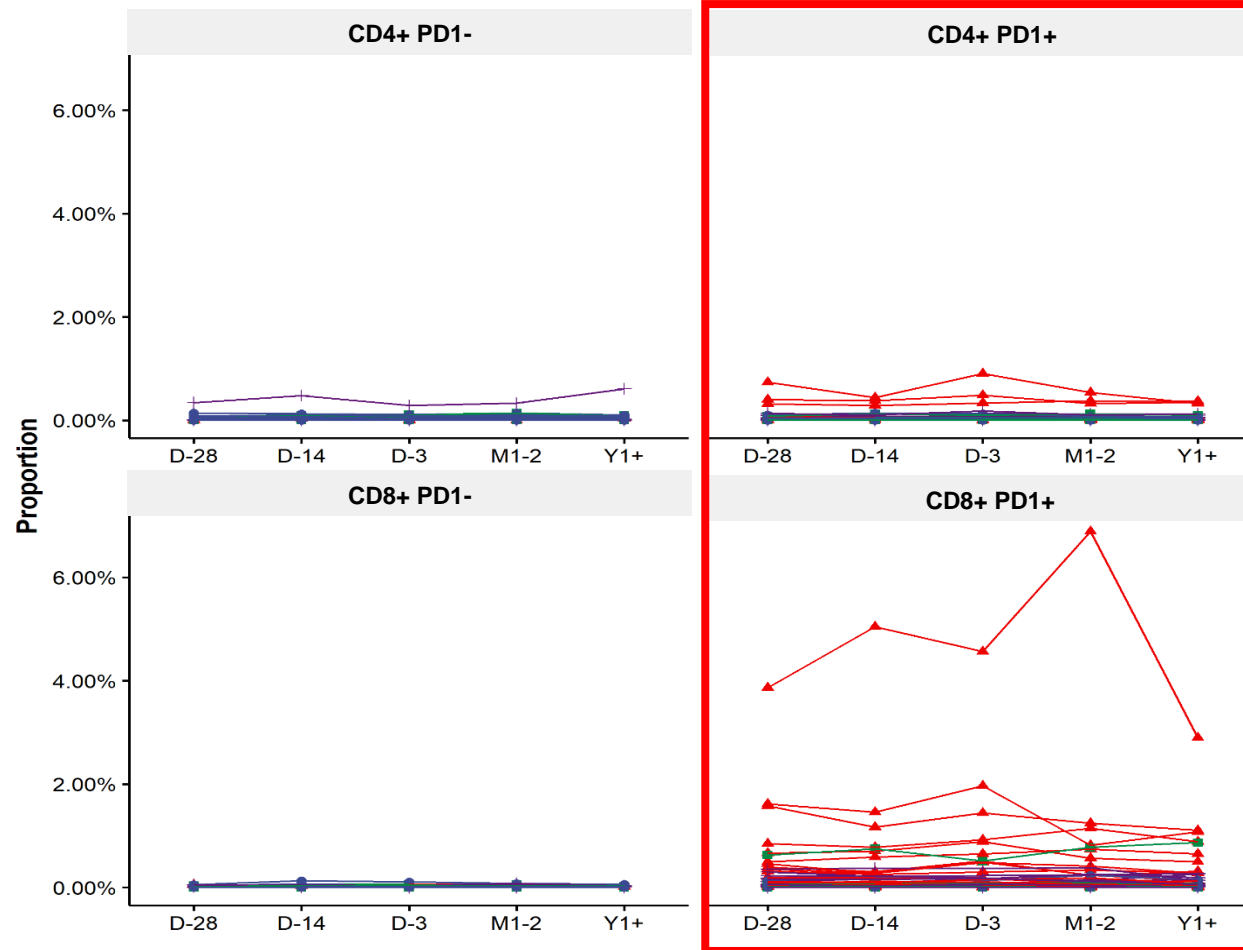


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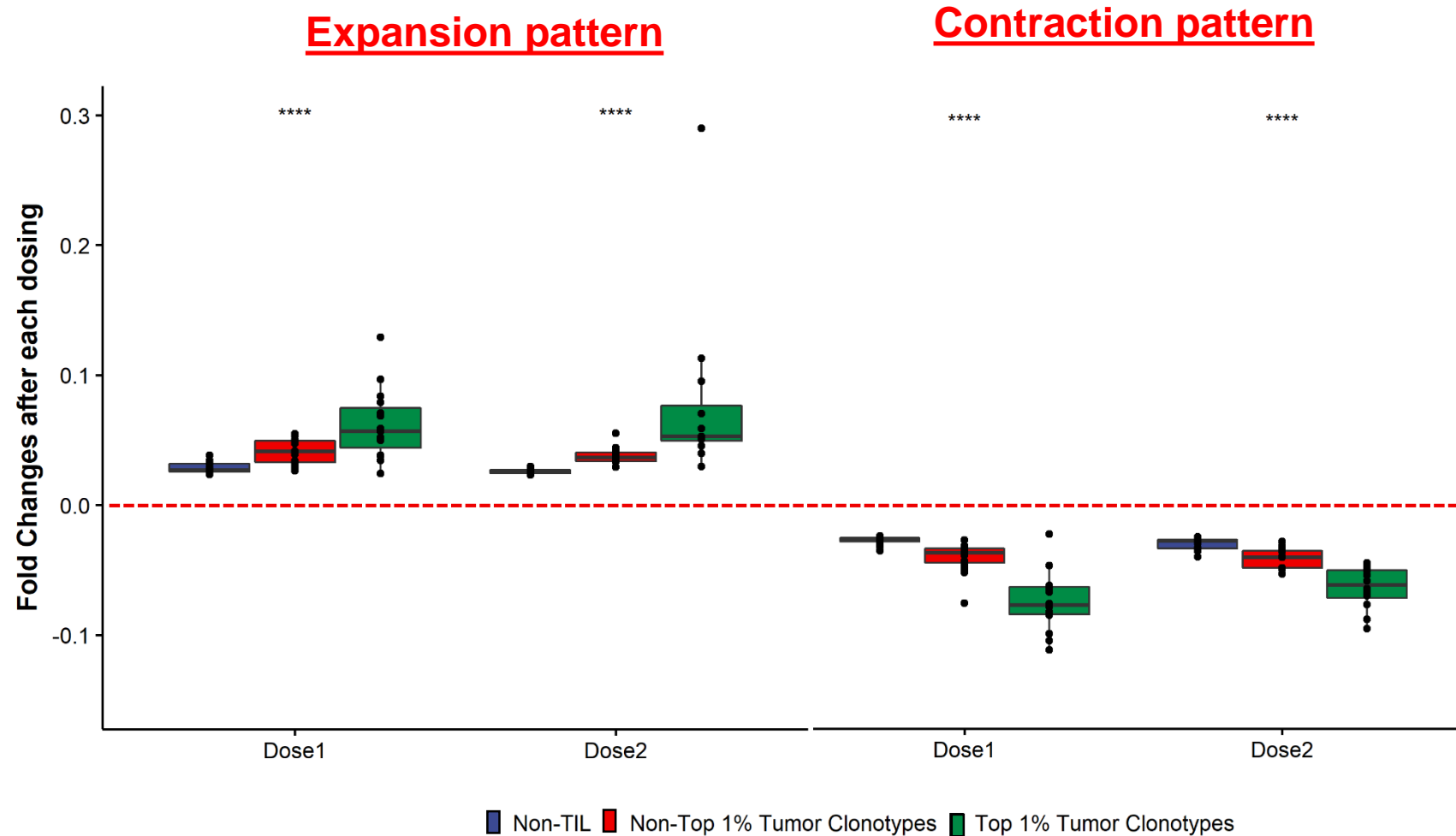
# Clones with systematic perturbations had PD1+ phenotype in pre-treatment PBMC (pt with MPR)



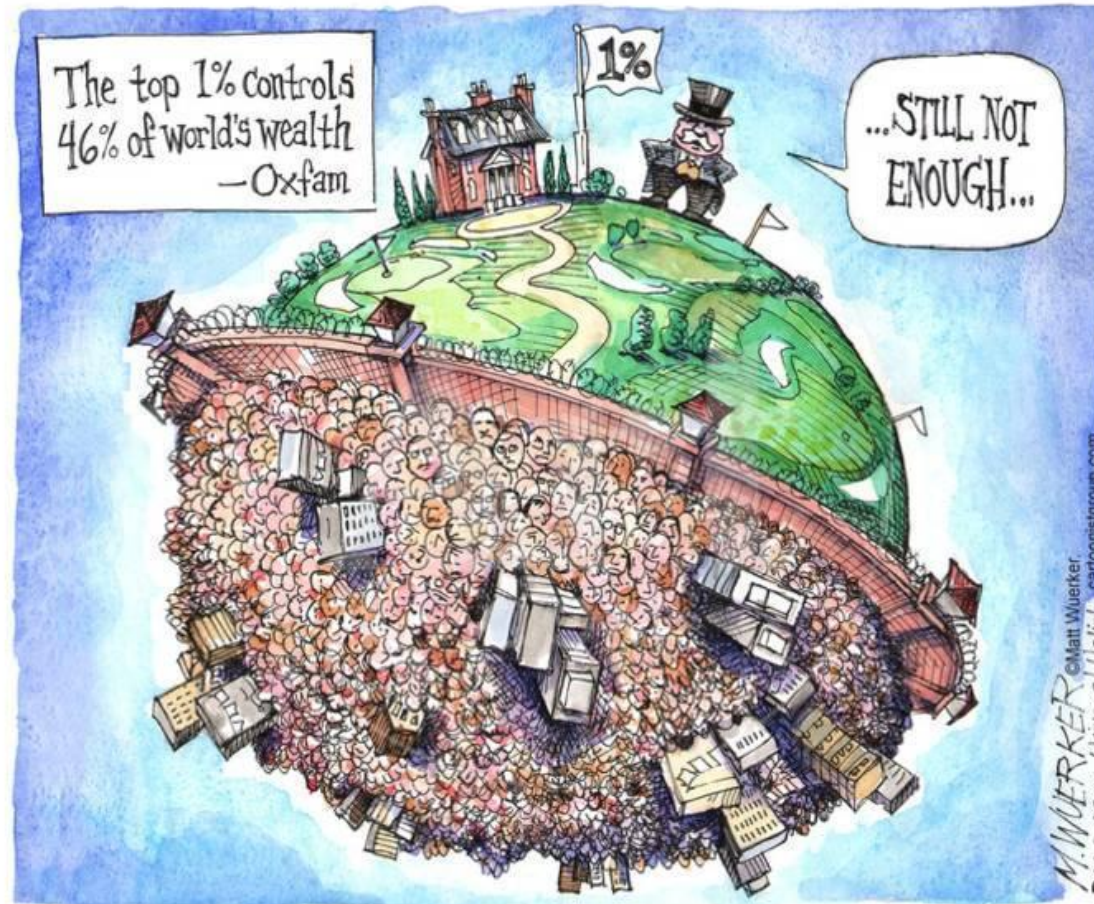
▲ Top 1% ranked clones    + Top 1-5% ranked clones    ■ > 5% ranked clones    ● Non-TIL

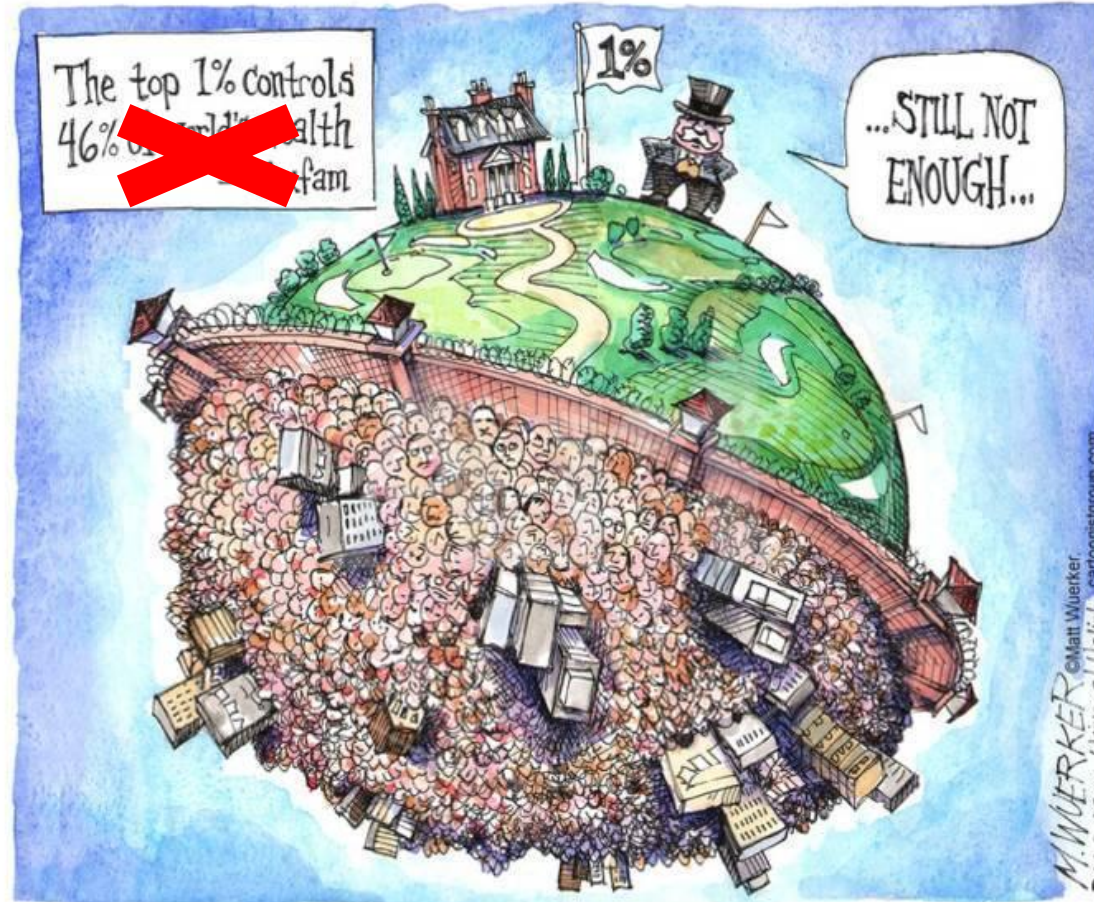


# Highest perturbations in the periphery for Top 1% TIL clones

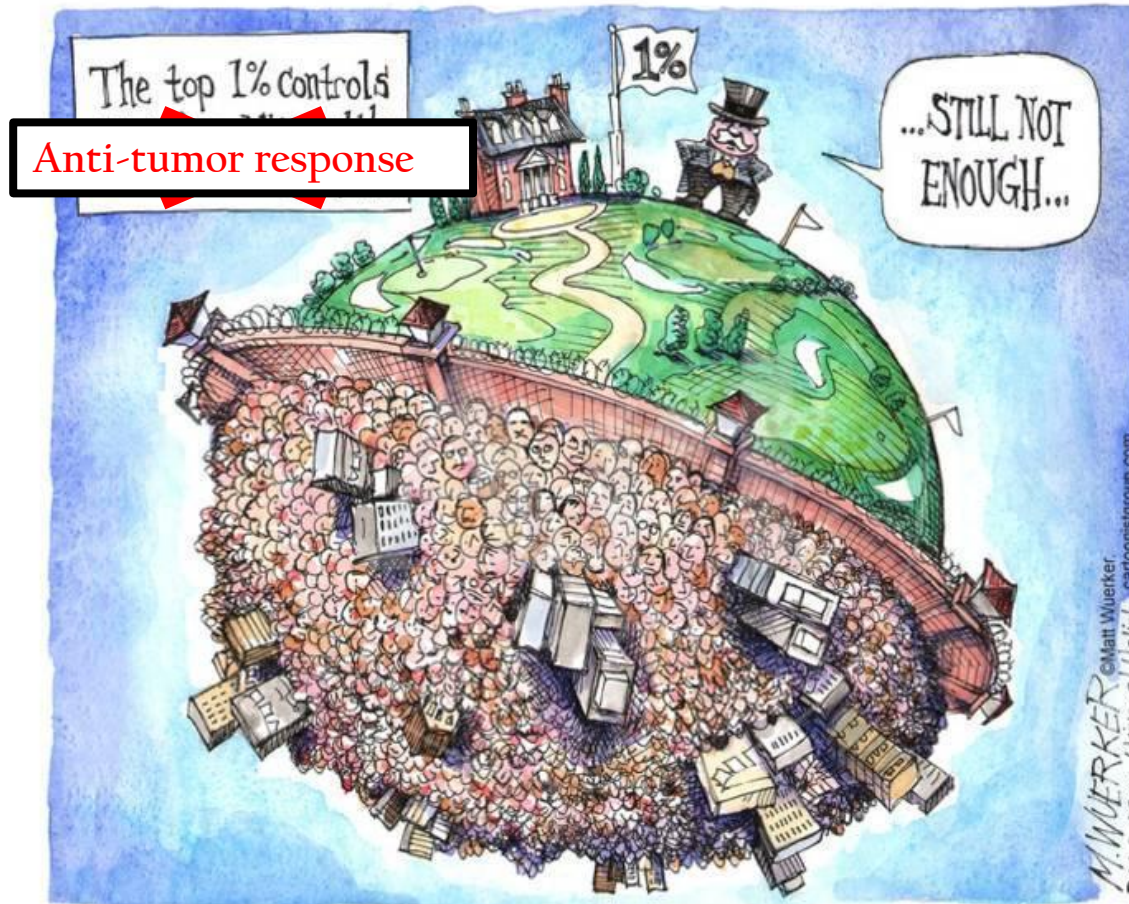






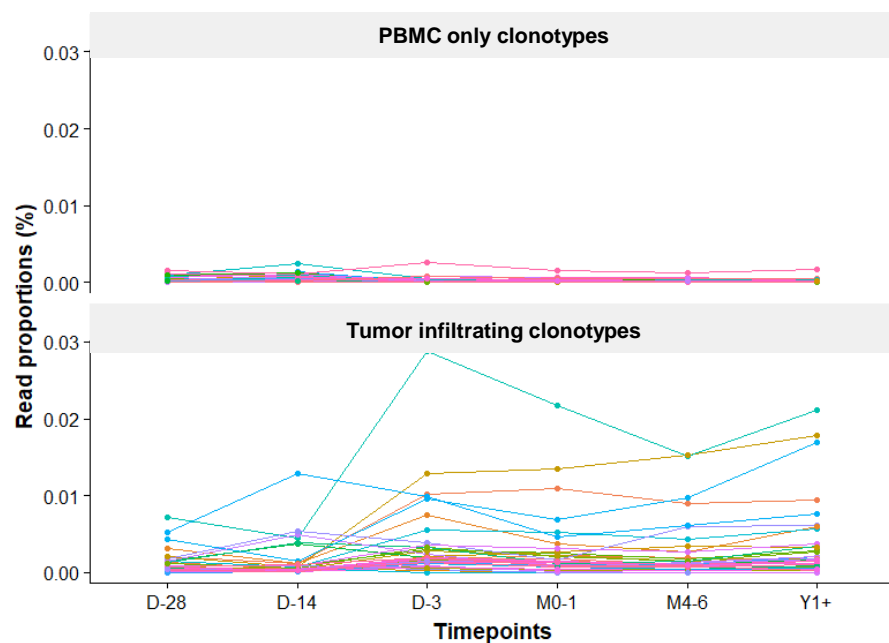




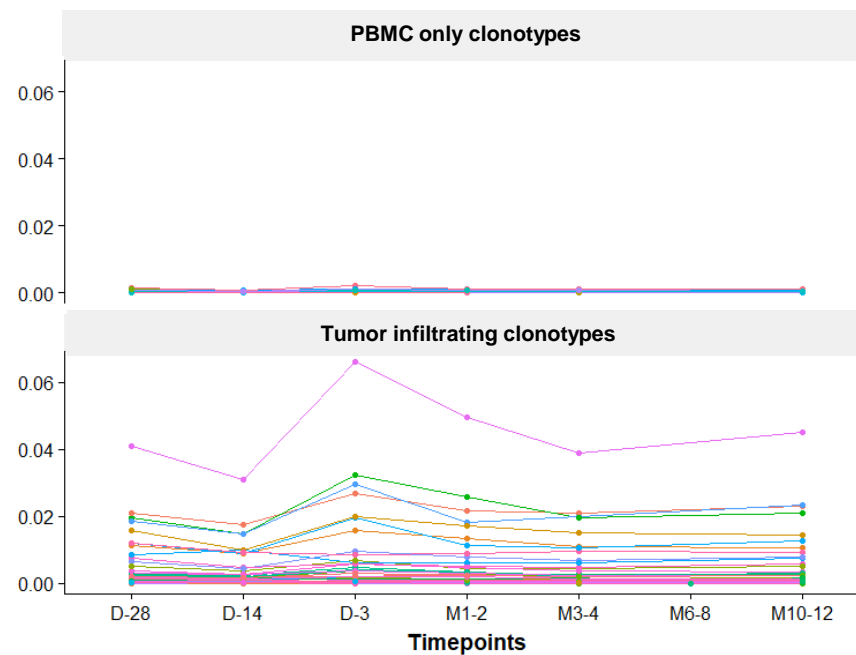


# Differentially changed clones identified in the periphery during PD-1 blockade

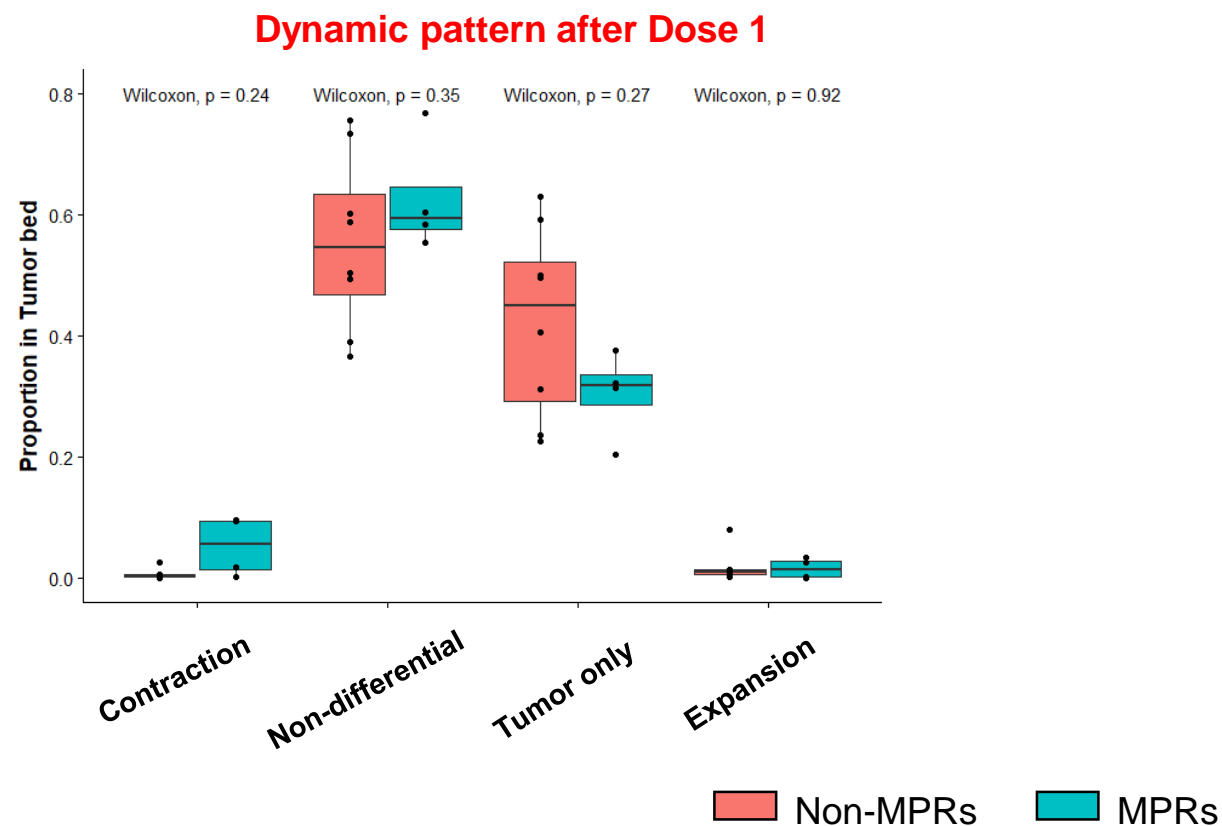
MPR, disease free



Non-MPR, disease free

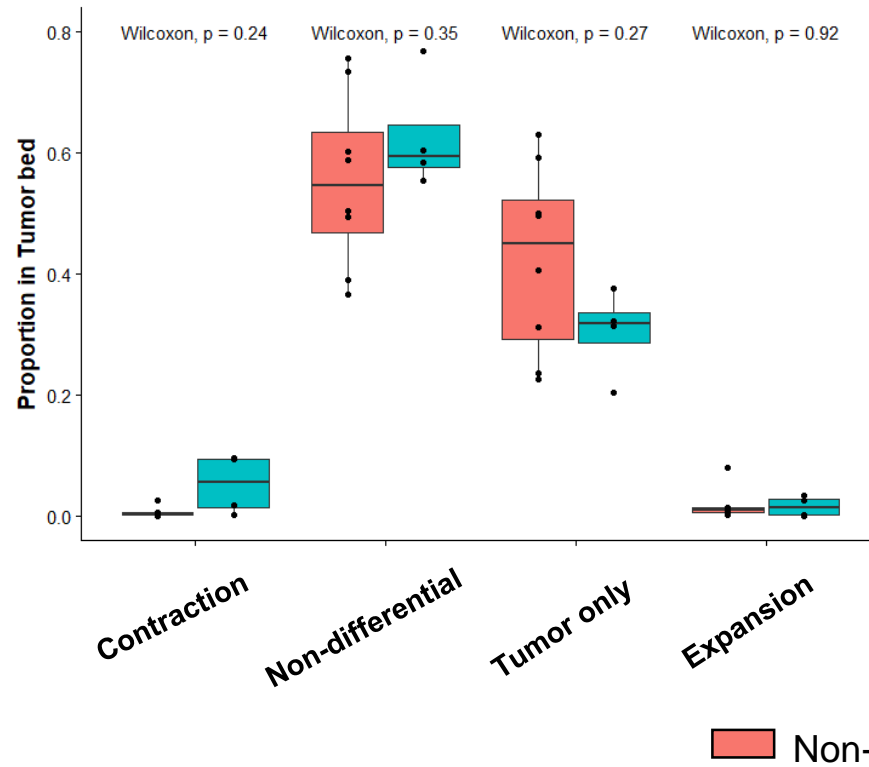


**Clones expanded in periphery after the 2<sup>nd</sup> dose (4w from treatment initiation) cumulate a significant greater proportion in post-tx tumor bed among responders**

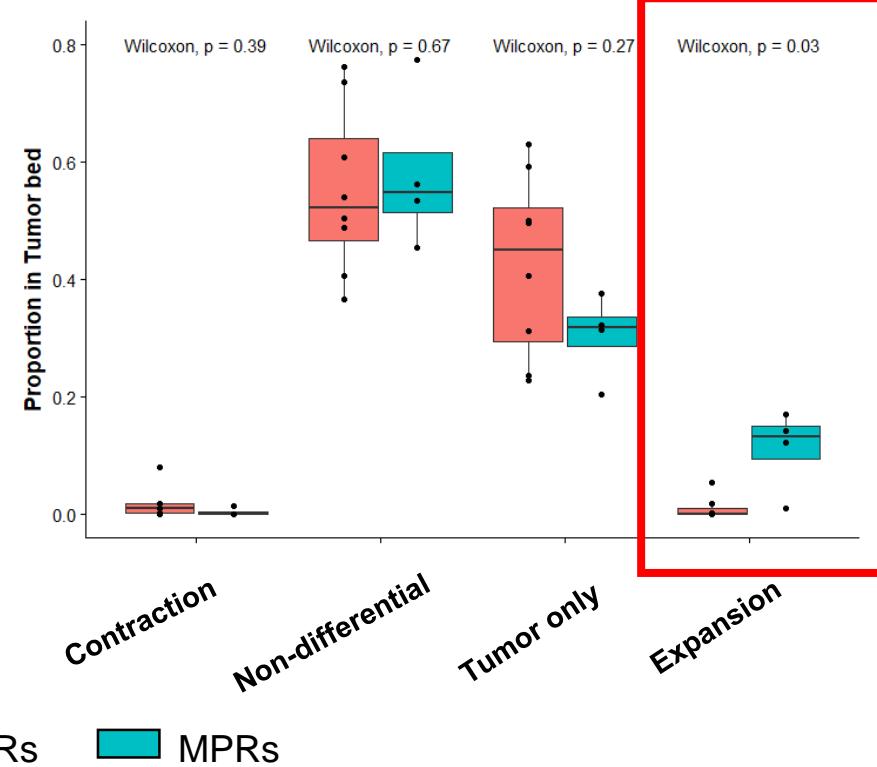


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Dynamic pattern after Dose 1



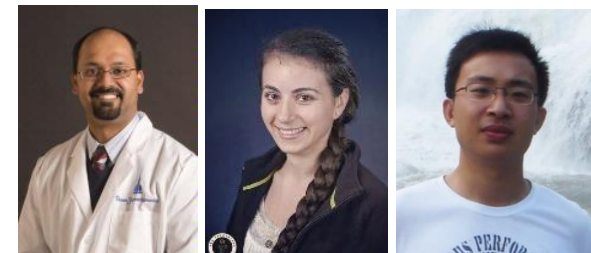
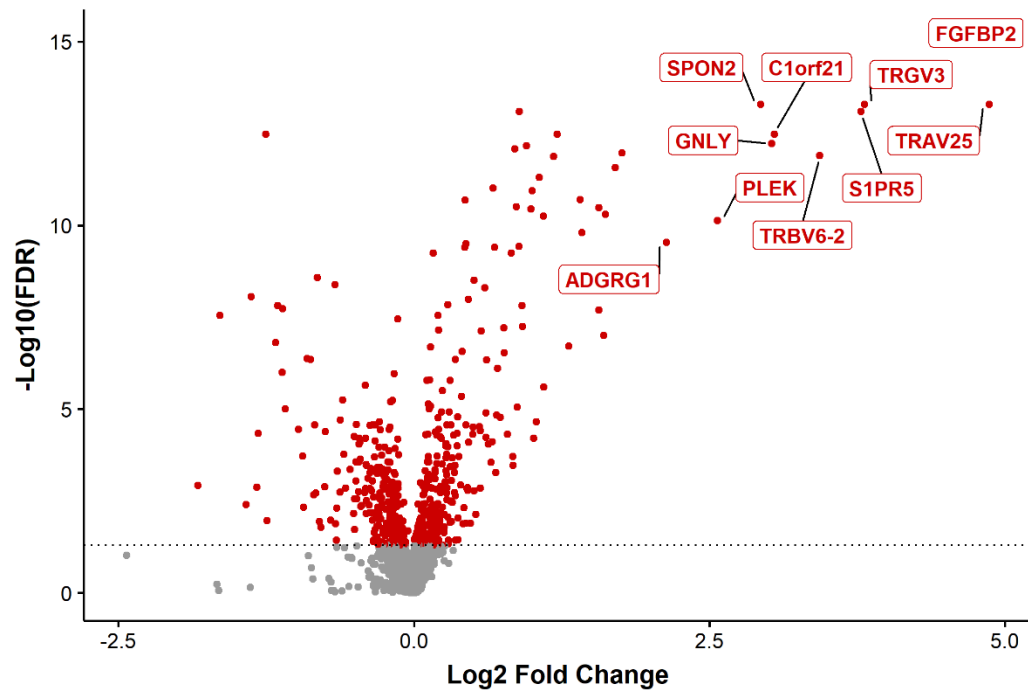
Dynamic pattern after Dose 2





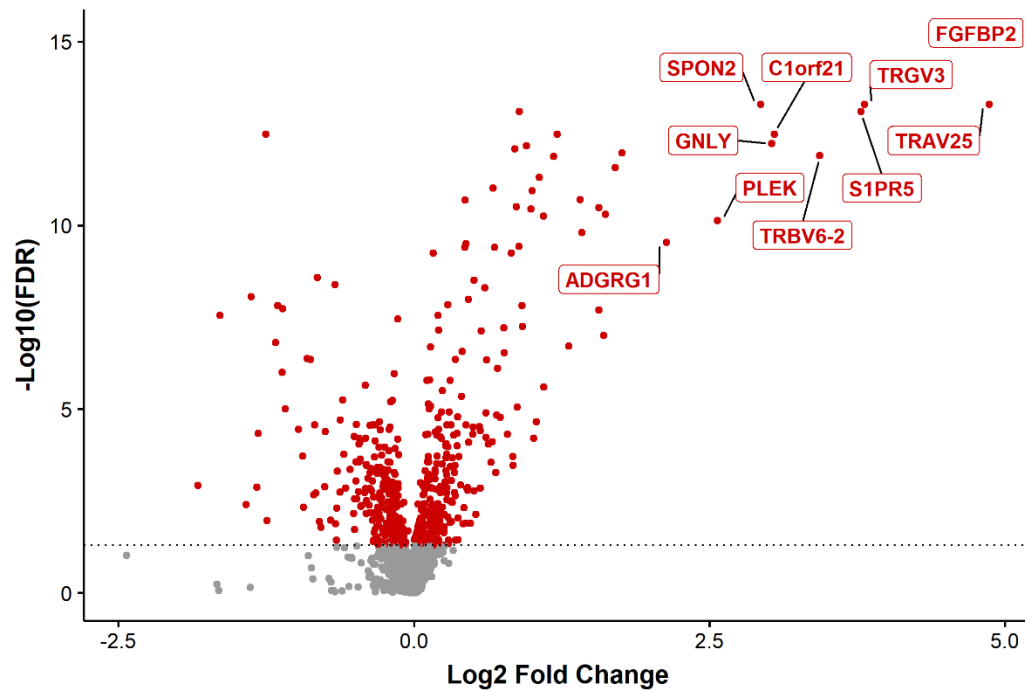
## Single cell RNAseq+TCRseq revealed differential phenotype of expanded clones as compared to non-differential clones (1 pt with non-MPR)

Cytotoxic phenotype (3 clones)

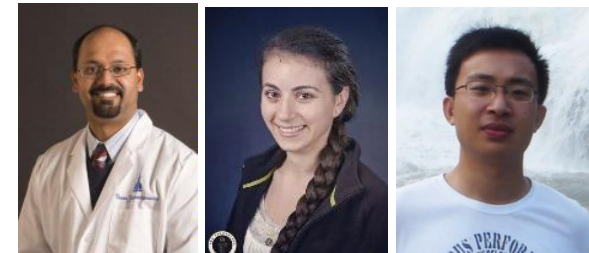
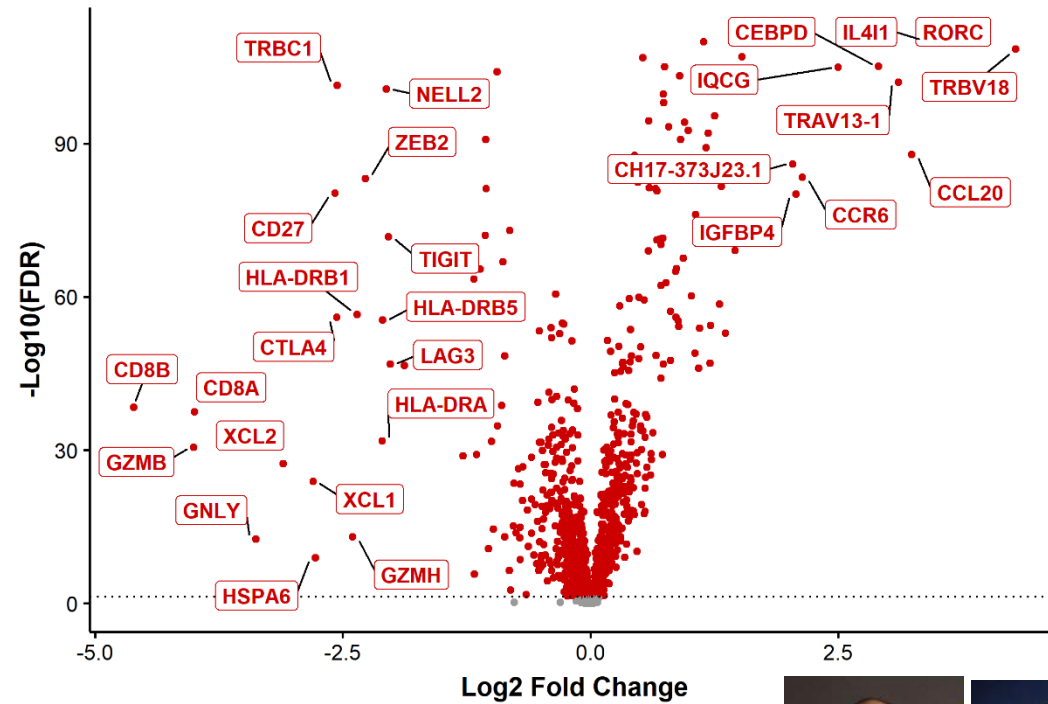


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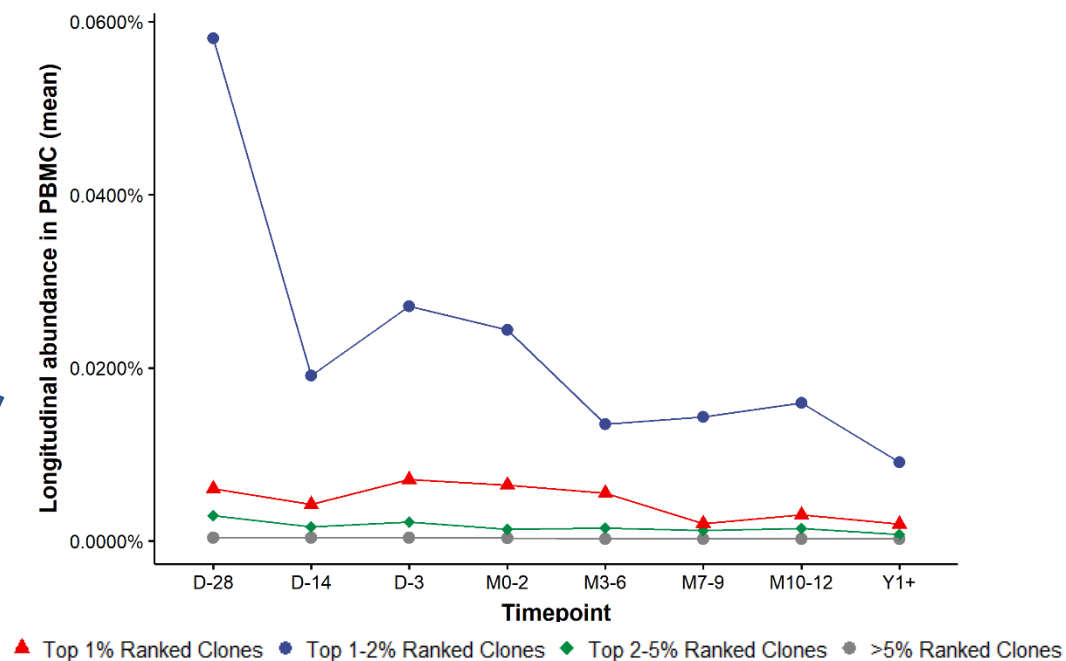
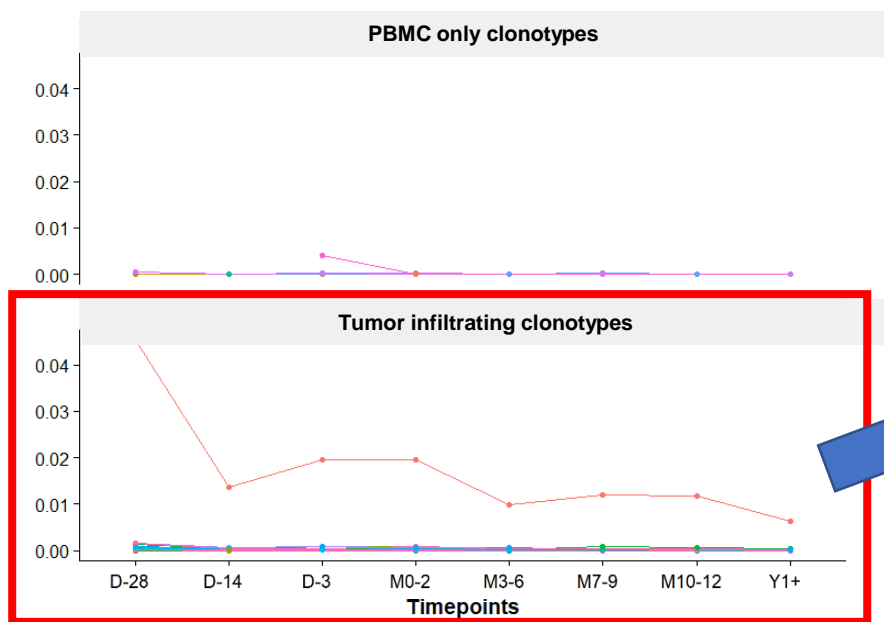
Cytotoxic phenotype (3 clones)



Th17 phenotype (1 clone)



## Majority of dynamic clones infiltrating tumor had low abundance in a patient with KRAS/STK11 co-mutations and had relapse



# Take Home Messages

- The periphery represents a vital biological compartment for the anti-tumor response
- Significant and systemic alterations in the peripheral anti-tumor T cell repertoire in NSCLC during neoadjuvant anti-PD-1
- Pattern and magnitude of repertoire reshaping correlates with tumor representation and pathologic response
- Impaired peripheral restructuring of the tumor infiltrating repertoire in patients with disease relapse highlights a potential immunological deficiency to overcome and warrants further investigation



# Acknowledgement

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