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Immune enrichment and functional T-cell receptor (TCR) frequencies predict response to immune checkpoint blockade (ICB) in selected fusion-associated sarcomas

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Disclosures

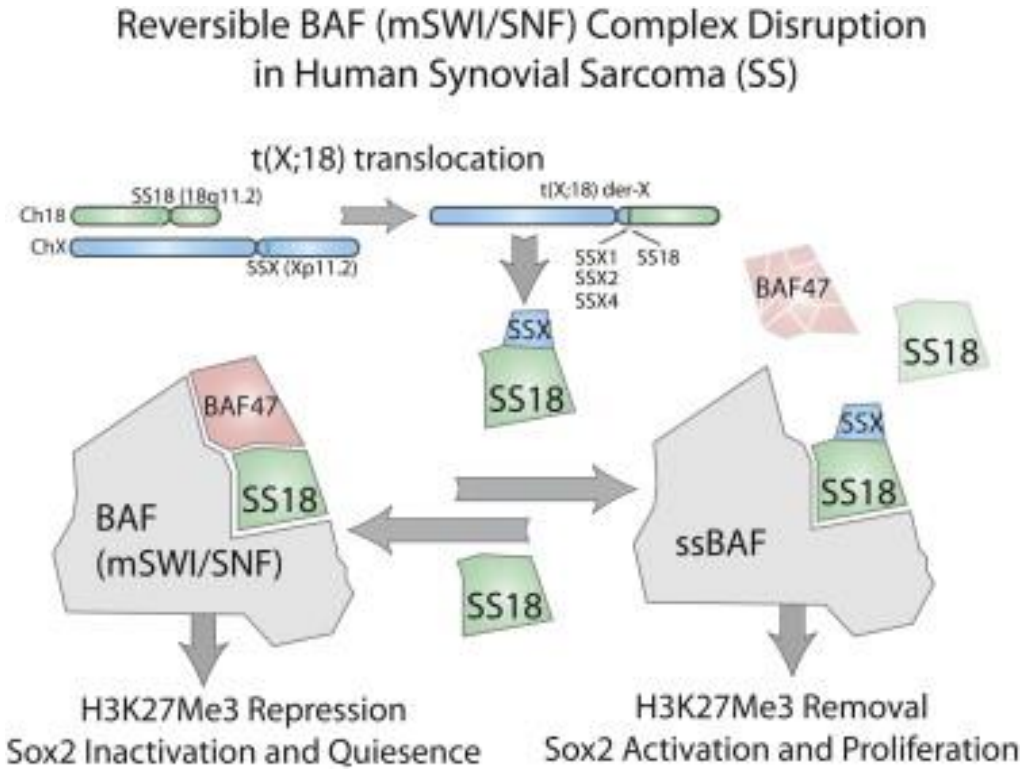
- I have no financial relationships to disclose.
- I will be discussing agents on investigational use in my presentation.

Synovial Sarcoma (SS)

- Predominantly affects adolescents and young adults (AYA)
- Characterized by oncogenic SS18-SSX fusion gene and loss of SMARCB1

- Current treatment modalities
  - Chemotherapy, RT and surgery standard of care
  - Pazopanib (VEGFi/PDGFRi) second line (ORR 6%)

Van Der Graaf, Winette TA, et al. "Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial." *The Lancet* 379.9829 (2012): 1879-1886.

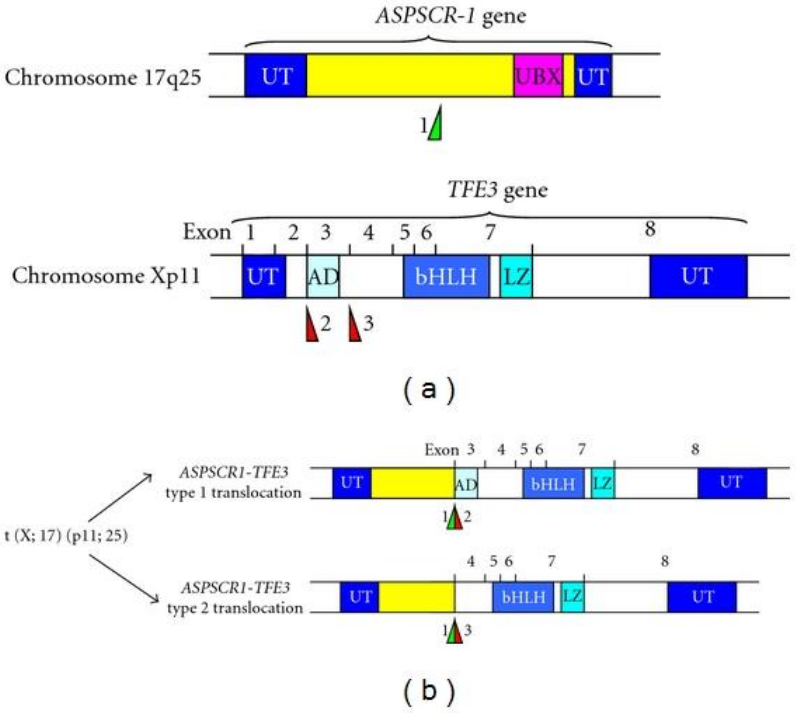


Kadoch, C., & Crabtree, G. R. (2013). Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma. *Cell*, *153*(1), 71-85.

Alveolar soft part sarcoma (ASPS)

- Involves an unbalanced translocation between *ASPSCR1* and *TFE3*
- The *TFE3* gene breaks off from the X chromosome and attaches onto the ASPSCR1 gene on chromosome 17

- Current treatment modalities
  - RT and surgery standard of care
  - Targeted VEGF receptor tyrosine kinases inhibitors: cediranib (ORR 11%)

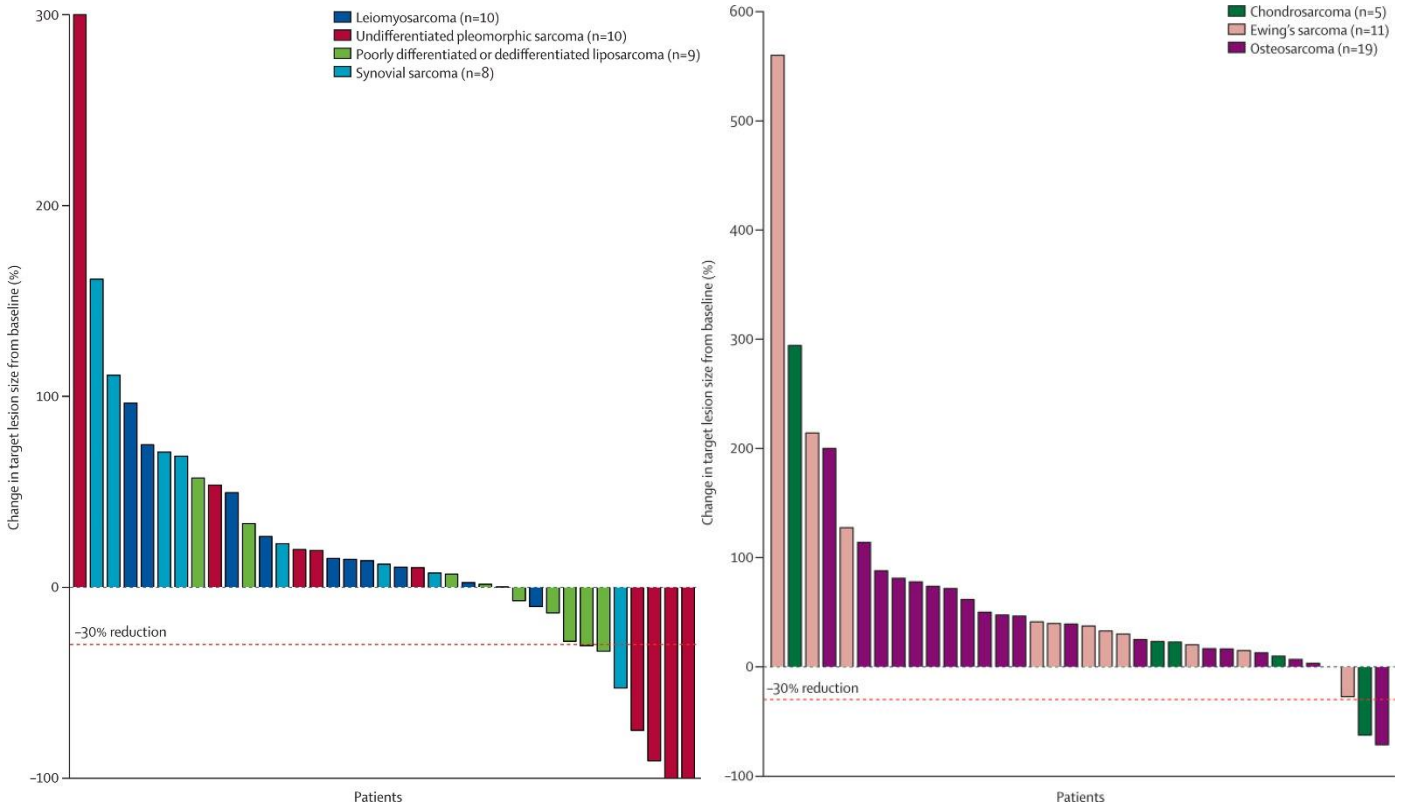


Mitton, B., & Federman, N. (2012). Alveolar soft part sarcomas: molecular pathogenesis and implications for novel targeted therapies. *Sarcoma*, *2012*.

Judson, Ian, et al. "Cediranib in patients with alveolar soft-part sarcoma (CASPS): a double-blind, placebo-controlled, randomised, phase 2 trial." *The Lancet Oncology* (2019).

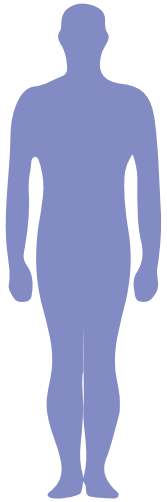
Role of ICB in sarcoma

- Phase 2 study investigating the role of pembrolizumab (anti-PD1) in the treatment of soft-tissue sarcoma (STS) and bone sarcoma
- Findings suggest that pembro is clinically active in patients with undifferentiated pleomorphic sarcoma or dedifferentiated liposarcoma
- Need to expand to other cohorts of both STS and bone sarcoma



Tawbi, Hussein A., et al. "Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial." *The Lancet Oncology* 18.11 (2017): 1493-1501.

Trial design: Anti-CTLA-4 in combination with anti-PD-L1



Sarcoma arms:
1. Adipocytic tumors
2. Vascular tumors
3. UPS
4. Synovial sarcoma
5. Osteosarcoma
6. ASPS
7. Chordoma
8. Others

Combo phase up to 4 doses.
Q4W durvalumab 1500mg and Q4W tremelimumab 75mg

Restaging every 8 weeks with confirmatorty scan at 12 weeks

Durvalumab monotherapy phase up to 50 weeks overall

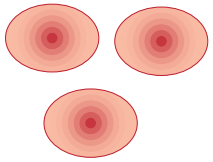
Follow-up

Blood draw and tumor biopsy at pre-treatment time point

Blood draw and tumor biopsy at 6 weeks on-treatment time point

Primary endpoint:
- PFS at 12 weeks greater than 40%

Secondary endpoint:
- irRC and irRECIST response rate
- PFS at 24 weeks and OS
- Safety and tolerability



Molecular correlates related to ICB:
- Whole exome sequencing
- RNA-sequencing
- TCR-sequencing
- Multiplex IF
- Flow cytometry

NCT02815995

Response criteria - irRC

- CR, complete disappearance of all lesions (whether measurable or not, and no new lesions)
- PR, decrease in tumor burden ≥50% relative to baseline
- SD, not meeting criteria for irCR or irPR, in absence of irPD

→ Responders

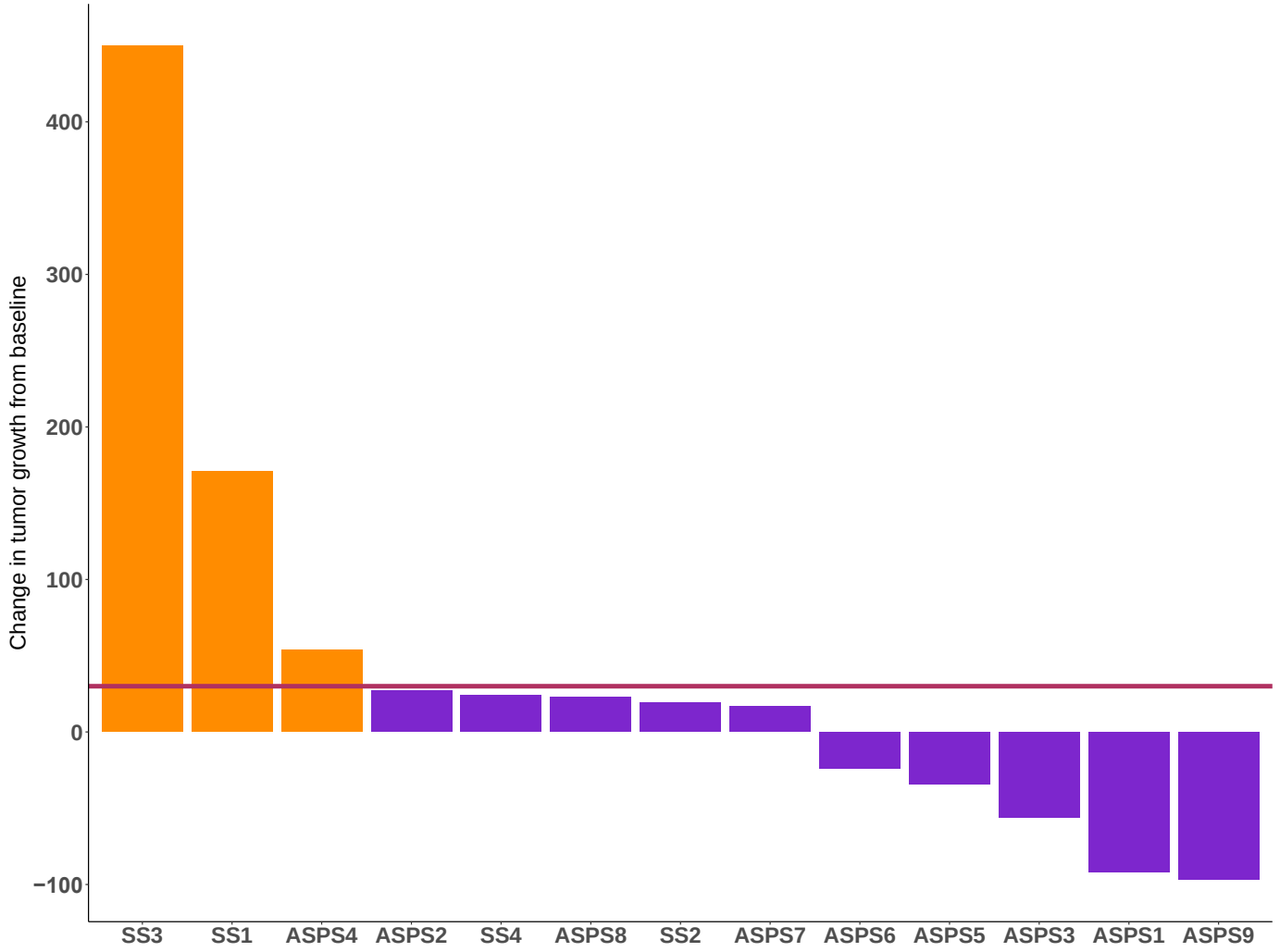
- PD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden)

→ Non-Responders

Molecular correlates under study

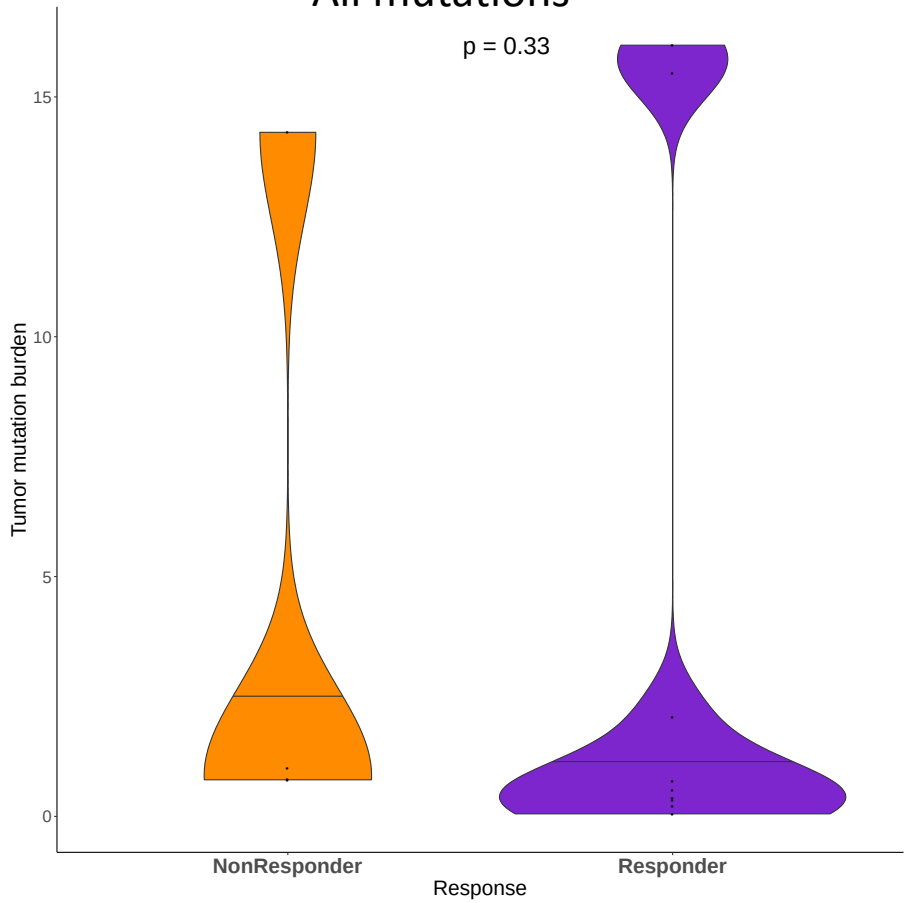
- Whole exome sequencing
- RNA-sequencing
- TCR-sequencing
- Multiplexed Immunofluorescence – Presented by Edwin Parra Cuentas Poster #360 on 11/9

Best response across both cohorts

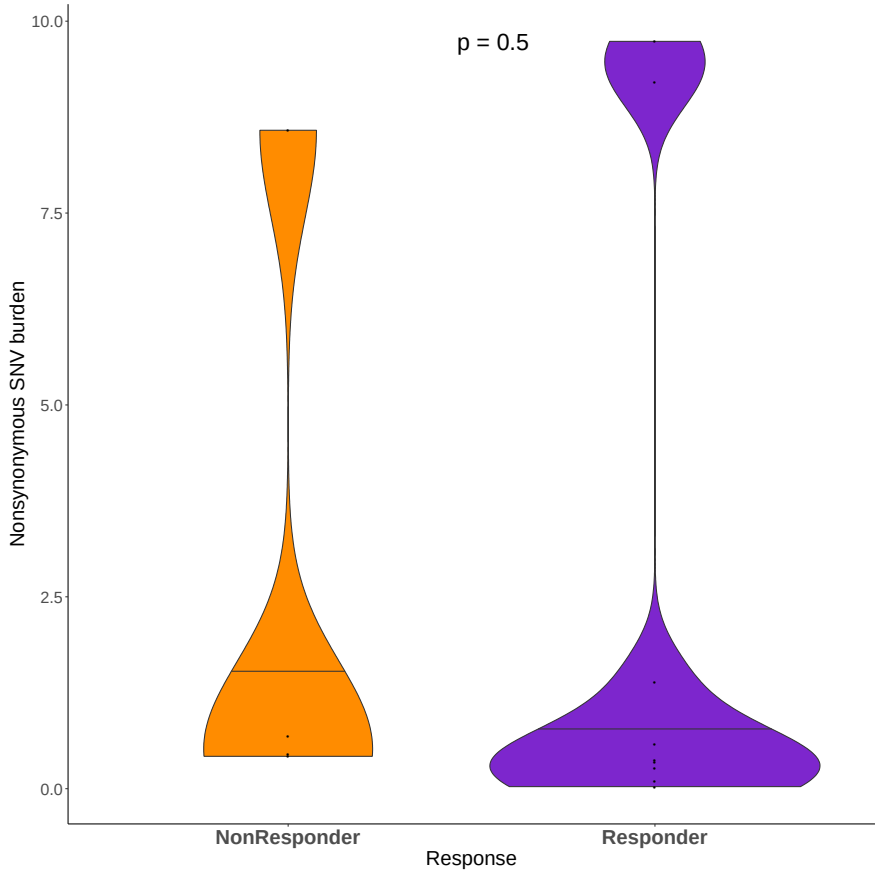


Tumor mutation burden was not predictive of response

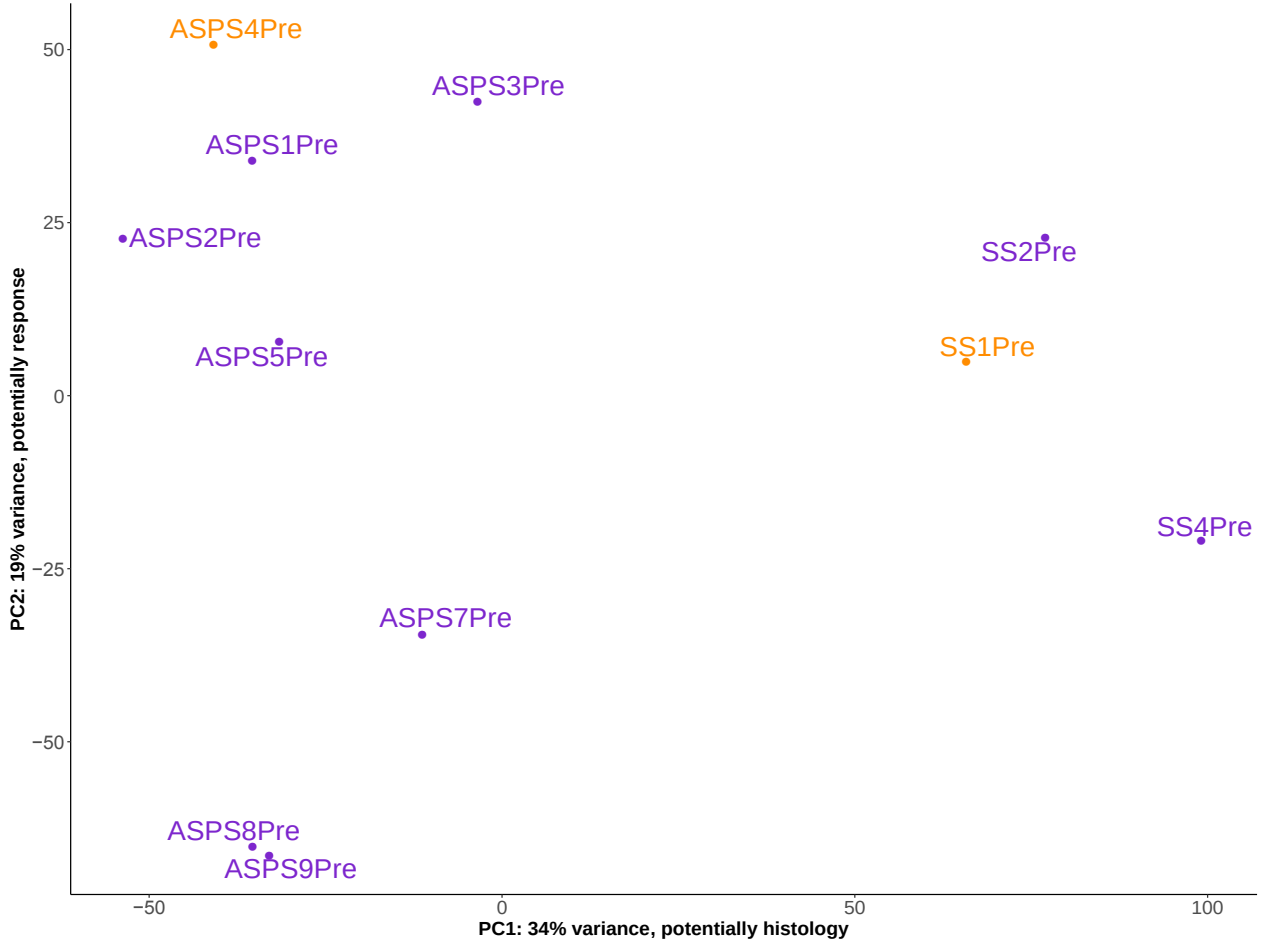
All mutations



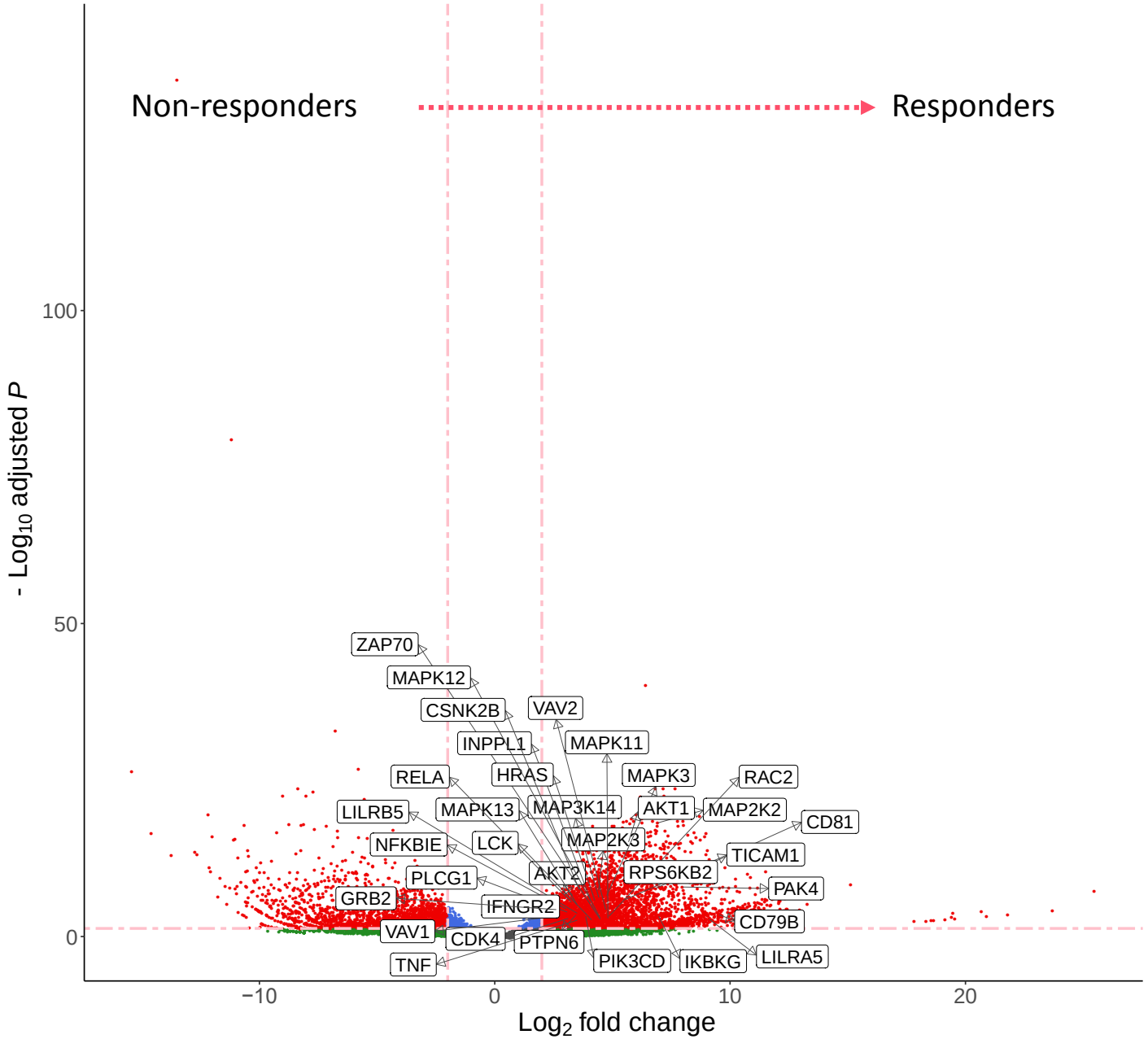
Nonsynonymous mutations



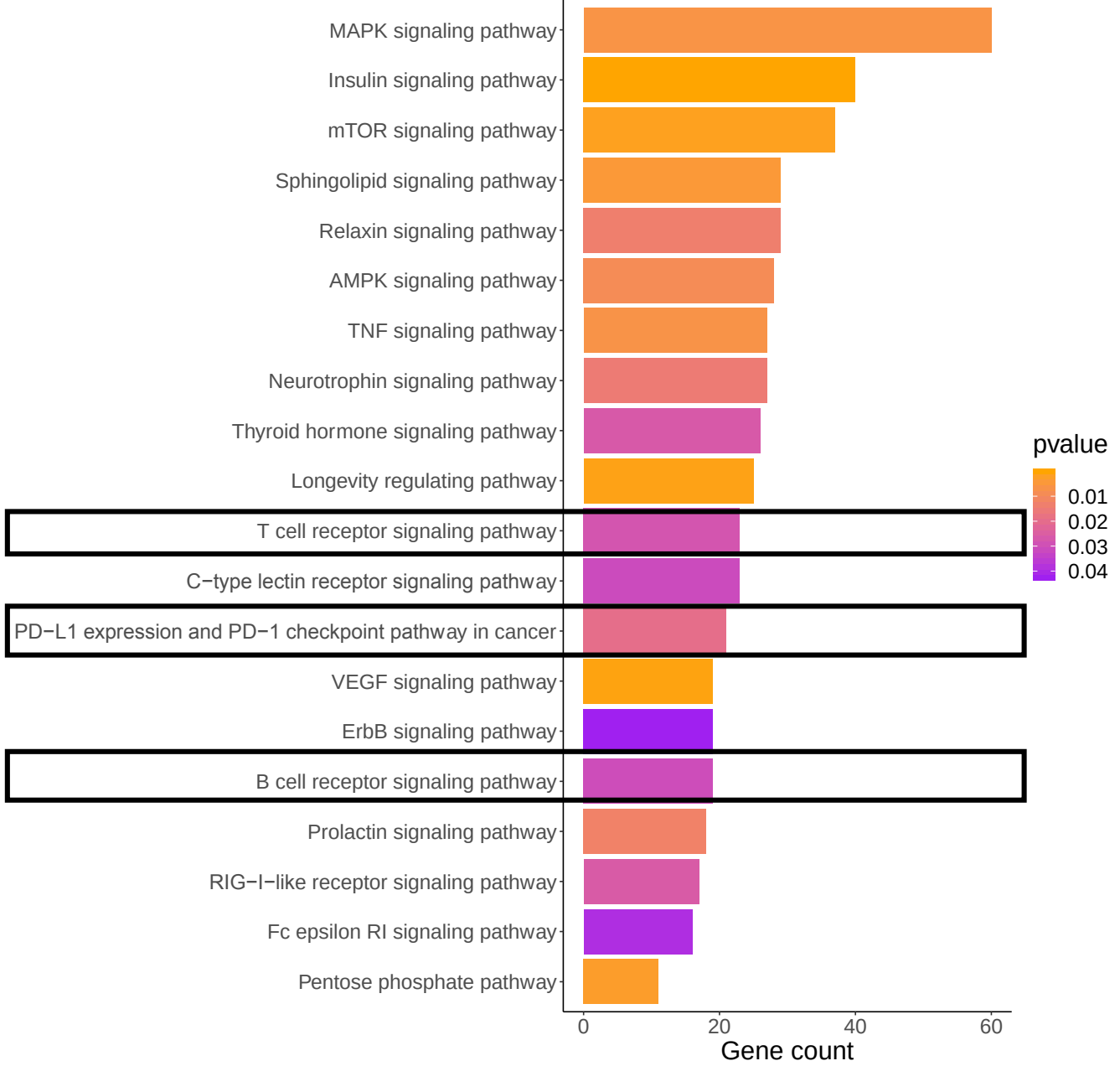
Overall transcriptomic clustering indicates a separation based on histology



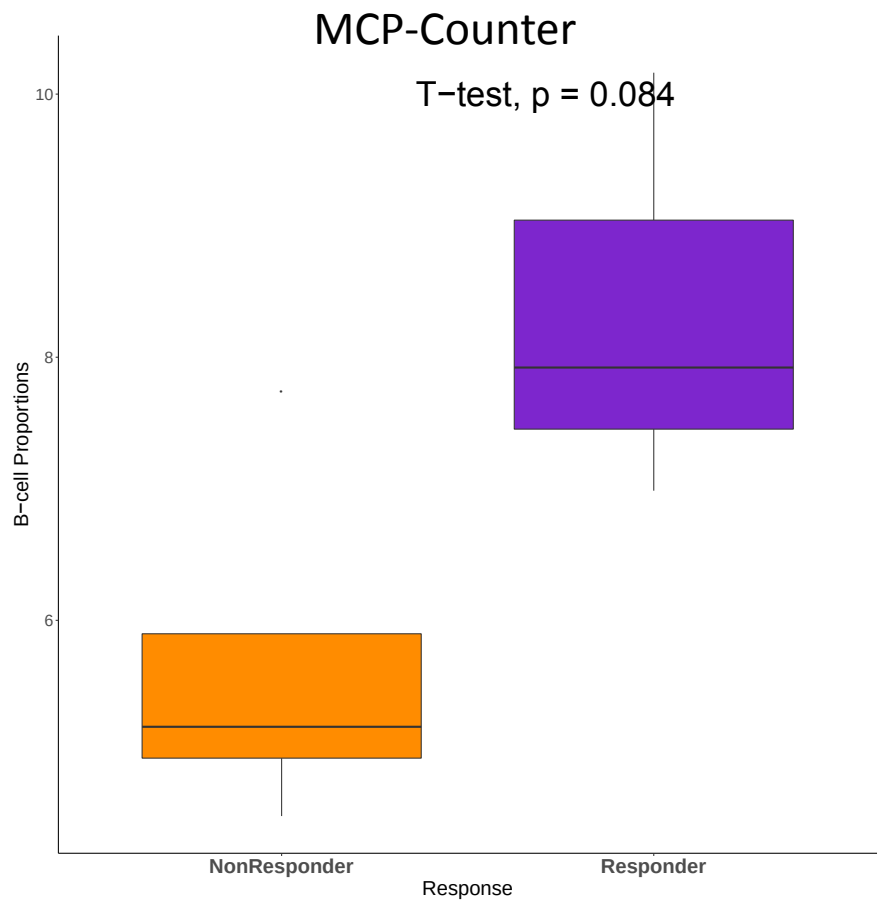
Differential expression is driven through an immune enrichment in pre-treatment samples of ASPS

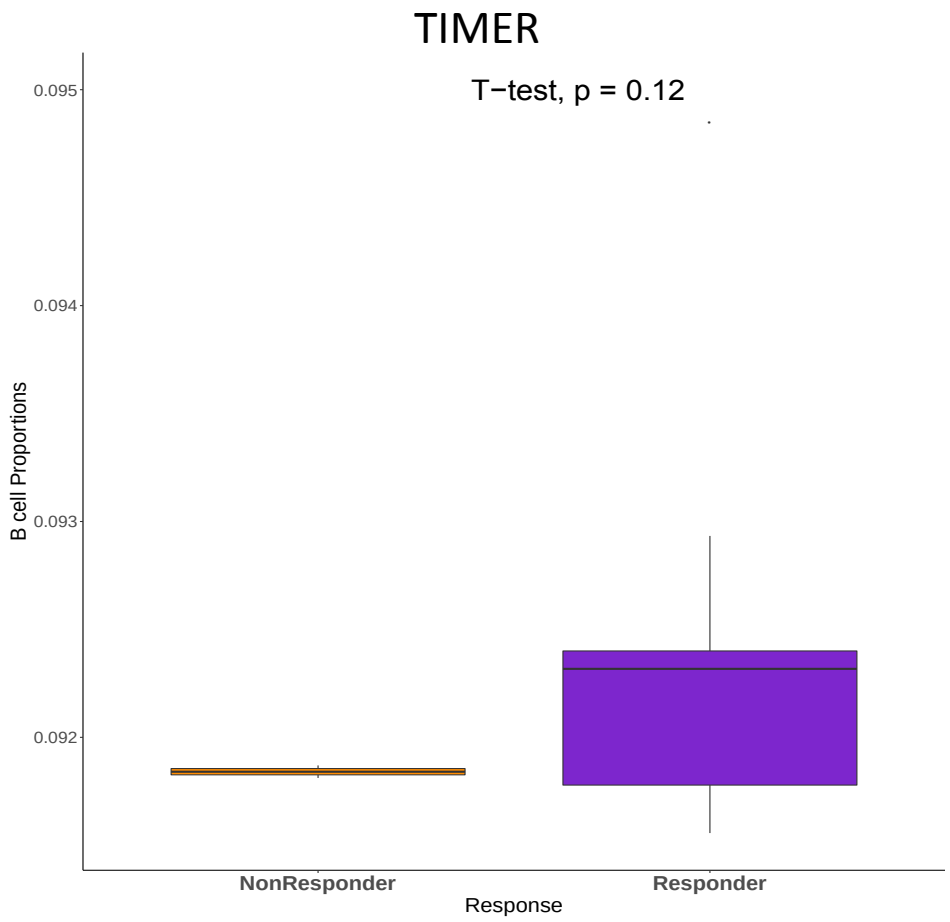


KEGG pathway level enrichment upregulated in responders with ASPS indicate an upregulation in immune response

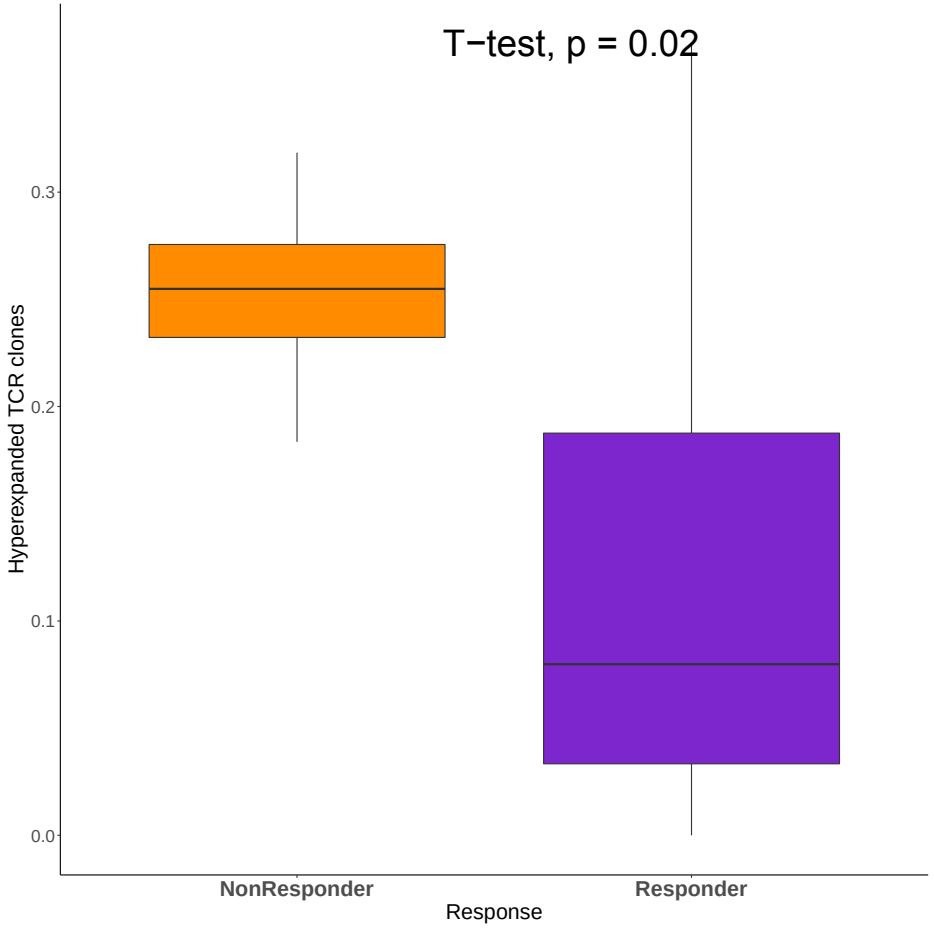


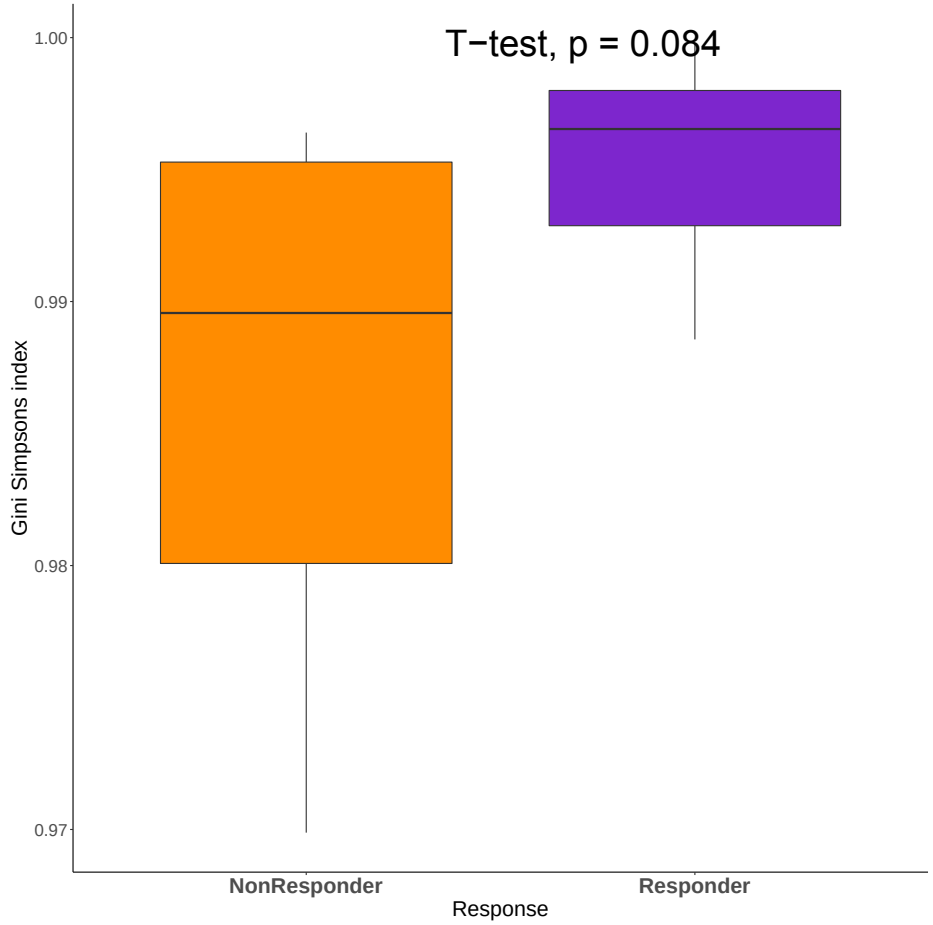
Increased levels of B-cell infiltration in pre-treated ASPS and SS responders



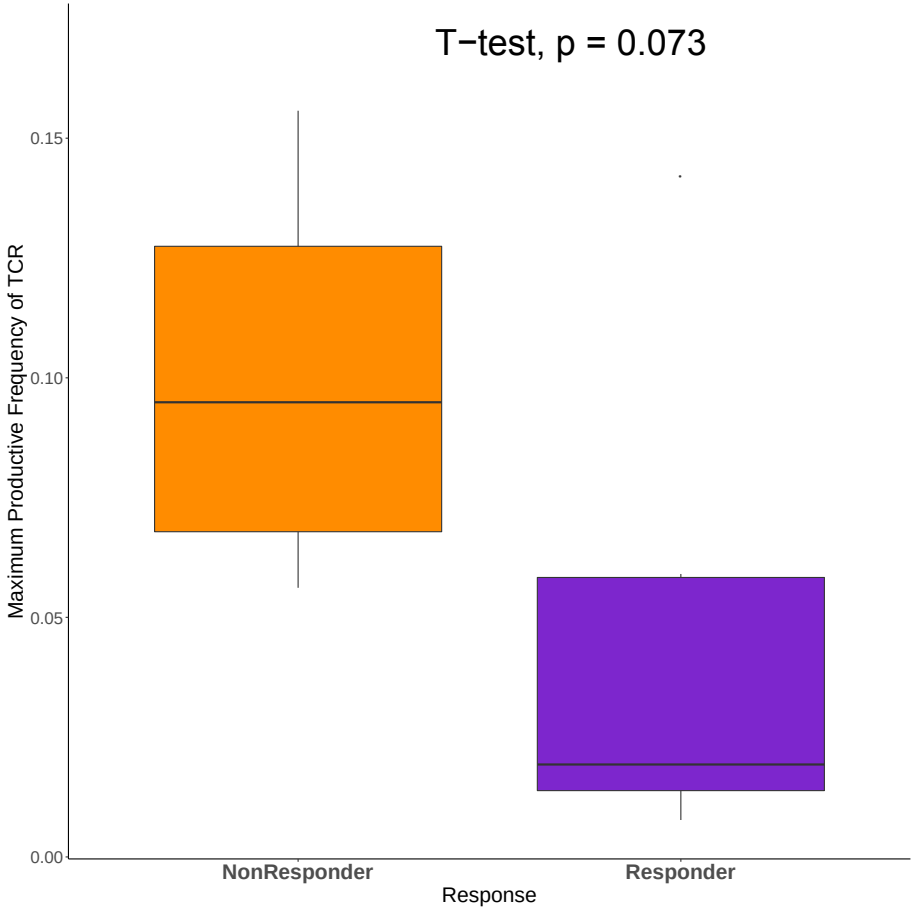


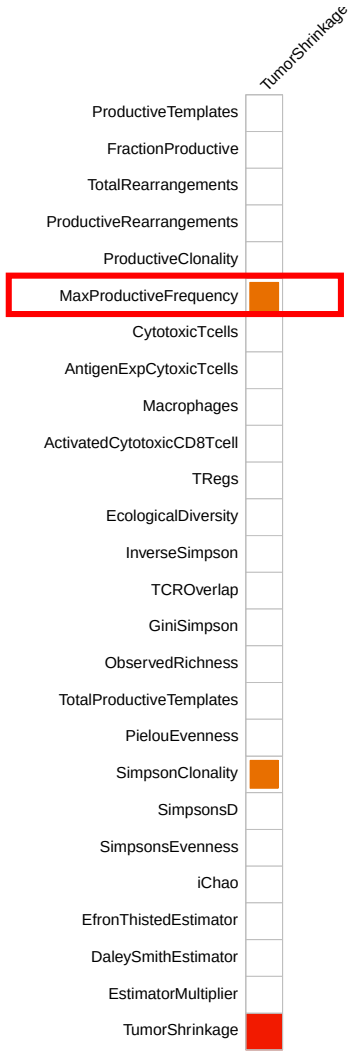
Diversity and not clonality of TCR correlates with response





Lower maximum productive frequency of the TCR correlates with tumor shrinkage





Conclusions and Future Directions

- Higher TMB and TCR clonality not predictive in response to ICB
- Immune enrichment in DEGs contributed to pathway enrichments in TCR signaling, BCR signaling and PD-L1 expression in cancer
- Increased levels of B-cells present in responders at the pre-treatment time point
- Lower maximum productive frequency of the TCR most correlates with a decrease in tumor volume
- Further immune deconvolution and BCR profiling
- Follow up studies will expand to further cohorts

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