KCRS 25
Kidney Cancer Research Summit

# Lower Checkpoint Gene Expression is Associated with Primary Resistance to Nivolumab-Ipilimumab Combination in Advanced Renal Cell Carcinoma

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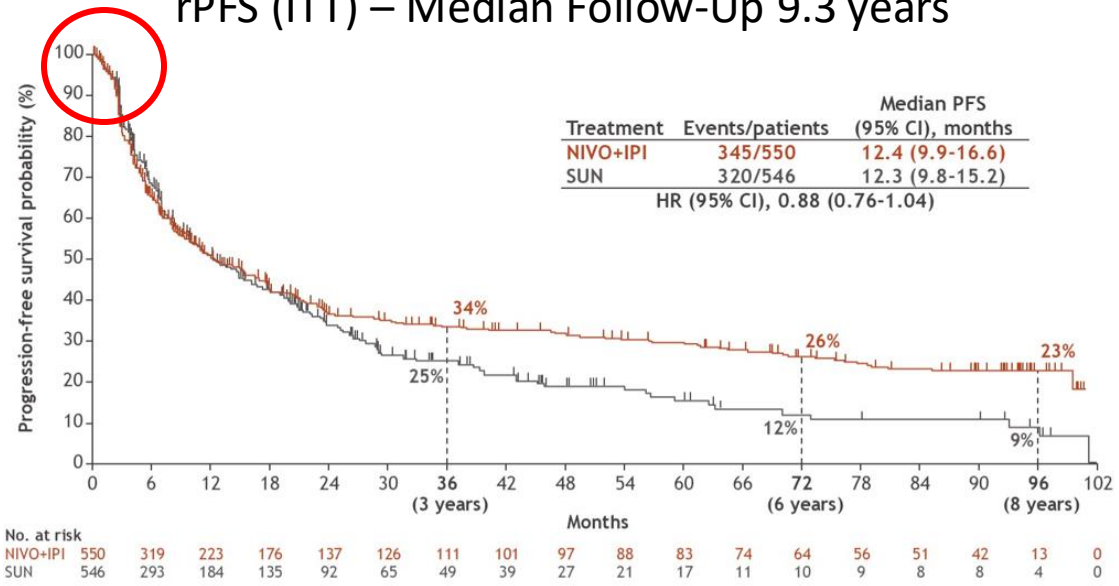
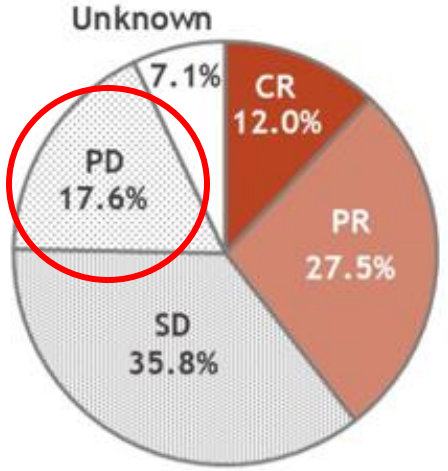
# Background

- Immunotherapy combinations have emerged as the standard of care for patients with advanced RCC
- Nivolumab-ipilimumab is associated with long-term durability, though a subset of patients do not derive any benefit from treatment

CheckMate 214
rPFS (ITT) – Median Follow-Up 9.3 years




CheckMate 214
Best Objective Response – ITT






RCC=Renal cell carcinoma; rPFS=Radiographic progression-free survival; ITT=Intent to treat.
Choueiri et al, ASCO Annual Meeting, 2025

# Rationale and Hypothesis

**Rationale: Urgent need to identify negative selection markers for treatment with nivolumab-ipilimumab**

**Hypothesis: Molecular differences exist among tumors with and without primary progression to nivolumab-ipilimumab**

# Methods

- Tempus Lens was used to select records for 106 patients with RCC who received 1L nivolumab-ipilimumab
- Eligible patients:
  - Tumor samples collected within one year of treatment initiation
  - Processed using xT (DNA-seq) and xR (RNA-seq) assays
- Treatment response:
  - Investigator-assessed within 90 days of therapy start
  - Categorized as PD versus non-PD
- RNA-seq data were normalized, log2-transformed, and batch-corrected
  - Measured checkpoint and angiogenic gene expression (TPM)
- Immunologic phenotype:
  - TMB (mt/Mb)
  - MSI status
  - PD-L1 (IHC, 22c3)
  - Immune infiltration estimated by quanTIseq (RNA)



RCC=Renal cell carcinoma; 1L=First-line; PD=Progressive disease; TMP=Transcripts per million; TMB=Tumor mutation burden; MSI=Microsatellite instability; PD-L1=Programed death ligand 1; IHC=Immunohistochemistry.

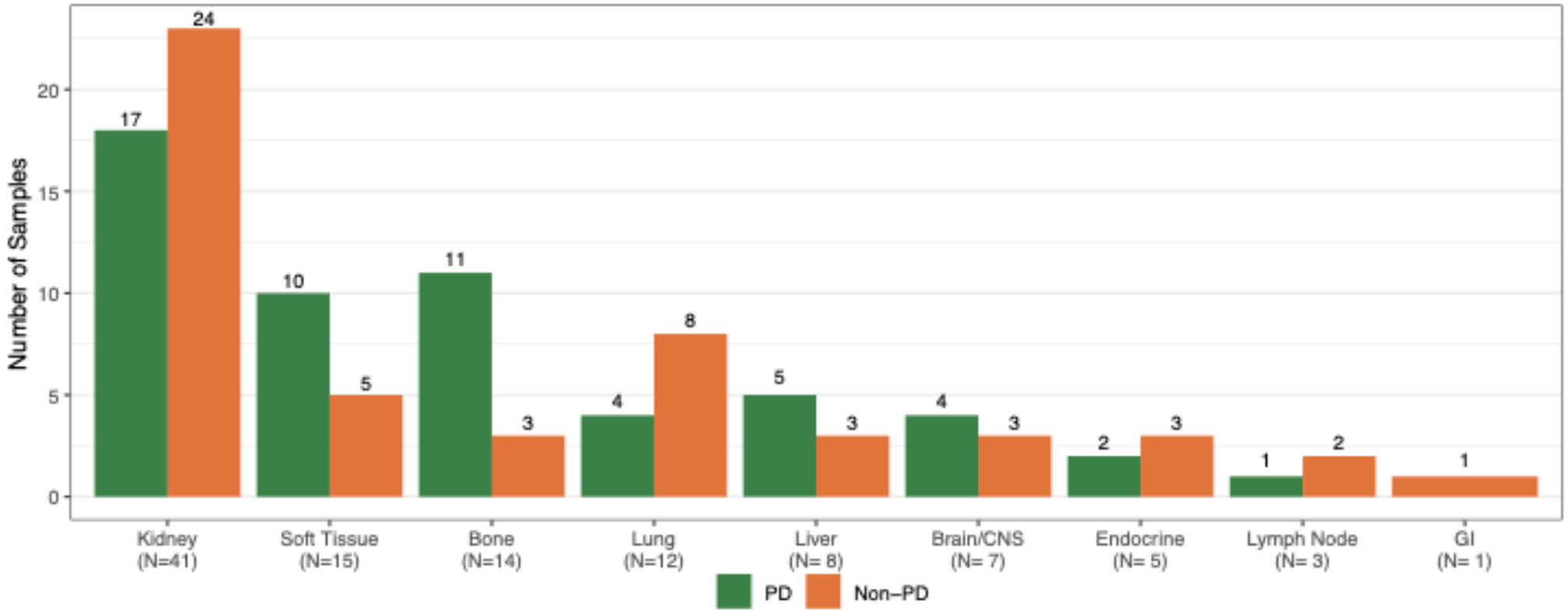
# Baseline Characteristics

| | PD (n=55) Median or N (%) | Non-PD (n=51) Median or N (%) | P-value |
|---|---|---|---|
| Age at Diagnosis, years | 59 | 58 | 0.962 |
| Male | 37 (67%) | 40 (78%) | 0.198 |
| White | 38 (83%) | 37 (90%) | 0.337 |
| Hispanic/Latino | 5 (15%) | 7 (25%) | 0.307 |
| Current/Former Smoker | 20 (36%) | 21 (41%) | 0.611 |
| Prior nephrectomy | 29 (53%) | 24 (47%) | 0.560 |
| Clear cell RCC | 42 (76%) | 42 (82%) | 0.480 |
| Metastases at Collection | 47 (94%) | 45 (96%) | >0.999 |
| Bone Metastases at Collection | 10 (18%) | 7 (14%) | 0.532 |
| Liver Metastases at Collection | 11 (20%) | 3 (5.9%) | 0.032 |



RCC=Renal cell carcinoma; PD=Progressive disease.

# Specimen Source (N=106)

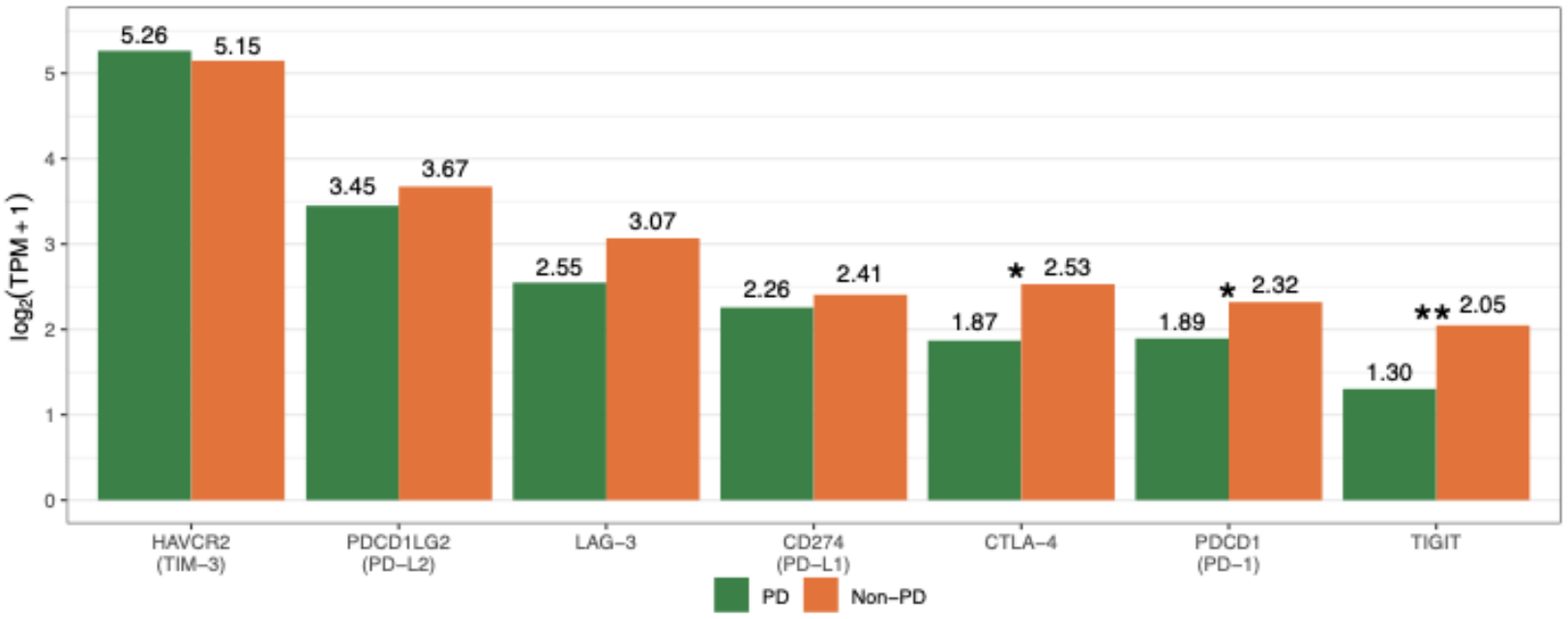


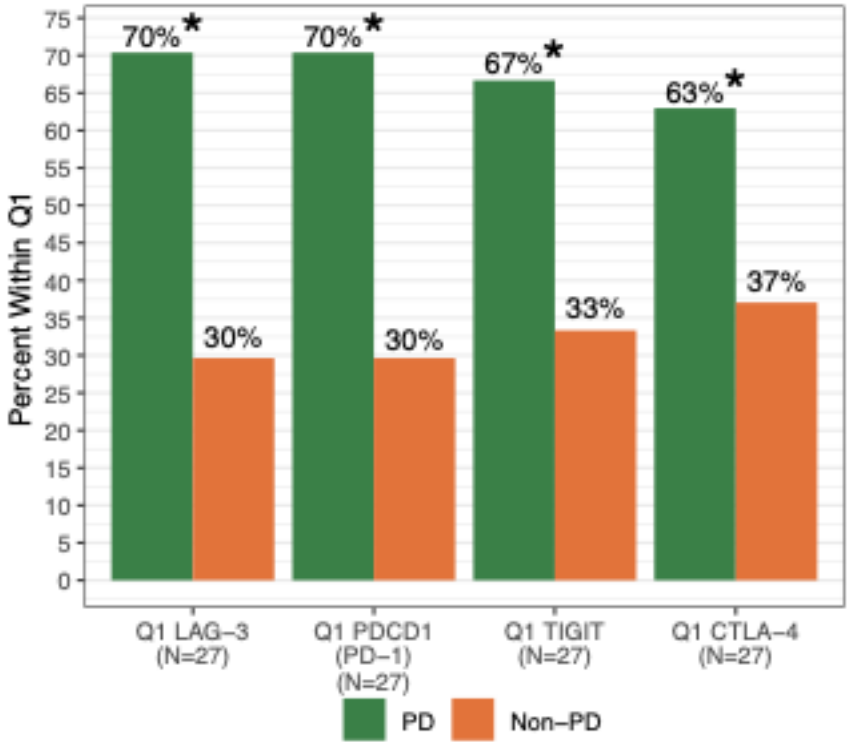

54% with matched normal DNA



CNS=Central nervous system; GI=Gastrointestinal; PD=Progressive disease.

# Checkpoint RNA Expression

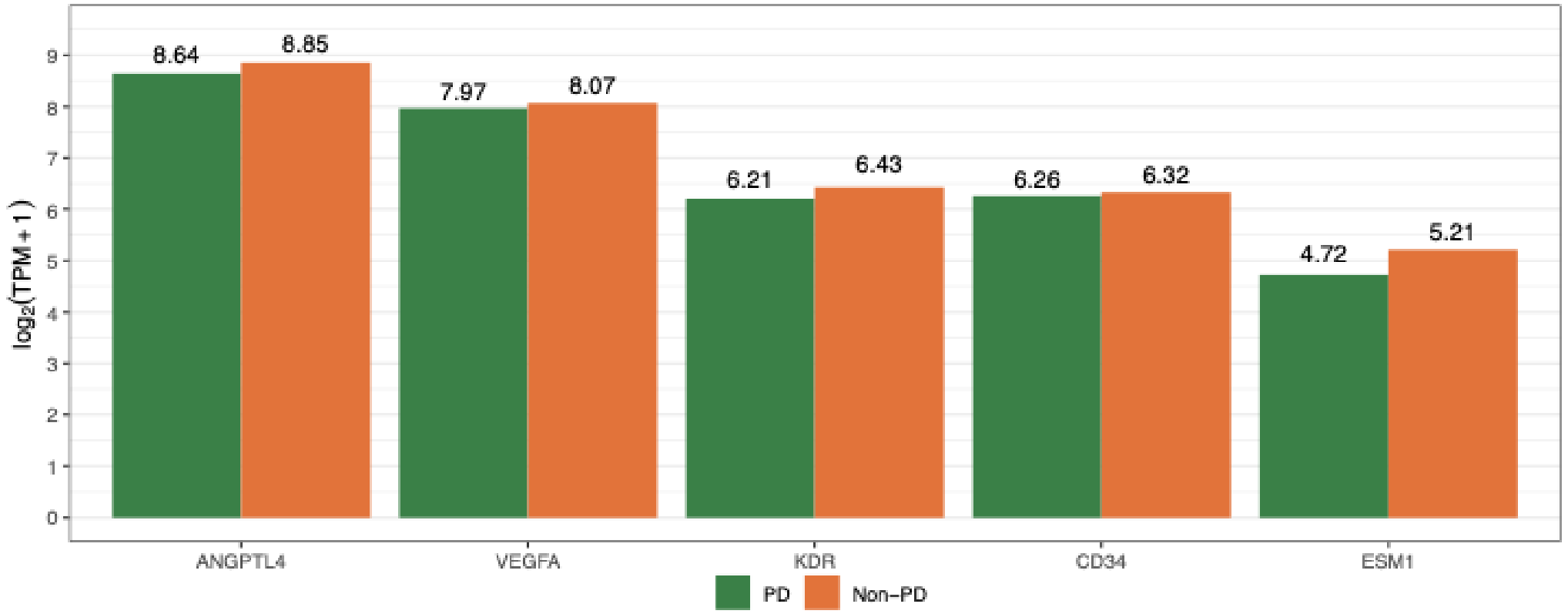





* p<0.05, **p<0.01.
CNS=Central nervous system; GI=Gastrointestinal; PD=Progressive disease.

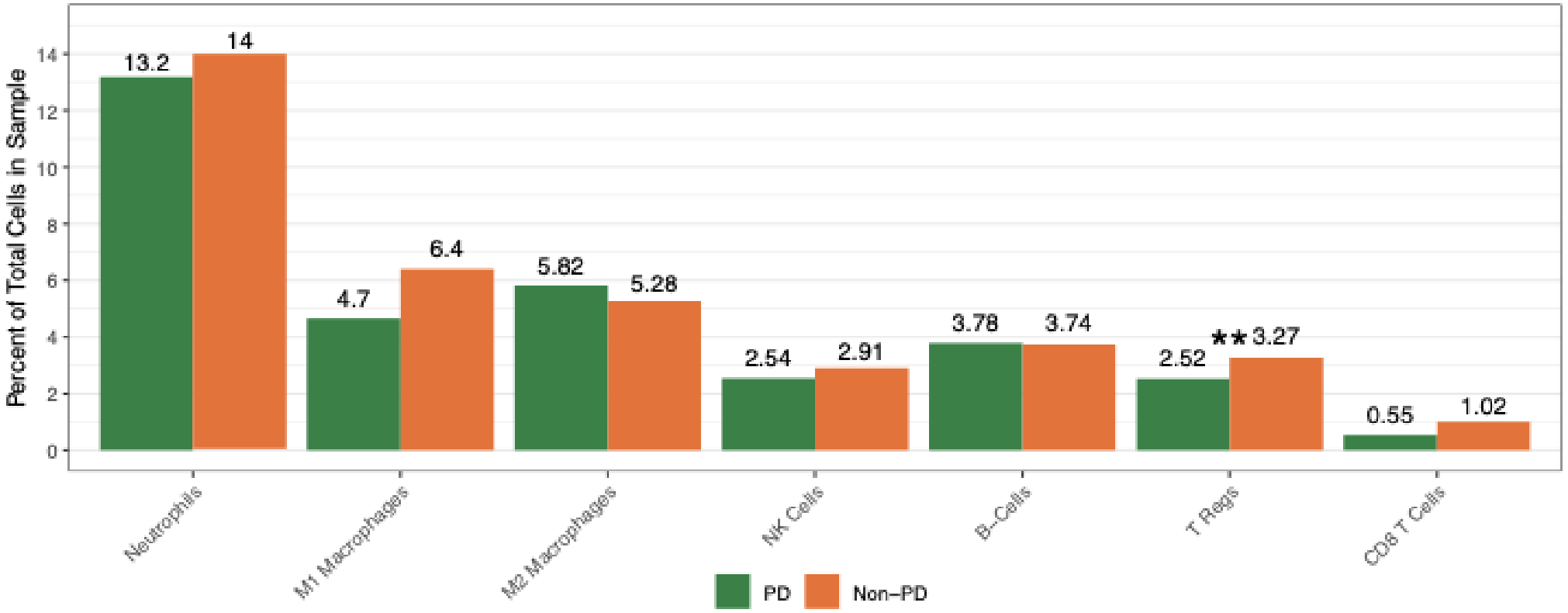
# Angiogenic Gene RNA Expression






PD=Progressive disease.

# Immune Cell Infiltrates




** p<0.01. Note – the following immune cell types had medians below 0 and were not included in this graph: Dendritic cells, monocytes, CD4 T cells.
PD=Progressive disease.

# Somatic Alterations

| | PD (n=55) | Non-PD (n=51) | P-value | Q-value |
|---|---|---|---|---|
| VHL, N (%) | 34 (67%) | 32 (58%) | 0.368 | 0.9 |
| PBRM1, N (%) | 15 (29%) | 16 (29%) | 0.971 | >0.9 |
| SETD2, N (%) | 8 (16%) | 15 (27%) | 0.148 | 0.9 |
| TP53, N (%) | 8 (16%) | 14 (25%) | 0.215 | 0.9 |
| CDKN2A, N (%) | 7 (14%) | 11 (20%) | 0.390 | 0.9 |
| BAP1, N (%) | 7 (14%) | 6 (11%) | 0.659 | 0.9 |
| CDKN2B, N (%) | 6 (12%) | 8 (15%) | 0.673 | 0.9 |
| TERT, N (%) | 7 (14%) | 5 (9.1%) | 0.452 | 0.9 |
| KDM5C, N (%) | 5 (9.8%) | 6 (11%) | 0.852 | >0.9 |
| PTEN, N (%) | 4 (7.8%) | 6 (11%) | 0.743 | 0.9 |
| MTAP, N (%) | 5 (9.8%) | 3 (5.5%) | 0.477 | 0.9 |
| TSC1, N (%) | 4 (7.8%) | 2 (3.6%) | 0.425 | 0.9 |
| ARID1A, N (%) | 3 (5.9%) | 2 (3.6%) | 0.670 | 0.9 |
| NF2, N (%) | 2 (3.9%) | 4 (7.3%) | 0.680 | 0.9 |



PD=Progressive disease.

# Conclusions

Primary resistant to nivolumab-ipilimumab characterized by lower RNA expression of immune checkpoints

This possibly reflects an immune-cold microenvironment with limited T-cell infiltration and activation

Future prospective studies, including IHC validation, is warranted to confirm these findings



IHC=Immunohistochemistry.

# Acknowledgements


- Patients and their families
- Collaborating institutions
- Tempus AI, Inc.