GENOMIC AND TRANSCRIPTOMIC CORRELATES OF HER3 EXPRESSION IN PROSTATE CANCER

OU Health | Stephenson Cancer Center
The UNIVERSITY of OKLAHOMA

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CARIS PRECISION ONCOLOGY ALLIANCE

INTRODUCTION

- HER3 (ERBB3) is a "pseudokinase" receptor that signals by heterodimerization with other receptor tyrosine kinases like HER2 to promote PI3K-AKT-mTOR mediated survival and adaptive resistance.
- It has emerged as a critical mediator of survival and resistance across a broad range of solid tumors, including advanced and castration resistant prostate cancer.
- Despite its biological relevance, the clinical and genomic significance of HER3 RNA expression in prostate cancer remains poorly defined.

OBJECTIVES

We performed a comprehensive multi-omic analysis to:

- Evaluate HER3 RNA expression in prostate cancer patients across tumor sites and clinical states.
- Evaluate commonly occurring DNA alterations in tumors with high and low HER3 expression.
- Evaluate overall survival in patients with high and low HER3 expression.

METHODS

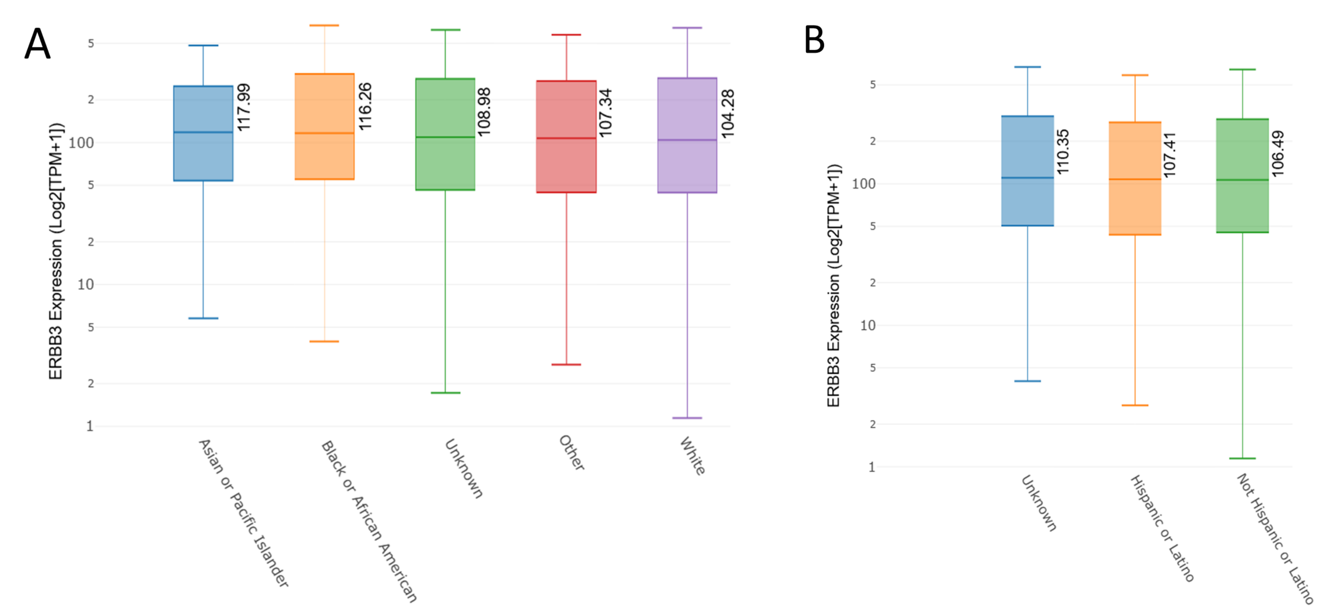
- DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing were performed on prostate tumor samples (n = 19,238) submitted to Caris Life Sciences. Analyzable HER3 data was present in 9684 samples.
- HER3 expression was quantified as transcripts per million (TPM) and stratified into high (HER3-H) and low (HER3-L) groups defined by the top and bottom quartiles, respectively.
- ADT exposure was defined as ≥3 months of androgen deprivation therapy before tissue collection.
- Real-world overall survival (rwOS) was obtained from insurance claims data and calculated from biopsy to last contact.
- Tumor microenvironment (TME) cell fractions were estimated by RNA deconvolution using quanTIseq.
- Group comparisons were conducted using Mann–Whitney U and chi-square tests as appropriate.
- Survival outcomes were evaluated using Cox proportional hazards models and log-rank testing, with false discovery rate correction for multiple comparisons.

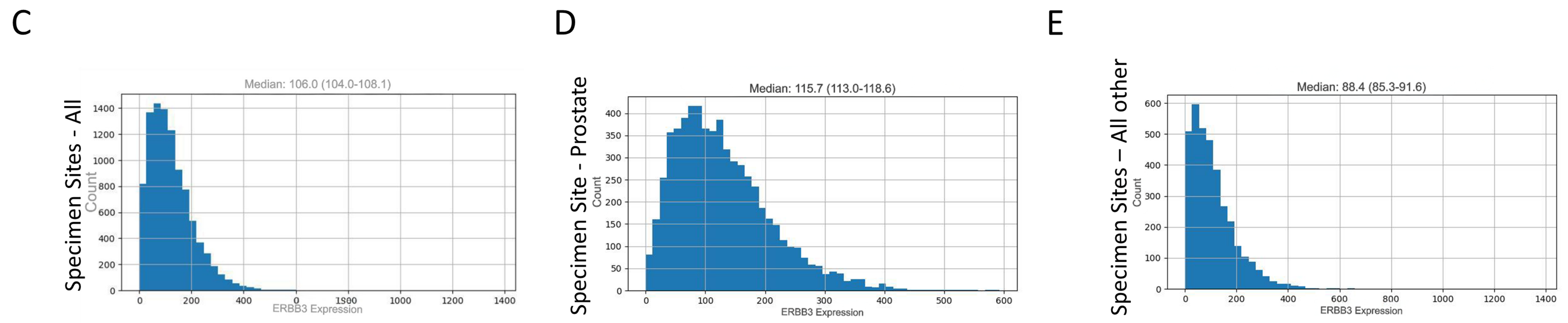
RESULTS

Table 1. Baseline Characteristics

Cohort Characteristics	N (%)
All Samples	9684
Median Age (range)	69(29- >89)
Race	
White	6301 (70)
Black	1275 (14)
Asian	205 (2)
Other	293 (3)
Unknown	932 (10)
Ethnicity	
Hispanic or Latino	670 (7)
Not Hispanic or Latino	7503 (83)
Unknown	833 (9)
Specimen Site	
Prostate	6187 (64)
Lymph Node	1105 (11)
Metastasis	2392 (25)

Figure 1. HER3 gene expression in prostate cancer by (A) Race, (B) Ethnicity, (C) All samples, (D) Primary Tumors, (E) Metastatic Tumors, and (F) Sites of metastases.





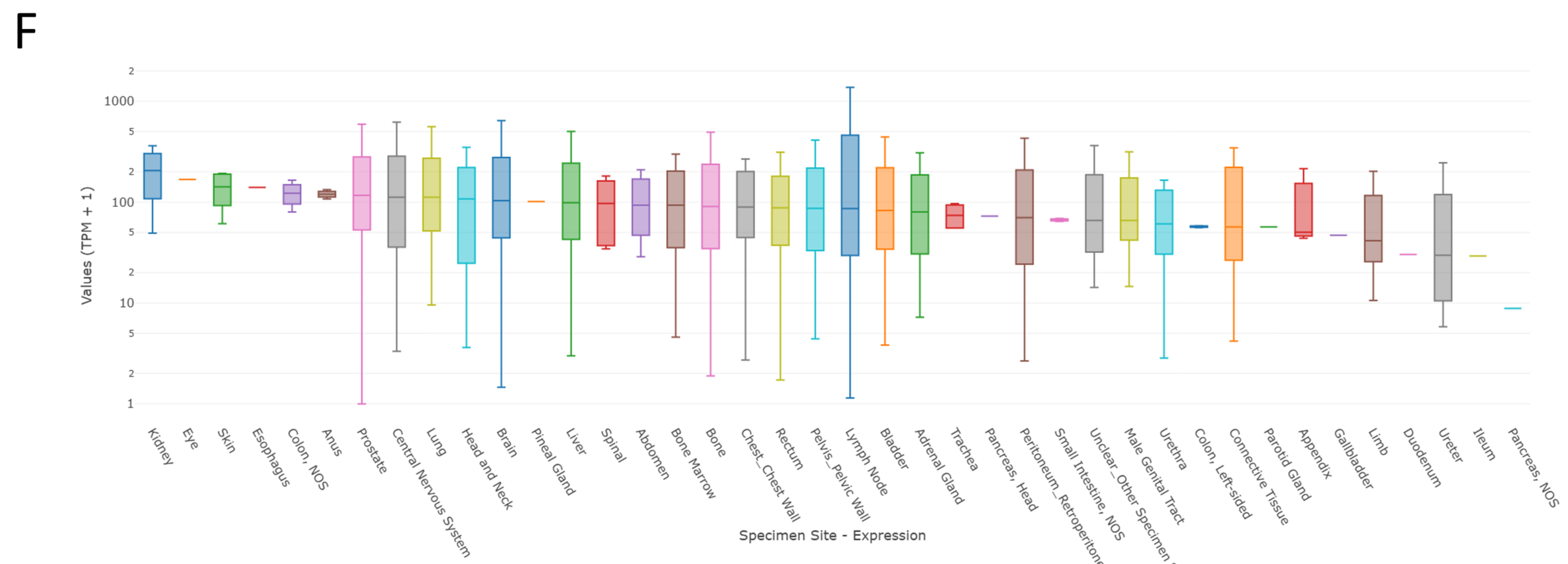
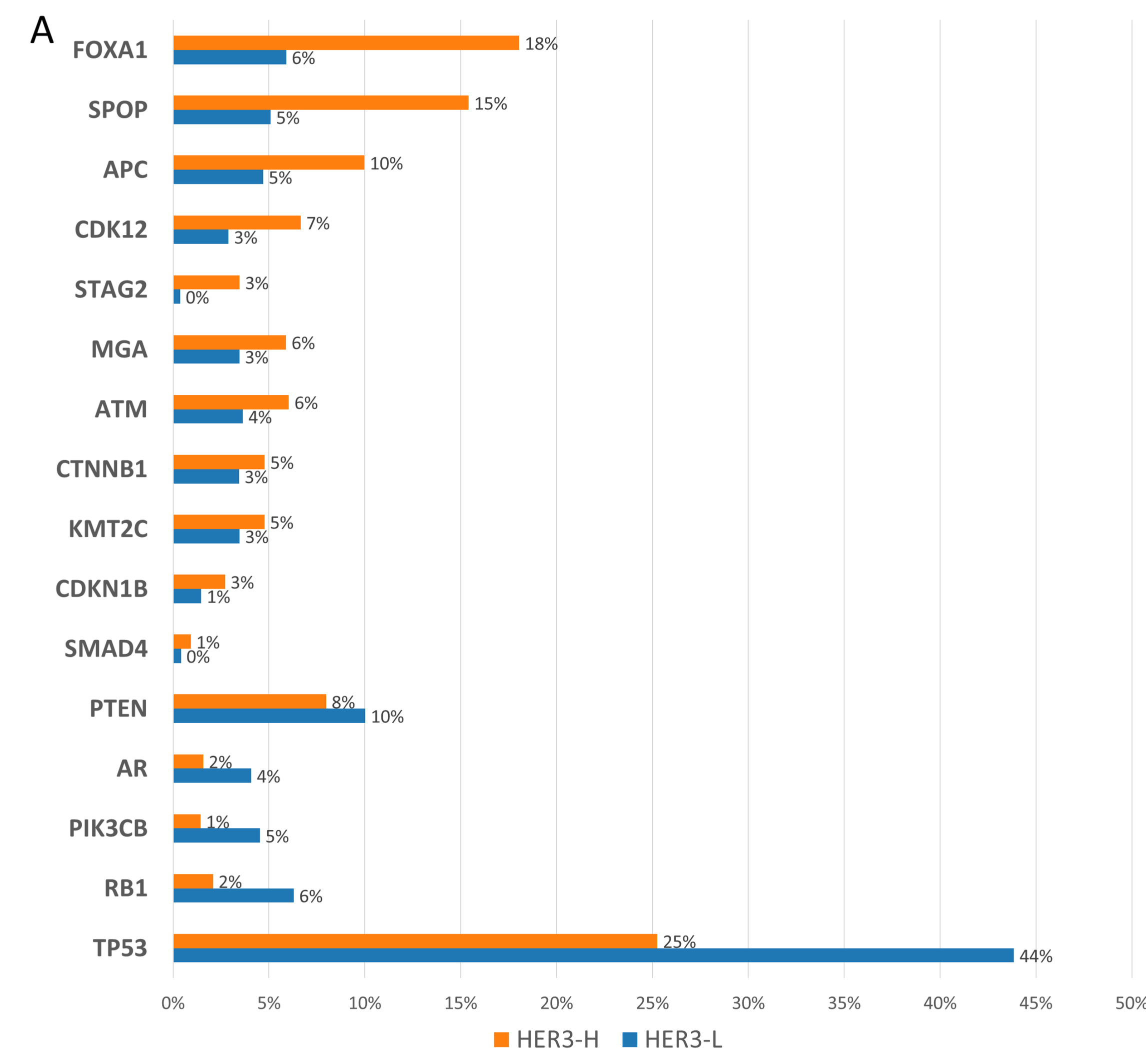
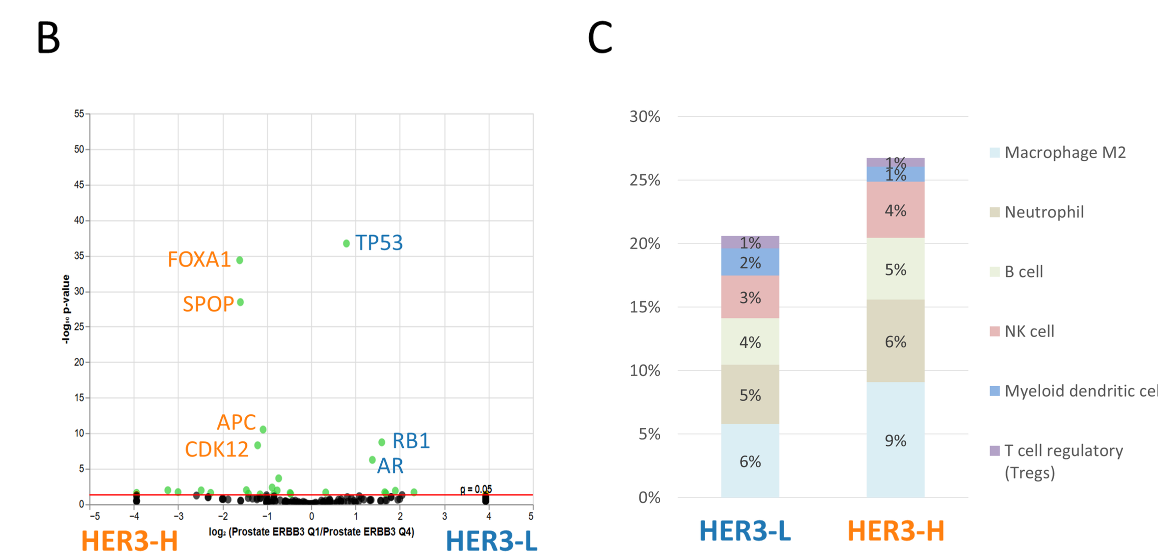


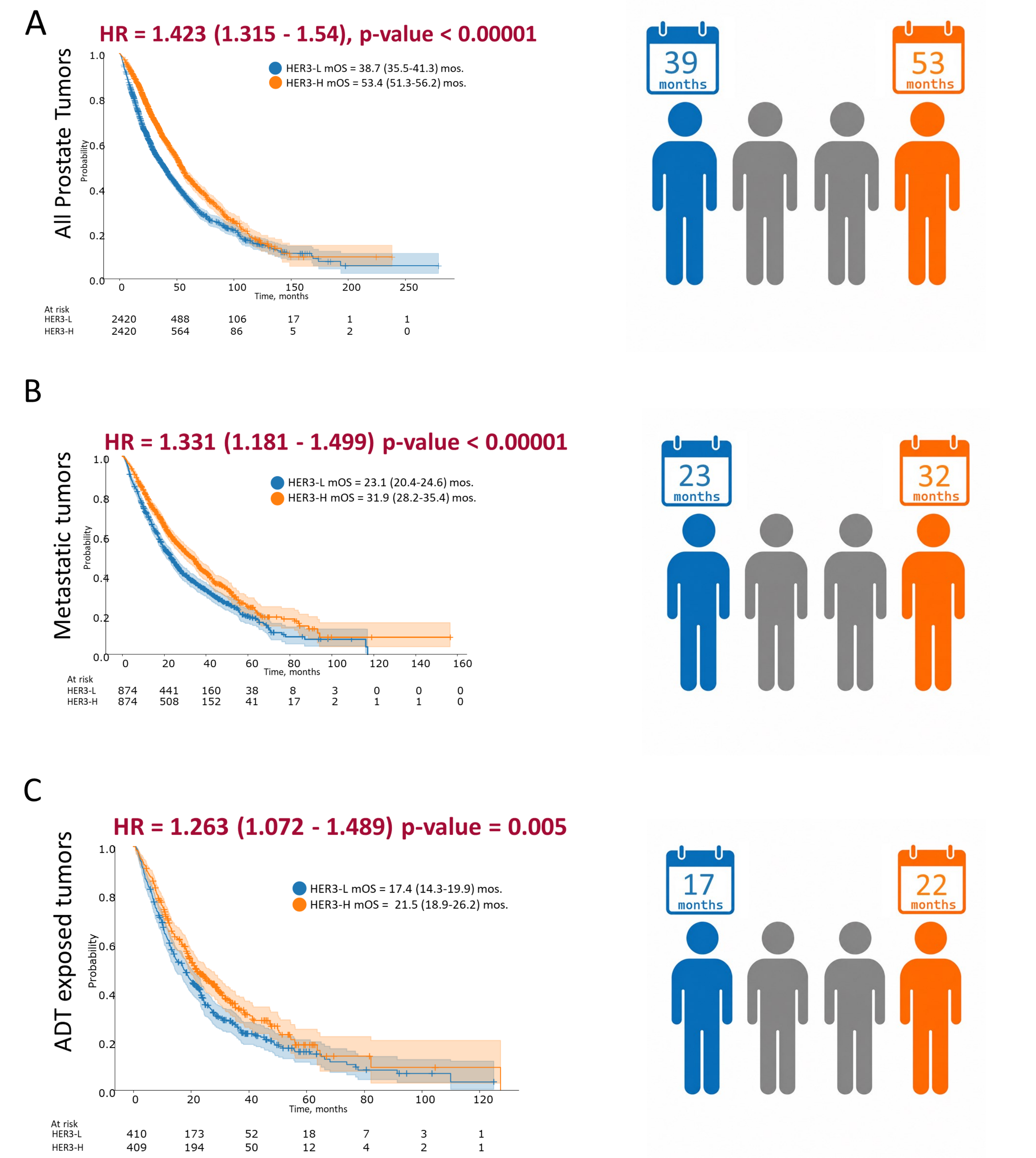
Figure 2. Direct comparison of HER3-L vs. HER3-H tumors in terms of (A) Composition of pathogenic mutations, (B) Volcano plot, and (C) Immune cell fractions in HER3-H vs HER3-L groups. (q-value <0.05)





OUTCOMES

Figure 3. KM analysis of median overall survival in (A) All Prostate Cancer samples, (B) Metastatic samples, and (C) ADT-exposed samples.



CONCLUSION

- HER3 expression identifies biologically distinct prostate cancer subsets.
- HER3-high tumors show primary-disease enrichment, luminal/AR-driven biology, mixed immune features, and better survival.
- HER3-low tumors harbor aggressive genomic alterations linked to lineage plasticity and resistance.
- These findings support further study of HER3-directed therapy.

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