Molecular hallmarks of prostate-specific membrane antigen in treatment-naïve prostate cancer

Running Title: PSMA and prostate cancer

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Background: Prostate cancer (PC) is extremely common and biologically diverse - necessitating avenues to further precision care. The advent of PSMA PET has helped augment staging for PC but not all PC is seen on PSMA PET. We hypothesize heterogeneity in PSMA expression might reflect differential tumor biology for treatment naïve PC and could thus be leveraged to help individualize targeted molecular tumor testing and treatment selection.

Methods: First, we correlated PSMA RNA abundance (*FOLH1*) with SUVmax in a prospective cohort who underwent surgery (NCT03392181; n=55). Using RNA abundance as a proxy for uptake on PET, we then compared differential molecular pathway enrichment using multivariable linear regressions in primary, treatment naïve PC from The Cancer Genome Atlas (TCGA; n=491) with validation in the GRID database (NCT02609269; n=2612). We validated those associations in independent cohorts (18 total; 5684 tumor samples) to characterize pathways and treatment responses associated with PSMA.

Results: PSMA RNA abundance correlates moderately with SUVmax (ρ= 0.41). In independent cohorts, androgen receptor signaling is more active in tumors with high PSMA. Accordingly, patients with high PSMA tumors experienced longer cancer-specific survival when managed with ADT for biochemical recurrence (adjusted hazard ratio [AHR] 0.54 [0.34-0.87]; n=174; **Figure 1**). PSMA low tumors possess molecular markers of stemness and resistance to radiotherapy. Consistent with this, Patients with high PSMA tumors experience longer time to recurrence following primary radiotherapy (AHR 0.50 [0.28-0.90]; n=248; **Figure 2**). In the SAKK09/10 trial (n=224), patients managed with salvage radiotherapy with high PSMA tumors experienced longer time to progression in the 64Gy arm (Restricted mean survival time [RMST] +7.60 [0.05-15.16]) but this effect was mitigated in the 70Gy arm (RMST 3.52 [-3.30-10.33]).

Conclusion: PSMA levels in treatment-naïve prostate cancer differentiate tumor biology and treatment susceptibilities. These results warrant validation using PET metrics to substantiate management decisions based on imaging.

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EMS is a consultant for Pfizer and Lantheus.

PCB sits on the Scientific Advisory Boards of Intersect Diagnostics Inc. and BioSymetrics Inc. and previously sat on the Scientific Advisory Board of Sage Bionetworks.

Figure 1

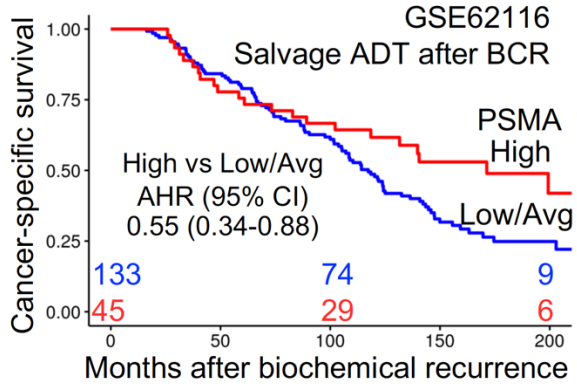

Figure 2