798PD | **In-depth assessment of metastatic prostate cancer with high tumour mutational burden**

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Background: A comprehensive assessment of biopsies from metastatic prostate cancer (mPCa) patients (pts) may identify a molecular subset of pts susceptible for immune checkpoint (IC) blockade (ICB).

Methods: 148 biopsies and germline DNA from 145 mPCa pts were whole genome sequenced (WGS) at an average of 114x and 38x. Tumour mutational (mut) burden (TMB) was defined as number of somatic single nucleotide variants and InDels per Mb of the genome, known mut signatures (Alexandrov, Nature 2013) extracted by non-negative least squares regression as well as recurrent mutations reported in mismatch repair (MMR) pts (Kim, Cell 2013). Selected pts with high TMB were further evaluated for; (a) MMR protein expression; (b) multiplex intratumoural (IT) immune cell phenotyping (VECTRA); (c) multiplex IC expression (VECTRA); (d) 8-color flow cytometry blood immune cell phenotyping, with high TMB pts compared with low TMB pts. Pts receiving anti-PD-1 ICB had additional immune phenotyping at C2, C3, C4 and at progression; 3 pts had post-progression biopsies analyzed.

Results: The median TMB was 2.9 (IQR 2.2 - 3.9); 12 pts (8.3%) had high TMB (>10 mut/Mb). In 11/12 pts with high TMB, corresponding MMR deficiency (MMRd) signatures (6, 15, 20 and 21) were identified. Recurrent mut in MMR genes were detected MSH2/MSH6, MSH3, MLH1; other recurrent mut were in POLE, and frameshift mut enriched (p < 0.001) in genes including TGFBR2, CLOCK, RPL22 and JAK1. Immunohistochemistry confirmed MMRd in 6/6 biopsies and in matched primary tissue in 5/5 evaluable pts. Five pts were referred for germline testing without MMR mut. A trend for increased IT CD3+ cells were seen in MMRd (p = 0.06); no relation was found between TMB and tumour PD-L1 expression. Pts were treated with anti-PD-1 ICB, with PSA>50% decline of 57% of hTMB pts (n = 7), and a significant decline in circulating T-cell populations during ICB, including CD4+PD-1 + (p = 0.02) and CD8+PD-1 + (p = 0.007). Response rate, duration of response, genomic and immune correlates will be presented for pts with low and high TMB.

Conclusions: 8% of mPCa pts display a high TMB with recurrent somatic mut in MMR genes and POLE. MMRd appears early in PCa evolution. High TMB pts witness a high response rate to monotherapy anti-PD-1 ICB.