Compound genomic alterations of *TP53*, *PTEN* and *RB1* tumor suppressors in localized and metastatic prostate cancer

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Background:
Alterations (alt) in *TP53*, *PTEN* and *RB1* TSGs have been identified in some prostate cancers. Preclinical data suggest that cooperative loss of 2 or more TSGs drives development of more aggressive disease.

Methods:
Patients who underwent targeted exome sequencing (Oncopanel) of CSPC (localized [L] and M1 presentation) and CRPC tissue samples were identified. Biomarker(BM)-positive(+) was defined as hemizygous or homozygous deletion and/or deleterious mutation of ≥1 TSG (*TP53*, *PTEN* or *RB1*). For pts presenting with L-CSPC, Kaplan-Meier method estimated time from biopsy to PSA relapse/metastasis/death (EFS), CRPC, and death (OS). Cox model assessed association of BM status and outcomes, adjusted for age, stage, Gleason score, tumor mutational burden and copy number (CN) burden in multivariable analyses (MVA). Time from ADT start for M1-CSPC to death was estimated. For M1-CRPC, duration on 1st line CRPC therapy and time from CRPC to death was estimated. Association of cumulative BM+ gene hits (0 vs 1 vs 2 vs 3) and outcomes was assessed.

Results:
TSG alt (including compound loss) and mutational/CN burden increased with metastatic and castration resistant disease (Table). In L-CSPC (n=205), *PTEN* (HR 1.76, p=0.04) and *TP53* (HR 1.92, p=0.01) alt were significantly associated with relapse and any BM+ had a shorter EFS (median 2.6 years, HR 1.95, p=0.005) and time to CRPC (HR 3.36, p=0.048). Mutational burden (HR 1.08, p=0.017) and CN burden (HR 1.18, p <0.001) were significantly associated with relapse. Increasing TSG hits (0 vs 1 vs 2-3) was associated with worse EFS (p=0.004) and TTCRPC (p=0.08) on UVA, but was not significant after adjusting for genomic instability in MVA (EFS: 1 hit vs 0 hits, HR 1.27, p=0.49; 2+ hits vs 0 hits, HR 1.90, p=0.175). None of the 43 M1-CSPC pts who were BM-neg had died with median follow-up of 3.3 yrs; BM+ 4-year OS was 64%. Only 4 (8%) of the CRPC cohort (n=48) were BM-neg and with a median follow-up 4.1 years, only 1 had died (5.2 yrs). A trend to poorer OS with increasing hits was observed (1 hit vs 0 hits, HR 5.89; 2+ hits vs 0 hits, HR 2.71; log-rank p=0.13).

Cohort	N	Median follow-up (yrs)	1 or more TSG-alt	2 or more TSG-alt	Mean mutation burden (mt/Mb)	Mean CN burden (est % genome)
L-CSPC	205	3.1	39%	8%	4.83	2.7
M1-CSPC	43	3.3	63%	18%	5.67	8.7
M1-CRPC	48	4.1	92%	63%	6.51	26.6

Conclusions:
Deleterious TSG variants are associated with poorer outcomes in CSPC and CRPC. Accounting for genomic instability, compound TSG loss shows a weaker trend to independent prognostic significance. Elucidating the mechanisms underlying TSG alt and genomic instability, and therapeutic implications, is an active area of investigation.

Conflict of Interest:
Nil

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