Genomic predictors of benefit of docetaxel (D) and next-generation hormonal therapy (NHT) in metastatic castration resistant prostate cancer (mCRPC)

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Background:
Predictive genomic biomarkers in mCRPC remain elusive. Prior studies suggest that tumor suppressor (TS) loss is prognostic, and may result in less benefit from NHT, but no impact on D efficacy. We assessed genomic predictors of differential benefit of androgen receptor-targeted therapy and chemotherapy for mCRPC.

Methods:
Retrospective cohort of men diagnosed with mCRPC (pooled, N=157) who underwent multigene sequencing (Dana-Farber Cancer Institute, Boston; n=102) and whole exome sequencing (Weill-Cornell Medicine, New York; n=55) of prostate adenocarcinoma biopsies obtained after metastatic disease. Patients with pure small cell histology were excluded. Time from NHT or D start to clinical/radiographic progression (time to treatment failure, TTTF) was estimated by Kaplan-Meier method, with censoring at next therapy or last follow-up for non-progressors.

Results:
75.8% of patients had bone and/or lymph node-only metastases at mCRPC diagnosis. In total, 135/157 (86%) and 100/157 (63.7%) received NHT and D for mCRPC, respectively. Median overall survival was 3.4 years from first mCRPC. Biallelic *RB1* loss was strongly predictive, conferring significantly shorter TTTF on both NHT (HR 1.76, p=0.06) and D (HR 2.3, p=0.02), and was also associated with poorer overall survival. *PTEN* alterations (alts) trended to association with worse TTTF on NHT (p=0.099), but not D. A dose effect with combined *PTEN* plus *RB1* or *TP53* plus *RB1* loss conferred significantly poorer outcomes on NHT and D, compared to single gene loss or no loss.

Conclusions:
This study confirms poor prognosis associated with biallelic *RB1* loss in mCRPC. We demonstrate that *RB1* loss with or without the compounding effect of *PTEN* or *TP53* alterations, leads to more rapid treatment failure on both NHT and D.

Conflicts of interest: None

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Table 1.

		Abiraterone/Enzalutamide N=86 Median TTTF=12.2 mo		Docetaxel N=61 Median TTTF=5.1 mo	
Gene	N=103	HR	p-val	HR	p-val
PTEN mo/bi	59.2%	1.68	0.029	0.83	0.52
PTEN bi	32%	1.25	0.39	0.96	0.89
TP53 mo/bi	65%	1.17	0.52	0.84	0.55
TP53 bi	47.6%	1.1	0.67	0.96	0.87
RB1 mo/bi	65%	1.29	0.28	1.04	0.88
RB1 bi	12.6%	2.86	0.003	3.17	0.007
BRCA2	11.7%	1.83	0.088	0.31	0.091
ATM	5.8%	0.84	0.7	0.52	0.37
AR amplification	30.1%	1.02	0.92	0.81	0.46
AR mutation	10.7%	0.36	0.017	1	0.99

Key: mo/bi, monoallelic or biallelic loss; bi, biallelic loss only

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