Prognostic and predictive utility of DNA damage response aberrations detected in cfDNA in metastatic castration-resistant prostate cancer (mCRPC)

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Background

The prognostic significance of DDR alterations in mCRPC remains unclear, with conflicting data from prior reports. Whether DDR alterations are predictive of outcomes with therapeutic agents other than PARP inhibitors in mCRPC is also poorly understood. With increasing use of molecular profiling in mCRPC, understanding the full prognostic and predictive utility of plasma DDR alterations is paramount.

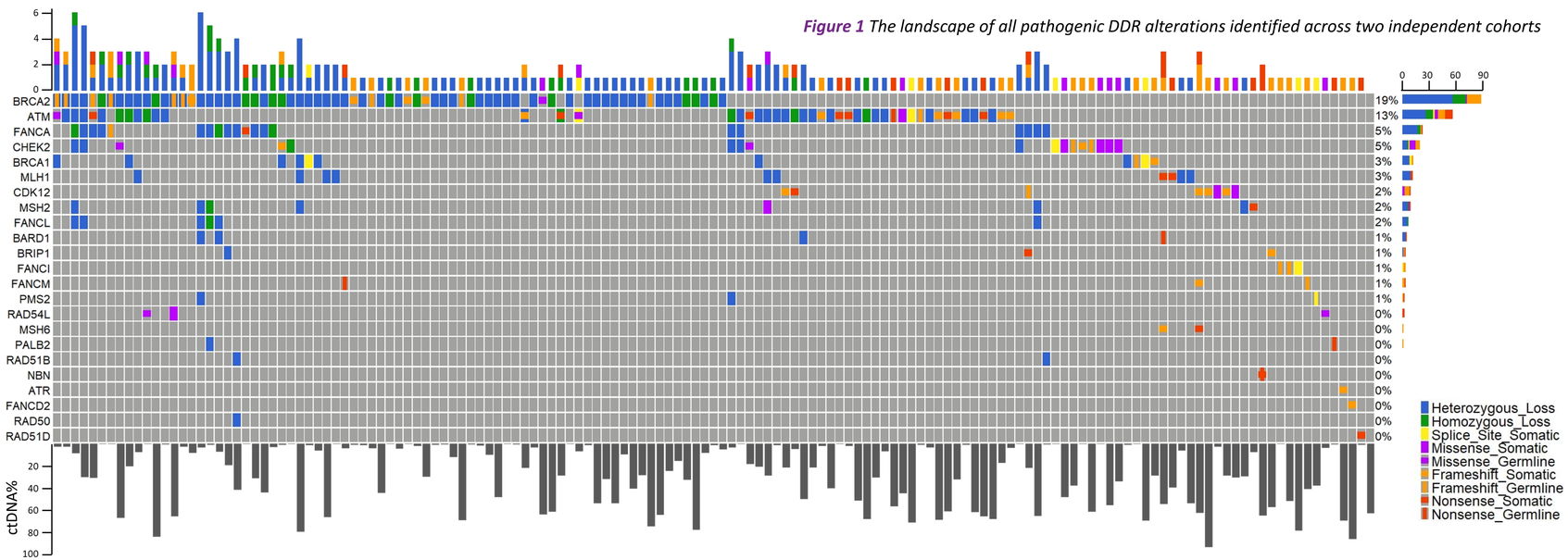
Methods

A next-generation sequencing Predicine liquid biopsy assay was used to profile pre-treatment cfDNA and germline DNA in 407 mCRPC patients (pts) from two independent international cohorts (n=162 Australia, n=245 US). DDR genes profiled are listen in Fig. 1. Kaplan-Meier survival estimates and multivariable Cox regression analyses were used to assess associations between DDR alterations and clinical outcomes including PSA response rate (PSA RR), progression-free survival and overall survival (OS).

Results

Median follow-up time and OS were 74 months and 23 months, respectively. Of the 38% of patients with a pathogenic DDR alteration (Fig. 1), the most commonly aberrant gene was *BRCA2*. Monoallelic loss of *BRCA2* was more common than biallelic loss/loss of heterozygosity (15% vs 6%). Unexpectedly, OS was similar for both types of *BRCA2* zygosity (12.5 vs 14.9 vs *wt* 31.4 months, Fig. 2). The presence of any pathogenic DDR alteration, any *BRCA2* alteration, and circulating tumour DNA (ctDNA) fraction were all independently associated with poor OS (Table 1). Patients with homozygous *BRCA2* deletion and detectable plasma ctDNA (>2%) were significantly less likely to experience a sustained PSA response (60 vs 0%, p=0.02; 83 vs 39%, p<0.001 respectively) on androgen receptor pathway inhibitors (ARPIs). This was not observed in the taxane chemotherapy-treated cohort 67 vs 29%, p=0.09; 64 vs 57%, p=0.7, respectively).

Figure 1 *The landscape of all pathogenic DDR alterations identified across two independent cohorts*



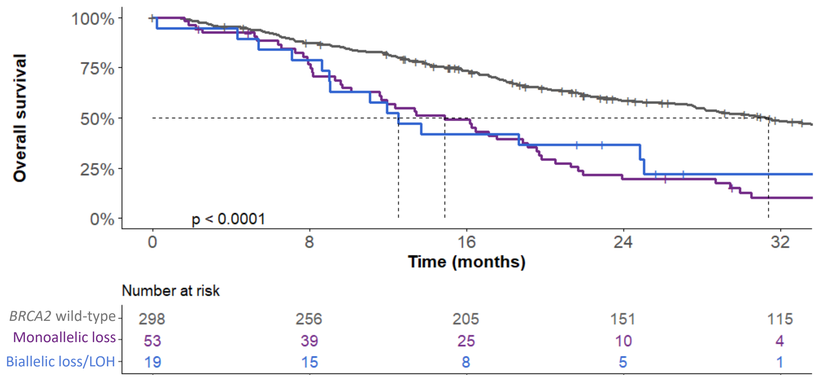


Figure 2 *Kaplan-Meier analysis of overall survival according to the number of BRCA2 alleles detected in the plasma of mCRPC patients*

Table 1 *Multivariable Cox analysis of OS based on plasma DDR aberrations. Clinical covariates: ctDNA fraction, prior chemotherapy, prior ARPI therapy, ECOG performance, visceral metastasis*

Variable	n	HR	95% CI	*p*
Any pathogenic DDR	146	3.6	2.2-6.0	**<0.001**
Any *BRCA2* alteration	72	2.4	1.5-4.1	**<0.001**
BRCA2 Heterozygous deletion	50	2.8	1.6-5.1	**<0.001**
BRCA2 Homozygous deletion	13	2.0	0.70-5.5	0.2
BRCA2 monoallelic loss	53	1.5	0.67-3.6	0.3
BRCA2 biallelic loss	19	3.1	1.8-5.6	**<0.001**

Conclusions and future directions

- A large array of pathogenic DDR alterations can be identified from patient plasma in mCRPC.
- Detection of any pathogenic DDR or *BRCA2* alteration in patient plasma was an independent poor prognostic factor across two large independent cohorts of mCRPC patients.
- Similar outcomes for mono- and biallelic *BRCA2* altered patients suggest that exonic DNA alterations may not identify all deleterious *BRCA2* defects. Future focus should be on concurrent identification and analysis of intronic regions, large structural variants and methylation patterns

Fully-funded PhD position available:

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