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Distinguishing clonal hematopoiesis (CH) from tumor homologous recombination repair (HRR) alterations in liquid biopsy: Implications for PARP inhibitor (PARPi) use in metastatic castration-resistant prostate cancer (mCRPC)

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Background

CH arises from fitness-enhancing hematopoietic mutations, occasionally involving HRR genes, which may confound liquid biopsy results. We evaluated the prevalence of CH HRR alterations and clinical outcomes on PARPi of patients (pts) with mCRPC, and assessed changes in CH prevalence following PARPi exposure.

Methods

This study included patients pts with prostate cancer who underwent FoundationOne®Liquid CDx comprehensive genomic profiling. Clinical data was obtained from the US-wide deidentified Flatiron Health-Foundation Medicine clinicogenomic database, from 280 cancer clinics (800 sites of care) between 01/2014-09/2025. A machine-learning variant origin prediction model classified mutations as predicted CH, germline, or tumor somatic. Time to next treatment (TTNT) and real-world overall survival (rwOS) were compared by Cox models between mCRPC pts receiving PARPi monotherapy with pre-therapy CH-only HRR mutations vs tumor HRR alterations in *BRCA1/2*, *PALB2*, *RAD51C/D*, or *BARD1*, adjusting for clinical covariates. CH mutation prevalence in common CH genes was compared pre vs post-PARPi exposure.

Results

Overall, 13% of HRR mutations (n=1368) were predicted to be CH-only, most commonly in *BRCA1* (30%) and *PALB2* (21%). Sixty-one mCRPC pts received PARPi monotherapy. Pts with predicted CH-only HRR mutations (n=8) had less favorable TTNT (median 5.8 vs 6.7 months (m); adjusted (a)HR 3.24, 95% CI 1.2–5.8, p 0.022) and rwOS (median 8.3 vs 15.3 m; aHR 3.52, 95% CI 1.1–11.4, p 0.036) vs those with tumor HRR alterations (n=53). Compared with pre-PARPi samples (n=366), post-PARPi samples (n=57) were nominally enriched for CH mutations in *TP53* (25.7% vs 33.3%; OR 1.45), *PTPN11* (4.1% vs 7.0%; OR 1.76), and *ASXL1* (3.6% vs 5.3%; OR 1.51).

Conclusions

CH alterations in HRR genes are detected in liquid biopsy and predicted CH-only mutations were associated with poorer PARPi outcomes, highlighting the importance of accounting for CH in therapy selection. Post-PARPi samples were enriched for CH mutations in genes previously linked to hematologic toxicities, supporting the value of CH monitoring after PARPi exposure.

Legal entity responsible for the study

Foundation Medicine, Inc.

Funding

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Disclosure

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