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Plasma ctDNA as standalone or adjunct to tumour tissue for HRR and PI3K/AKT genotyping in mCRPC: PROMPT (NCT04746300)

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Background

Liquid biopsy is reshaping genotyping in mCRPC, but its role as a replacement for, rather than a complement to, tumour tissue (TT) sequencing remains undefined. PROMPT (NCT04746300), is a prospective matched-pair concordance series in mCRPC, enrolled patients at the clinical decision point of progression on/before 1L or 2L therapy with pre-planned matched TT and plasma sampling.

Methods

301 mCRPC patients underwent matched TT (archival / fresh; TSO500) and plasma ctDNA plus matched PBMC sequencing for germline and clonal hematopoiesis control on a 57-gene custom targeted panel. Pathogenic SNVs/indels and biallelic copy losses in *BRCA1/2*, HRRm (*ATM*, *CDK12*, *CHEK2*, *PALB2*, *RAD51B/C/D*, *RAD54L*, *MRE11*, *NBN*) and PI3K/AKT (*PTEN*, *PIK3R1*, *PIK3CA*, *PIK3CB*, *AKT1*, *AKT2*) were assessed. Concordance was assessed by OPA, PPV and NPV using TT as the reference.

Results

Combined *BRCA1/2* or HRRm alterations occurred in 21% (62/301) and were SNV/indel-dominated (51 vs 8 biallelic). ctDNA captured 50/58 TT cases and identified 4 not seen in TT: OPA 95%, PPV 92%, NPV 95%; *BRCA1/2* alone 98%/85%/99%. As standalone, ctDNA detected 81% (50/62) of all *BRCA1/2*+HRRm-positive patients; as adjunct to TT, ctDNA added +7% incremental yield (all SNV/indel). PI3K/AKT alterations occurred in 27% (81/301), dominated by biallelic losses (n=50, mostly *PTEN*) over SNV/indel (n=23). CtDNA captured 32/81 (OPA 80%, PPV 63%, NPV 82%), only detecting 8 of 50 TT biallelic losses. Tumour fractions 1–68%; missed alterations clustered at TF <5%.Table: 2220R0

Pathway-specific concordance and bidirectional discordance by alteration class (TT as reference; n=301)

Pathway	Class	TT+ C+	Concordant	ctDNA-unique	OPA/PPV/NPV
<i>BRCA1/2</i> + HRRm	SNV/indel	51 46 42	4		96 / 91 / 96%
<i>BRCA1/2</i> + HRRm	Biallelic loss	8 4 4	0		99 / 100 / 99%
PI3K / AKT	SNV/indel	23 20 13	7		94 / 65 / 96%
PI3K / AKT	Biallelic loss	50 16 8	8		83 / 50 / 85%

C+ = ctDNA-positive; ctDNA-unique = ctDNA-positive / TT-negative. OPA = overall percent agreement; PPV = positive predictive value; NPV = negative predictive value

Conclusions

In this prospective, CHIP-controlled mCRPC cohort, plasma ctDNA achieves high concordance with TT for *BRCA1/2* and HRRm and is a credible standalone biomarker for PARPi eligibility (81% sensitivity) when TF is adequate, or an adjunct delivering +7% yield over TT alone. PI3K/AKT alterations are dominated by biallelic copy losses which are under-detected in plasma; PI3K/AKT genotyping should remain tissue-anchored, with ctDNA used cautiously as adjunct only.

Clinical trial identification

NCT04746300.

Legal entity responsible for the study

Radboud University Medical Center.

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Disclosure

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