

ORIGINAL RESEARCH

Durable benefit from poly(ADP-ribose) polymerase inhibitors in metastatic prostate cancer in routine practice: biomarker associations and implications for optimal clinical next-generation sequencing testing[☆]

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Background: Controlled trials have consistently demonstrated the efficacy of poly(ADP-ribose) polymerase inhibitors (PARPi) in patients with metastatic castration-resistant prostate cancer (mCRPC) and *BRCA1* or *BRCA2* alterations (*BRCAalt*). However, the reported efficacy of PARPi for alterations in other homologous recombination repair (HRR) genes is less consistent. We sought to evaluate the routine practice effectiveness of PARPi between and within these groups.

Design: Patient-level data from a deidentified nationwide (USA-based) cancer clinico-genomic database between January 2011 and September 2023 were extracted. Patients with mCRPC and comprehensive genomic profiling by liquid biopsy [circulating tumor DNA (ctDNA)] or tissue (tumor) biopsy and who received single-agent PARPi were included and grouped by *BRCAalt*, *ATMalt*, other HRR, or no HRR. We further subcategorized *BRCAalt* into homozygous loss (*BRCALoss*) and all other deleterious *BRCAalt* (other*BRCAalt*).

Results: A total of 445 patients met inclusion criteria: 214 with tumor and 231 with ctDNA. *BRCAalt* had more favorable outcomes to PARPi compared with *ATM*, other HRR, and no HRR groups. Within the *BRCAalt* subgroup, compared with other *BRCAalt*, *BRCALoss* had a more favorable time to next treatment (median 9 versus 19.4 months, $P = 0.005$), time to treatment discontinuation (median 8 versus 14 months, $P = 0.006$), and routine practice overall survival (median 14.7 versus 19.4 months, $P = 0.016$). Tumor *BRCALoss* prevalence (3.1%) was similar to ctDNA prevalence in liquid biopsy specimens with high tumor fraction (>20%). *BRCALoss* was not detected in orthogonal germline testing.

Conclusions: PARPi routine practice effectiveness between groups mirrors prospective trials. Within the *BRCAalt* group, *BRCALoss* had the best outcomes. Unless the ctDNA tumor fraction is very high, somatic tissue testing (archival or metastatic) should be prioritized to identify patients who may benefit most from PARPi. When tissue testing is not clinically feasible, sufficient ctDNA tumor fraction levels for detection are enriched at clinical timepoints associated with tumor progression.

Key words: mCRPC, PARPi, BRCA, homozygous loss

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) is a genetically heterogeneous disease and 20%-30% of men with mCRPC harbor somatic or germline loss-of-function mutations in genes involved in DNA damage repair.^{1,2} Deleterious mutations in homologous recombination repair (HRR) genes are often associated with distant metastases and worse overall survival (OS).³ HRR-deficient prostate cancers are dependent on alternative

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mechanisms to prevent deleterious accumulation of DNA damage. One such mechanism for maintaining genomic stability is mediated via poly(ADP-ribose) polymerases (PARPs), which are enzymes involved in the repair of single-strand DNA breaks. Inhibition of PARP in HRR-deficient cancer cells leads to the creation of DNA double-strand breaks and resultant synthetic lethality in prostate tumor cells with HRR deficiency.⁴ Randomized clinical trials have shown efficacy for the inhibition of PARP in men with HRR-deficient mCRPC.^{5,6} On the basis of these trials, rucaparib was approved by the United States Food and Drug Administration (FDA) as a single agent for men with mCRPC and *BRCA1/2* mutations (*BRCAalt*) previously treated with next-generation androgen receptor directed therapy and prior taxane therapy.⁷ Olaparib was approved for men with mCRPC and any germline or somatic HRR mutations previously treated with next-generation androgen receptor directed therapy.⁸ More recently, talazoparib plus enzalutamide and niraparib or olaparib plus abiraterone have been approved by the FDA for patients with mCRPC with any HRR mutation (talazoparib) or *BRCA1/2* mutations only (niraparib and olaparib) based on phase III data from TALAPRO-2, MAGNITUDE, and PROPEL, respectively.⁹⁻¹¹

The varying results surrounding the importance of different HRR alterations in driving sensitivity to PARP inhibitor (PARPi) therapy¹² leave open key questions surrounding the role of these treatments beyond the *BRCAalt* setting. This is reflected in the different criteria for olaparib and talazoparib use (any HRR mutation) compared with the criteria for rucaparib and niraparib (only *BRCAalt*). Although this may reflect differences in the drugs themselves, it also may be related to the study design in each of the pivotal trials.^{9,11,13} In addition, there is an emerging hypothesis that homozygous *BRCA1* or *BRCA2* loss may be associated with more favorable responses to PARPi compared with other types of *BRCA* alterations^{14,15} because deletions are irreversible^{16,17} which may result in prolonged patient benefit.¹⁸ Scar-based homologous recombination deficiency (HRD) biomarkers based on patterns of chromosomal instability, such as those approved in ovarian cancer, are hypothesized to have utility in identifying genomic subsets of prostate cancer most likely to respond to PARPi.^{4,19}

The routine clinical use patterns of PARPi are not well described, nor is the routine practice effectiveness of PARPi across HRR subsets and *BRCA* alteration types. There is a need to more precisely define the molecular determinants that confer durable PARPi benefit to ensure appropriate patient selection for targeted PARPi therapy, as well as the mode of assessment: tissue biopsy or liquid biopsy. Certain types of alterations, such as copy number losses, are more challenging to reliably detect than mutations, not universally validated or reported by next-generation sequencing (NGS) assays,²⁰ and when assessed with liquid biopsy, additionally require a higher level of circulating tumor DNA (ctDNA) tumor fraction to detect.²¹⁻²³ Here we describe routine practice outcomes of patients with mCRPC undergoing PARPi therapy according to molecular subgroups stratified by specific HRR mutation status or a scar-based

HRD signature (HRDsig). In addition, we sought to assess the association of specific *BRCA* alterations with PARPi effectiveness.

METHODS

Study design and patient selection

The cohort consisted of patients with a confirmed diagnosis of mCRPC included in the USA-wide Flatiron Health—Foundation Medicine Inc. (FMI) deidentified clinico-genomic database between January 2011 and September 2023. All patients underwent genomic testing using Foundation Medicine comprehensive genomic profiling (CGP) assays (described later) with molecular data linked directly.

Deidentified clinical data originated from ~280 United States cancer clinics (~800 sites of care). Retrospective longitudinal clinical data were derived from electronic health records, comprising patient-level structured and unstructured data, curated via technology-enabled human abstraction of clinical notes and radiology/pathology reports, which were linked to genomic data derived from FMI testing by deidentified, deterministic matching.^{24,25}

Clinical data included demographics, clinical and laboratory features, timing of treatment exposure, treatment progression, survival, and orthogonal unstructured somatic and germline molecular testing abstracted from PDF reports of non-Foundation Medicine testing.²⁶ Lines of therapy in the database were oncology clinician-defined and rule-based. Patients with a birthyear of 1938 or earlier may have an adjusted birthyear in Flatiron datasets due to patient deidentification requirements. All data elements used in this study have undergone a rigorous quality assessment against published frameworks.²⁷

Patients were included in this study if they received a first-line single-agent PARPi (olaparib, rucaparib, or niraparib) in the mCRPC setting and genomic profiling by tissue or liquid biopsy. Patients were grouped by genes with deleterious alterations detected: *BRCA1/2* (*BRCAalt*), *ATM*, other HRR (*ATR*, *ATRX*, *BAP1*, *BARD1*, *BRIP1*, *CHEK1*, *CHEK2*, *CDK12*, *FANCA*, *FANCL*, *MRE11*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*, *PALB2*), or no HRR (if negative by tissue or liquid profiling). We further subclassified *BRCAalt* into *BRCA* homozygous loss (*BRCAloss*) and all other *BRCA* alterations (other*BRCA*), including point mutations, small sequence deletions, and rearrangements. While homozygous loss is always biallelic, other *BRCA* alterations may be mono-allelic. Institutional Review Board approval of the study protocol was obtained before conducting the study and included a waiver of informed consent based on the observational, noninterventive nature of the study (WCG IRB, Protocol No. 20225562).

Comprehensive genomic profiling

Hybrid capture-based NGS assays were carried out on patient tumor or blood specimens in a Clinical Laboratory Improvement Amendments (CLIA)-certified, College of American Pathologists-accredited laboratory (FMI, Cambridge, MA). FoundationOne and FoundationOne CDx assays

report single-nucleotide variants, insertions/deletions, genomic rearrangements, copy number amplifications, and homozygous losses.²⁸ FoundationOne Liquid CDx is an NGS panel assay interrogating 324 cancer-related genes, and reporting single-nucleotide variants, insertions/deletions, genomic rearrangements, copy number amplifications, and homozygous losses. Cell-free DNA was extracted from whole blood and CGP was carried out using hybridization-captured, adaptor ligation-based libraries.²²

HRDsig is a machine learning algorithm developed to predict genomic scarring consistent with homologous repair deficiency.²⁹ HRDsig utilizes a broad set of copy number features, including absolute modeled copy number, segment size, oscillation patterns, and breakpoints per chromosome arm with features examined genomewide and specifically within the telomeric and centromeric portions of chromosome arms.³⁰ The broad set of copy number features was used as inputs into an extreme gradient boosting machine learning model. HRDsig is a continuous factor from 0 to 1 and a cut-off of 0.7 was prespecified for calling a sample HRDsig(+) based on 90% sensitivity to detect biallelic *BRCA1/2* alterations in canonically *BRCA*-driven diseases (ovary, prostate, pancreas, and breast cancers).

Predominant genetic ancestry was assigned by training a random forest classifier to distinguish the five ancestral superpopulations of the 1000 Genomes Project,³¹ as previously described,³² and then determining the closest match for each specimen.

Time-to-event outcomes

Time to next treatment (TTNT) was calculated from the treatment start date to the start of the next treatment line (due to any cause) or death. Patients not yet reaching the next treatment line or death were censored at the date of the last clinical visit. Time to PARPi discontinuation (TTD) was calculated from the treatment start date to the cessation of PARPi use (due to any cause), or death. Patients still on PARPi were censored at the date of the last clinical visit or structured activity. OS was calculated from the start of PARPi to death from any cause, and patients with no record of mortality were right censored at the date of the last clinic visit. As patients cannot enter the database until a CGP report is delivered, OS risk intervals were left truncated to the date of the CGP report to account for immortal time. Truncation independence with censoring was evaluated with Kendall's tau, with $P < 0.05$ considered acceptable. Flatiron Health database mortality information is a composite derived from three sources: documents within the electronic health records, the Social Security Death Index, and a commercial death dataset mining data from obituaries and funeral homes, with validations reported in comparison to the National Death Index.³³

Prostate-specific antigen response

A line of PARPi therapy was eligible for prostate-specific antigen (PSA) response assessment if a PSA result was available within 60 days before PARPi initiation and a

separate PSA result was available 1-180 days after. If multiple results were available, respective values most proximal to treatment initiation and 12 weeks of treatment were used. PSA response calculated as previously described³⁴: $(\text{on treatment PSA} - \text{baseline PSA}) / (\text{baseline PSA} + 0.01)$.

Statistical analysis

Differences in time-to-event outcomes were assessed using the log-rank test and Cox proportional hazard models. Chi-square tests and Wilcoxon rank-sum tests were used to assess differences between groups of categorical and continuous variables, respectively. Multiple comparison adjustments were not carried out; P values were reported to quantify the strength of association for biomarker and each outcome, not for null hypothesis significance testing, and interpretations adopted broadly considering the consistency of multiple outcome measures in concert (TTNT, TTD, PSA response, and OS), with no outcome measure standing on its own.

Missing values were handled by simple imputation with expected values determined using random forests with the R package 'missForest.' In subsequent analyses, imputed values were treated identically to measured values. R software (R Foundation, Vienna, Austria) was used for all statistical analyses.

RESULTS

Characteristics of the analysis cohort

We included 4559 patients with mCRPC and CGP data, of whom 445 unique patients were treated with single-agent PARPi and met inclusion criteria (Figure 1). There were 214 patients who had tumor tissue CGP and 231 who had liquid biopsy CGP; 68 (15%) patients were predicted of majorly African ancestry, 337 (76%) of majorly European ancestry, and 40 (9%) other. Of these patients, 170 (38.2%) had *BRCA*alt, 110 (24.7%) had *ATM* mutations, 109 (24.5%) had other HRR mutations, and 56 (12.6%) had no known HRR alteration (Table 1). *BRCA*alt was more highly represented in the tissue CGP cohorts compared with liquid CGP (46.7% versus 30.3% respectively, $P < 0.001$). Timing of PARPi therapy was variable: it was administered as a first-line mCRPC treatment in 10.1% (45 patients), second-line in 28.3% (126 patients), third-line in 23.1% (103 patients), and fourth-line in 38.4% (171 patients). This was similar between men with tissue or liquid biopsy genomic profiling. The vast majority of patients ($n = 390$, 87.6%) had records of prior novel hormonal therapy, 225 (50.6%) had records of prior taxane therapy, and 29 (6.5%) had records of prior platinum therapy. Most patients were treated with olaparib (95.5%) and the remainder received rucaparib (4.0%) and niraparib (0.5%). Differences between molecular subgroups are listed in Supplementary Table S1, available at <https://doi.org/10.1016/j.esmoop.2024.103684>.

Outcomes of PARPi stratified by molecular subgroup

We next assessed TTNT, TTD, and OS stratified by molecular subgrouping. A granular analysis of gene alterations associated with outcomes of individual patients is shown with

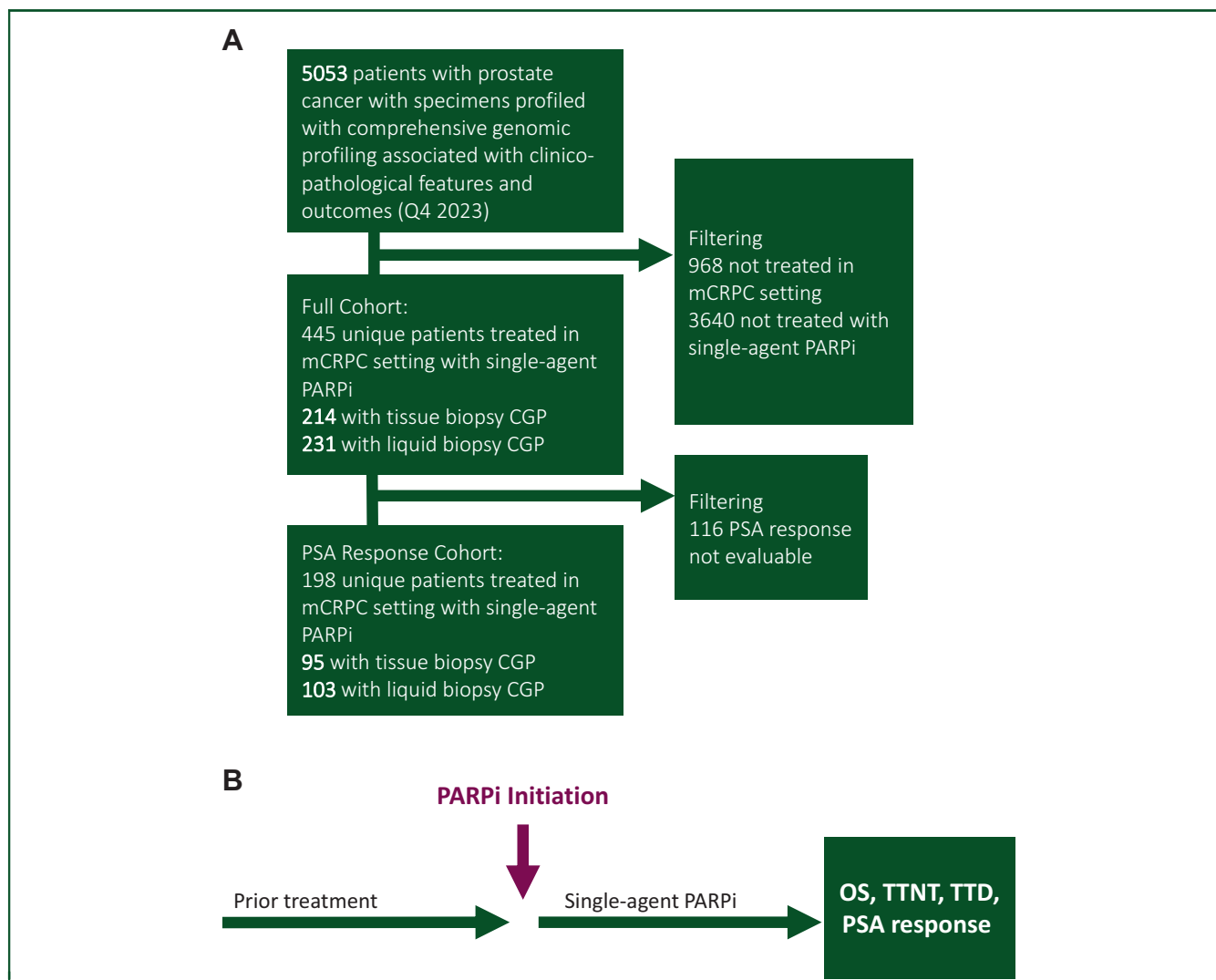


Figure 1. Cohort overview. (A) Cohort selection diagram and (B) overview diagram of outcome associations assessed from (A).

CGP, comprehensive genomic profiling; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor; PSA, prostate-specific antigen (pre-PARPi PSA level); TTD, time to PARPi discontinuation; TTNT, time to next treatment.

swimmer plots for TTNT for patients with tissue biopsy CGP (Figure 2A) and liquid biopsy CGP (Figure 2B). In the tissue cohort, several patients with the longest TTNT (>12 months) were patients with *BRCA1* or *BRCA2* homozygous loss, which were less commonly detected in the liquid cohort. Several patients with non-*BRCA* alterations (*FANCA*, *RAD51C*, *PALB2*, *CHEK2*, *CDK12*, and *BRIP1*) had >12 months' TTNT. A small group of patients were administered PARPi without the detection of any HRR subgroup. No significant differences in PARPi outcomes were found between genetic ancestry groups.

A population ($n = 56$) of patients received PARPi without a positive HRR alteration from Foundation Medicine (somatic) testing. Of these, half ($n = 28$) were assessed with tissue testing and half ($n = 28$) with liquid testing (Supplementary Figure S1A, available at <https://doi.org/10.1016/j.esmooop.2024.103684>). The group baseline PSA levels (median 155.5, interquartile range 22.2-242.2) were qualitatively higher than other groups, without other substantive differences in other baseline clinical features

(Supplementary Table S1, available at <https://doi.org/10.1016/j.esmooop.2024.103684>). As many as 37 patients in this group had orthogonal (germline or somatic) *BRCA* testing from laboratories other than Foundation Medicine. Of these, 12 had a *BRCA* mutation detected. The median TTNT of these three groups (*BRCA* mutation detected, no *BRCA* mutation detected, and no record of orthogonal testing) were 4.3, 4.4, and 4.4 months, respectively (log-rank $P = 0.80$; Supplementary Figure S1B, available at <https://doi.org/10.1016/j.esmooop.2024.103684>).

Using the no HRR group as a reference, we next carried out multivariable analyses for TTNT, TTD, and OS in the tissue and liquid CGP cohorts, adjusting for clinical factors that might confound time-to-event analyses [e.g. pre-tx PSA, Eastern Cooperative Oncology Group (ECOG) performance status]. In the tissue CGP cohort, *BRCA*alt was associated with more favorable TTNT compared with men with no HRR alterations [$n = 100$, hazard ratio (HR) 0.30, 95% confidence interval (CI) 0.18-0.51, $P < 0.001$]. *ATM*alt was not associated with more favorable TTNT ($n = 35$, HR

Table 1. Characteristics of patients included in the study, by method of genomic profiling				
Characteristics	LBx (n = 231)	TBx (n = 214)	Total (n = 445)	P value
Age, years				<0.001
Median (Q1-Q3)	75.0 (69.0-80.0)	71.0 (65.0-77.0)	73.0 (67.0-79.0)	
ECOG, n (%)				0.14
1	73 (31.6)	83 (38.8)	156 (35.1)	
2	44 (19.0)	26 (12.1)	70 (15.7)	
3+	66 (28.6)	66 (30.8)	132 (29.7)	
Unknown	48 (20.8)	39 (18.2)	87 (19.6)	
Treatment setting, n (%)				0.51
1st line mCRPC	21 (9.1)	24 (11.2)	45 (10.1)	
2nd line mCRPC	61 (26.4)	65 (30.4)	126 (28.3)	
3rd line mCRPC	59 (25.5)	44 (20.6)	103 (23.1)	
4th+ line mCRPC	90 (39.0)	81 (37.9)	171 (38.4)	
Biopsy site, n (%)				<0.001
Blood	231 (100.0)	0 (0.0)	231 (51.9)	
Metastatic	0 (0.0)	107 (50.0)	107 (24.0)	
Prostate	0 (0.0)	107 (50.0)	107 (24.0)	
HRR category, n (%)				<0.001
No HRR alteration	28 (12.1)	28 (13.1)	56 (12.6)	
ATMalt	75 (32.5)	35 (16.4)	110 (24.7)	
BRCA1/2 alt	70 (30.3)	100 (46.7)	170 (38.2)	
Other HRR alt	58 (25.1)	51 (23.8)	109 (24.5)	
Pre-Tx PSA				0.80
Median (Q1-Q3)	75.7 (17.9-293.5)	79.3 (16.8-310.7)	77.4 (17.1-307.2)	
N-Miss, n	109	105	214	
Pre-Tx albumin, n (%)				0.90
Below LLN	30 (15.7)	28 (16.2)	58 (15.9)	
Normal	161 (84.3)	145 (83.8)	306 (84.1)	
N-Miss, n	40	41	81	
Pre-Tx alkaline phosphatase, n (%)				0.62
Above ULN	62 (32.5)	57 (35.0)	119 (33.6)	
Normal	129 (67.5)	106 (65.0)	235 (66.4)	
N-Miss, n	40	51	91	
Pre-Tx hemoglobin, n (%)				0.45
Below LLN	154 (81.5)	147 (84.5)	301 (82.9)	
Normal	35 (18.5)	27 (15.5)	62 (17.1)	
N-Miss, n	42	40	82	
Practice type, n (%)				0.66
Academic	47 (20.3)	40 (18.7)	87 (19.6)	
Community	184 (79.7)	174 (81.3)	358 (80.4)	
Prior novel hormonal therapy, n (%)				0.66
No	27 (11.7)	28 (13.1)	55 (12.4)	
Yes	204 (88.3)	186 (86.9)	390 (87.6)	
Prior taxane, n (%)				0.14
No	122 (52.8)	98 (45.8)	220 (49.4)	
Yes	109 (47.2)	116 (54.2)	225 (50.6)	
Prior platinum, n (%)				0.13
No	212 (91.8)	204 (95.3)	416 (93.5)	
Yes	19 (8.2)	10 (4.7)	29 (6.5)	
Pre-Tx opioid use, n (%)				0.76
No evidence	166 (71.9)	151 (70.6)	317 (71.2)	
Yes	65 (28.1)	63 (29.4)	128 (28.8)	
Treatment received, n (%)				0.32
Niraparib	2 (0.9)	0 (0.0)	2 (0.4)	
Olaparib	221 (95.7)	204 (95.3)	425 (95.5)	
Rucaparib	8 (3.5)	10 (4.7)	18 (4.0)	
PSA response, n (%)				0.97
Evaluable	103 (44.6)	95 (44.4)	198 (44.5)	
Unevaluable	128 (55.4)	119 (55.6)	247 (55.5)	
Genetic ancestry, n (%)				0.21
African	42 (18.2)	26 (12.1)	68 (15.3)	
European	169 (73.2)	168 (78.5)	337 (75.7)	
Other	20 (8.7)	20 (9.3)	40 (9.0)	

ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; LBx, liquid biopsy; LLN, lower limit of normal; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; TBx, tissue biopsy; Tx, treatment; ULN, upper limit of normal.

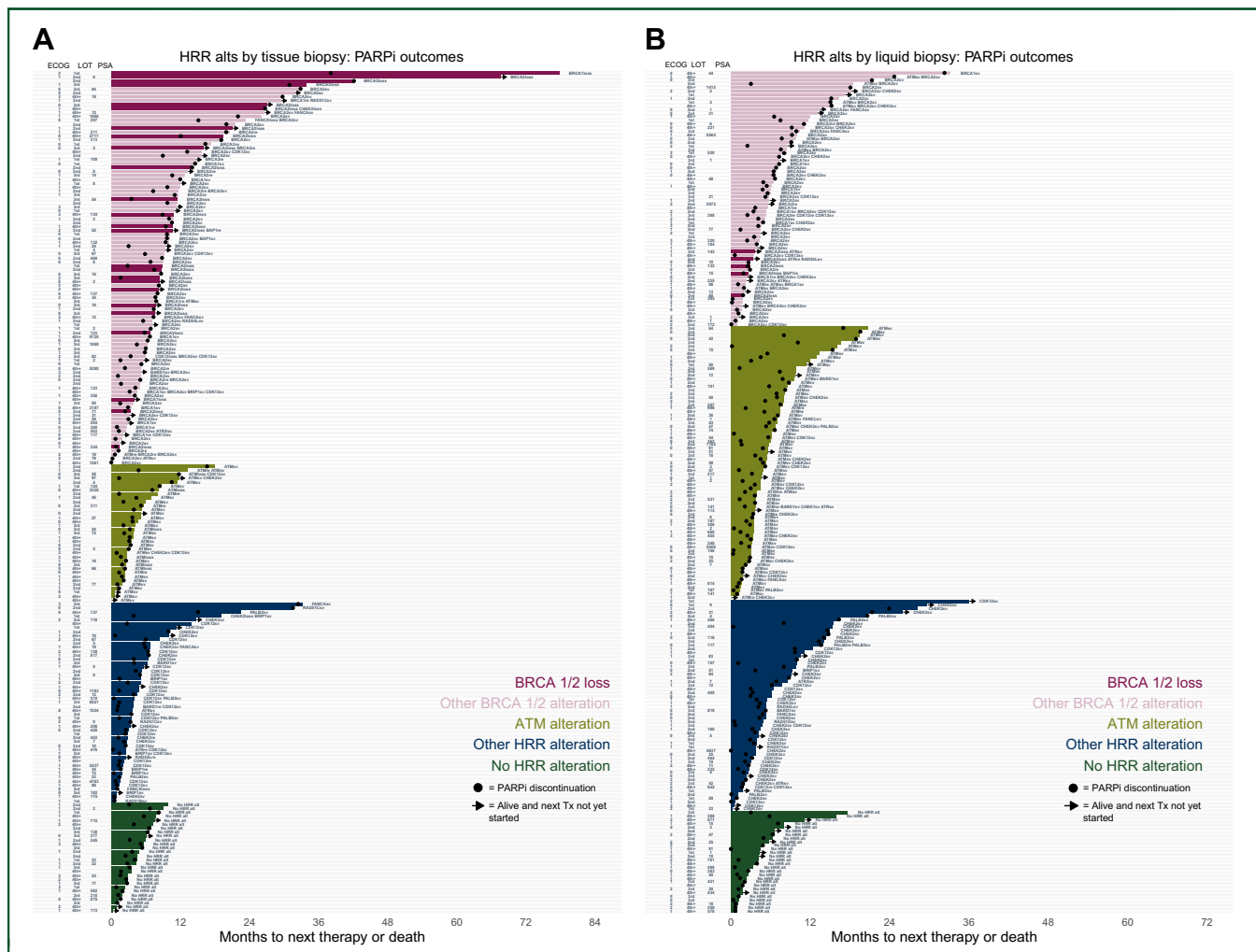


Figure 2. Outcomes on PARPi by biomarker group. Swimmer's plots of TTNT per patient receiving single-agent PARPi and receiving genomic profiling via (A) tissue biopsy or (B) liquid biopsy.

ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; loss, homozygous loss; LOT, line of therapy in the mCRPC setting; mCRPC, metastatic castration-resistant prostate cancer; PARPi, poly(ADP-ribose) polymerase inhibitor; PSA, prostate-specific antigen (pre-PARPi PSA level); re, rearrangement; sv, short variant mutation; TTNT, time to next treatment; Tx, treatment.

1.00, 95% CI 0.56-1.78, $P = 0.999$), consistent with prior reports,³⁵ and similarly other HRR mutations ($n = 51$, HR 0.75, 95% CI 0.44-1.28, $P = 0.296$) were not associated with more favorable TTNT compared with the no HRR cohort (Supplementary Figure S2A, available at <https://doi.org/10.1016/j.esmooop.2024.103684>). OS was also more favorable in the *BRCAalt* group relative to no HRR ($n = 100$, HR 0.43, 95% CI 0.24-0.75, $P = 0.003$). *ATM* ($n = 35$, HR 0.73, 95% CI 0.38-1.41, $P = 0.351$) and other HRR ($n = 51$, HR 1.08, 95% CI 0.58-1.92, $P = 0.854$) cohorts were not statistically different than no HRR (Supplementary Figure S2C, available at <https://doi.org/10.1016/j.esmooop.2024.103684>).

In the liquid CGP cohort, adjusted TTNT was more favorable in the *BRCAalt* subgroup ($n = 70$, HR 0.46, 95% CI 0.26-0.82, $P = 0.009$) and similarly in the other HRR subgroup ($n = 58$, HR 0.51, 95% CI 0.29-0.88, $P = 0.017$) compared with no HRR. *ATM* was not statistically different than no HRR (Supplementary Figure S2D, available at <https://doi.org/10.1016/j.esmooop.2024.103684>). In addition, OS was similarly favorable in *BRCAalt* ($n = 70$, HR 0.50, 95% CI 0.25-1.01, $P = 0.053$) and other HRR subgroups

($n = 58$, HR 0.53, 95% CI 0.27-1.04, $P = 0.064$) compared with no HRR. No difference was observed in the *ATM* subgroup ($n = 75$, HR 0.95, 95% CI 0.51-1.78, $P = 0.877$; Supplementary Figure S2F, available at <https://doi.org/10.1016/j.esmooop.2024.103684>).

The multivariable model for TTD for both tissue and liquid cohorts was very similar to TTNT (Supplementary Figure S2C and D, available at <https://doi.org/10.1016/j.esmooop.2024.103684>). Unadjusted, univariable associations between HRR groups can be found in Supplementary Figure S3, available at <https://doi.org/10.1016/j.esmooop.2024.103684>.

PSA response

Baseline and 12-week PSA responses were evaluable in 198 patients ($n = 95$ with tissue biopsy and $n = 103$ with liquid biopsy). In the tissue CGP cohort, 16 (34.7%) patients with *BRCAalt* had a >50% decline in PSA at 12 weeks after PARPi initiation. By contrast, 0 patients in the *ATM* alteration subgroup, 1 patient in the other HRR subgroup (4.2%), and

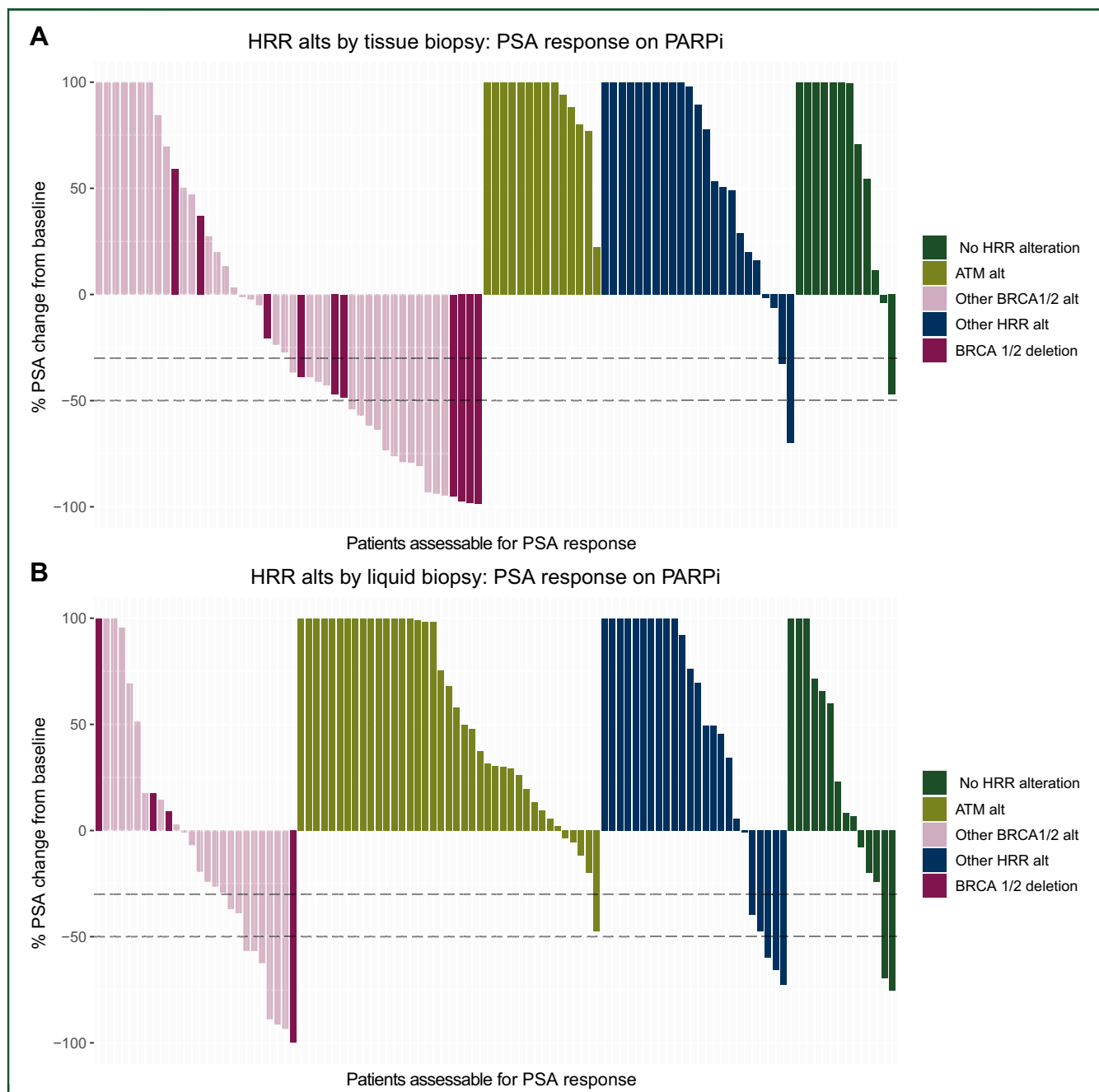


Figure 3. PSA response at week 12. The change in PSA from baseline to most proximal PSA assessment to 12-week timepoint on-therapy (see Methods) is shown for patients with evaluable baseline and on-therapy PSA with alterations identified via (A) tissue biopsy and (B) liquid biopsy. Dashed horizontal lines represent 30% and 50% PSA declines from the baseline.

HRR, homologous recombination repair; PARPi, poly(ADP-ribose) polymerase inhibitor; PSA, prostate-specific antigen (pre-PARPi PSA level); TBx, tissue biopsy; LBx, liquid biopsy.

0 patients in the no HRR subgroup had a PSA decline of $\geq 50\%$ (Figure 3A). Several of the exceptional responders had *BRCA* loss. In the liquid CGP cohort, 7 patients (26.9%) with *BRCA* alt had a 12-week 50% PSA response (Figure 3B). In this cohort, 0 patients with *ATM* alterations, 3 patients (12.5%) with other HRR alterations, and 2 patients (14.0%) with no HRR alterations had a 50% PSA response. Patient characteristics were broadly similar between those with an evaluable PSA response ($n = 198$) and those with an unevaluable for PSA response ($n = 247$; Supplementary Table S2, available at <https://doi.org/10.1016/j.esmooop.2024.103684>).

Outcomes stratified by *BRCA* alteration type

We next assessed if homozygous *BRCA* loss detected on tissue CGP is associated with more favorable outcomes to single-agent PARPi compared with other *BRCA* alt. For men with homozygous *BRCA* loss, there was more favorable TTNT (adjusted HR 0.4, 95% CI 0.21-0.76, $P = 0.005$) and OS (adjusted HR 0.42, 95% CI 0.21-0.85, $P = 0.016$) compared with other *BRCA* alt (Figure 4A and B). Time-to-treatment discontinuation associations were similar to TTNT (Supplementary Figure S4, available at <https://doi.org/10.1016/j.esmooop.2024.103684>), and multivariable

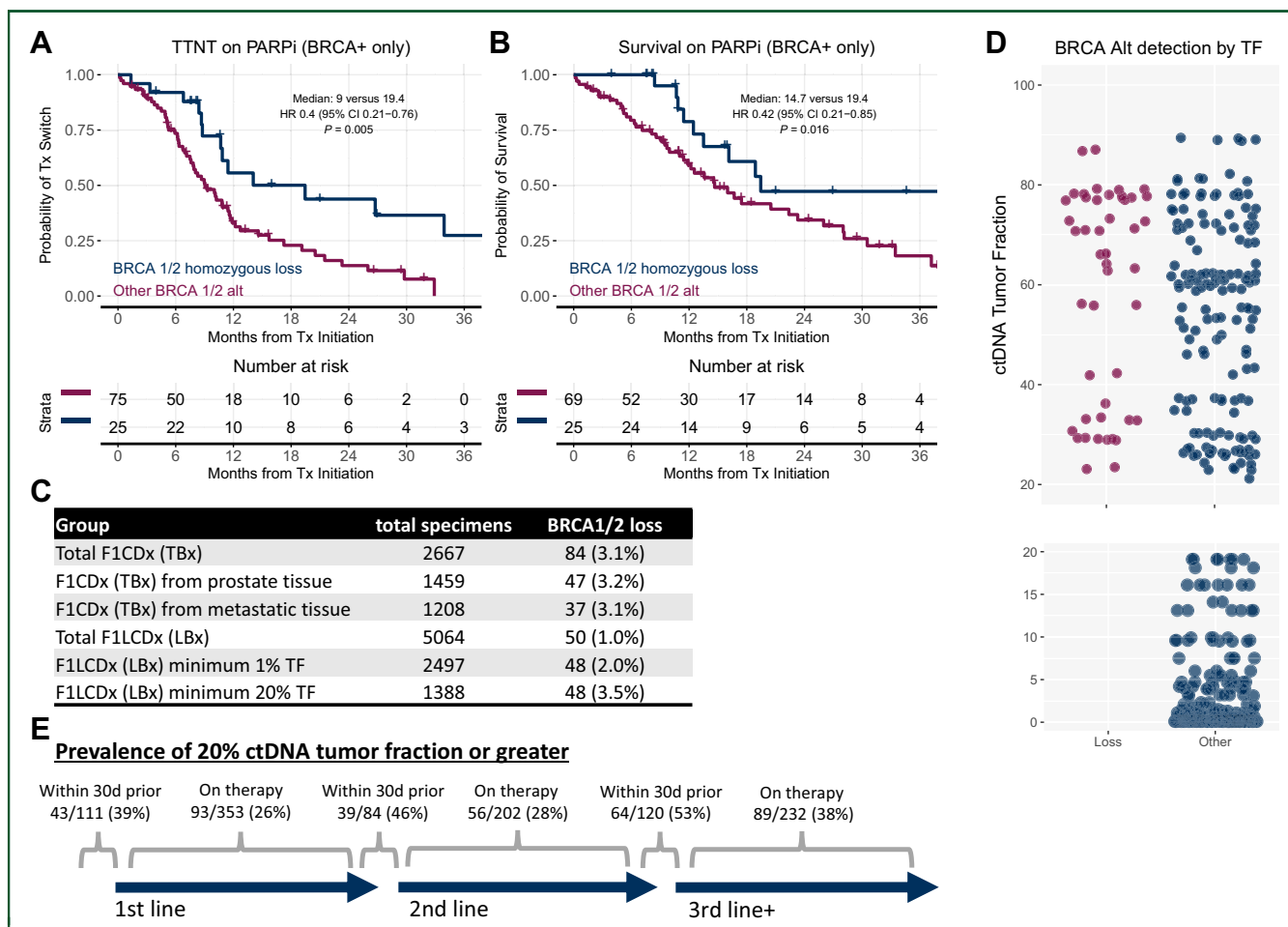


Figure 4. Outcomes on PARPi by BRCA alteration type. Among the subset of patients with tissue biopsy and BRCA 1/2 alterations, the outcomes associated with BRCA 1/2 homozygous loss versus other alterations are shown for (A) TTNT and (B) OS. (C) Prevalence of BRCA 1/2 homozygous loss among FDA-approved assays included in the database. (D) Distribution of ctDNA tumor fraction associated with the detection of BRCA alterations in liquid biopsy. (E) Prevalence of ≥20% ctDNA tumor fraction by the timing of blood draw relative to the start of a line of therapy. CI, confidence interval; ctDNA, circulating tumor DNA; FDA, Food and Drug Administration; HR, hazard ratio; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor; TF, ctDNA tumor fraction; TTNT, time to next treatment; Tx, treatment.

assessments adjusting for standard baseline prognostic factors estimate a similar magnitude of effect as seen in univariable assessments (Supplementary Figure S5, available at <https://doi.org/10.1016/j.esmooop.2024.103684>), including when adjusting for co-occurring alterations in other commonly altered pathways in prostate cancer (Supplementary Figures S6 and S7, available at <https://doi.org/10.1016/j.esmooop.2024.103684>).

To further evaluate the hypothesis that BRCA homozygous loss is challenging to detect in liquid biopsy in the absence of high levels of ctDNA tumor fraction (TF), we explored the frequency of detection of BRCA homozygous loss in FDA-approved CGP assays for tissue and liquid biopsy, regardless of the treatment. We identified 2667 tissue specimens profiled with FoundationOne CDx. Among these, 3.1% have BRCA homozygous loss. Among 5064 liquid biopsy specimens profiled with FoundationOne Liquid CDx, 1.0% had homozygous BRCA loss. Considering only the specimens with a minimum of 1% TF and 20% TF, the prevalence is 2% and 3.5%, respectively (Figure 4C). A visualization of the TF associated with BRCA alteration types in liquid biopsy is also shown (Figure 4D). We further

evaluated the prevalence of ≥20% ctDNA tumor fraction as determined by FoundationOne Liquid CDx, with respect to the timing of initiation of first, second, and third lines of therapy, and found the respective prevalences of 39%, 46%, and 53% when assessed within 30 days before when a new line of therapy began (Figure 4E). When ctDNA tumor fraction was assessed outside of these ranges, the respective prevalences were 26%, 28%, and 38%, respectively.

BRCA loss was highly associated with genomic scarring (HRDsig), consistent with it being biallelic loss (Supplementary Figure S8 and S9, available at <https://doi.org/10.1016/j.esmooop.2024.103684>). While the presence of HRDsig was significantly associated with more favorable outcomes in the tissue cohort (TTNT, TTD, and OS all $P < 0.001$) the associations with outcome within the BRCA altered, and separately, the non-BRCA altered groups, were less clear in this cohort.

As BRCA1 and BRCA2 knockout mice are embryonic lethal,³⁶ it is hypothesized that BRCA loss in human cancers is a somatic-only event. We sought to evaluate if orthogonal germline testing would identify BRCA loss. Among the tissue cohort, 88 patients had germline BRCA testing results

available (Supplementary Figure S10, available at <https://doi.org/10.1016/j.esmooop.2024.103684>). Of those with *BRCA* mutations or rearrangements in tumor tissue, 22 of 39 (56%) were positive for germline *BRCA* mutations. Notably, 0 of 9 (0%) patients with *BRCA* loss detected by Foundation Medicine tumor tissue testing had positive germline *BRCA* results.

DISCUSSION

Multiple lines of level 1 evidence support PARPi therapy in the context of certain HRR alterations. However, questions have remained with regard to PARPi efficacy across the spectrum of alterations in HRR pathway genes and the use of tumor versus liquid CGP for the detection of alterations. In this routine practice cohort study, we show that men with mCRPC treated with single-agent PARPi were most likely to have favorable outcomes and durable benefits in the setting of homozygous *BRCA1* or *BRCA2* loss compared with those in other biomarker-defined subgroups (other *BRCA* alterations, *ATM* alterations, other HRR alterations, or no HRR alterations). These findings were robust across multiple endpoints—PSA response, TTNT, TTD, and OS—and are in line with previous reports: the greatest benefit was most consistently observed in patients whose tumors had evidence of deleterious *BRCA1/2* alterations, and smaller cohorts reporting extreme benefit in the presence of homozygous *BRCA* loss.^{14,18} There is an existing body of biological evidence to suggest that reversion mutations are a common mechanism of resistance to PARPi³⁷ and that complete loss of *BRCA1* or *BRCA2* confers an inability to evolve this resistance mechanism. We report and further validate this phenomenon in a larger cohort more reflective of routine clinical practice.

In contrast to prior evaluations of the effectiveness of PARPi in *BRCA1*- versus *BRCA2*-altered groups,³⁸ we observed similar relative outcomes between these groups when additionally adjusting for routine clinical prognostic factors, alteration type (homozygous loss versus other), and TP53 status (Supplementary Figure S5, available at <https://doi.org/10.1016/j.esmooop.2024.103684>). This was also observed when further adjusting for additional commonly coaltered genes (Supplementary Figure S6, available at <https://doi.org/10.1016/j.esmooop.2024.103684>). A recent report suggested potential extreme benefit from the coalteration of *SPOP* and *BRCA2* mutations,³⁹ and while we did not observe this finding here (Supplementary Figure S6, available at <https://doi.org/10.1016/j.esmooop.2024.103684>), such inferences must be interpreted with caution given the small number with *SPOP* mutations in our cohort. Further exploratory assessments of non-HRR alterations (Supplementary Figure S7, available at <https://doi.org/10.1016/j.esmooop.2024.103684>) did not suggest an association with PARPi effectiveness for other non-HRR-altered genes or pathways, with the notable exception of *TP53*, which was consistently associated with less favorable outcomes. This was true both the overall cohort (Supplementary Figure S7, available at <https://doi.org/10.1016/j.esmooop.2024.103684>)

and in just those with *BRCA1* or *BRCA2* alterations (Supplementary Figure S6, available at <https://doi.org/10.1016/j.esmooop.2024.103684>).

A surprising finding in our study was the non-insignificant ($n = 56$) population of patients who received PARPi without a positive Foundation Medicine test for HRR gene alteration. All *BRCA* results as available in the electronic health record are abstracted. As results are not always available in the electronic health record, it is possible that more patients than reflected received testing. A total of 37 patients had orthogonal testing results available: 12 had positive *BRCA* test results and 25 had negative *BRCA* results. The lack of TTNT differences observed between these groups (log-rank $P = 0.80$) is consistent with the possibility that these orthogonal test results might represent false-positive results.

While liquid biopsy CGP offers a less invasive alternative to tissue biopsy, liquid biopsy approaches may be more prone to false-negative and false-positive results. Clonal hematopoiesis (CH) is a well-described process that can lead to the accumulation of somatic mutations in blood cells, and these can confound the interpretation of ctDNA results. In a retrospective study of 69 patients with mCRPC, 7 had detectable CH mutations in HRR genes (5 *ATM*, 1 *BRCA2*, and 1 *CHEK2*).⁴⁰ It is possible a subset of liquid CGP patients had CH interference which may also impact interpretation of PARPi outcomes.

Liquid biopsy CGP assay sensitivity is dependent on the amount of ctDNA shed and measured by tumor fraction on liquid biopsy assays.^{21,22,41} Detection of homozygous loss is particularly challenging with the current generation of liquid biopsy technologies. In a *post hoc* analysis of the PROfound study, Chi et al. found that while the concordance of liquid CGP for the detection of nonsense, splice, and frameshift mutations on matched tissue CGP was high (each >85%), the concordance of homozygous loss was only 27%.⁴² Corroborating this, we observed a similar prevalence of *BRCA* loss detection between tissue biopsy (TBx) and liquid biopsy (LBx) when the ctDNA tumor fraction is very high ($\geq 20\%$; Figure 4C). This is consistent with the differences observed between the cohort of outcomes associated with TBx and LBx detection of HRR alterations (Figure 2). At the face value, without consideration of confounders, in men who underwent liquid biopsy CGP, the *BRCA*alt group did not have more favorable outcomes compared with the other HRR alterations. Our interpretation is that, because *BRCA* homozygous losses are only detectable in liquid biopsy with a level of ctDNA tumor fraction that many patients in routine practice will not have, potential extreme responders are underrepresented in the liquid biopsy cohort presented here.

Our data support the use of tumor tissue for CGP for the detection of HRR alterations in mCRPC that can improve care. However, biopsy is not always feasible, and biopsies of bone metastases, in particular, have a high rate of failure of CGP.^{42,43} Previous studies suggest that HRR alterations are largely truncal, and would be present in an archival prostate tissue biopsy,^{44,45} suggesting that it would be valid to use archival specimens to guide decisions for PARPi use in

metastatic settings. Corroborating this, we observed a similar prevalence of *BRCA* loss in specimens originating from the prostate and from other tissues (Figure 4C). In our cohorts of patients treated with PARPi, among the 214 with tissue biopsy, exactly half of the biopsies were obtained from the prostate and half from metastatic tissue (Table 1). We did not observe differences in outcomes associated with either group (Supplementary Figures S2 and S5-S7, available at <https://doi.org/10.1016/j.esmooop.2024.103684>). While prospective, longitudinal assessments of *BRCA* loss would be able to more definitively assess whether it can be acquired over the course of treatments, current data support a truncal nature and the appropriateness of using an archival prostate biopsy to assess *BRCA* loss status.

In cases where fresh biopsy is not feasible and archival tissue is not available, liquid biopsy is an important alternative. Certain liquid biopsy assays are validated to detect *BRCA* loss, but even when these tools are used, the lack of detection of *BRCA* loss should be interpreted as 'indeterminate' rather than 'negative' in the absence of very high ctDNA fraction, whereas properly validated tissue biopsy assays can definitively rule out the presence of *BRCA* loss. However, liquid biopsy assays have much higher sensitivity (requiring less ctDNA tumor fraction) to detect mutations and rearrangements. Detection of other types of *BRCA* alterations via liquid biopsy was associated with improved OS compared with control in a *post hoc* analysis of the PRO-found study.^{46,47}

Providers should be aware of the inherent limitations of liquid biopsy with regard to ctDNA tumor fraction and the detection of homozygous *BRCA* loss. Providers should also be aware that not all NGS tumor tissue assays have the ability to report copy number losses in *BRCA1* and *BRCA2*.²⁰ Lastly, it is also important to note that blood-based germline testing is also unlikely to detect homozygous *BRCA* loss; *BRCA1* and *BRCA2* knockout mice are embryonic lethal,³⁶ suggesting a somatic-only origin. In this study, all patients ($n = 9$) with detected *BRCA* loss in tumor tissue who underwent orthogonal germline testing were negative for germline *BRCA* alterations (Supplementary Figure S10, available at <https://doi.org/10.1016/j.esmooop.2024.103684>).

Consistent with prior reports⁴⁸ we observed that ctDNA tumor fraction was enriched in specimens obtained within 30 days before the initiation of a new line of therapy (Figure 4E), with prevalence rates of $\geq 20\%$ tumor fraction present in 39%, 46%, and 53% of specimens, respectively, obtained within 30 days before first-, second-, and third-line treatment initiations in our cohort, consistent with the hypothesis that progressing tumors will shed more DNA into circulation compared with points in the patient journey where disease may be slower growing. This observation supports current treatment guideline recommendations to prioritize liquid biopsy CGP testing at times of progression.

Notably, there were no differences in clinical outcomes to PARPi for patients across genetic ancestry cohorts. Each registrational trial of PARPi enrolled $< 5\%$ of patients of African descent. This routine care population with 15% of patients of African ancestry having similar treatment effects

and outcomes to PARPi is reassuring for clinical practice, supporting the use of PARPi agents for patients of African descent.

The PARPi monotherapy has not shown a consistent clinical benefit for patients with *ATM* mutations,³⁵ and our results are consistent with prior reports. Single-agent PARPi has shown some efficacy in a small subset of other HRR mutations. In the TRITON2 study, 6/11 patients with *PALB2* alterations treated with rucaparib had a 50% PSA response.⁴⁹ There were also occasional responses in patients with other HRR genes (*RAD51B*, *FANCA*, and *BRIP1*). Similarly, in the TOPARP-B trial, 4/7 patients with mCRPC and *PALB2* mutations had either a radiographic or 50% PSA response to single-agent olaparib.⁵⁰ A United States FDA pooled analysis of six trials of PARPi in mCRPC, which included studies of single-agent PARPi and dual PARPi plus androgen receptor pathway inhibitors, found that PARPi benefit was greatest for patients with *BRCA*, *PALB2*, and *CDK12* mutations.⁵¹ In our study, the small fraction of men with non-*BRCA* HRR and durable TTNT and TTD had alterations in these genes as well. A total of nine patients in our cohort tested positive for HRDsig who were negative for *BRCA* alterations (Supplementary Figure S9, available at <https://doi.org/10.1016/j.esmooop.2024.103684>), and two of these had *PALB2* mutations. While more favorable outcomes were not strongly enriched in this small cohort, larger cohorts may yield more insights.

Limitations

Observational and/or retrospective analyses are more prone to false discovery than prospective randomized trials, due to multiple hypothesis testing and potential imbalances between groups. We carried out rigorous adjustments of prognostic factors to reduce potential imbalances between groups that might confound time-to-event comparisons. However, these adjustments do not account for all potential imbalances, and there are some biases that are known that must be carefully considered to generalize results, such as *BRCA* loss being easier to detect with tissue biopsy. Results abstracted from unstructured data, such as orthogonal (non-Foundation Medicine) somatic and germline testing can be subject to degrees of human or machine reader error, especially around *BRCA* loss. We recognize that clinical annotation, bioinformatic pipelines, and reporting can vary between laboratories. Therefore the results from our study may not be generalizable to the biomarker performance of all NGS platforms.

CONCLUSIONS

In this analysis of the effectiveness of PARPi, patients with *BRCA* alterations identified on tissue biopsy CGP had more favorable outcomes across all endpoints relative to other patient subgroups in the setting of PARPi monotherapy. Patients with homozygous *BRCA* loss had significantly more favorable outcomes relative to all other *BRCA* alterations. While *BRCA* loss can be detected with validated liquid biopsy assays, many patients with mCRPC do not have high-enough

ctDNA tumor fraction to rule out the presence of *BRCA* loss using liquid biopsy. However, when tumor tissue testing is not feasible, the greater signal in liquid biopsy is anticipated when tumors are progressing. No patients with *BRCA* loss detected in tumor tissue had germline *BRCA* alterations detected, consistent with the existing biological understanding of *BRCA* loss. Our results suggest that tumor tissue CGP should be prioritized when clinically feasible for the detection of alterations in HRR genes, especially for those associated with durable benefits from PARPi.

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DISCLOSURE

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DATA SHARING

The data that support the findings of this study were originated by Flatiron Health, Inc. and Foundation Medicine, Inc. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to PublicationsDataaccess@flatiron.com and cgdb-fmi@flatiron.com.

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