B23

Real world comparison of time-to-next-treatment, time-to-castration-resistance, and overall survival among patients with BRCA1/2 positive and homologous recombination repair negative metastatic castration-sensitive prostate cancer

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Key Takeaways

- This study demonstrates worse outcomes for patients with *BRCA*+ mCSPC, particularly more rapid treatment changes and progression to castration resistant PC by 24 months
- Given that *BRCA* mutations are the most prevalent HRR mutations observed in men with PC, these results support early identification and a need for more effective therapies for this population

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Poster

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Disclosures

H.H. Cheng, G. Brown, N. Shore, B. Lowentritt, D.W. Lin, and M.A. Bilen received consulting fees from Johnson & Johnson. S. Burbage and I. Khilfeh are employees of Johnson & Johnson and are stockholders of Johnson & Johnson. C. Rossi, L. Diaz, Y. Wang, and D. Pilon are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Johnson & Johnson.

Background

- Prostate cancer (PC) is the second most common cancer among men, with advanced metastatic disease linked to poor outcomes, including a 5-year survival rate of 36.6%[1,2]
- Molecular heterogeneity is a notable challenge in the treatment of metastatic PC; patients who harbor mutations in homologous recombination repair (HRR) genes, particularly *BRCA1* or *BRCA2* (hereafter "*BRCA+*") have poorer disease prognosis[3,4]
- Targeted therapy, including poly ADP-ribose polymerase (PARP) inhibitors, are currently under investigation for treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC), also known as hormone-sensitive PC, harboring HRR mutations[5,6]
- There are limited real-world data on clinical outcomes among patients with mCSPC harboring *BRCA+* mutations

Objective

- This study compared real-world time-to-next-treatment (TTNT), time-to-castration-resistance (TTCR), and overall survival (OS) between *BRCA+* patients and those without any HRR mutations (HRR-) in mCSPC

Methods

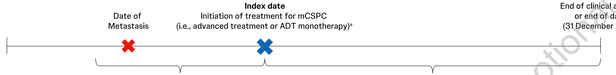
Data source

- Data from oncology centers included in the nationwide (US-based) Flatiron Health-Foundation Medicine, Inc. (FMI) Metastatic PC Clinico-Genomic Database (CGDB) were used (study period: 1 January 2017 to 31 December 2022)
- Data were de-identified and Health Insurance Portability and Accountability Act (HIPAA) compliant
- Flatiron Health, Inc. and FMI did not participate in data analyses

Study design

- A retrospective longitudinal cohort study design was used (**Figure 1**)
- Patients receiving their first treatment for mCSPC were included if they had results from ≥1 HRR mutation test and:
  1. The start date of an advanced PC treatment (e.g., androgen receptor pathway inhibitors [ARPIs], chemotherapy) after the date of metastasis detection, with or without ADT, was on or after 1 January 2018 (index date)
  2. The start date of ADT monotherapy was on or after 1 January 2018, with the index date defined as the latter of ADT initiation or the date of metastasis detection
- Patients were classified as *BRCA+* (i.e., *BRCA1* or *BRCA2*) or HRR- (i.e., tested but not found to have any HRR mutation) based on testing results for both germline and somatic mutations, observed prior to the index date as well as those post-index until castration resistance progression, if observed
  - The following non-*BRCA* HRR mutations were assessed: *BRIP1, CHEK2, FANCA, PALB2, RAD51B, RAD54L*
- Baseline patient characteristics were evaluated in the 12 months preceding the index date
- Study outcomes were assessed during the observation period which spanned from the index date until the end of clinical activity or data availability (31 December 2022)

Figure 1: Study design



ADT: androgen deprivation therapy; mCSPC: metastatic castration-sensitive prostate cancer; OS: overall survival; TTCR: time-to-castration resistance; TTNT: time-to-next-treatment.
Note: a. For patients who started ADT monotherapy before the date of metastasis, the index date was changed to the date of metastasis.

Patient selection criteria

- The inclusion and exclusion criteria used to select patients with mCSPC are shown in **Figure 2**

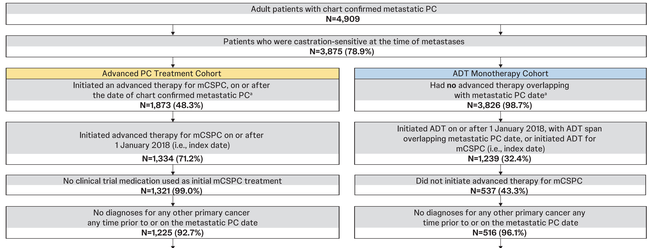
Study outcomes

- TTNT was defined as the time from first mCSPC treatment (index date) to the start of subsequent therapy, including the use of clinical trial medication
  - TTNT was only assessed among patients with advanced PC treatment (i.e., excluded ADT monotherapy patients)
- TTCR was defined as the time from first mCSPC treatment (index date) to the development of castration resistance
- OS was defined as the time from the initial PC diagnosis date to the date of death from any cause
  - OS was only assessed among patients who did not receive a platinum-based chemotherapy or a PARP inhibitor as first mCSPC treatment

Statistical analysis

- Based on the propensity score, inverse probability of treatment weighting (IPTW) was used to account for differences in baseline characteristics between the *BRCA+* and HRR- cohorts (**Table 1**)[7]
- Baseline characteristics between cohorts were considered balanced after weighting, as indicated by standardized differences of <10%[8]
- Weighted Kaplan-Meier (KM) analysis and weighted Cox proportional hazards models were used to compare TTNT, TTCR, and OS between the *BRCA+* and HRR- cohorts

Figure 2: Sample selection



ADT: androgen deprivation therapy; HRR: homologous recombination repair; mCSPC: metastatic castration-sensitive prostate cancer; NGS: next-generation sequencing; PC: prostate cancer.
Note: a. Not mutually exclusive.

Results

Baseline characteristics

- A total of 149 *BRCA+* and 1,066 HRR- patients were included (**Figure 2**)
- Baseline patient characteristics were generally well-balanced between the *BRCA+* and HRR- cohorts after weighting (**Table 1**)

Table 1: Baseline demographic and clinical characteristics

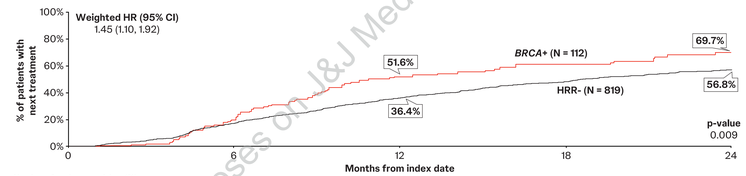
	After weighting[a,b]		
	BRCA+ N=149	HRR- N=1,066	Std. diff %
Age, years, mean ± SD [median]	70 ± 9 [70]	70 ± 9 [70]	1.1
Age group, n (%)			
≤50	2 (1.5)	19 (1.8)	2.1
51-60	22 (15.0)	167 (15.7)	1.9
61-70	53 (35.3)	376 (35.3)	0.0
71-80	52 (34.9)	352 (33.0)	4.1
≥81	20 (13.3)	152 (14.2)	2.8
Race, n (%)			
White	90 (60.4)	653 (61.2)	1.7
Black	18 (11.9)	121 (11.3)	2.0
Other	24 (15.9)	161 (15.1)	2.3
Unknown	18 (11.7)	132 (12.4)	1.9
Insurance plan type, n (%)			
Commercial	54 (36.4)	412 (38.7)	4.8
Medicare	53 (35.7)	387 (36.3)	1.3
Medicaid	5 (3.3)	32 (3.0)	2.2
Dual coverage or unknown	37 (24.5)	234 (22.0)	6.1
Practice type, n (%)			
Academic only	24 (15.9)	178 (16.7)	2.2
Community only	119 (79.9)	837 (78.5)	3.3
Both academic and community	6 (4.2)	51 (4.8)	2.6
Time from metastasis to index date, days, mean ± SD [median]	114 ± 261 [44]	128 ± 278 [46]	4.9
Year of index date, n (%)			
2018	23 (15.1)	160 (15.0)	0.3
2019	35 (23.2)	241 (22.6)	1.4
2020	35 (23.4)	249 (23.4)	0.0
2021	36 (24.4)	257 (24.2)	0.7
2022	21 (13.8)	158 (14.8)	2.8
Gleason score at initial PC diagnosis, n (%)			
≤6	4 (2.6)	26 (2.5)	0.7
7	16 (10.6)	132 (12.4)	5.5
8	23 (15.4)	159 (14.9)	1.3
9	58 (38.0)	419 (39.3)	0.6
10	13 (9.0)	97 (9.1)	0.4
Not available	35 (23.3)	232 (21.8)	3.7
Quan-CCI score, mean ± SD [median]	3.2 ± 2.8 [2.0]	3.3 ± 2.8 [2.0]	1.8
Localized PC therapy[c], n (%)	34 (22.9)	259 (24.3)	3.2
Medication used on the index date, n (%)			
ARI[d]	39 (26.4)	296 (27.7)	3.1
Chemotherapy	30 (19.9)	213 (20.0)	0.3
Abiraterone acetate	45 (30.2)	327 (30.7)	1.2
ADT monotherapy	37 (25.1)	247 (23.1)	4.5

ADT: androgen deprivation therapy; ARI: androgen receptor inhibitor; *BRCA+*: BRCA positive; CCI: Charlson Comorbidity Index; HRR-: homologous recombination repair negative; PC: prostate cancer; SD: standard deviation.
Notes: a. Baseline characteristics were balanced between cohorts using inverse probability of treatment weighting. Propensity scores were generated using probability estimates from a logistic regression model including age, race, insurance plan type, practice type, time from metastasis to index date, index year, index medication use, Gleason score, Quan-CCI score, and localized PC therapy. Weights were truncated at the 95th percentile and defined as follows: 1/(propensity score) (*BRCA+*) and 1/(1-propensity score) (HRR-). **b.** The number of patients reported in this weighted population represents the sum of weights for the corresponding non-weighted patients, rounded to the nearest integer. The proportions displayed were calculated before the rounding and may be slightly different than if they were calculated based on rounded numbers. **c.** Receipt of any localized PC therapy was evaluated at any time prior to index. **d.** ARI included apalutamide, enzalutamide, and darolutamide.

Time-to-next-treatment

- By 24-months post-index, a significantly higher proportion of *BRCA+* patients progressed and received a next PC therapy relative to HRR- patients (59.0% vs. 46.7%; HR: 1.45 [95% CI: 1.10, 1.92]; p=0.009 **[Figure 3]**)
- Median TTNT was shorter among *BRCA+* patients relative to HRR- patients (10.9 months vs. 18.7 months)

Figure 3: Time-to-next-treatment[a]



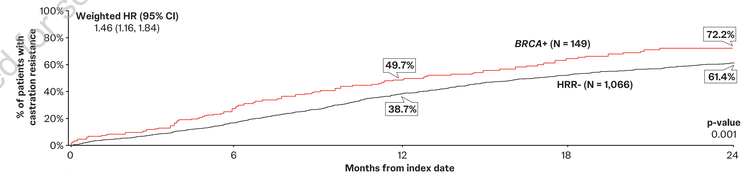
Number of patients at risk, n (%)					
BRCA+	112 (100.0)	77 (69.2)	41 (36.4)	24 (21.8)	14 (13.0)
HRR-	819 (100.0)	580 (70.7)	369 (45.0)	241 (29.4)	149 (18.2)

BRCA+: *BRCA1* or *BRCA2* positive; CI: confidence interval; HR: hazard ratio; HRR-: homologous recombination repair negative; mCSPC: metastatic castration-sensitive prostate cancer; TTNT: time-to-next-treatment.
Note: a. Patients were not considered to move to a subsequent line if the exact same treatments were re-initiated after a gap of >90 days. TTNT was censored at the end of the observation period (i.e., end of clinical activity or data availability).

Time-to-castration-resistance

- By 24-months post-index, a significantly higher proportion of *BRCA+* patients progressed to castration-resistance relative to HRR- patients (66.0% vs. 53.3%; HR: 1.46 [95% CI: 1.16, 1.84]; p=0.001 **[Figure 4]**)
- Median TTCR was shorter among *BRCA+* patients relative to HRR- patients (12.9 months vs. 16.9 months)

Figure 4: Time-to-castration-resistance[a]



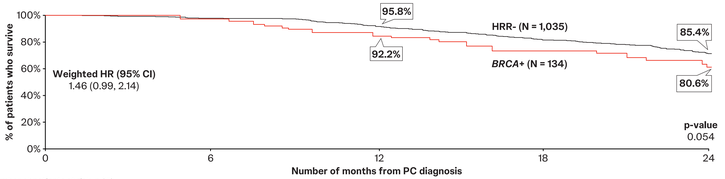
Number of patients at risk, n (%)					
BRCA+	149 (100.0)	96 (64.7)	58 (38.9)	34 (23.0)	22 (15.0)
HRR-	1,066 (100.0)	775 (72.7)	488 (45.7)	319 (29.9)	201 (18.9)

BRCA+: *BRCA1* or *BRCA2* positive; CI: confidence interval; HR: hazard ratio; HRR-: homologous recombination repair negative; mCRPC: metastatic castration-resistant prostate cancer; mCSPC: metastatic castration-sensitive prostate cancer; TTCR: time-to-castration resistance.
Note: a. TTCR was censored at the earliest of initiation of a clinical trial drug or the end of the observation period (i.e., end of clinical activity or data availability).

Overall survival

- Numerically fewer *BRCA+* patients survived 24 months after PC diagnosis (80.6%) than the HRR- cohort (85.4%; HR: 1.46 [95% CI: 0.99, 2.14]; p=0.054 **[Figure 5]**)

Figure 5: Overall survival[a]



Number of patients at risk, n (%)					
BRCA+	134 (100.0)	128 (95.5)	105 (78.2)	85 (63.5)	67 (49.6)
HRR-	1,035 (100.0)	986 (95.3)	892 (86.2)	779 (75.3)	659 (63.7)

N.: first-line; *BRCA+*: *BRCA1* or *BRCA2* positive; CI: confidence interval; HR: hazard ratio; HRR-: homologous recombination repair negative; OS: overall survival; PARP: poly-ADP ribose polymerase; PC: prostate cancer.
Note: a. *BRCA+* status was treated as time-varying exposure in the weighted Cox proportional hazard model for OS. OS was censored at the earliest of initiation of a PARP inhibitor or platinum-based chemotherapy, initiation of a clinical trial drug, or the end of the observation period (i.e., end of clinical activity or data availability).

Limitations

- The Flatiron algorithm for identifying castration resistance relied on physician report or observed rising PSA values and did not incorporate an evaluation of testosterone levels; as such, the evaluation of castration resistance may be subject to misclassification or reporting inaccuracies
- This study relied upon clinical data that may contain inaccuracies or omissions (e.g., specimen collection dates, HRR mutation positivity rates, treatment start dates) and does not capture any diagnoses, testing services, or prescription fills obtained outside of the oncology network

Conclusions

- In this real-world study comparing *BRCA+* and HRR- patients with mCSPC during the time of ARPI availability for the treatment of mCSPC, a significantly higher proportion of *BRCA+* patients progressed to subsequent treatment and castration-resistance, relative to HRR- patients
- While not statistically significant, observed OS results may signal more adverse survival outcomes for patients with *BRCA+* mCSPC
- These results highlight an unmet treatment need for patients with mCSPC with *BRCA+*, that may be addressed with novel targeted therapies

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