Real-world time-to-next-treatment and time-to-castration-resistance among patients with metastatic castration-sensitive prostate cancer using androgen-receptor pathway inhibitors with and without homologous recombination repair mutations

Daniel W. Lin[1], Sabree Burbage[2], Carmine Rossi[3], Ibrahim Khilfeh[2], Lilian Diaz[3], Yuxi Wang[3], Dominic Pilon[3], Gordon Brown[4], Neal Shore[5], Benjamin Lowentritt[6], Heather H. Cheng[1], Mehmet A. Bilen[7]

Presenter:
Dr. Daniel W. Lin

[1] Fred Hutch Cancer Center, Seattle, Washington
[2] Johnson & Johnson, Horsham, Pennsylvania
[3] Analysis Group, Inc., Montréal, Canada
[4] New Jersey Urology, Sewell, New Jersey
[5] Carolina Urologic Research Center, Myrtle Beach, South Carolina
[6] Chesapeake Urology, Baltimore, Maryland
[7] Emory University School of Medicine, Atlanta, Georgia

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Acknowledgements & Disclosures

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DISCLOSURES

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Background

- The treatment of mCSPC is challenged by molecular heterogeneity of the disease
  - Patients harboring HRR mutations, particularly *BRCA1* and *BRCA2*, experience more aggressive disease course and are less responsive to traditional treatments[1,2]
- Novel treatments such as poly ADP-ribose polymerase (PARP) inhibitors are currently being investigated for the treatment of HRR positive mCSPC[3,4]
- While ARPIs are a common treatment for patients with mCSPC, real-world evidence of clinical outcomes among patients treated with ARPIs with HRR mutations is limited

1. Huang X, et al. *J Hematol Oncol.* 2012;5:35. 2. Leith A, et al. *Future Oncol.* 2022;18(8):937-951. 3. Rathkopf DE, et al. *J Clin Oncol.* 2021;39 (6_suppl).4. Agarwal N, et al. *Future Oncol.* 2024;20(9):493-505.

Objective

A descriptive analysis using retrospective data evaluating real-world clinical outcomes among patients with mCSPC treated with ARPIs with and without HRR mutations

- To assess real-world time-to-next-treatment (TTNT) and time-to-castration resistance (TTCR) among patients with metastatic castration-sensitive prostate cancer (mCSPC) using androgen receptor pathway inhibitors (ARPIs) with and without homologous recombination repair (HRR) mutations

Methods

STUDY DESIGN

- Retrospective, longitudinal cohort analysis
- Patients were classified into cohorts (HRR positive [HRR+][1], including *BRCA1/2* positive [*BRCA*+] subgroup, or HRR negative [HRR-]) based on testing results observed any time prior to progression to castration resistance, if observed
- The observation period spanned from the ARPI initiation (index date) to the end of clinical activity or data availability (12/31/2022)

DATA SOURCES

- Data from the US-based Flatiron Health-Foundation Medicine, Inc. (FMI) Metastatic PC Clinico-Genomic Database were evaluated
- Flatiron Health, Inc. and FMI did not participate in data analyses

1. HRR genes assessed included *BRCA1, BRCA2, BRIP1, CHEK2, FANCA, PALB2, RAD51B, RAD54L*.

Methods

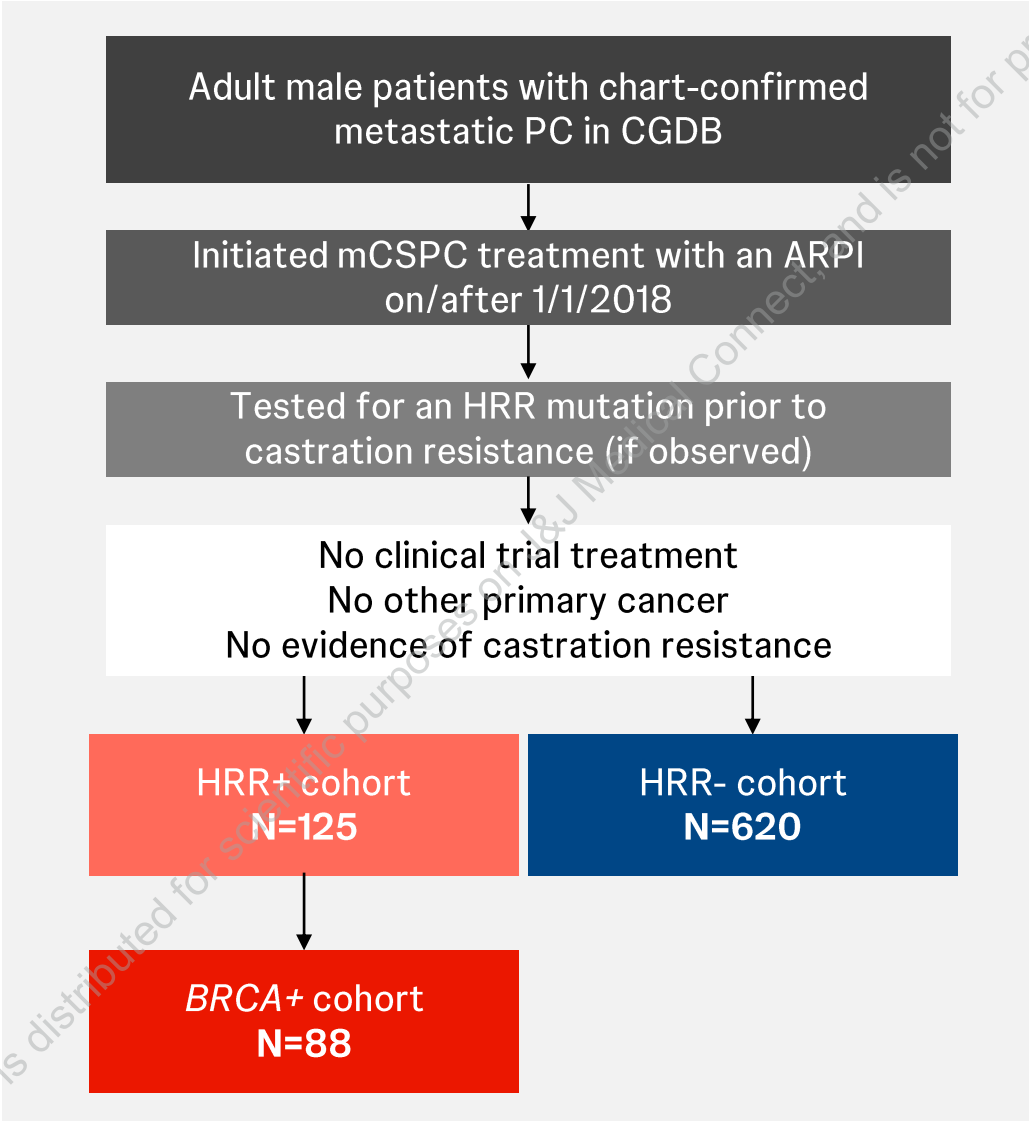
PATIENT SELECTION

- Patients with mCSPC who initiated an ARPI on/after 1/1/2018 and were tested for an HRR mutation were included
- Patients were excluded if they had evidence of progression to castration resistance prior to/on the index date, clinical trial medication as initial mCSPC treatment, or diagnosis for another primary cancer prior to metastasis

STATISTICAL ANALYSES

- TTNT and TTCR were described using Kaplan-Meier analyses

Methods



ARPI: androgen receptor pathway inhibitor; CGDB: Clinico-Genomic Database; HRR: homologous recombination repair; HRR+: homologous recombination repair positive; *BRCA+: BRCA1* or *BRCA2* positive; mCSPC: metastatic castration-sensitive prostate cancer; PC: prostate cancer.

Results

Patient Characteristics

- Mean age was similar across cohorts (71 years HRR+ and *BRCA+*, 70 years HRR-)
- Approximately two-thirds of patients in each cohort were White
- The majority of patients were treated in community-based oncology practices
- Across all cohorts, enzalutamide and abiraterone acetate were the most frequently used ARPIs
- Overall, 5.5% of patients received ≥2 HRR tests

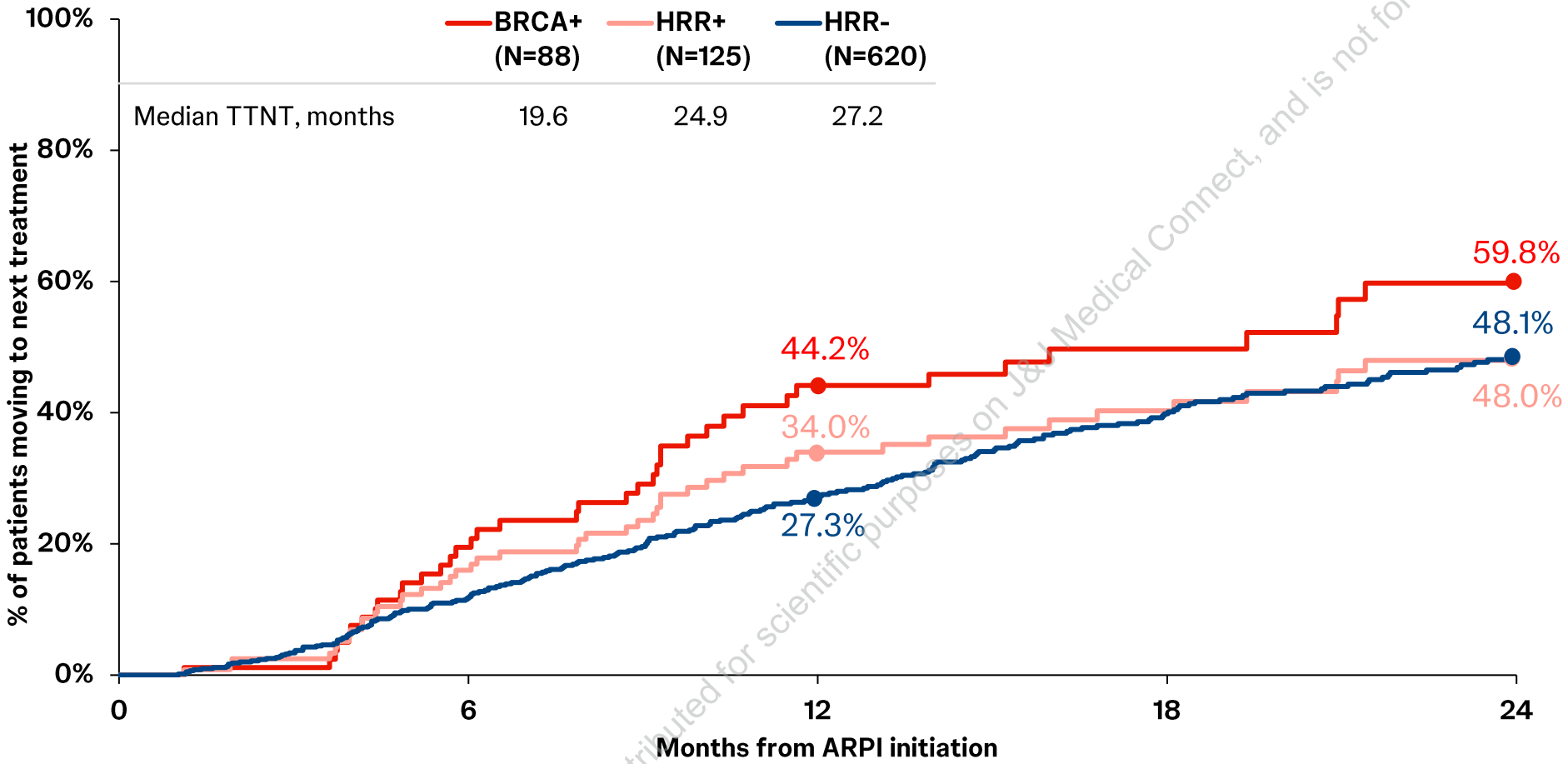
Patient characteristics	*BRCA+* N=88	HRR+ N=125	HRR- N=620
Mean age, years	71	71	70
Race			
White	68.2%	64.8%	60.5%
Black	6.8%	8.0%	11.1%
Other	17.0%	17.6%	14.8%
Unknown	8.0%	9.6%	13.5%
Year of ARPI initiation			
2018	10.2%	9.6%	11.0%
2019	13.6%	15.2%	18.9%
2020	26.1%	28.8%	23.1%
2021	30.7%	27.2%	26.9%
2022	19.3%	19.2%	20.2%
Practice type			
Community only	84.1%	82.4%	78.4%
Academic only	11.4%	13.6%	16.6%
Both community and academic	4.5%	4.0%	5.0%
Median time from metastasis to ARPI initiation, months	2.1	2.1	2.0
Mean Quan-CCI score	3.2	3.1	3.5
Localized PC therapy	27.3%	30.4%	25.2%
Initial ARPI used[1]			
Enzalutamide	45.5%	37.6%	32.3%
Abiraterone acetate	38.6%	44.0%	54.5%
Apalutamide	10.2%	12.8%	11.1%
Darolutamide	5.7%	5.6%	3.2%

ARPI: androgen receptor pathway inhibitor; HRR: homologous recombination repair; HRR+: homologous recombination repair positive; *BRCA+: BRCA1* or *BRCA2* positive; PC: prostate cancer; Quan-CCI: Quan-Charlson Comorbidity Index.

1. Categories are not mutually exclusive; patients may have used multiple ARPIs in combination or with other agents.

Results

Time-to-next-treatment (TTNT)

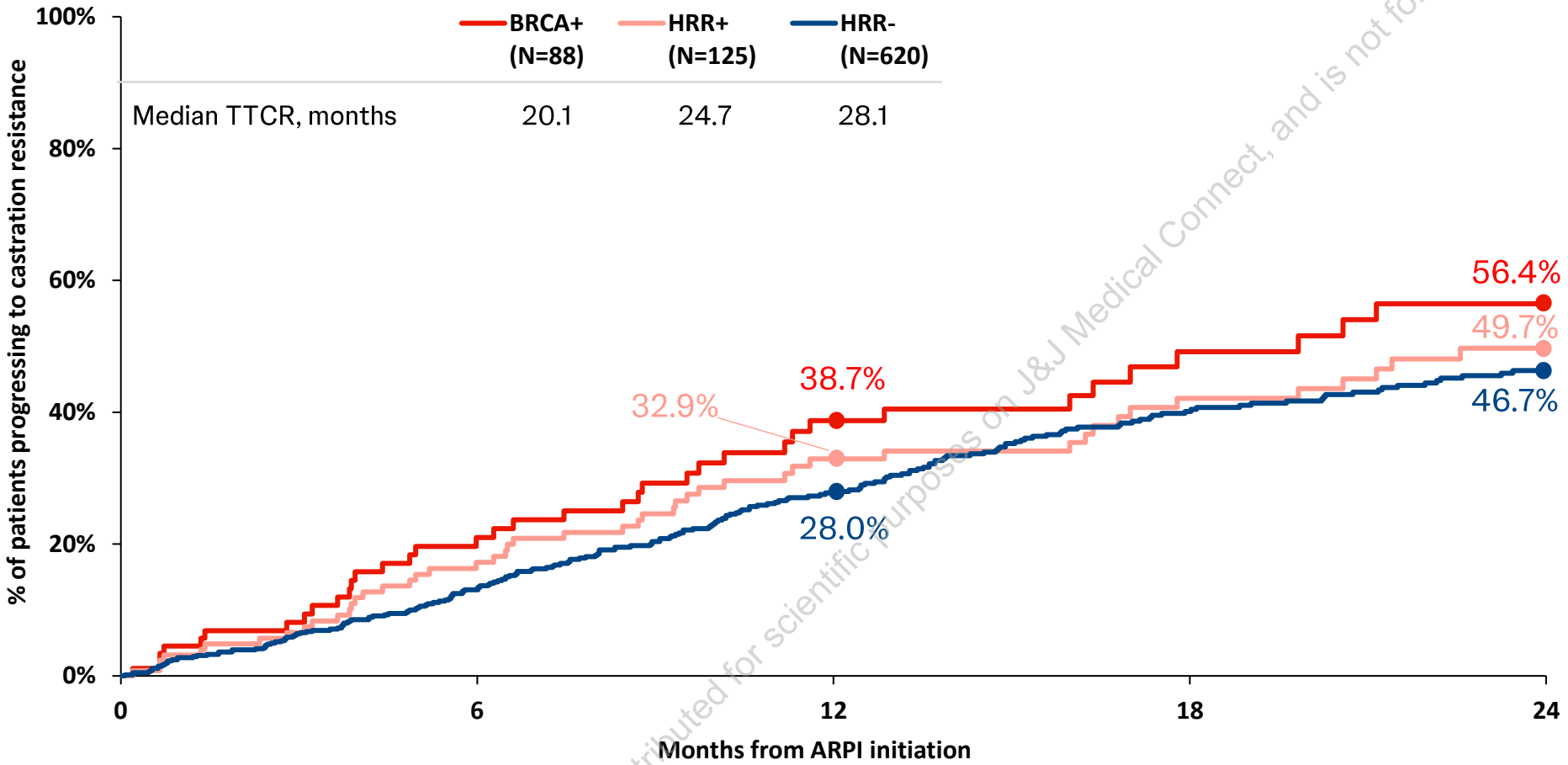


Number at risk, n (%)	6 months	12 months	18 months	24 months
BRCA+	59 (67.0)	35 (39.8)	22 (25.0)	14 (15.9)
HRR+	90 (72.0)	59 (47.2)	42 (33.6)	28 (22.4)
HRR-	461 (74.4)	308 (49.7)	202 (32.6)	125 (20.2)

- By 24 months, **59.8% of *BRCA+* patients received a next treatment**, which was a higher proportion relative to 48.0% of HRR+ and 48.1% of HRR- patients
- ***BRCA+* patients had a median TTNT of 19.6 months,** which was shorter relative to 24.9 months among HRR+ and 27.2 months among HRR- patients

Results

Time-to-castration resistance (TTCR)



Number at risk, n (%)	6 months	12 months	18 months	24 months
BRCA+	60 (68.2)	37 (42.0)	23 (26.1)	16 (18.2)
HRR+	92 (73.6)	59 (47.2)	43 (34.4)	30 (24.0)
HRR-	445 (71.8)	302 (48.7)	200 (32.3)	133 (21.5)

- By 24 months, **56.4% of *BRCA+* patients progressed to castration resistance**, which was a higher proportion relative to 49.7% of HRR+ patients and 46.7% of HRR- patients
- ***BRCA+* patients had a median TTCR of 20.1 months**, shorter relative to 24.7 months among HRR+ patients and 28.1 months among HRR- patients

Conclusions

- This retrospective study utilized real-world genomic data from a major oncology network in the US to evaluate clinical outcomes among **patients with mCSPC tested for HRR mutations**

- Among patients treated with an ARPI, those with ***BRCA1/2* mutations** experienced descriptively **faster progression to next treatment**, and **higher rates of progression to castration resistance**

- These findings indicate that currently **available treatments for mCSPC may be suboptimal** for patients with *BRCA* mutations and highlight the **need for novel therapies** such as PARP inhibitors in the mCSPC setting

- These results support the need for ongoing clinical trials such as AMPLITUDE[1] and TALAPRO-3[2] investigating the use of PARP inhibitors in HRR-positive mCSPC

1. Rathkopf DE, et al. *J Clin Oncol.* 2021;39 (6_suppl). 2. Agarwal N, et al. *Future Oncol.* 2024;20(9):493-505.