

Association of somatic/germline homologous recombination repair (HRR) alterations with prostate-specific antigen, radiographic and second progression-free survival (PSA-PFS, rPFS and PFS2) in metastatic hormone-sensitive prostate cancer by disease volume

David Lorente¹, Daniel Tello Velasco², Ana Jambriana², Ignacio Gonzalez-Ginel², Nuria Romero-Laorden^{3,4}, Diogo Nunes-Carneiro⁵, Casilda Llácer⁶, Manuel Balongo^{2,6}, Rocio Santos^{6,7}, David Hernández⁸, Alexandra Jürgens⁹, Camille Capone¹⁰, Marco Trevisan¹¹, Suzy Van Sanden¹², Gabriel Stulnig¹³, Pedro P. López-Casas², Daniel E. Castellano², Bernardo Herrera-Imbroda^{6,7}, David Olmos², Elena Castro²

¹Instituto Valenciano de Oncología, Valencia, Spain; ²H2 Biomedical Research Institute, Hospital Universitario 12 de Octubre, Madrid, Spain; ³Hospital Universitario La Princesa, Madrid, Spain; ⁴Universidad Autónoma de Madrid, Madrid, Spain; ⁵Centro Hospitalar e Universitario de Santo António, Porto, Portugal; ⁶Instituto de Investigación Biomédica de Málaga (IBIMA-Plataforma BIONAND), Málaga, Spain; ⁷Hospital Universitario Virgen de la Victoria de Málaga, Málaga, Spain; ⁸Hospital Regional Universitario de Málaga, Málaga, Spain; ⁹Janssen, Neuss, Germany; ¹⁰Janssen Inc., Issy Les Moulineaux, France; ¹¹Janssen Pharmaceuticals, Zug, Switzerland; ¹²Janssen Pharmaceutica NV, Beerse, Belgium; ¹³Janssen-Cilag Pharma GmbH, Vienna, Austria

Key Takeaways

Patients with BRCA mutations experienced significantly earlier PSA progression compared with those without mutations, regardless of tumour burden (low or high volume disease); a similar, but less pronounced, trend was observed for patients with other HRR mutations

Patients with HRR mutations, particularly those with BRCA alterations, more frequently progressed to second-line standard treatments for mCRPC, suggesting a faster progression through initial therapy

This further evidence that patients with BRCA mutations progress more rapidly on second-line treatments than patients without mutations, reinforces the need for tailored therapeutic strategies in this population

Conclusions

Biochemical progression events occurred earlier in patients with HRR alterations, particularly BRCA mutations, and were followed by radiographic progression notably earlier than in patients without mutations

These poor outcomes are not compensated with standard second-line therapies, as benefit was also short lived among patients receiving subsequent treatment (where PARPi use was scarce)

Our findings highlight the need for novel targeted therapies such as PARPi to reverse the poor outcomes in this population



Please scan QR code

Poster

<https://www.congresshub.com/Oncology/ESMO2025/Niraparib/Lorente>

Supplementary material

Copies of this poster obtained through QR, AR and/or text key codes are for personal use only and may not be reproduced without written permission of the authors



Acknowledgements

The authors thank the patients, physicians, and investigators who participated in this study. We would also like to thank the ACHILLES study/PROCURE platform of CRIS contra el cáncer, as well as the ISCIII, Fundación FERO and Fundación Científica de la AEC, for the ongoing support to David Olmos' and Elena Castro's research teams. Editorial assistance was provided by Natalie Nkwor, MSc, of Excerpta Medica BV, Netherlands, and was funded by Janssen Pharmaceutica NV.

Disclosures

This study was funded by Janssen Pharmaceutica NV. All authors had access to the data, were involved in the design and conduct of the study.

David Lorente has taken on consultant or advisory role for AstraZeneca, Bayer, Bristol Myers Squibb, Janssen (J&J) and Pfizer; received speaker fees from Astellas, AstraZeneca, Bayer, Janssen, MSD, Pfizer and Sanofi; and received travel support from Astellas, AstraZeneca, Bayer, F. Hoffmann-La Roche, Janssen and Pfizer.

Background

- Patients with mCRPC who carry mutations in HRR genes, particularly *BRCA1/2* (BRCA), face a poor prognosis¹
- In the CAPTURE observational study, we extended these findings to the mHSPC setting, showing that BRCA mutations and other HRR alterations are associated with shorter rPFS and OS, independent of disease volume²
- These insights underscore the urgent need for therapies tailored to patients with HRR/BRCA mutations; recent studies have demonstrated that PARPis can improve survival outcomes in patients with these alterations, both in mCRPC³ and mHSPC⁴
- Building on this evidence, we present new analyses of additional disease progression events to further evaluate the prognostic impact of HRR/BRCA mutations in mHSPC
- We also report on subsequent treatments received, highlighting that disease in patients with BRCA mutations tends to progress faster than in those without mutations, reinforcing the potential benefit of targeted therapy in this population

Results

Patient population

- Of 556 patients, 159 (28.6%) had HRR gene alterations: 69 (12.4%) with BRCA and 90 (16.2%) with HRR non-BRCA mutations (Figure 2)²
- Observed baseline characteristics, for all patients and by mutational subgroups, are shown in Table 1²
 - mHSPC was classified by conventional imaging as high volume in 306 (55.0%) and low volume in 250 (45.0%) patients
 - The most common treatment regimen was ADT plus an androgen receptor pathway inhibitor (44.8%), while 30.4% received ADT plus docetaxel, and 11.3% were treated with triplet therapy (ADT plus docetaxel plus an androgen receptor pathway inhibitor); only 13.5% received ADT alone
 - Baseline patient characteristics and treatments administered were similar across all subgroups after adjustment

Figure 2. Distribution of subgroups according to mutation type

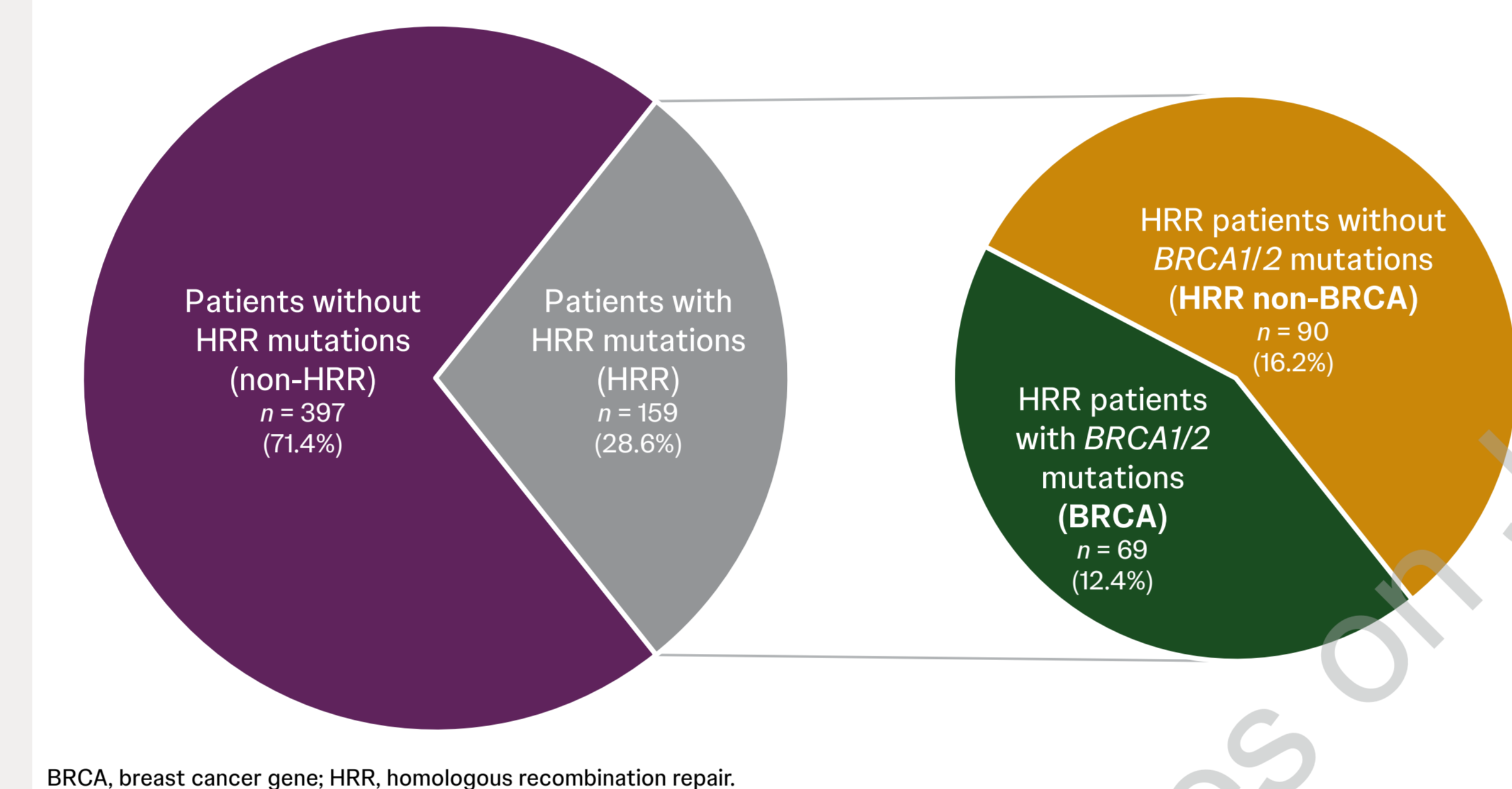


Table 1. Observed baseline characteristics, overall and by subgroups

Characteristic	All patients (N = 556)	BRCA (n = 69)	Non-BRCA (n = 487)	HRR (n = 159)	Non-HRR (n = 397)
Age at study entry, years, n (%)					
Median	70.2	70.4	70.0	70.4	69.9
<75	384 (69.1)	48 (69.6)	336 (69.0)	111 (69.8)	273 (68.8)
≥75	172 (30.9)	21 (30.4)	151 (31.0)	48 (30.2)	124 (31.2)
ECOG PS at study entry, n (%)					
0	341 (61.3)	41 (59.4)	300 (61.6)	91 (57.2)	250 (63.0)
≥1	215 (38.7)	28 (40.6)	187 (38.4)	68 (42.8)	147 (37.0)
Metastatic status at entry, n (%)					
Synchronous	451 (81.1)	56 (81.2)	395 (81.1)	136 (85.5)	315 (79.3)
Metachronous	105 (18.9)	13 (18.8)	92 (18.9)	23 (14.5)	82 (20.7)
Bone metastases at study entry, n (%)					
No	114 (20.5)	16 (23.2)	98 (20.1)	32 (20.1)	82 (20.7)
Yes	442 (79.5)	53 (76.8)	389 (79.9)	127 (79.9)	315 (79.3)
Visceral metastases at study entry, n (%)					
No	462 (83.1)	59 (85.5)	403 (82.8)	135 (84.9)	327 (82.4)
Yes	94 (16.9)	10 (14.5)	84 (17.2)	24 (15.1)	70 (17.6)
Treatment, n (%)					
ADT only	75 (13.5)	11 (15.9)	64 (13.1)	24 (15.1)	51 (12.8)
DOCE + ADT	169 (30.4)	26 (37.7)	143 (29.4)	55 (34.6)	114 (28.7)
ARPi + ADT	249 (44.8)	26 (37.7)	223 (45.8)	66 (41.5)	183 (46.1)
ARPi + DOCE + ADT	63 (11.3)	6 (8.7)	57 (11.7)	14 (8.8)	49 (12.3)
CHAARTED volume score, n (%)					
High volume	306 (55.0)	42 (60.9)	264 (54.2)	86 (54.1)	220 (55.4)
Low volume	250 (45.0)	27 (39.1)	223 (45.8)	73 (45.9)	177 (44.6)

ADT, androgen-deprivation therapy; ARPi, androgen receptor pathway inhibitor; BRCA, breast cancer gene; DOCE, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair.

Abbreviations

ABI, abiraterone; ADT, androgen-deprivation therapy; ARPi, androgen receptor pathway inhibitor; BRCA, breast cancer gene; CABA, cabazitaxel; CI, confidence interval; DOCE, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; ENZA, enzalutamide; HR, hazard ratio; HRR, homologous recombination repair; IPTW, inverse probability treatment weighting; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; PFS, progression-free survival; PFS2, second PFS; PSA, prostate-specific antigen; Ra223, radium-223; rPFS, radiographic progression-free survival; TTRC, time to castration resistance.

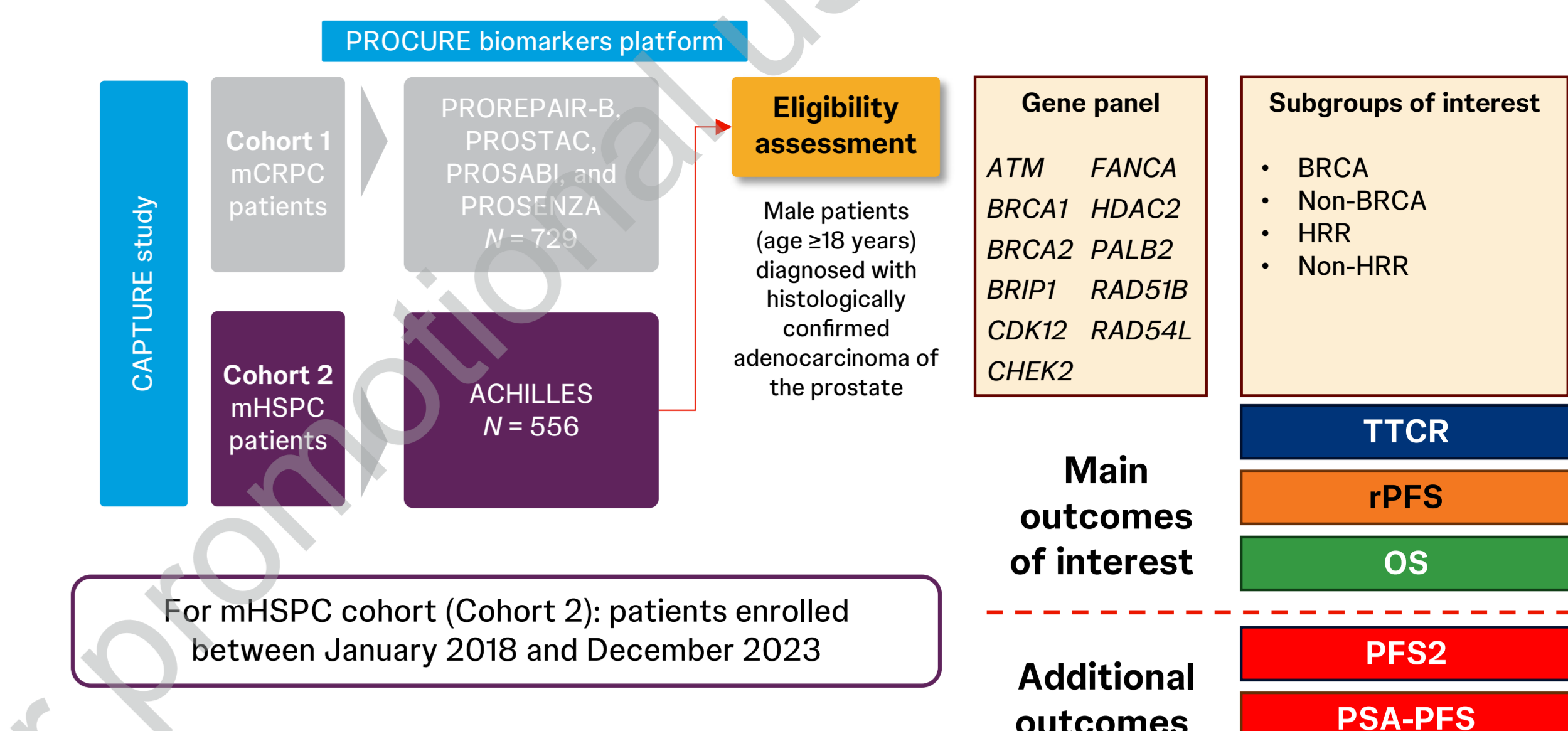
References

1. Olmos D, et al. *Ann Oncol*. 2024;35:458-472. 2. Olmos D, et al. *Ann Oncol*. 2025;36:1190-1202. 3. Chi KN, et al. *Ann Oncol*. 2023;34:772-782. 4. Attard G, et al. *Nat Med*. 2025. doi:10.1038/s41591-025-03961-8.

Methods

- CAPTURE is an observational, multicohort study using data, derived from an ongoing low-intervention study and collated in the PROCURE Biomarkers Platform, to investigate outcomes based on HRR mutation status in patients with prostate cancer (Figure 1)²
- Eligible patients with mHSPC, who were originally enrolled in the ACHILLES study between January 2018 and December 2023, underwent paired somatic/germline DNA sequencing²
- Cases with alterations in ≥ 1 HRR gene were classified as BRCA or non-BRCA and HRR or non-HRR²
- Main outcomes of interest (rPFS, time to castration resistance, and OS) for all subgroups have previously been reported²
- Here we present second PFS (PFS2), rPFS, and prostate-specific antigen PFS (PSA-PFS) data for all subgroups; associations between mutations and outcomes were assessed after controlling for treatment modality and baseline characteristics using inverse probability of treatment weighting models

Figure 1. Study design

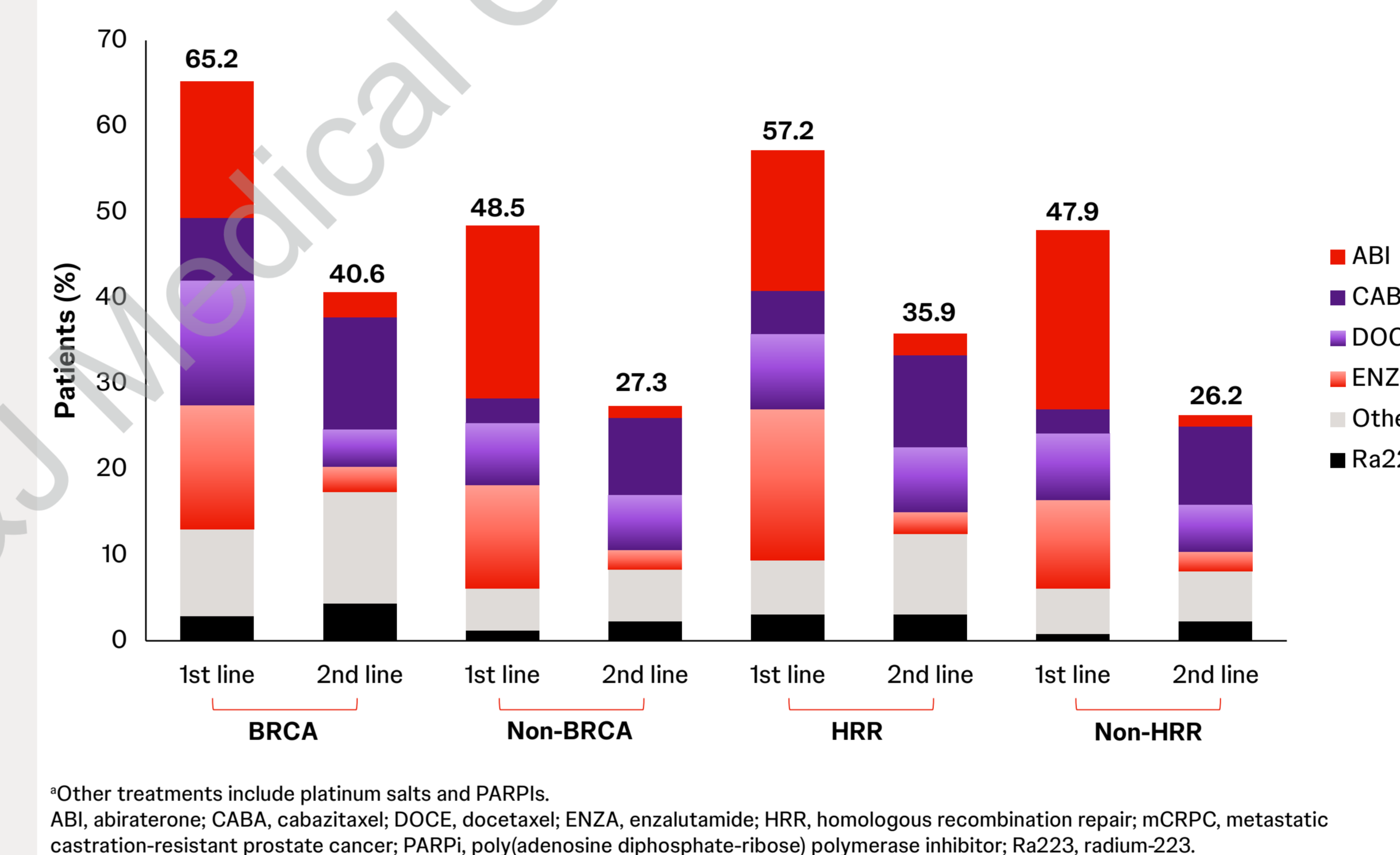


BRCA, breast cancer gene; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PFS2, second progression-free survival; PSA-PFS, prostate-specific antigen progression-free survival; rPFS, radiographic progression-free survival; TTRC, time to castration resistance.

Subsequent treatments

- More patients with alterations received subsequent treatments (including novel hormone therapy and taxanes) for mCRPC than patients without mutations (Figure 3)
- First line
 - BRCA: 65.2%; non-BRCA: 48.5%
 - HRR: 57.2%; non-HRR: 47.9%
- Second line
 - BRCA: 40.6%; non-BRCA: 27.3%
 - HRR: 35.9%; non-HRR: 26.2%

Figure 3. Subsequent first- and second-line treatments for mCRPC

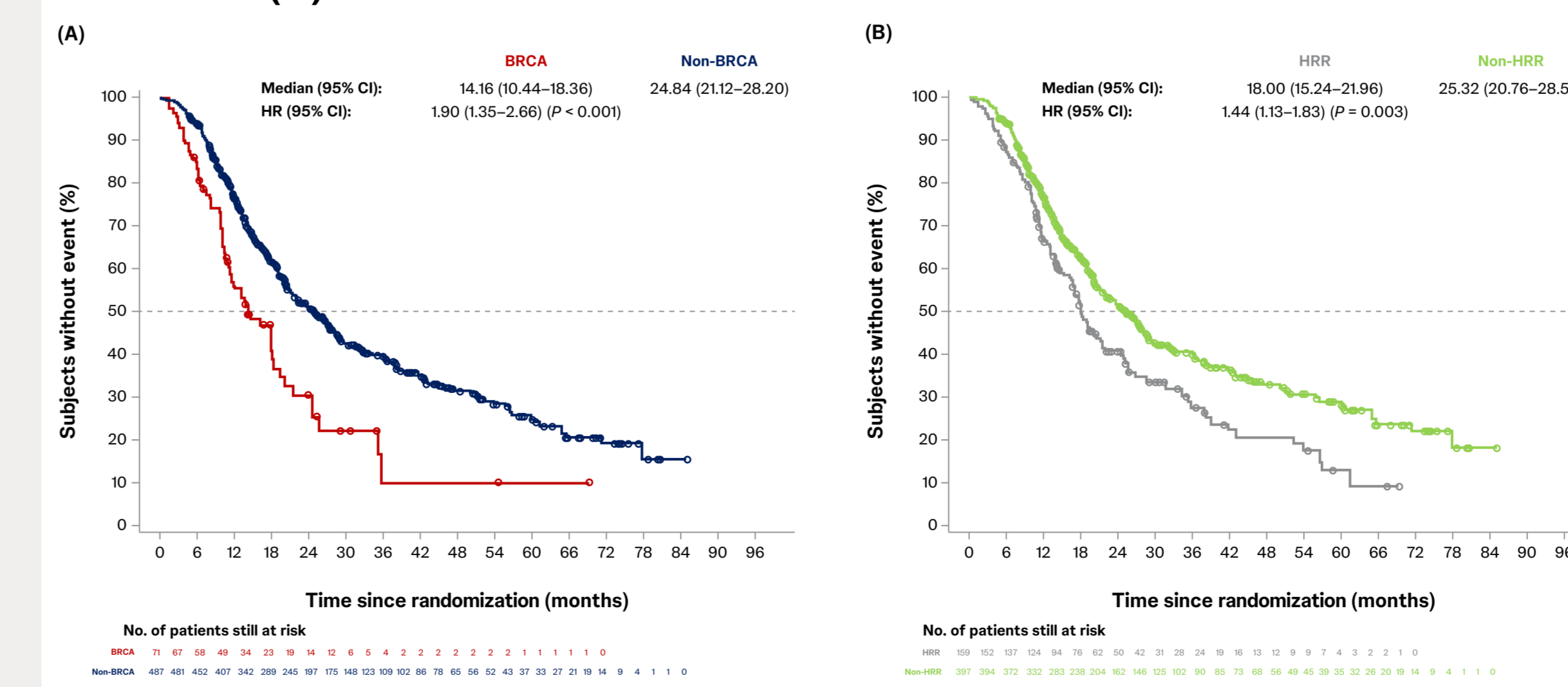


*Other treatments include platinum salts and PARPis. ABI, abiraterone; CABA, cabazitaxel; DOCE, docetaxel; ENZA, enzalutamide; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; PARPi, poly(adenosine diphosphate-ribose) polymerase inhibitor; Ra223, radium-223.

Comparison of outcomes between mutational subgroups

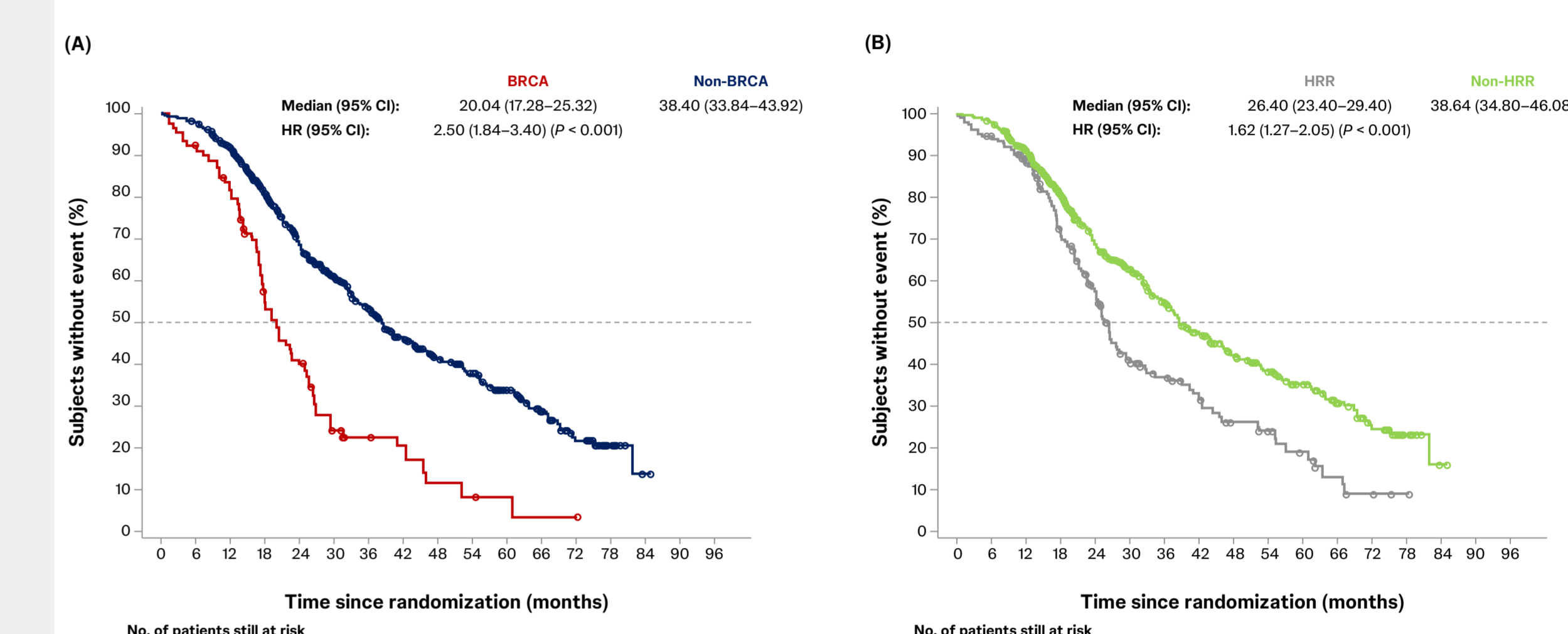
- After IPTW adjustment, all survival outcomes were significantly shorter in patients with BRCA mutations compared with the non-BRCA subgroup
 - Median PSA-PFS was 14.2 vs 24.8 months (HR 1.9 [95% CI 1.4–2.7]; $P < 0.001$; Figures 4A and 6A)
 - Median rPFS was 13.6 vs 30.4 months (HR 2.4 [95% CI 1.8–3.3]; $P < 0.001$; Supplementary Figure 1A and Figure 6A)²
 - Median PFS2 was 20.0 vs 38.4 months (HR 2.5 [95% CI 1.8–3.4]; $P < 0.001$; Figures 5A and 6A)
- The presence of HRR mutations, when compared with the non-HRR subgroup, was also associated with an adverse impact, but of a smaller magnitude
 - Median PSA-PFS was 18.0 vs 25.3 months (HR 1.4 [95% CI 1.1–1.8]; $P = 0.003$; Figures 4B and 6B)
 - Median rPFS was 20.5 vs 30.6 months (HR 1.6 [95% CI 1.3–2.0]; $P < 0.001$; Supplementary Figure 1B and Figure 6B)²
 - Median PFS2 was 26.4 vs 38.6 months (HR 1.6 [95% CI 1.3–2.1]; $P < 0.001$; Figures 5B and 6B)

Figure 4. PSA-PFS by subgroups:^a BRCA vs non-BRCA (A) and HRR vs non-HRR (B)



*Results presented are from IPTW analysis. CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IPTW, inverse probability treatment weighting; PSA-PFS, prostate-specific antigen progression-free survival.

Figure 5. PFS2 by subgroups:^a BRCA vs non-BRCA (A) and HRR vs non-HRR (B)

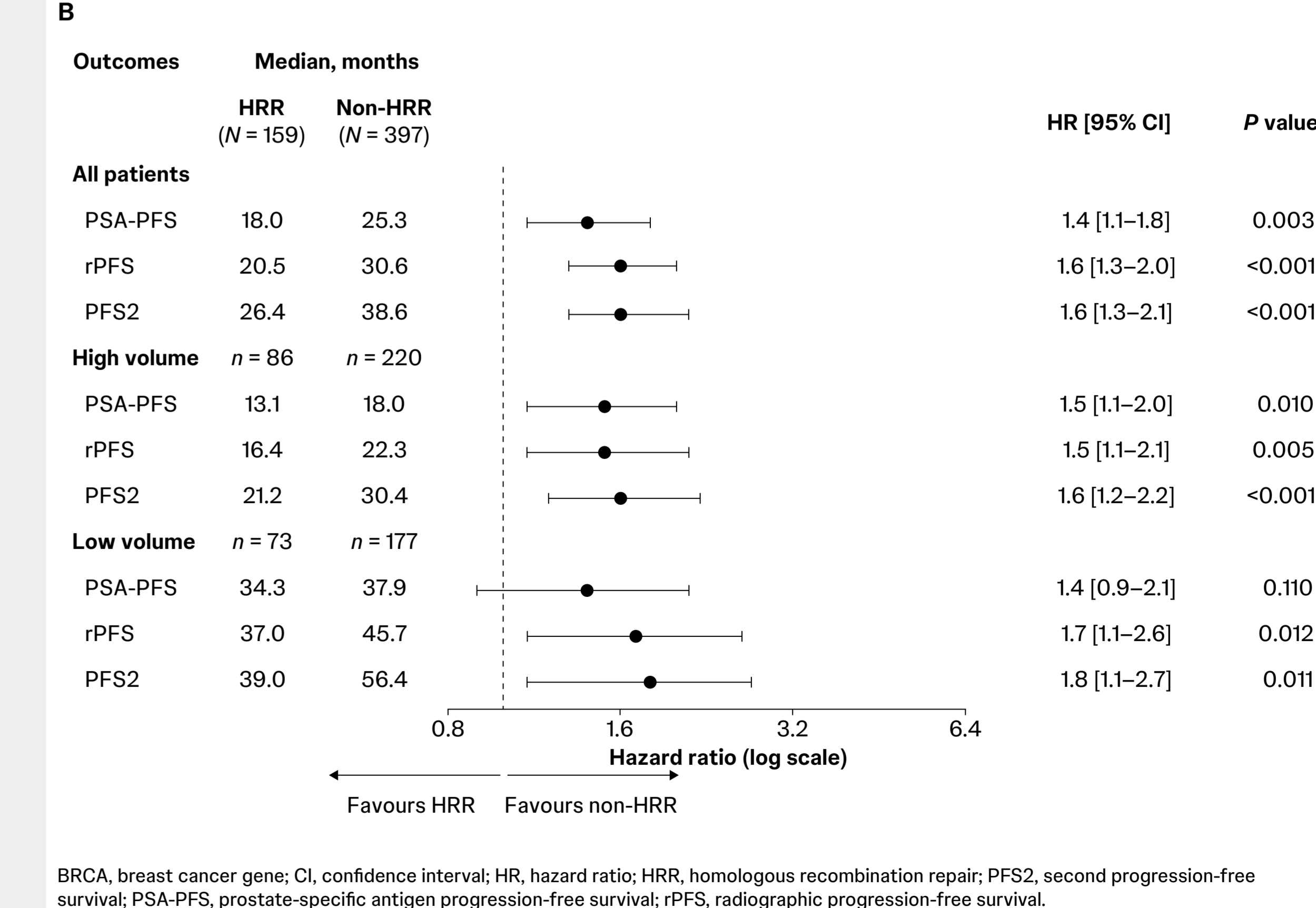
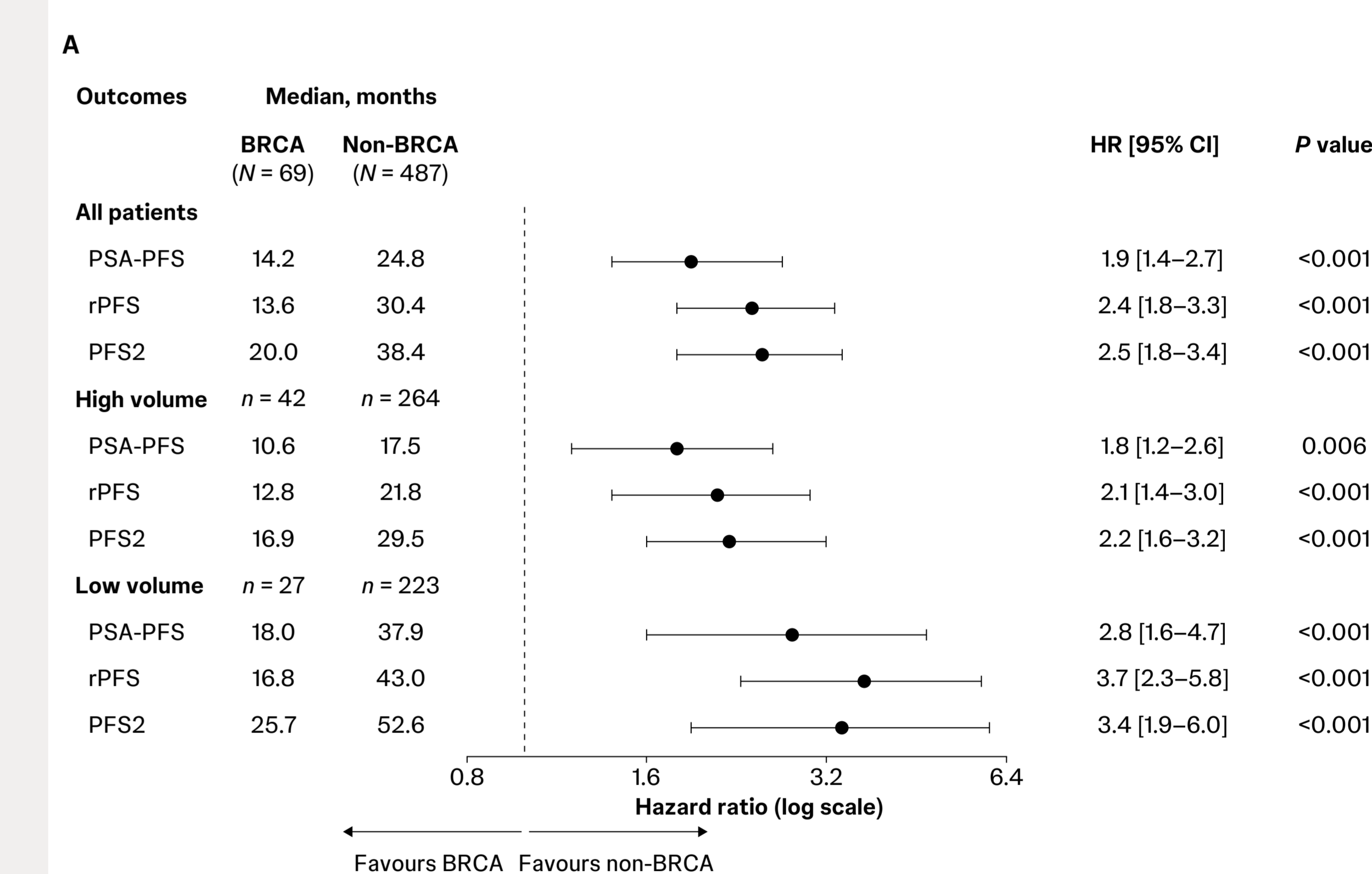


*Results presented are from IPTW analysis. CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IPTW, inverse probability treatment weighting; PFS2, second progression-free survival.

Comparison of outcomes between mutational subgroups by tumour burden

- PFS2 and PSA-PFS were significantly shorter in the presence of BRCA mutations across low- and high-volume disease; notably, this effect was more pronounced in patients with low-volume disease (Figure 6A)
- Similar differences were observed when the HRR and non-HRR subgroups were compared; however, the PSA-PFS difference did not reach statistical significance for low-volume disease (Figure 6B)

Figure 6. Treatment outcomes by high-volume and low-volume disease: BRCA vs non-BRCA (A) and HRR vs non-HRR (B)



BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; PFS2, second progression-free survival; PSA-PFS, prostate-specific antigen progression-free survival; rPFS, radiographic progression-free survival.

