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Impact of somatic/germline homologous recombination repair (HRR) alterations on metastatic hormone-sensitive prostate cancer (mHSPC) outcomes by disease volume

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Key takeaways

- Over 12% of patients with mHSPC had *BRCA1/2* (BRCA) alterations and a further 16% had alterations in other HRR genes
- The overall HRR prevalence rate in mHSPC was comparable to that seen in mCRPC
- Patients with HRR mutations, particularly BRCA alterations, showed significantly worse outcomes than those without, regardless of tumour burden
- ARPis improved outcomes compared with docetaxel in non-HRR patients, but not in BRCA/HRR patients, indicating a high unmet need in this latter population

Conclusions

Presence of HRR mutations, particularly BRCA alterations, significantly worsened prognosis with more aggressive progression patterns, regardless of disease volume or treatment regimen

These findings highlight the need for early HRR screening and underscore the importance of integrating tumour biology for accurate risk stratification in mHSPC and the design of new treatment strategies

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Supplementary material

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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.

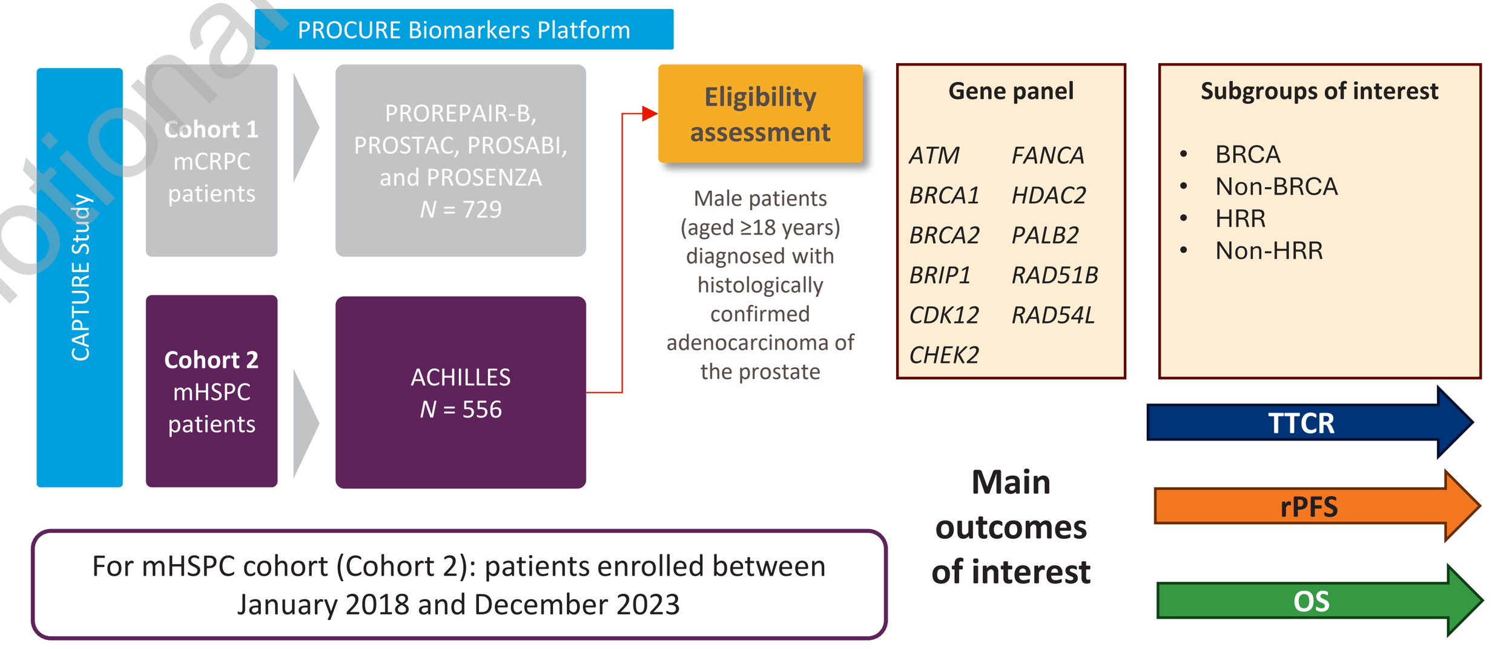
Background

- Alterations in *BRCA1/2* (BRCA) and other HRR genes have previously been shown to exert a negative impact on outcomes in patients with mCRPC[1]
- Poly(adenosine diphosphate-ribose) polymerase inhibitors, the only treatment demonstrated to improve the prognosis of patients with mCRPC,[2–5] are also being developed for the treatment of patients with mHSPC
- To fully assess their potential benefit in this setting, it is essential to understand how BRCA and HRR defects may influence the prognosis of conventionally treated patients with low- and high-disease volume
- Here we report the prevalence of somatic and germline alterations in HRR genes (including BRCA) in patients with mHSPC, and their impact on disease-onset characteristics and clinical outcomes, specifically exploring the associations between these mutations and tumour burden

Methods

- CAPTURE is an observational, multi-cohort 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**)
- Treatment patterns and outcomes by HRR status in patients with mCRPC have previously been reported[1]
- Here, we focus on the analysis of eligible mHSPC patients who were originally enrolled in the ACHILLES study between January 2018 and December 2023 and underwent paired somatic/germline DNA sequencing
- Cases with alterations in ≥1 HRR gene were classified as BRCA or non-BRCA and HRR or non-HRR
- rPFS, TTCR, and OS were reported 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



Results

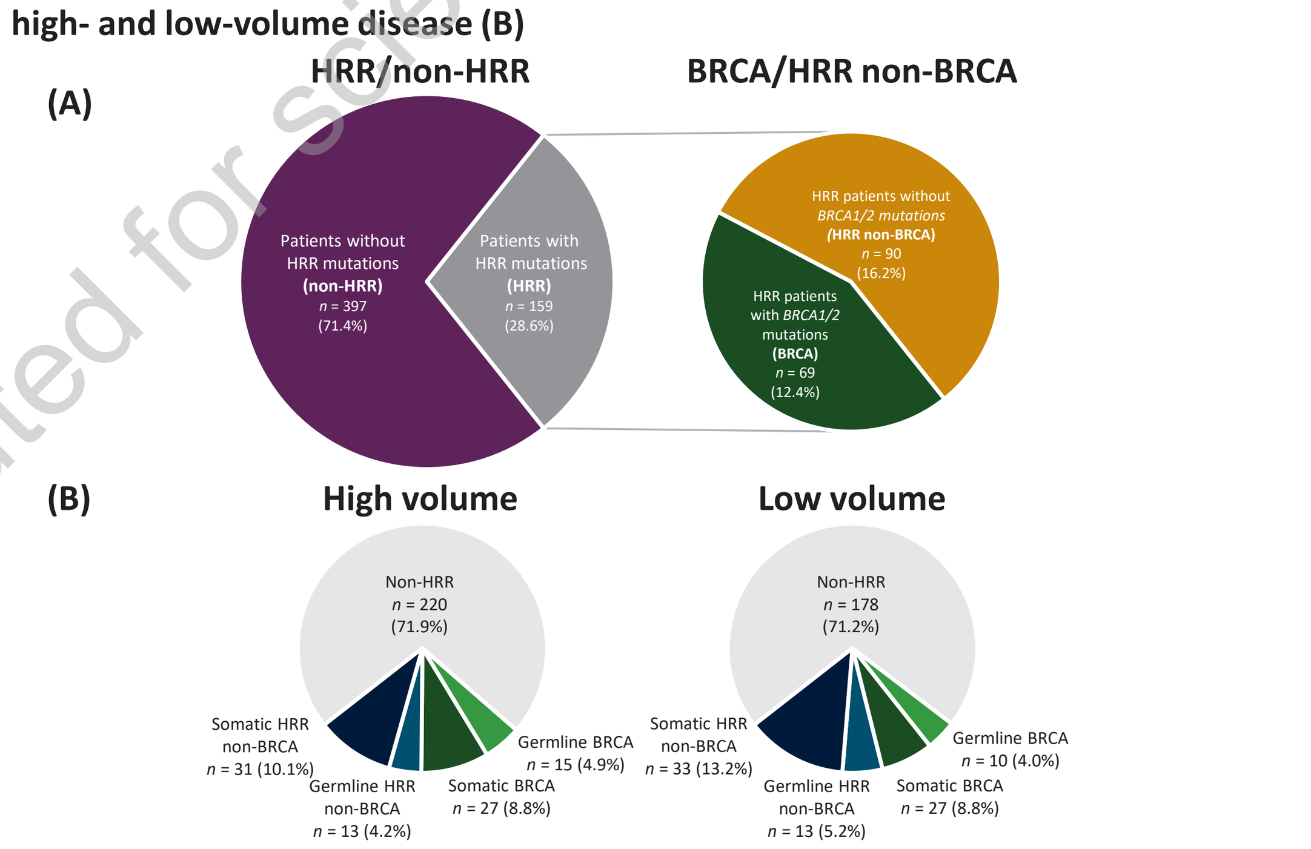
Patient population

- Observed baseline characteristics are shown in **Table 1**
- 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**)
- mHSPC was classified by conventional imaging as high volume in 306 (55.0%) and low volume in 250 (45.0%) patients
- mHSPC was synchronous in 451 patients (81.1%) and metachronous in 105 patients (18.9%)
- The most common treatment regimen was ADT plus ARPi (44.8%), while 30.4% received docetaxel plus ADT, and 11.3% were treated with triplet therapy. Only 13.5% received ADT alone
- Baseline patient characteristics and treatments administered were similar across all subgroups after adjustment

Table 1: Observed baseline characteristics, overall and by subgroups

	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)

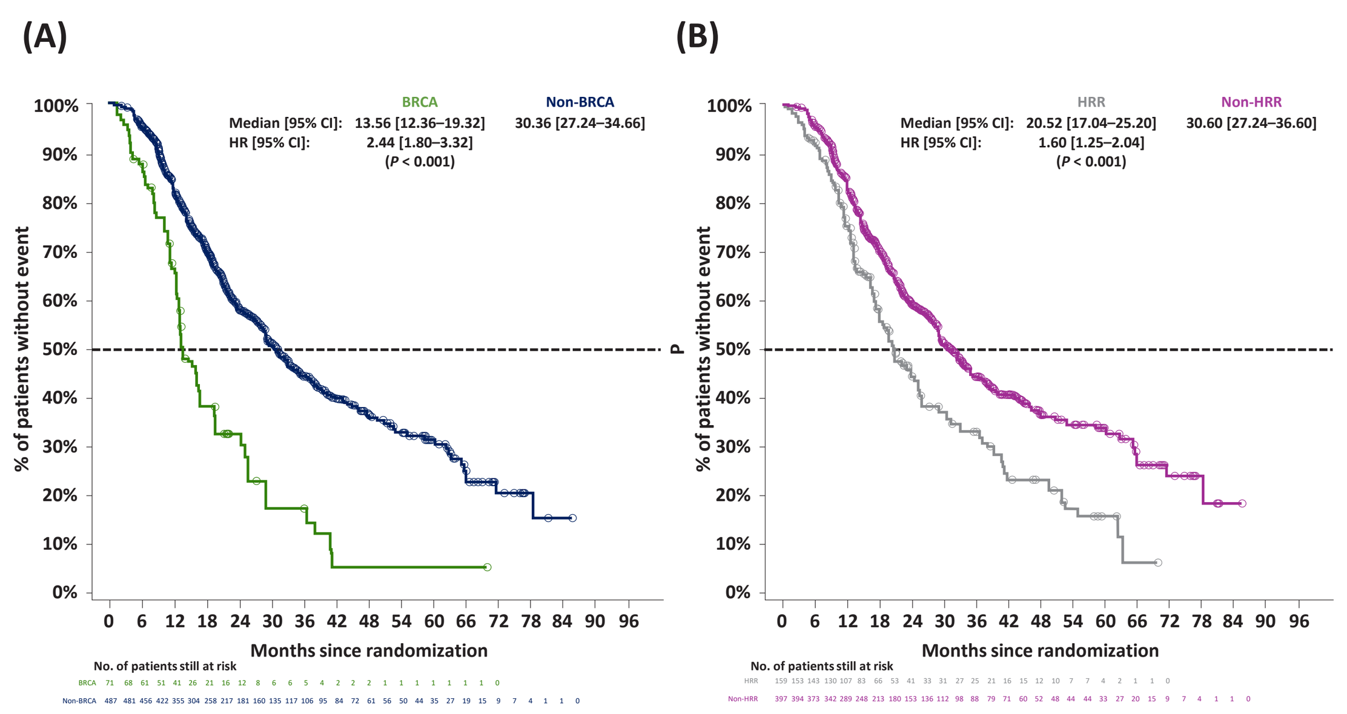
Figure 2: Distribution of subgroups according to mutation type (A) and frequency of HRR alterations by germline versus somatic in the subgroups of patients with high- and low-volume disease (B)



Comparison of outcomes between mutational subgroups

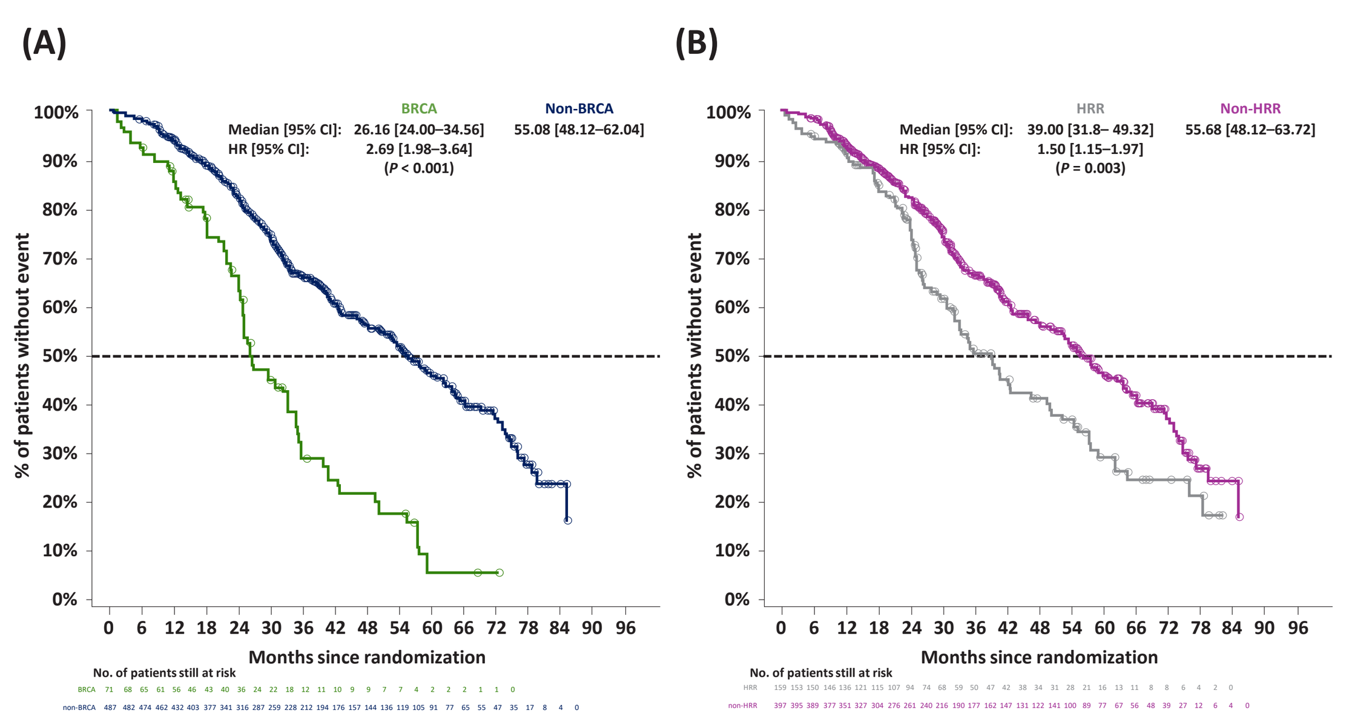
- All survival outcomes analysed after inverse probability treatment weighting adjustment were significantly shorter in the BRCA than in the non-BRCA subgroup:
  - Median rPFS were 13.6 vs 30.4 months (HR 2.4 [95% CI 1.8–3.3]; $P < 0.001$; **Figures 3A** and **5A**)
  - Median TTCR were 12.4 vs 22.3 months (HR 2.2 [95% CI 1.7–3.0]; $P < 0.001$; **Supplementary Figure 1A** and **Figure 5A**)
  - Median OS were 26.2 vs 55.1 months (HR 2.7 [95% CI 2.0–3.6]; $P < 0.001$; **Figures 4A** and **5A**)
- A similar, but less-pronounced, trend of significantly shorter outcomes was observed when comparing HRR and non-HRR subgroups:
  - Median rPFS were 20.5 vs 30.6 months (HR 1.6 [95% CI 1.3–2.0]; $P < 0.001$; **Figures 3B** and **5B**)
  - Median TTCR were 17.0 vs 22.9 months (HR 1.4 [95% CI 1.1–1.8]; $P = 0.003$; **Supplementary Figure 1B** and **Figure 5B**)
  - Median OS were 39.0 vs 55.7 months (HR 1.5 [95% CI 1.1–2.0]; $P = 0.003$; **Figures 4B** and **5B**)

Figure 3: rPFS by subgroups:[a] BRCA versus non-BRCA (A) and HRR versus non-HRR (B)



[a]Results presented are from IPTW analysis.

Figure 4: OS by subgroups:[a] BRCA versus non-BRCA (A) and HRR versus non-HRR (B)

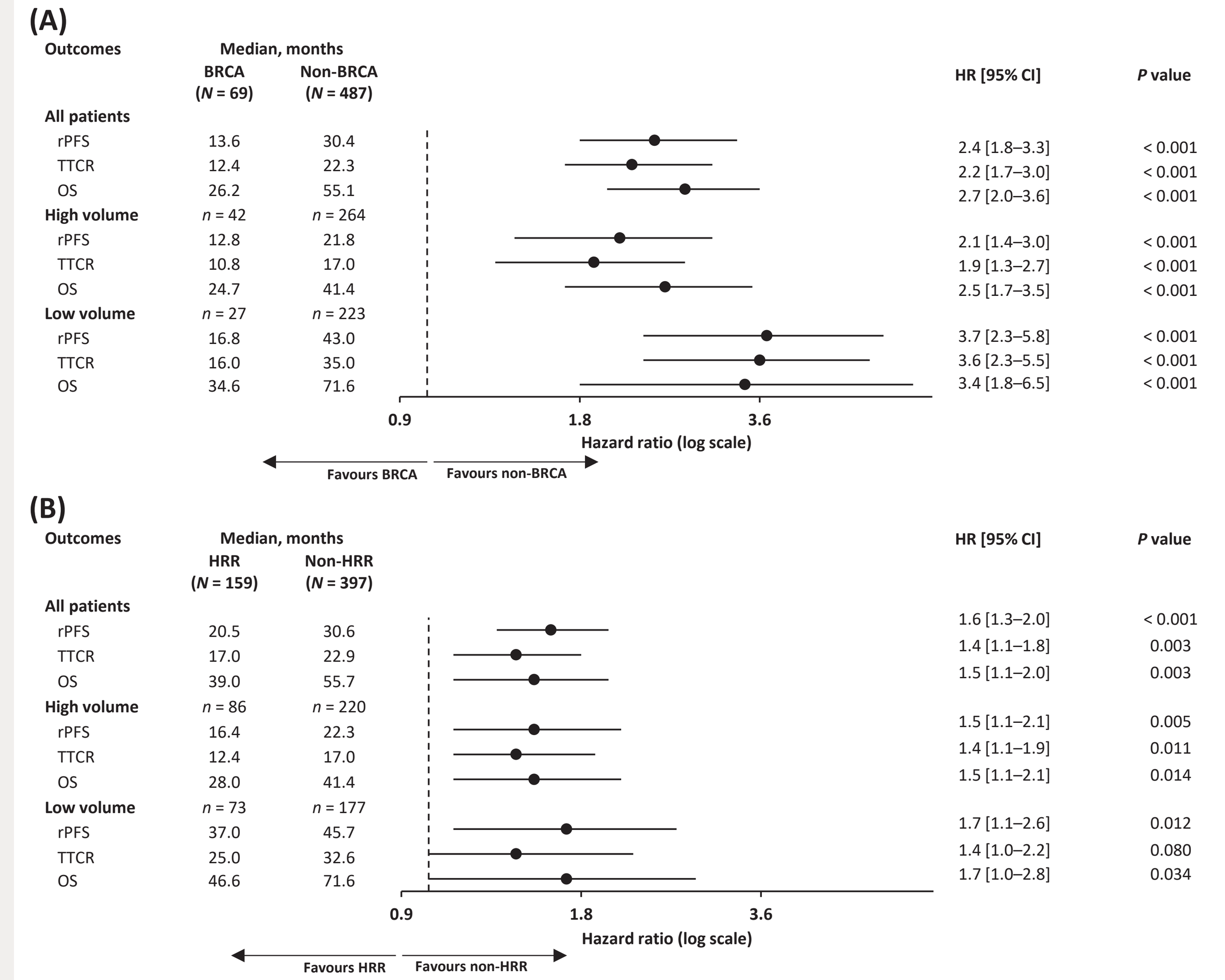


[a]Results presented are from IPTW analysis.

Comparison of outcomes between mutational subgroups by tumour burden

- The presence of BRCA and HRR alterations was associated with poor prognosis in both low- and high-volume subgroups; this adverse impact was stronger in the low-volume population (**Figure 5**)

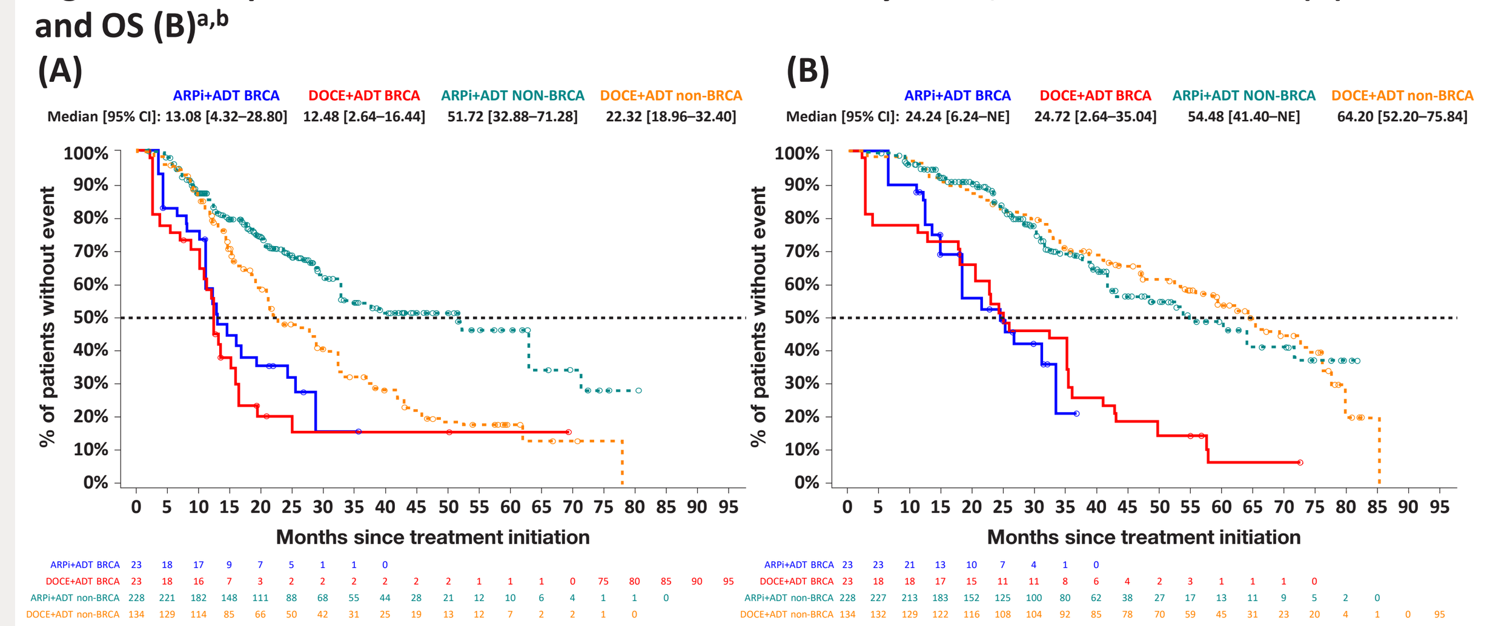
Figure 5. Treatment outcomes by high-volume and low-volume disease: BRCA versus non-BRCA (A) and HRR versus non-HRR (B)



Comparison of outcomes between treatments by mutational subgroups

- In a sensitivity analysis, ADT plus ARPi was compared with ADT plus docetaxel. Patients with BRCA had the worst outcomes, with no difference between treatment regimens (**Figure 6**)

Figure 6. Comparison of ADT+ARPi vs ADT+docetaxel by BRCA/non-BRCA for rPFS (A) and OS (B)[a,b]



Treatment comparison in BRCA (HR [95% CI]: 0.8 [0.3–1.7])
Treatment comparison in non-BRCA (HR [95% CI]: 0.5 [0.4–0.7])

Treatment comparison in BRCA (HR [95% CI]: 1.1 [0.4–2.8])
Treatment comparison in non-BRCA (HR [95% CI]: 1.1 [0.7–1.7])

[a]Results presented are from IPTW analysis.
[b]Balancing between treatment groups was performed within the BRCA and non-BRCA subgroups separately.

Abbreviations
ADT, androgen-deprivation therapy; ARPi, androgen receptor pathway inhibitor; CI, confidence interval; DOCE, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; 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; rPFS, radiographic progression-free survival; TTCR, time to castration resistance.

References
1. Olmos D, et al. *Ann Oncol.* 2024;35:458-472. 2. De Bono JS, et al. *Lancet Oncol.* 2021;22:1250-1264. 3. Mateo J, et al. *Lancet Oncol.* 2020;21:162-174.
4. Chi KN, et al. *Ann Oncol.* 2023;34:772-782. 5. Clarke NW, et al. *Eur Urol Oncol.* 2025;8:394-406.

Prostate Cancer

Presented by Dr David Olmos (@dolmos77, dolmos.imas12@h12o.es) at the 2025 American Society of Clinical Oncology Annual Meeting; May 30–June 3, 2025; Chicago, IL, USA.

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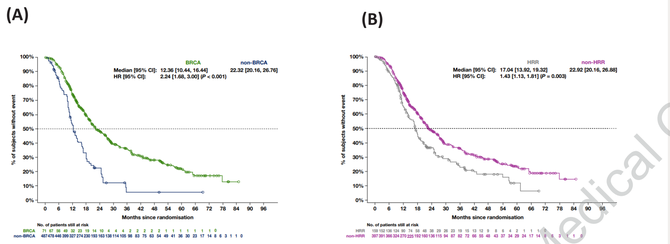
Supplementary page

(This page provides additional online content, that can only be accessed by scanning the QR code on the main poster)

Supplementary Figure 1: TTCR by subgroups:[a] BRCA versus non-BRCA (A) and HRR versus non-HRR (B)



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