Check for updates

BRCA-Altered High-Volume mHSPC: Which Intensification Should Come First?

Giandomenico Roviello,[1] Chiara Calandrelli,[3] Lorenzo Antonuzzo[2,3]

Clinical Genitourinary Cancer, Vol. 24, No.xxx, 102668 © 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Keywords: BRCA1/2 alterations, Docetaxel, High-volume disease, Metastatic hormone-sensitive prostate cancer, PARP inhibitors

For a fit patient with high-volume metastatic hormone-sensitive prostate cancer (mHSPC) harboring a BRCA1 or BRCA2 alteration, the problem is no longer whether to intensify treatment, but how. Docetaxel-based triplet therapy improves overall survival in high-volume populations, whereas early PARP inhibition markedly delays radiographic progression in molecularly selected populations enriched for BRCA alterations. These evidence streams were generated in parallel rather than against one another. The patient eligible for both strategies is therefore the patient for whom current trials provide the least direct guidance. High-volume disease is a clinical marker of early lethality, while BRCA1/2 loss identifies aggressive biology and sensitivity to PARP inhibition or platinum. When both coexist, accumulating active agents may appear attractive. However, the unanswered question is whether PARP inhibition should replace docetaxel, precede it, follow it, or be integrated with it, and whether additional disease control justifies cumulative toxicity and cost. The chemotherapy evidence is clinically persuasive but genomically uninformative. In PEACE-1, adding abiraterone to androgen-deprivation therapy (ADT) and docetaxel improved radiographic progression-free survival and overall survival in the docetaxel-treated population.[1] In ARASENS, darolutamide added to ADT and docetaxel reduced the risk of death, including in high-volume disease.[2,3] However, neither trial prospectively tested whether BRCA1/2 status modifies the benefit of triplet therapy. The PARP evidence has the opposite limitation. In AMPLITUDE, niraparib plus abiraterone improved radiographic progression-free survival in the BRCA subgroup compared with abiraterone alone (hazard ratio [HR], 0.52), but overall survival was immature (HR, 0.75; 95% CI, 0.51-1.11). Although 78% had high-volume disease, only 16% received docetaxel before study treatment.[4] TALApro3 showed a major radiographic benefit from talazoparib plus enzalutamide in HRR-altered disease (HR, 0.48), while overall survival remained immature. Prior docetaxel was prohibited after a protocol amendment and only approximately 1% had received it.[5] Neither trial determines whether PARP-based intensification is preferable to a docetaxel-based triplet for BRCA-mutated high-volume disease (Table 1). The hazard ratios invite informal ranking, but the trials differed in control regimens, eligibility, metastatic presentation, follow-up, subsequent therapies, and endpoints. An HR near 0.5 for radiographic progression cannot establish superiority over an HR near 0.7 for overall survival. A high-volume subgroup also cannot substitute for a BRCA-mutated high-volume subgroup. Early PARP inhibition may exploit sensitivity before resistant BRCA reversions emerge, but later use may retain activity and avoid exposing every patient to years of treatment. Current data support efficacy, not an optimal sequence. Docetaxel concentrates toxicity into 6 cycles. In ARASENS, grade 3 or 4 adverse events occurred in 66.1% with darolutamide triplet therapy and 63.5% with ADT plus docetaxel, mainly during chemotherapy.[2] In PEACE-1, grade 3 or worse events occurred in 63% with abiraterone triplet therapy versus 52% with ADT and docetaxel, largely because of hypertension.[1] PARP toxicity is chronic and surveillance intensive. In TALApro3, grade 3 or higher anemia occurred in 51%, serious adverse events in 42%, and 2 treatment-related deaths were reported.[5] In AMPLITUDE, grade 3 or 4 adverse events occurred in 75.2% with niraparib plus abiraterone; 29.1% developed grade 3 or higher anemia and 25.1% required transfusion.[4] Duration, reversibility, dose modifications, transfusions, quality of life, and the feasibility of later chemotherapy matter more than the maximum grade alone.

The economic contrast is similarly asymmetric. Docetaxel requires infusion capacity and acute supportive care, but its delivery is finite. PARP and ARPI combinations require continuous acquisition until progression, molecular testing, laboratory monitoring, transfusions, and toxicity management. Delayed progression may offset later care, but radiographic progression-free survival alone cannot establish value. Quality-adjusted survival, treatment-free time, cumulative healthcare use, and budget impact should be assessed across the entire sequence. A biomarker-defined strategy trial should enroll only fit patients with pathogenic BRCA1/2-altered, high-volume mHSPC. With ADT plus a common ARPI backbone, patients could be randomly assigned to upfront PARP inhibition or 6 cycles of docetaxel followed by protocol-defined

[1]Department of Health Sciences, University of Florence, Florence, Italy
[2]Clinical Oncology Unit, Careggi University Hospital, Florence, Italy
[3]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

Submitted: Aug 26, 2026; Accepted: Sep 6, 2026; Epub: 7 September 2026

Address for correspondence: Giandomenico Roviello, MD, PhD, Department of Health Sciences, Section of Clinical Pharmacology and Oncology, University of Florence, Viale Pieraccini 6, Florence 50139, Italy
E-mail contact: giandomenico.roviello@unifi.it

1558-7673/$ - see front matter © 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.
https://doi.org/10.1016/j.clgc.2026.102668

Table 1 What the Evidence Does and Does Not Resolve

Strategy	Evidence Signal	Critical Gap	Burden and Cost Pattern
Docetaxel triplet	OS benefit in high-volume disease[1-3]	No informative BRCA comparison	Finite treatment; acute toxicity and delivery costs
PARP plus ARPI	BRCA/HRR rPFS benefit[4,5]	OS immature; little docetaxel exposure	Chronic anemia, monitoring, transfusions, and drug costs
Sequential strategy	Biologically plausible	No randomized BRCA high-volume test	Potential cumulative toxicity and resource use

PARP inhibition at progression. A third arm of docetaxel followed by PARP maintenance before progression could test whether finite cytoreduction and early synthetic lethality are complementary, after safety is established. Pending this prospective evidence, this sequential approach might be explored in carefully selected fit patients with exceptionally high disease burden, particularly those with visceral or liver metastases, using 6 cycles of docetaxel for rapid cytoreduction followed by PARP inhibitor maintenance on an ADT–ARPI backbone, preferably within a clinical trial or prospective registry. Future studies should stratify by BRCA1 versus BRCA2, germline versus somatic status, biallelic loss, de novo presentation, visceral disease, and baseline anemia. Overall survival should remain decisive, supported by second progression-free survival, symptomatic progression, cumulative grade 3 or higher toxicity, transfusion burden, patient-reported outcomes, time without symptoms or toxicity, and quality-adjusted survival. Serial circulating tumor DNA should evaluate BRCA clearance and reversion mutations. Cost-effectiveness and budget impact should be embedded prospectively. Current evidence supports early intensification but not a universal hierarchy. For symptomatic, rapidly progressive, visceral, or otherwise threatening high-volume disease, finite docetaxel-based triplet therapy remains compelling because it has demonstrated an overall-survival benefit in the relevant clinical phenotype. For clearly pathogenic, preferably biallelic BRCA1/2 loss, a PARP and ARPI combination offers a large radiographic benefit and strong biologic rationale, particularly when chemotherapy is unsuitable or declined. Both are reasonable choices, but neither is proven optimal. Precision medicine has identified the BRCA-mutated high-volume patient as both high risk and potentially treatment sensitive, but has not identified which intensification should come first. The answer requires randomizing patients eligible for both strategies and measuring survival, lived toxicity, treatment-free time, and cost across the entire therapeutic sequence.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

AI tools were used solely for language editing of original schematic figures, and all content was reviewed and approved by the authors.

Data Availability Statement

No new datasets were generated or analyzed during the preparation of this manuscript.

Disclosure

GR: Scientific advisory boards, consulting, travel expenses: MSD, Merck Serono, Bayer, BMS, AAA, Astra Zeneca, Pfizer, Astellas. LA has received honoraria or consultation fees for speaker, consultancy, or advisory roles from Amgen, Bayer, Eisai, Merck Serono, Pierre Fabre, Roche, Servier, Incyte, Ipsen, and MSD; has also received travel grants from AstraZeneca, MSD, Merck Serono, and Ipsen; research funding was provided to LA's institution by Novartis and AstraZeneca.

CRediT authorship contribution statement

Giandomenico Roviello: Conceptualization, Data curation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Chiara Calandrelli:** Data curation, Writing – original draft. **Lorenzo Antonuzzo:** Conceptualization, Data curation, Writing – review & editing.

Acknowledgments

This work received no external funding.

References

1. Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1). *Lancet*. 2022;399:1695–1707. doi:10.1016/S0140-6736(22)00367-1.
2. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med*. 2022;386:1132–1142. doi:10.1056/NEJMoa2119115.
3. Hussain M, Tombal B, Saad F, et al. Darolutamide plus androgen-deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer by disease volume and risk subgroups in the phase III ARASENS trial. *J Clin Oncol*. 2023;41:3595–3607.
4. Attard G, et al. Niraparib and abiraterone acetate plus prednisone for HRR-deficient metastatic castration-sensitive prostate cancer: a randomized phase 3 trial. *Nat Med*. 2025;31:4109–4118. doi:10.1038/s41591-025-03961-8.
5. Agarwal N, Matsubara N, Azad AA, et al. PARP and androgen-signaling inhibition plus ADT in metastatic prostate cancer. *N Engl J Med*. 2026;395:427–439. doi:10.1056/NEJMoa2604126.