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Comments and Controversies

Re: Rohan Garje, Irbaz Bin Riaz, Syed Arsalan Ahmed Naqvi, et al. Systemic Therapy in Patients with Metastatic Castration-resistant Prostate Cancer: ASCO Guideline Update. J Clin Oncol 2025;43:2311–34

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The therapeutic landscape for metastatic prostate cancer has evolved rapidly in recent years, driven by advances in molecular profiling, the development of novel agents, and a growing emphasis on treatment personalization. Given the expanding arsenal of therapeutic options—including hormonal agents, radiopharmaceuticals, and targeted therapies—recent clinical guidelines have been proposed to support optimal sequencing of treatment. Among these, the updated American Society of Clinical Oncology guideline on systemic management of metastatic castration-resistant prostate cancer (mCRPC) by Garje et al [1] provides a structured framework for therapy selection that incorporates prior treatments and key genomic alterations, particularly *BRCA1/2* mutations. According to the proposed treatment algorithm, PARP inhibitor (PARPi) monotherapy is recommended for patients with *BRCA*-mutated mCRPC with previous androgen receptor pathway inhibitor (ARPI) exposure, while ARPI + PARPi combination therapy is recommended for ARPI-naïve patients.

While this sequencing reflects current clinical trial data, I believe that the role of combined ARPI + PARPi therapy could be reconsidered in selected patients with *BRCA*-mutated mCRPC who have previously received an ARPI, especially those who experienced a long response duration in the hormone-sensitive setting. In particular, long responders to upfront ARPI therapy (eg, >12 mo) and patients with no visceral crisis or rapidly evolving symptoms may still benefit from rechallenge of the AR axis (Table 1). In fact, tumors harboring BRCA1/2 mutations remain largely dependent on AR signaling even in advanced stages, and preclinical and clinical data suggest that early PARPi addition might delay acquired resistance to AR-targeted therapies [2].

Crucially, the pivotal PROpel, TALAPRO-2, and MAGNITUDE combination trials primarily enrolled ARPI-naïve patients [3–5]. As a result, data on the efficacy of ARPI + PARPi combinations in previously treated patients are limited. For example, MAGNITUDE excluded patients with prior novel ARPI therapy from its biomarker-positive cohort, while PROpel and TALAPRO-2 similarly selected ARPI-naïve participants. This evidence gap makes it difficult to determine whether exclusion of these patients from combination therapy is truly warranted or merely a byproduct of trial design.

Preclinical and translational studies suggest that BRCA-deficient tumors remain heavily reliant on AR signaling, even in later disease stages [2,6]. Moreover, early PARPi co-administration may mitigate the development of ARPI resistance mechanisms [2]. These observations provide a compelling biological rationale for administering ARPI

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Table 1 – Eligibility for continuation of ARPI + PARP inhibitor therapy in patients with *BRCA*-mutated metastatic castration-resistant prostate cancer

Clinical parameter	Eligible to continue ARPI + PARP inhibitor
Response to prior ARPI	Prolonged response (≥12 mo)
Symptoms	No visceral crisis or rapidly evolving symptoms
Performance status	Clinically stable profile

ARPI = androgen receptor pathway inhibitor.

therapy in selected patients with *BRCA* mutations, regardless of prior exposure.

I argue that ARPI + PARPi therapy should not be categorically withheld for patients with prior ARPI exposure, particularly those who responded well initially and have favorable clinical features (eg, absence of a visceral crisis). Continuing to target the AR pathway in this setting may extend the window of clinical benefit [7].

As the treatment landscape evolves, the current "either/or" approach to sequencing may soon become obsolete. I advocate for a more flexible, biology-driven strategy that takes treatment duration, depth of response, and underlying tumor AR dependence into account. Prospective trials specifically designed to test ARPI + PARPi in previously treated patients are urgently needed to close this evidence gap and guide personalized decision-making.

Conflicts of interest: The author has nothing to disclose.

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