Reshaping Prostate Cancer Therapies with Biomarker-Driven Strategies

Author: Katrina Thornber, EMJ, London, UK

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TARGETED treatments for prostate cancer were a central theme at the European Society for Medical Oncology (ESMO) Congress 2025, where speakers highlighted how advances in biomarker-driven approaches are reshaping patient management across the metastatic disease spectrum. Two presentations in particular, one on overcoming resistance through next-generation androgen receptor (AR) targeting, and another on exploiting vulnerabilities in homologous recombination repair (HRR), revealed both the opportunities and ongoing challenges of tailoring therapy based on tumour biology, from decoding AR alterations to expanding the role of poly (ADP-ribose) polymerase (PARP) inhibition.

TARGETING ANDROGEN RECEPTOR ALTERATIONS

Alice Bernard-Tessier, Institut Gustave Roussy, Villejuif, France, gave an insightful overview of the evolving landscape of targeting AR alterations in metastatic castration-resistant prostate cancer (mCRPC). Her talk highlighted the importance of the AR axis in prostate cancer pathology, and the clinical complexity of overcoming resistance driven by AR pathway reactivation.

Bernard-Tessier explained that AR alterations are the most frequent genomic events that occur in mCRPC, and that they accumulate as the disease progresses under the selective pressure of AR-targeted therapies.[1] Describing the role of the androgen receptor as both a problem and a solution, Bernard-Tessier explained that, although AR alterations are well established as prognostic markers, they have not yet consistently demonstrated predictive value for treatment selection. She outlined the three main classes of AR alterations: amplification, splicing variants, and mutations, explaining that each have different prevalences and prognostic implications. AR amplification is common (present in 40–60% of patients), and is associated with worse prognosis.[2,3] Splicing variants, particularly AR-V7, are also prognostic, and emerging evidence suggests that their presence may predict greater efficacy of chemotherapy compared to AR pathway inhibitors.[4] AR mutations increase in frequency with cumulative AR-directed treatment exposure, and are likewise associated with poorer outcomes.[5] These alterations have been known about for decades, Bernard-Tessier revealed, yet developing targeted agents remains an ongoing challenge.

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Challenges in Targeting Androgen Receptor Alterations

Bernard-Tessier described the challenges in translating the biological understanding of AR alterations into therapeutic success. Several targeted approaches have failed to progress, including galeterone, a CYP17 inhibitor evaluated in patients with AR-V7-positive mCRPC, which was terminated early due to a high screening failure and early dropout.[6] Additionally, third-generation AR antagonists, including compounds designed to more effectively inhibit the ligand-binding domain, have failed to demonstrate efficacy in patients who have experienced disease progression on an AR pathway inhibitor.[7]

Emergence of Androgen Receptor Degraders

In contrast, AR degraders have recently emerged as a promising therapeutic avenue. Bernard-Tessier highlighted BMS-986365, a novel drug candidate that is a dual AR degrader and antagonist capable of inducing AR degradation while retaining antagonistic activity.[8] In an early-phase trial in patients with heavily pre-treated mCRPC, progression-free survival responses in both AR-wild-type and AR-mutant disease were achieved, with particularly notable activity in the mutant subgroup. Among patients with AR mutations, prostate-specific antigen ≥50% was achieved in 55% of patients, with a median progression-free survival of 8 months. A similar pattern was observed with the AR degrader ARV-766, in which prostate-specific antigen ≥50% was achieved in 43% of patients with AR ligand-binding-domain mutant tumours.[9] Why AR degraders demonstrate enhanced activity in mutant disease remains under investigation, Bernard-Tessier explained, but hypotheses include increased binding affinity and a heightened dependency of mutated tumours on AR signalling. Despite this promising research, Bernard-Tessier emphasised that toxicity associated with AR degraders remains an important consideration, with common side effects including gastrointestinal adverse events and prolonged QT on ECGs.[8,9]

Ongoing Research

Looking ahead, Bernard-Tessier explained that most upcoming trials have not been designed to target AR alterations specifically. Instead, for some of them, AR mutations are a stratification biomarker, and for others, they are “not even part of the pre-plan analysis.” On reflection, she stated that we are still a long way from achieving precision medicine in this space. Advancing precision medicine will require more refined biomarkers and better detection methods. She highlighted circulating tumour DNA as a promising biomarker technique, although optimal timing and reimbursement remain unresolved challenges.

EXPLOITING HOMOLOGOUS RECOMBINATION WITH POLY (ADP-RIBOSE) POLYMERASE THERAPY

In the next session, the spotlight fell on HRR alterations and the rapidly evolving role of PARP inhibitors across the prostate cancer continuum. Neeraj Agarwal, Huntsman Cancer Institute, University of Utah Health, Salt Lake City, USA, began by establishing the prevalence of HRR alterations, noting that around 12% of men with metastatic prostate cancer carry germline pathogenic variants.[10] His own large somatic sequencing study, conducted with Foundation Medicine, Boston, Massachusetts, USA, and involving more than 3,400 patients, identified HRR alterations in roughly 25% of tumours,[11] emphasising the clinical importance of this population and the urgent need to expand genomic testing.

Evidence from Key Trials

Agarwal then outlined how PARP inhibitors (drugs that target DNA-repair defects) entered the mCRPC landscape. He highlighted a Phase II trial that was the first prospective evidence of their efficacy in this setting, whereby patients demonstrated radiographic progression-free survival and overall survival.[12] He then moved on to the pivotal Phase III PROfound and TRITON3 trials, explaining that both olaparib and rucaparib significantly improved radiographic progression-free survival compared with alternate AR pathway inhibitors, with TRITON3 also showing superiority over docetaxel.[13,14] The PROfound trial, he emphasised, demonstrated an overall survival benefit despite a 67% crossover rate from the control arm. These findings led to regulatory approvals for both agents in patients with mCRPC and HRR alterations.

Next, Agarwal devoted much of his session to combination strategies, explaining the rationale behind this approach being that AR inhibition appears to upregulate PARP activity, while PARP inhibition suppresses AR signalling. He explained that the link between these pathways inspired the PROpel, MAGNITUDE, and TALAPRO-2 trials.[15-17] Although their designs differed, ranging

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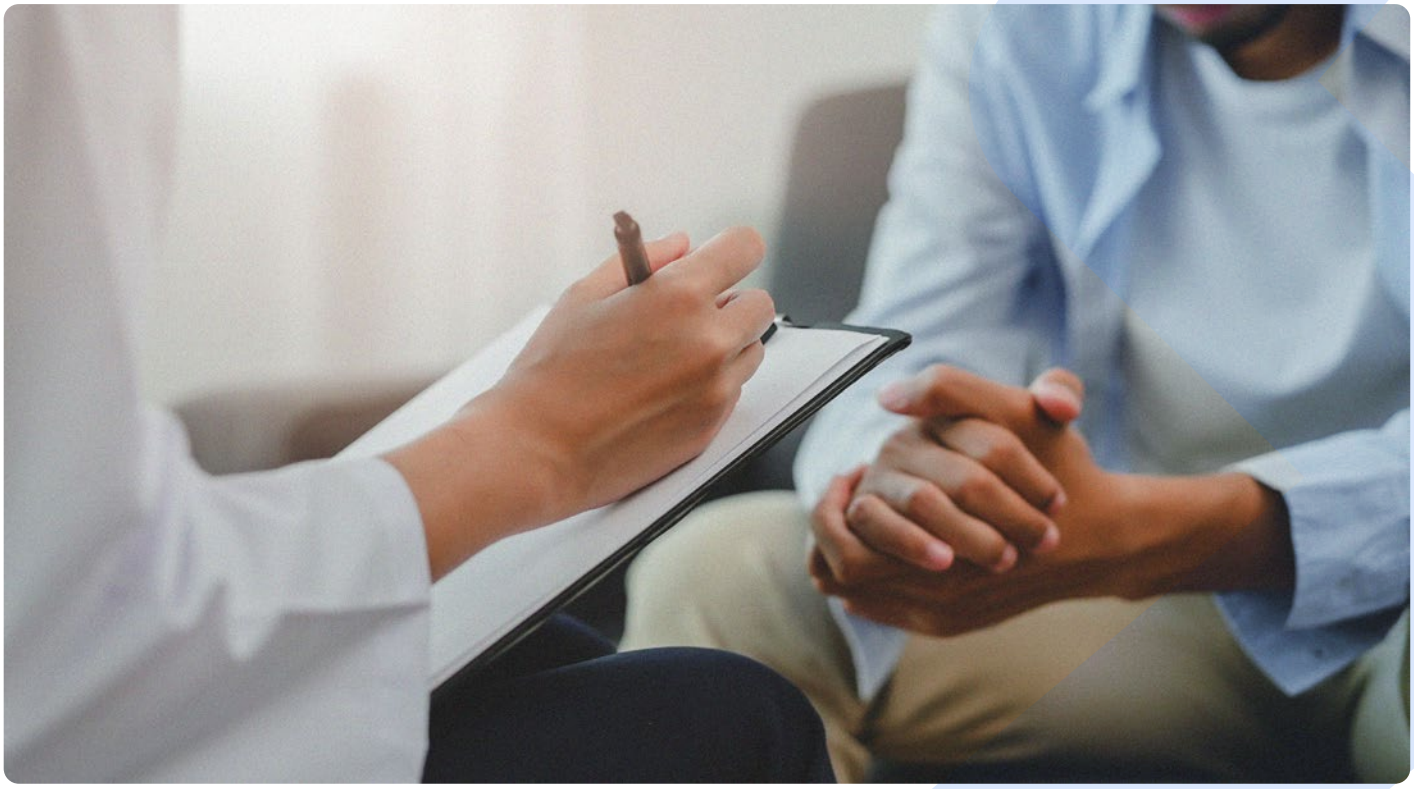

from all-comer cohorts to strictly biomarker-selected populations, and they involved different PARP inhibitors, all three trials showed substantial reductions in the risk of progression when a PARP inhibitor was added to an AR pathway inhibitor. The most significant effects were seen in *BRCA1/2*-mutated tumours, where PROpel and TALAPRO-2 demonstrated risk reductions of up to 80% for risk of progression or death. In TALAPRO-2, Agarwal added, for patients with HRR-altered mCRPC, enzalutamide plus talazoparib reduced the risk of death by 40%, extending median survival from around 31 months to 45 months. He described the data as "striking, with an unprecedented survival benefit."

Sequencing versus Upfront Combination

On the question of sequencing versus upfront combination, Agarwal acknowledged the absence of direct comparative trials to answer this question, but pointed to the Phase II BRCAAway study for insight.[18] In this study, sequential therapy yielded combined progression-free survivals of about 16 months, whereas upfront abiraterone plus olaparib extended this to 39 months. Although the trial was small, he described the difference as convincing. He also highlighted high attrition rates as a reason to use upfront combination, as real-world data show that fewer than half of patients proceed to second-line therapy.[19]

"If we don't combine upfront, we lose half the patients to prostate cancer," Agarwal said. Looking ahead, he described emerging data in metastatic hormone-sensitive prostate cancer, which are expected to further define the role of these agents earlier in the disease course.

Agarwal closed with a call to action, stressing that the advantages of PARP inhibition can only be realised through broader adoption of genomic testing. "It is unacceptable that NGS testing happened in fewer than 30% of patients in the USA in 2023," he said, urging clinicians to improve identification of biomarker-eligible patients and maximise benefits.

IN SUMMARY

Together, the presentations by Bernard-Tessier and Agarwal illustrated the expanding possibilities of biomarker-guided therapy in prostate cancer while highlighting persistent gaps in precision implementation. Both speakers emphasised that therapeutic innovation must go hand-in-hand with better biomarker detection. As the field moves towards next-generation AR degraders, earlier PARP inhibitor use, and more refined genomic stratification, the future of prostate cancer therapy will increasingly depend on integrating biological insights into routine clinical decision-making.

References

1. Watson PA et al. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nat Rev Cancer. 2015;15(12):701-11.
2. Robinson D et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015;161(5):1215-28.
3. Conteduca V et al. Androgen receptor gene status in plasma DNA associates with worse outcome on enzalutamide or abiraterone for castration-resistant prostate cancer: a multi-institution correlative biomarker study. Ann Oncol. 2017;28(7):1508-16.
4. Antonarakis ES et al. Androgen receptor splice variant 7 and efficacy of taxane chemotherapy in patients with metastatic castration-resistant prostate cancer. JAMA Oncol. 2015;1(5):582-91.
5. Bernard-Tessier A et al. Androgen receptor (AR) mutations in men with metastatic castration-resistant prostate cancer (mCRPC): incidence and natural history. J Clin Oncol. 2023;41:221.
6. Taplin ME et al. Clinical factors associated with AR-V7 detection in ARMOR3-SV, a randomized trial of galeterone (Gal) vs enzalutamide (Enz) in men with AR-V7+ metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol. 2017;35:5005.
7. De Bono JS et al. PI3K/AKT pathway biomarkers analysis from the phase III IPATential150 trial of ipatasertib plus abiraterone in metastatic castration-resistant prostate cancer. J Clin Oncol. 2021;39:13.
8. Rathkopf DE et al. Safety and clinical activity of BMS-986365 (CC-94676), a dual androgen receptor ligand-directed degrader and antagonist, in heavily pretreated patients with metastatic castration-resistant prostate cancer. Ann Oncol. 2025;36(1):76-88.
9. Petrylak DP et al. ARV-766, a proteolysis targeting chimera (PROTAC) androgen receptor (AR) degrader, in metastatic castration-resistant prostate cancer (mCRPC): initial results of a phase 1/2 study. J Clin Oncol. 2024;42:5011.
10. Pritchard CC et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med. 2016;375(5):443-53.

11. Chung JH et al. Prospective comprehensive genomic profiling of primary and metastatic prostate tumors. JCO Precis Oncol. 2019;3:PO.18.00283.
12. Mateo J et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med. 2015;373(18):1697-708.
13. de Bono J et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med. 2020;382(22):2091-102.
14. Fizazi K et al. Targeted inhibition of CYP11A1 in castration-resistant prostate cancer. NEJM Evid. 2024;3(1):EVIDoa2300171.
15. Clarke NW et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. NEJM Evid. 2022;1(9):EVIDoa2200043.
16. Chi KN et al. Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer. J Clin Oncol. 2023;41(18):3339-51.
17. Agarwal N et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet. 2023;402(10398):291-303.
18. Hussain M et al. Abiraterone, olaparib, or abiraterone + olaparib in first-line metastatic castration-resistant prostate cancer with DNA repair defects (BRCAAway). Clin Cancer Res. 2024;30(19):4318-28.
19. Swami U et al. Treatment pattern and outcomes with systemic therapy in men with metastatic prostate cancer in the real-world patients in the United States. Cancers (Basel). 2021;13(19):4951.