

# Testing and Treating Metastatic Castration-Resistant Prostate Cancer

In this **CancerNetwork® OncView™** program, faculty panelist Alicia Morgans, MD, MPH, explains the treatment options in this disease space and discusses recent drug approvals.



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A recent *OncView™* conversation presented by CancerNetwork® featured **Alicia Morgans, MD, MPH**, medical director of the Survivorship Program at Dana-Farber Cancer Institute in Boston, who discussed her perspective on genomic testing, treatment, and the use of PARP inhibitors in metastatic castration-resistant prostate cancer (mCRPC).

“There’s so much that we’re learning and figuring out, and it is only the beginning,” Morgans explained. “There are advances coming one after the other, and it’s quite a hopeful time for mCRPC.”

Morgans started the conversation by focusing on testing for homologous recombination repair (HRR) gene alterations, then moving on to treatment options with PARP inhibitors, and finally looking toward the future of treating metastatic prostate cancer.

## Germline and Somatic Testing for Prostate Cancer

The use of PARP inhibitors is not possible without first finding out if a patient is a candidate.

“Make sure that you’re doing testing for germline and somatic mutations, because if we don’t test, we won’t be able to find a patient who may benefit from therapies,” Morgans explained.

Morgans noted that patients and caregivers should consider germline or somatic testing for metastatic prostate cancer.

“For any patient with metastatic prostate cancer, we [encourage] germline genetic testing and [want] to ensure that this is done as soon as we meet the patient, because [these results] could have implications for his family members at the time of initial testing,” Morgans detailed.

Germline testing is utilized to target DNA repair defect mutations, which Morgans says can be involved with inheritable cancer syndromes. She mentioned that mutations in *BRCA1*, *BRCA2*, *PALB2*, as well as *MSH* and *MLH*, can put patients at risk for tumors that are high expressors of microsatellite instability (MSI) or tumor mutational burden (TMB).

“It’s important, as we think about these inheritable mutations, to recognize that they can be associated not just with prostate cancer, but with [other] cancers, including breast and ovarian,” Morgans said.

Somatic testing, Morgans explained will yield “twice the number of patients who may be eligible for ultimate treatment with targeted therapies like PARP inhibitors.”

Somatic testing is crucial for identifying indications like MSI-high status and TMB in patients with metastatic prostate cancer, which can only be found through this type of testing.

“It’s important for us to make sure that we are [testing], because for the 1% to 3% of patients who may have MSI-high

status, treatment [with] pembrolizumab [Keytruda] can be extremely effective. We won't know this is potentially an option unless we do the testing," said Morgans.

As for timing of the tests, germline testing should be done "as soon as the patient has metastatic disease," whereas timing for somatic testing is more variable, according to Morgans.

"That can depend on an individual clinician and their workflow, but it's necessary for treatment decision-making when we think about patients in the mCRPC space," she explained.

### Treatment Options and PARP Inhibitors for mCRPC

In mCRPC, Morgans mentioned a handful of potential treatment combinations with androgen deprivation therapy (ADT).

"One of the main purposes of our treatment plan for men with prostate cancer is that we want to change the mechanism of action of the treatments that we combine with our ADT. [This helps] target evolving mutations that may [make] a patient's cancer resistant to the prior therapy that they may have seen, in terms of their last treatment," Morgans explained.

Chemotherapy or immunotherapy in combination with sipuleucel-T (Provenge) can be an alternative approach that allows providers to change the mechanism of action used instead of administering another androgen receptor-targeted drug.

The chemotherapy agents docetaxel and cabazitaxel (Jevtana) are commonly used in mCRPC. Morgans mentioned that she takes clinical and patient factors into consideration for determining what treatment is best for each patient.

"I use a combination of clinical factors associated with the cancer, patient factors associated with his fitness, as well as patient preferences and needs, to make the decision for each individual patient," she explained.

Looking at safety, Morgans focused on preventing treatment-associated

cytopenias, which are common with some mCRPC therapy options. She added that kidney and liver function are also closely monitored during treatment.

"We as oncologists and urologists recognize that we need to monitor 2 things. First is safety and to ensure that the treatment we're giving is not causing complications that could put an individual at risk. We also monitor for disease response or progression," Morgans explained.

PARP inhibitors are an alternative treatment option in certain cases, with olaparib (Lynparza) and rucaparib (Rubraca) approved by the FDA for treating mCRPC.

The approval for olaparib came from the phase 3 PROfound trial (NCT02987543), which compared olaparib treatment with physician's choice of therapy for patients with mCRPC who progressed on enzalutamide (Xtandi) or abiraterone (Zytiga) and harbored HRR gene mutations.<sup>1</sup>

The defect mutations referenced from the trial for patients in both cohort A and cohort B included any of the following prespecified genes: *BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.

Results found that median imaging-based progression-free survival was significantly longer among patients who received olaparib vs control treatment with enzalutamide (Xtandi) or abiraterone (Zytiga) (7.4 months vs 3.6 months, respectively; HR, 0.34; 95% CI, 0.25-0.47;  $P < .001$ ).

The phase 2 TRITON study (NCT02952534) led to the approval of the PARP inhibitor rucaparib. The study evaluated oral rucaparib for patients with mCRPC who had evidence of a homologous recombination gene deficiency.<sup>2</sup>

"The indication for approval for rucaparib is for *BRCA1* or *BRCA2* alterations because those patients very

clearly had a significant response to treatment with rucaparib. This was a single-arm study, so that may have had a role in that targeted indication of *BRCA1/BRCA2*," Morgans explained.

The confirmed overall response rates via independent radiology review and investigator assessment were 43.5% (95% CI, 31.0%-56.7%) and 50.8% (95% CI, 38.1%-63.4%), respectively. The research concluded that rucaparib demonstrated antitumor activity and maintained a tolerable safety profile for patients with mCRPC who have deleterious *BRCA* mutations.

As for the safety of PARP inhibitors, Morgans said they are "generally well tolerated," with most patients not needing to discontinue treatment with these agents.

### Practical Treatment Considerations for Patients

Top of mind for Morgans was a patient's access to treatment for their disease. She mentioned that efficacy in a clinical trial and efficacy in the real-world setting are 2 different things, as access in the latter plays a role in patients receiving potentially lifesaving treatment.

"Patient access is always one of the most important things that we must think about because the treatment doesn't work if it's still in the bottle, in the bag, or in the pharmacy," Morgans said.

Further, Morgans touched on the treatment decision-making process, where she emphasized the need for dialogue with a patient to determine their needs and their specific treatment plan.

"At each decision time point, it's incumbent upon us to have those conversations with our patients and to find the right match for him," Morgans said. "If we don't pick the right match, we make a change and we choose the treatment that's going to be the right one for him moving forward." ■

For full references visit [cancernetwork.com/Morgans\\_1.22](https://cancernetwork.com/Morgans_1.22)