

PARP INHIBITION THERAPY — Clinical importance of genetic variants of BRCA 1/2 and ATM in men with metastatic castration-resistant prostate cancer.

Something big is emerging in the management of men with metastatic (often heavily pre-treated) castration-resistant prostate cancer: A new potential entry into the regimens of standard-of-care treatment of men with BRCA 1/2 and ATM mutations with PARP inhibitor therapy.

This Commentary is offered as a heads-up to seed *clinical awareness* that this rapidly evolving category of management is an option. It should be considered for all men with metastatic cancer who harbor these gene variants and are progressing despite current therapies.

Background:

An adult human has about 30 trillion cells that are continuously undergoing replication — albeit at different rates in different tissues. This process randomly creates mutations, most of which are inconsequential (‘passenger’ mutations). Other, far less frequent mutations predispose patients to cancer and accelerate cancer growth (‘driver’ mutations).

The BRCA family of genes, i.e., BRCA 1&2, ATM, CHEK2, CDK12, and others, when mutated, increase cancer aggressiveness and lessen the response to conventional hormone therapy. When functioning normally, these genes generate the enzymatic templates that repair the continuously damaged DNA. When mutations inactivate these first-line DNA repair genes, the responsibility for repair falls to the second-line PARP system. A family of drugs, including olaparib (‘Lynparza’) and others, has been developed to inhibit the rescue by the second-line PARP repair enzymes. A high mutational rate is characteristic of advanced cancer, making these cancers especially vulnerable to the combined malfunction of the first- and second-line repair systems — and un-repaired DNA damage induces cell death.

Prevalence of DNA repair mutations:

The commonly accepted figure for men with prostate cancer who have inherited mutations (‘germline’) in the BRCA2 gene is ~6% (higher in some studies). Other inherited mutated genes in the BRCA family include: BRCA1, 1.25%; ATM, 2%; CHEK2, 2.88%; and PALB2, 0.56%. This means that there is a total of 17% of men with a pathologic germline variant in the BRCA family. (Nicolosi et al., *JAMA Oncol.* 2019).

Based on tissue biopsies of metastatic lesions, Prichard et al., (*NEJM*. 2016) found that the cancers of 11.8% of men with metastases were enriched with BRCA2 and other BRCA-like germline variants. These men have a significant likelihood of responding to one of the family of PARP inhibitors.

The recent ‘PROfound’ trial reported impressive results in heavily pretreated men selected for BRCA1/2, ATM, and 12 other variants in the DNA damage repair family (Mateo et al., “TOPARP-B: A phase II randomized trial of the poly (ADP)-ribose polymerase (PARP) inhibitor olaparib for metastatic castration-resistant prostate cancers (mCRPC) with DNA damage repair (DDR) alterations. *J Clin Oncol*, 37 [suppl.5005].)

One portion of the trial tested 92 heavily pre-treated men with BRCA1/2 and ATM variants who had progressed through at least one hormone therapy and possibly a taxane chemotherapy and had imageable sites of metastatic disease. Randomization was between two dose levels of olaparib or a newer hormonal agent that had not been previously employed. Response was declared if the PSA declined by 50% or more, the scan abnormalities improved, or the numbers of circulating tumor cells decreased from >5/7.5 ml blood to <5 cells measured at 4-weeks.

Findings:

- Overall response rate was 54% in the 400 mg/day group and 37% in men taking 300mg per day.
- At 17.6 months of follow-up in patients with BRCA1/2 and ATM mutations, the median radiographic progression-free survival was extended by 7.4 months over 3.5 months in the hormone therapy control group. The overall survival in the olaparib cohort was 18.5 months compared to 15.1 months in the control group — a 66% reduction in risk of death and substantial reduction in pain. The survival data is not yet mature. These men who progressed on a hormone therapy were allowed treatment with olaparib.
- Response rate by mutational subgroups analyzed the percent meeting one of the response criteria: BRCA 1/2, 80%; ATM, 37%; PALB2 57%; and CDK12, 25%.
- Response measured specifically by >50% PSA decline: BRCA1/2, 73%; and 67% in patients with the PALB2 variant.

Quotes regarding this study from two respected prostate cancer researchers:

- “This is a truly practice-changing study ...we’re entering into the targeted-therapy era.”
– Eleni Efstathiou, MD, PhD, MD Anderson Cancer Center
- “I think... we’ve entered a new era and I call it a new world order for prostate cancer... And this is the first time we’re actually in a mode of targeted, based on pre-selection for potential responsiveness to treatment.”
– Maha Hussain, MD, Director Lurie Cancer Center, Northwestern University. (Interview with Alicia Morgans, *UroToday*)

Looking toward the future – liquid biopsies:

In the PROfound study, the variants were identified by biopsies into metastatic tissue, a sometimes hazardous, invasive, and expensive procedure. Tissue biopsies capture ~90% of the germline mutations and, additionally, identify new mutations that have evolved as a result of treatment pressure (i.e., ‘somatic’ mutations). Coming online, but not commercially available as yet, is a ‘liquid biopsy,’ a blood sample which analyzes for small fragments of tumor DNA and RNA. The ‘liquid biopsy’ has the advantage of sampling the contribution of genetic variants from all tumor sites. It is currently employed in some institutional studies and was used in the PROfound trial. Information from liquid biopsies in men with metastatic CRPC expands the number of men harboring defective DNA repair genes to ~25%-30%. These are men who might benefit from PARP inhibitor drugs.

How to access PARP inhibitor therapy?

Step one is having the test to identify BRCA-like mutations. This is germline information and is addressed in most institutional genomic testing of the tumor. Commercial labs offer the test.

Although the results of the PROfound study likely will accelerate FDA approval for olaparib for metastatic prostate cancer, currently PARP inhibitors are only available on protocols. As of the time of this Commentary, there are 24 trials listed in [ClinicalTrials.gov](https://clinicaltrials.gov) testing PARP inhibitors of various types and in various clinical settings. This should be discussed with the treating oncologist.

BOTTOM LINE:

- A new therapeutic era is underway based on the significant results of the PROfound trial in men with metastatic CRPC.

Yf Reading, Pennsylvania. After graduating from Princeton University in 1956 with a BA in History, Dr. Edward Weber attended medical school at the University of Pennsylvania. His internship training took place at the University of Vermont in Burlington, Vermont. A tour of service as a Naval Flight Surgeon positioned him on Whidbey Island, Washington, and this introduction to the Pacific Northwest ultimately proved irresistible. Following naval service, he received postgraduate training in internal medicine in Philadelphia at the Pennsylvania Hospital and then he pursued a fellowship in hematology and oncology at the University of Washington. His career in medical oncology was at the Tumor Institute of the Swedish Hospital in Seattle where his practice focused largely on the treatment of patients experiencing lung, breast, colon, and genitourinary cancer and malignant lymphoma. Toward the end of his career he developed a particular concentration on the treatment of prostate cancer. Since retirement in 2002 he has authored the PCa Commentary, published by the Prostate Cancer Treatment Research Foundation, an analysis of new developments in the prostate cancer field with essays discussing and evaluating treatment management options in this disease. He is a regular speaker at various prostate cancer support groups around Seattle.