# PARP Inhibitor Delays Prostate Cancer Progression

First targeted therapy may prolong survival of men with advanced prostate cancer.

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The PARP inhibitor Lynparza (olaparib) delayed progression of metastatic prostate cancer more than standard-of-care hormone therapy in people with faulty DNA repair genes, according to study results presented at the recent European Society for Medical Oncology Congress (ESMO 2019) in Barcelona.

The PROfound trial showed that metastatic prostate cancer patients with extensive prior treatment took longer to experience disease progression with Lynparza compared with Xtandi (enzalutamide) or Zytiga (abiraterone acetate). While preliminary survival results showed an improvement of only a few months, this represents a "clinically meaningful" advance for a group without good treatment options, researchers said. Prostate cancer treatment is now tailored based on the extent of metastasis and response to prior hormone therapy, but so far it has no targeted therapies aimed at specific genetic characteristics.

"To see such a significant effect on disease progression and other clinically relevant effects, such as pain progression and objective response rate, is a remarkable achievement in such heavily pretreated patients with prostate cancer," said co–principal investigator Maha Hussain, MD, of Robert H. Lurie Comprehensive Cancer Center at Northwestern University in Chicago. "Prostate cancer has lagged behind all other common solid tumors in the use of molecularly targeted treatment, so it is very exciting that now we can personalize an individual's treatment based on specific genomic alterations in their cancer cells."

Lynparza and other PARP inhibitors work by blocking poly (ADP-ribose) polymerase proteins, which play a role in DNA repair. Interfering with PARP leads to more DNA breaks in cancer cells, which can halt cancer cell division. People with BRCA gene mutations—best known for their role in raising breast cancer risk—or alterations in other DNA repair genes are unable to fix this kind of damage, so their cancer is especially susceptible to PARP inhibitors. Lynparza, from AstraZeneca and Merck, is currently approved for advanced ovarian and breast cancer.

The Phase III PROfound study enrolled 387 men with metastatic castration-resistant prostate cancer in North America, South America, Europe, Asia and Australia. The median age was 68 years.

Testosterone and other male hormones stimulate prostate cancer growth. Treatment for advanced cancer that has spread beyond the prostate typically includes androgen deprivation therapy (ADT), which stops testosterone production; this is referred to as castration, though today it is usually done with medications rather than surgical removal of the testicles. Prostate cancer that no longer responds to ADT is known as castration-resistant.

Study participants had already tried Xtandi or Zytiga, two newer hormone therapies that interfere with the production or activity of androgens other than testosterone. These medications are the current standard of care for metastatic castration-resistant prostate cancer. About two thirds had also been treated with taxane chemotherapy.

One cohort of participants (Cohort A) had mutations in BRCA1, BRCA2 or another DNA repair gene called ATM. A second cohort (Cohort B) had alterations in any one of a dozen other less well studied homologous recombination repair genes known to play a direct or indirect role in DNA repair. Up to 30% of men with metastatic castration-resistant prostate cancer have these mutations, according to AstraZeneca.

The participants were randomly assigned to receive Lynparza or their doctor's choice of Xtandi or Zytiga taken as pills once or twice daily. The median duration of treatment was 7.4 months for Lynparza recipients and 3.9 months for those who received the hormone therapies. Patients who experienced disease progression while on hormone therapy could cross over to receive Lynparza.

In Cohort A, the median progression-free survival time, meaning patients were still alive without worsening of disease according to scans, was 7.4 months for Lynparza recipients compared with 3.6 for those taking Xtandi or Zytiga. That is, Lynparza reduced the risk of disease progression or death by 66%. After 12 months of treatment, 28% of Lynparza recipients had not yet experienced disease progression, compared with 9% of hormone therapy recipients.

In the full study population (Cohorts A and B combined), progression-free survival time was 5.8 months with Lynparza versus 3.5 months with the hormone therapies, or a 51% risk reduction. Both differences were statistically significant, meaning they probably were not driven by chance alone.

The researchers were not yet able to report mature overall survival (OS) results because a majority of study participants are still alive. However, a preliminary analysis found that in Cohort A, the median overall survival was 18.5 months with Lynparza compared with 15.1 months with the comparison medications. After a year on treatment, 73% of Lynparza recipients and 57% of hormone therapy recipients were still alive. In Cohort B, the median OS was 17.5 versus 14.3 months, respectively. These differences did not reach the threshold for statistical significance.

Because participants who progressed on hormone therapy could cross over to Lynparza—and more than 80% did so—they experienced some benefit too, reducing the survival difference between the two groups. While allowing such crossover is ethically the right approach and helps the greatest number of patients, it makes it harder to see an overall survival advantage.

Looking at secondary endpoints, the overall response rate—meaning complete or partial tumor shrinkage—was 33% with Lynparza versus 2% with Xtandi or Zytiga in Cohort A, and 22% versus 5%, respectively, in Cohort B. Further, men taking the hormone therapies experienced worsening pain in a median of 9.9 months, while the median was not reached for Lynparza recipients. Pain commonly results from cancer spreading to the bones or other organs.

Treatment was generally safe, but side effects were common. Men treated with Lynparza were more likely than those taking Xtandi or Zytiga to experience anemia (47% versus 15%), nausea (41% versus 19%), fatigue and weakness (41% versus 32%) and loss of appetite (30% versus 18%). The most common severe side effect was anemia (22% versus 5%, respectively). Nearly twice as many Lynparza recipients stopped treatment because of adverse events (16% versus 9%, respectively).

Despite the modest advantages of Lynparza, some experts said it represents a clear improvement over the current standard of cancer for metastatic prostate cancer.

“This is a landmark trial as it is the first Phase III [prostate cancer] trial looking specifically at tumors harboring a targetable molecular alteration,” Eleni Efstathiou, MD, of MD Anderson Cancer Center in Houston, commented in an ESMO press release. “In patients with such tumors, treatment with olaparib resulted in a 66% greater delay in progression than the new hormonal agents which were used in PROfound. This is impressive because it is considerably higher than the 35% to 40% improvements with which we’ve been very satisfied in previous prostate cancer studies in this more advanced disease setting.”

Overall, she continued, “these data show that, like breast and lung cancers, prostate cancer is not one but many different diseases and we need to start identifying different groups of patients and treating them with targeted therapy.”

This study “finally brings prostate cancer medicine into the 21st century by giving us, for the first time ever, a therapy that makes use of genetic testing of the tumor to work out which men will benefit,” Matthew Hobbs, MD, of Prostate Cancer UK, said in a statement. “This kind of precision medicine approach is already used to treat other cancers, and we hope olaparib will become the first of many treatments for prostate cancer which are based on this sort of detailed understanding of an individual man’s tumor.”

In addition to this study of patients with prior treatment experience, Lynparza is also being evaluated in the Phase III PROpel trial as a first-line therapy for previously untreated people with metastatic castration-resistant prostate cancer, according to an AstraZeneca press release.

Click here to learn more about prostate cancer.

Click here for full prescribing information for Lynparza.

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