# Combination Therapy for Metastatic Prostate Cancer Helps Some Men Live Longer

A combo of Xtandi (enzalutamide) and Talzenna (talazoparib) does improve overall survival for men with advanced prostate cancer, compared with Xtandi alone.

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By Edward Winstead

For men with metastatic castration-resistant prostate cancer, an initial treatment that combines enzalutamide (Xtandi) and talazoparib (Talzenna) may help them live longer than just getting enzalutamide alone, according to updated results from a large clinical trial. Enzalutamide is a type of drug known as an androgen receptor antagonist and talazoparib is part of a group of drugs called PARP inhibitors.

In 2023, the Food and Drug Administration (FDA) approved the enzalutamide–talazoparib combination for men with this form of prostate cancer whose tumors have an alteration that disrupts a specific DNA repair process. These are often called HRR-deficient tumors.

FDA's approval was based on earlier results from the trial, called TALAPRO-2. Researchers recruited two groups, or cohorts, of patients. The "all-comers" group enrolled 805 patients with metastatic castration-resistant prostate cancer, including 169 patients with HRR-deficient tumors. The "HRR-deficient" group included those 169 patients and another 230 patients with HRR-deficient tumors who were subsequently enrolled in the study.

Participants were randomly assigned to receive talazoparib plus enzalutamide or placebo plus enzalutamide.

Talazoparib works by blocking a protein called PARP, which normally provides an alternative route for DNA repair. Blocking PARP makes it harder for HRR-deficient cancer cells to survive. Enzalutamide works in a different way, by blocking hormones from fueling tumor growth (which can happen to some extent even in castration-resistant prostate cancer).

The earlier results showed that the combination treatment increased how long people in both groups lived without their cancers getting worse as documented by imaging (radiographic progression-free survival) compared with patients treated with enzalutamide alone. The

improvement was greater in the HRR-deficient group.

When the FDA approval was announced, however, trial participants hadn't been followed long enough to know if the combination treatment helped patients live longer overall. So, it was unclear whether the combination provided more benefit to patients than using enzalutamide as an initial treatment followed by a PARP inhibitor if the cancer started to worsen.

According to the trial's updated results, the enzalutamide–talazoparib combination does substantially improve overall survival compared with enzalutamide alone, and it does so in all patients, not just in those with HRR-deficient tumors. The findings were presented February 13 at the American Society of Clinical Oncology Genitourinary Cancers Symposium.

In the all-comers cohort, at a median follow-up of about 53 months, participants in the combination-therapy group lived a median of 8.8 months longer than those in the control group, 45.8 months versus 37.0 months.

In the HRR-deficient cohort, at a median follow-up of 44 months, participants in the combination-therapy group lived a median of 14 months longer than those in the control group, 45.1 months versus 31.1 months.

William Kelly, DO, a urologist at Thomas Jefferson University who was not involved in the trial, called the trial results "impressive."

Importantly, the new results didn't reveal any previously unknown side effects of the combination therapy, Dr. Kelly said during a press briefing on the trial results. The most common side effect of talazoparib was a substantial drop in red blood cells, or anemia. Oncologists typically manage this condition by lowering the drug's dose, Dr. Kelly explained.

Since the TALAPRO-2 trial began to enroll patients in 2019, treatment approaches for advanced prostate cancer have evolved considerably, Dr. Kelly noted. "Further work is needed to show how the [enzalutamide–talazoparib] combination therapy will be integrated into today's treatment paradigm for patients," he said.

More information about the trial, which was funded by Pfizer, the maker of talazoparib, is available in this Cancer Currents story.

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