New Androgen Blocker Slows Prostate Cancer Progression

Darolutamide delays metastasis and reduces the risk of death in men with high-risk prostate cancer.

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An experimental anti-androgen medication more than doubled the time it took for cancer to spread in men with high-risk prostate cancer that no longer responds to initial hormone therapy, according to a study presented at the American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium this week in San Francisco.

Among men with nonmetastatic castration-resistant prostate cancer, darolutamide reduced the likelihood of disease spreading to a distant part of the body, worsening pain, needing to start chemotherapy or death. What's more, the treatment was well tolerated, Karim Fizazi, MD, PhD, of the Gustave Roussy Institute and University of Paris reported.

Prostate cancer is the second leading cause of cancer death in men, according to the American Cancer Society. In some cases, the disease progresses slowly and "watchful waiting" with regular surveillance can be a good approach. But in others, it is more aggressive and can spread to the bones, brain or elsewhere.

Cancer that has not yet spread is usually treated with surgery or radiation therapy followed by androgen deprivation therapy (ADT). Testosterone and other androgens (male hormones) promote prostate cancer growth, and depriving tumors of these hormones slows disease progression.

But prostate cancer can develop resistance to ADT and progress despite low testosterone levels, known as being castration-resistant. Cancer that has spread beyond the prostate is treated with chemotherapy and medications that interfere with androgen production or signaling. However, it is not clear how best to treat men with rising prostate-specific antigen (PSA) levels but no obvious metastasis, who may in fact have progressive cancer that can't yet be seen on scans.

Darolutamide blocks the activity of male hormones by interfering with androgen receptor signaling. It is in the same class as the approved medications Erleada (apalutamide) and Xtandi (enzalutamide), but it has a distinct structure. It shows little penetration across the blood-brain barrier, which could mean less central nervous system toxicity and improved tolerability, according to Fizazi.

Although Erleada and Xtandi have been shown to delay disease progression in men with high-risk nonmetastatic castration-resistant prostate cancer, they are associated with fatigue, falls, bone fractures and other side effects. Because men with nonmetastatic disease often don't have cancer symptoms, it is important that treatment doesn't diminish their quality of life, Fizazi said.

The Phase III ARAMIS trial enrolled 1,509 men with nonmetastatic castration-resistant prostate cancer; the median age was 74. Participants had a rapid PSA doubling time—usually six months or less—indicating aggressive disease. Three fourths had used two or more prior hormone therapies.

Participants were randomly assigned to receive darolutamide or placebo tablets taken twice daily while continuing on ADT. Radiographic scans were repeated every 16 weeks to look for disease progression. The primary study endpoint was metastasis-free survival, meaning the men were still alive without cancer spreading to a distant part of the body. The study is ongoing to determine if the treatment ultimately improves overall survival.

Men who received darolutamide had a median metastasis-free survival time of 40.4 months compared with 18.4 months for placebo recipients—a 59 percent reduction in the risk of distant metastasis or death. Benefits were seen across all subgroups. Progression-free survival—defined here as no distant metastasis, local progression or death—showed a 62 percent improvement, from 14.8 months in the placebo group to 36.8 months in the darolutamide group.

Men in the darolutamide group also went longer before they experienced worsening pain (40.3 months versus 25.4 months) or skeletal events such as fractures or spinal cord compression, which can occur when cancer reaches the bones. Placebo recipients started cytotoxic chemotherapy after a median of 38.2 months, but the median was not reached in the darolutamide group because a majority had not yet done so.

Overall survival data are not yet mature—83 percent of darolutamide recipients and 73 percent of placebo recipients were still alive—but the interim data show a 29 percent reduction in the risk of death.

Treatment was generally safe and well tolerated. Adverse events were common in both groups but mostly mild or moderate. A quarter of darolutamide recipients and one in five placebo recipients experienced severe adverse events. The most common events in both groups were fatigue, back pain and joint pain. The proportion of men who stopped treatment because of side effects was the same in both groups, at 9 percent.

Fizazi noted that several side effects associated with other androgen receptor inhibitors—including seizures, bone fractures and falls, and cardiovascular events—occurred at similar rates in the darolutamide and placebo groups. Using standard assessment scales, men taking darolutamide reported lower pain severity, less pain interference and fewer urinary symptoms than placebo recipients.

"Pain progression was delayed and quality of life was meaningfully preserved with darolutamide compared to placebo," the researchers concluded. Based on these results, Fizazi suggested,

darolutamide “should become the new standard of care” for men with nonmetastatic castration-resistant prostate cancer.

Click here to read the study abstract.

Click here to read the full report in The New England Journal of Medicine.

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