New Treatment for Nonmetastatic Castration-Resistant Prostate Cancer

Can apalutamide significantly improve outcomes for some prostate cancer patients?

Androgen deprivation therapy (ADT) is the cornerstone of medical treatment for prostate cancer. Each year, more than 50,000 men in the United States develop castration-resistant prostate cancer (CRPC), with rising levels of the prostate-specific antigen (PSA) despite ongoing ADT for their cancer. There are a variety of approved treatments for men with metastatic CRPC. But for men without CRPC and no detectable metastases, also known as nonmetastatic CRPC (nmCRPC), there were no approved drugs.

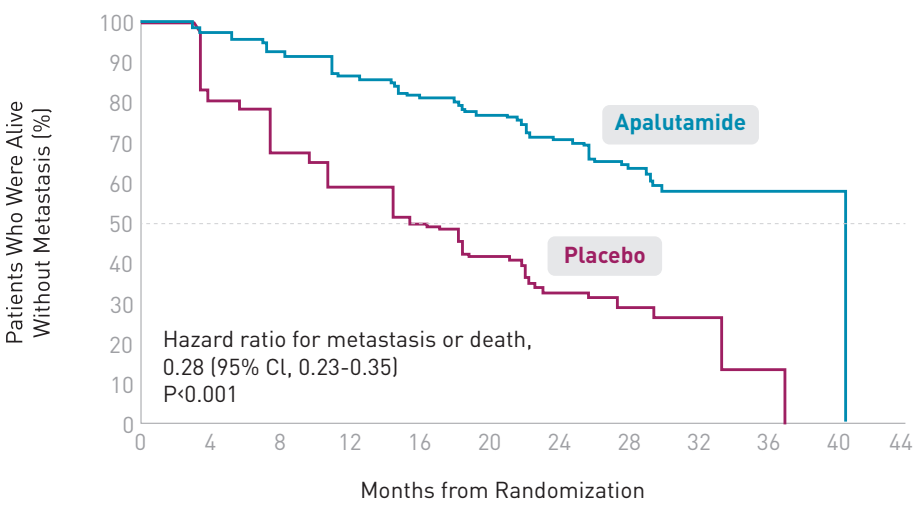
"Safe and effective treatment for nmCRPC was an important unmet medical need," says Matthew Smith, MD, PhD, director of the Genitourinary Malignancies Program at Mass General Cancer Center. For nmCRPC, patients and clinicians were faced with the decision of using unproved therapies or simply monitoring the patient. But waiting is risky for these patients because the cancer can advance to other parts of the body. Most men with nmCRPC progress to detectable metastases within a couple of years and die from their cancer within 4 to 5 years.

Now, new research by Dr. Smith and colleagues has identified a therapy, apalutamide, that can significantly delay the spread of cancer in nmCRPC patients. Findings were published in *The New England Journal of Medicine*[1] in April, and the therapy has received approval from the Food and Drug Administration, the first time the FDA has approved a drug for nmCRPC.

A PIONEERING DRUG FOR NMCRPC

In the phase 3 trial, Dr. Smith's team found that apalutamide, an androgen receptor inhibitor, delayed the development of visible metastases for more than two years

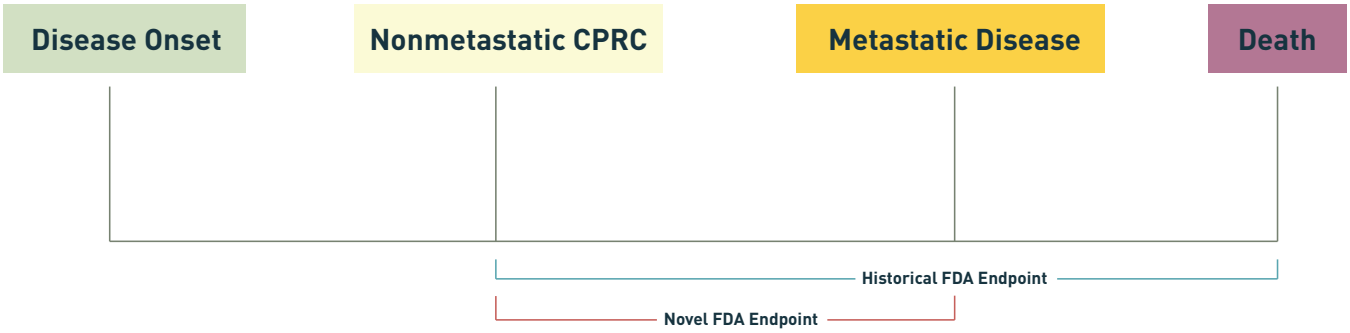
Apalutamide Improves Metastasis-Free Survival



No. at Risk												
Apalutamide	806	713	652	514	398	282	180	96	36	16	3	0
Placebo	401	291	220	153	91	58	34	13	5	1	0	0

Apalutamide Improves Metastasis-Free Survival

In men with non-metastatic castration-resistant cancer receiving apalutamide plus hormone therapy, it took, on average, 40.5 months for cancer to spread to the point where it showed up on conventional imaging. For men receiving the placebo plus hormone therapy, the cancer spread in 16.2 months, on average.



Metastasis as Endpoint

Treatments for prostate cancer have historically measured overall patient survival. But in 2011, an FDA committee recognized that the transition from nmCRPC to detectable metastatic disease was a clinically relevant event that might be used as an alternative endpoint. Apalutamide was the first drug to qualify for approval by this measure.

in these patients. "That's a very large treatment effect," says Dr. Smith. He also notes that there was a trend for improved overall survival, though cautions that longer followup is needed to be certain about the impact on mortality.

The study evaluated 1,207 men, enrolled from 332 sites in 26 countries. For those receiving apalutamide, the cancer took 40.5 months on average to spread to the point where it showed up on conventional imaging. For men receiving the placebo, the cancer spread in an average of 16.2 months. The men receiving apalutamide were also 72% less likely to develop metastasis or die over the course of the study.

Apalutamide was generally well tolerated by patients, an important factor in FDA approval. The most common side effects included fatigue, weight loss, rashes, falls and fractures. "The relative benefits and harms should be considered in making treatment decisions with each patient," says Dr. Smith.

Today, apalutamide is in development in several other phase 3 clinical trials in other prostate cancer settings. One trial will evaluate the addition of apalutamide to abiraterone acetate for patients with metastatic castration-resistant prostate cancer. A second study will examine whether adding apalutamide to standard hormone therapy and radiation therapy improves outcomes for metastatic castration-resistant prostate cancer patients. A third study will examine the impact of adding apalutamide to androgen deprivation therapy as initial therapy for men with metastatic castration-sensitive prostate cancer.

A NOVEL FDA ENDPOINT

In addition to being the first drug approved for nmCRPC, apalutamide was also notable for being the first cancer drug that the FDA has approved on the basis of a primary end point of metastasis-free survival, a subject covered in a separate perspective article in *The New England Journal of Medicine*.

Patients can survive many years after detection of rising PSA levels, and efforts to test a drug's effectiveness by measuring how long a patient lives can run into many confounding factors. These can include the use of other treatments over the course of a patient's life and death from non-cancer related causes, both of which make using the benchmark of overall survival "increasingly difficult," the authors note.

By establishing an intermediary endpoint—the advent of metastases—apalutamide creates a helpful framework for future studies. "It's a regulatory precedent," says Dr. Smith, one

(continued from page 2)

that may help future drugs come to market more quickly. "Through looking at time to metastasis, we could be setting the precedent for a path to early approval," he says.

The advantage of bringing new treatments to this non-metastatic window of the disease should not be understated. "Our study confirmed that this is an important disease stage—that if we catch it, there's benefit to intervening early," says Dr. Smith.

[1] Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med.* 2018; 378:1408-1418.

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December 2018

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