EDITORIALS

Progress in Nonmetastatic Prostate Cancer

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Since 2010, the Food and Drug Administration (FDA) has approved five new drugs for the treatment of metastatic, castration-resistant prostate cancer on the basis of a primary end point of overall survival.[1] Progress in the treatment of nonmetastatic prostate cancer has been slower. A series of phase 3 trials that were designed to investigate treatments for the prevention of bone metastases either were stopped early or did not reach their primary end point.[2-4] In a later, placebo-controlled, phase 3 trial, denosumab significantly prolonged bone metastasis–free survival among patients with nonmetastatic, castration-resistant prostate cancer.[5] However, in February 2012, an Oncology Drugs Advisory Committee of the FDA voted not to approve denosumab for the prevention of metastasis because the prolongation in median bone metastasis–free survival was small, no benefits were noted with regard to progression-free or overall survival, and denosumab was associated with osteonecrosis of the jaw.[6] Although unsuccessful, these trials served to better characterize the natural history of nonmetastatic, castration-resistant prostate cancer and to inform the design of subsequent phase 3 clinical trials.

In February 2018, the FDA approved apalutamide, a next-generation antiandrogen, for the treatment of men with nonmetastatic, castration-resistant prostate cancer.[7] Apalutamide is the first drug that was approved by the FDA on the basis of a primary end point of metastasis-free survival and is the first drug that was approved for the treatment of nonmetastatic, castration-resistant prostate cancer. The approval of apalutamide was based on the results of the SPARTAN (Selective Prostate Androgen Receptor Targeting with ARN-509) trial.[8] In that trial, apalutamide plus androgen-deprivation therapy led to a 72% lower risk of metastasis or death and a 24-month delay in the development of metastases, as compared with placebo plus androgen-deprivation therapy.

In this issue of the *Journal*, Hussain and colleagues[9] report the results of a phase 3 trial with a design similar to that of the SPARTAN trial. In the PROSPER trial, enzalutamide plus androgen-deprivation therapy led to a 71% lower risk of metastasis or death and a 22-month delay in the development of metastases, as compared with placebo plus androgen-deprivation therapy. In March 2018, the FDA granted priority review for a supplemental new drug application for enzalutamide in nonmetastatic, castration-resistant prostate cancer. Another phase 3 trial of similar design, for the evaluation of the effects of darolutamide on metastasis-free survival, is ongoing (ARAMIS; ClinicalTrials.gov number, NCT02200614).

The distinction between nonmetastatic and metastatic depends on the type of imaging used. In the SPARTAN and PROSPER trials, nonmetastatic disease was defined as the absence of identifiable metastases on conventional imaging (technetium-99m bone scanning and computed tomography or magnetic resonance imaging). Newer imaging tests, including positron-emission tomography with choline or fluciclovine or the targeting of prostate-specific membrane antigen, are substantially more sensitive for metastasis detection.[10] Many of the patients who were enrolled in these two trials would have had detectable metastases according to more sensitive

imaging tests. The trials that supported regulatory approvals for metastatic prostate cancer, however, identified metastases by means of conventional imaging and do not provide meaningful evidence about the benefit–risk ratio among patients with metastases that are detectable only by more sensitive tests. In contrast, the SPARTAN and PROSPER trials provide important new information about the appropriate treatment of patients with that novel category of disease (negative on conventional imaging yet positive on newer imaging techniques).

The key clinical decision in patients with nonmetastatic, castration-resistant prostate cancer is whether to start additional treatment in men who have rising prostate-specific antigen (PSA) levels as the only manifestation of worsening disease or to continue androgen deprivation alone until metastases become detectable by imaging. Although the SPARTAN and PROSPER trials were not designed to evaluate sequential treatment formally, these two trials provide valuable evidence about early versus later therapy. The majority of the patients in the placebo group in each trial subsequently received approved therapy for metastatic disease. Despite the high rates of subsequent therapy, both trials showed improvements in all secondary end points, including late clinical events that followed radiographic progression by many months. In the SPARTAN trial, for example, apalutamide was associated with prolongation in the time to symptomatic progression and in the time to the initiation of cytotoxic chemotherapy. Apalutamide and enzalutamide were also each associated with longer overall survival, although longer follow-up is required in order to evaluate their effects on mortality reliably.

Treatment for nonmetastatic, castration-resistant prostate cancer also has potential harms. Apalutamide and enzalutamide are associated with fatigue, falls, and fractures. Both drugs have been associated with a small seizure risk (<1%). The SPARTAN and PROSPER trials included patients with a PSA doubling time of 10 months or less, and the median PSA doubling time in each trial was approximately 4 months. The benefit–risk ratio for either drug is not well characterized in patients with longer PSA doubling times.

In summary, the FDA approval of apalutamide for nonmetastatic prostate cancer and the anticipated approval of enzalutamide in the same context represent important steps forward for men with rising PSA levels during androgen-deprivation therapy. The benefit–risk evaluation suggests that treatment with either drug is better than waiting until the appearance of metastases.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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1. Sartor O, de Bono JS. Metastatic prostate cancer. N Engl J Med 2018;378:645-57.
2. Smith MR, Kabbinavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol 2005;23:2918-25.
3. Mason MD, Sydes MR, Glaholm J, et al. Oral sodium clodronate for nonmetastatic prostate cancer--results of a randomized double-blind placebo-controlled trial: Medical Research Council PR04 (ISRCTN61384873). J Natl Cancer Inst 2007;99:765-76.
4. Nelson JB, Love W, Chin JL, et al. Phase 3, randomized, controlled trial of atrasentan in patients with nonmetastatic, hormone-refractory prostate cancer. Cancer 2008;113:2478-87.
5. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet 2012;379:39-46.
6. Xgeva (denosumab) prescribing information. Silver Spring, MD: Food and Drug Administration, 2018 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125320s185lbl.pdf).
7. FDA approves new treatment for a certain type of prostate cancer using novel clinical trial endpoint. News release of the Food and Drug Administration, Silver Spring, MD, February 14, 2018 (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm596768.htm).
8. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018;378:1408-18.
9. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2018;378:2465-74.
10. Maurer T, Eiber M, Schwaiger M, Gschwend JE. Current use of PSMA-PET in prostate cancer management. Nat Rev Urol 2016;13:226-35.

DOI: 10.1056/NEJMe1805733