2- Chou R et al. "Preexposure prophylaxis for the prevention of HIV infection. Evidence report and systematic review for the US Preventive Services Task Force" *JAMA* 2019; **321** (22): 2214-2230.

3- Owens DK et al. "Preexposure prophylaxis for the prevention of HIV infection: US Preventive Services Task Force. Recommendation Statement" *JAMA* 2019; **321** (22): 2203-2213.

4- Prescrire Editorial Staff "Emtricitabine + tenofovir disoproxil - Truvada° for prevention of HIV infection in adolescents" *Prescrire Int* 2019; **39** (426): 249.

Non-metastatic, castration-resistant prostate cancer

Survival extended with the addition of apalutamide or enzalutamide

● **After longer follow-up, an analysis of two placebo-controlled trials, one of which evaluated *apalutamide* and the other *enzalutamide*, has shown that median survival was extended by about one year when one of these drugs was added to medical or surgical castration in patients at high risk of developing prostate cancer metastases. This clinical benefit was accompanied by an increase in serious, or even fatal, adverse effects.**

For patients with non-metastatic prostate cancer, androgen deprivation therapy is sometimes proposed either by orchiectomy (surgical castration) or administration of a gonadotropin-releasing hormone (GnRH) agonist (medical castration). In some patients, the serum prostate specific antigen (PSA) concentration continues to rise despite a very low serum testosterone level. The cancer is then said to be castration-resistant. When the serum PSA doubling time is less than or equal to 10 months, the risk of developing metastases is considered to be high. In this situation, addition of either *apalutamide* or *enzalutamide* (nonsteroidal antiandrogens) to castration delayed the appearance of metastases in a double-blind, randomised, placebo-controlled trial (1,2).

In late 2020, results with longer follow-up became available for these two trials. As planned in the protocol, after an initial interim analysis, the patients in the placebo groups were allowed to receive the antiandrogen being evaluated (about 19% of patients in each of these trials). This could reduce the observed difference in mortality between the two groups (3,4).

Apalutamide: median survival extended by 14 months. As of late 2020, the results concerning *apalutamide* were only available in the form of a conference abstract that provided few details (3).

This trial ("Spartan") included 1207 patients. After a median follow-up of at least 4 years, estimated median survival was about 74 months in the *apalutamide* group versus 60 months in the placebo group (p=0.016) (3).

Enzalutamide: median survival extended by 11 months. The "Prosper" trial which evaluated *enzalutamide* included 1401 patients (4). After a median follow-up of at least 4 years, mortality was 31% in the *enzalutamide* group versus 38% in the placebo group, with an estimated median survival of 67 months in the *enzalutamide* group versus 56 months in the placebo group (p=0.001). 33% of patients in the *enzalutamide* group received at least one antineoplastic drug following cancer progression (after a median delay of 67 months) versus 65% of those in the placebo group (after a median delay of 19 months). There was no notable difference between the groups regarding the nature of the antineoplastic therapy received (4).

Adverse effects of antiandrogens: sometimes fatal. The initial data from the Spartan and Prosper trials had shown that the adverse effect profiles of *apalutamide* and *enzalutamide* were in general the same as those of other nonsteroidal antiandrogens, with mainly: hot flushes, gynaecomastia, breast tenderness, galactorrhoea, breast cancer, osteoporosis and fractures, cardiovascular disorders, and type 2 diabetes (1-3,5). Interstitial lung disease was reported after marketing of *apalutamide* and *enzalutamide* (see also: "Enzalutamide, apalutamide: interstitial lung disease" p. 158) (6).

During the longer follow-up of the Prosper trial, a serious event, possibly linked to treatment, occurred in 40% of patients in the *enzalutamide* group (leading to death in 5%), versus 22% of patients in the placebo group (leading to death in 1%) (2,4).

In practice For patients with non-metastatic prostate cancer, when castration is insufficient and the risk of metastasis is high, addition of *apalutamide* or *enzalutamide* is an option which delays the appearance of metastases and extends survival by about one year. It is crucial to provide patients with information and to share decision-making with them, because serious adverse effects are common with these antiandrogens and are sometimes fatal.

▶ Translated from *Rev Prescrire* **March 2021**
Volume 41 N° 449 • Pages 204-205

Selected references from Prescrire's literature search

1- Prescrire Editorial Staff "Apalutamide - Erleada°. Non-metastatic prostate cancer: delayed appearance of metastases in case of castration-resistant disease" *Prescrire Int* 2020; **29** (218): 201-203.

2- Prescrire Editorial Staff "Enzalutamide - Xtandi° and non-metastatic, castration-resistant prostate cancer" *Prescrire Int* 2020; **29** (218): 203-204.

3- Small EJ et al. "Final survival results from SPARTAN, a phase III study of apalutamide versus placebo in patients with nonmetastatic castration-resistant prostate cancer". www.urotoday.com accessed 19 November 2020: 3 pages.

4- Sternberg CN et al. "Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer" *N Engl J Med* 2020; **382** (23): 2197-2206.

5- Prescrire Rédaction "Enzalutamide" Interactions Médicamenteuses Prescrire 2021.

6- EMA "Suspected adverse drug reaction reports. Enzalutamide and Apalutamide" December 2020. www.adrreports.eu accessed 14 December 2020: 2 pages.