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Recent Updates in the Treatment of Non-Metastatic Castration Resistant Prostate Cancer

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Mini Review

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Abstract

Non-metastatic castration-resistant prostate cancer (nmCRPC) is a heterogeneous disease affecting a particular group of patients, by definition men with biochemically recurrent disease (PSA elevation), even if under treatment with LHRH agonists or antagonists (ADT) but with no detectable distant metastasis when valuated with conventional CT and bone scan. For this very reason, it would be better talking of a "castration-resistant prostate cancer without detectable distant metastases".

Recently, The Food and Drug Administration, after the results showed in three "twins" trials, approved three respective new second-generation androgen receptor antagonists (Apalutamide, Darolutamide, Enzalutamide) in this peculiar setting of patients.

All three trials (SPARTAN, ARAMIS and PROSPER, respectively) showed improvements in metastasis-free survival (primary endpoint) and also important results in terms of secondary endpoints (Overall survival, Time to PSA progression, Time to subsequent therapy, etc). This short review will illustrate these trials, including the respective latest updates, and will discuss the different therapeutic options.

Keywords: Apalutamide; Darolutamide; Enzalutamide; Nonmetastatic castration-resistant prostate cancer

Abbreviations: DT: Definitive Therapy; RP: Radical Prostatectomy; PSA: Prostate Specific Antigen; ADT: Androgen-Deprivation Therapy; NMCRPC: Non-Metastatic, Castration-Resistant Prostate Cancer; MFS: Metastasis-Free Survival; OS: Overall Survival; PD: Progression of Disease.

Introduction

Prostate cancer can be differentiated into localized disease (which can be divided into low risk, intermediate risk, poor risk), locally advanced disease and metastatic disease.

From a hormonal prospective, it can also be divided into hormone-sensitive and castration-resistant disease. Localized prostate cancer is frequently treated with definitive therapy (DT): radical prostatectomy (RP), radiotherapy (RT), or both. About 27 to 53% of all patients undergoing DT will develop biochemical recurrence. [1]. Patients with biochemical recurrence after definitive therapy will be treated with locally directed rescue therapy. Many of these patients will, eventually, develop increasing levels of prostate specific antigen (PSA) and start and hormonal therapy (androgen-deprivation therapy, ADT) with a gonadotropin releasing hormone (GNRH) agonist or antagonist. ADT is the standard therapy for patients whose prostate cancer relapses after definitive therapy (DT) [2-4].

A condition characterized by rising PSA levels under continuous ADT therapy but with castrated levels of testosterone (by definition, <50 ng/dl) and no evidence of metastatic disease when the disease is valuated with CT and bone scan is defined as non-metastatic, castration-resistant prostate cancer (nmCRPC) [1]. The number of patients

affected by nmCRPC is valued to be around 50,000 and 60,000 in the United States alone [5].

In this set of patients, the main goal is to delay the onset of distant metastases [5,6]: here we will discuss the several and recently approved therapeutic options available.

Prior to 2018, treatment options for nmCRPC patients were observation, use of first generation androgen receptor antagonists, such as bicalutamide or flutamide, estrogen or ketoconazole, but none of these demonstrated a survival benefit [7,8].

In 2018, three "twins" phase III trials took the nmCRPC side of the disease by storm. In 2020, these trials have been updated and completed.

All these trials include almost the same type of patients: non-metastatic castration resistant patients with serum testosterone levels <50 ng/dl and a PSA doubling-time (PSADT) ≤10 months.

As said, the introduction of these new second-generation androgen receptor antagonists into clinical practice will change the treatment landscape for nmCRPC.

Enzalutamide

Enzalutamide is a new second-generation androgen receptor antagonists, it was approved by the FDA and European Medicines Agency in 2013. It is a potent inhibitor of the androgen receptor signal which is blocked at several levels. Enzalutamide competitively inhibits the binding of androgens to androgen receptors, inhibits the nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA [9,10]. At first two trials (Affirm and Prevail) showed the power of enzalutamide in patients with Mcrpc [11,12]. In 2016 the Strive trial compared enzalutamide with bicalutamide, demonstrating the superiority of enzalutamide in patients with mCRPC in terms of risk of progression or death [13]. The approval of enzalutamide for non-metastatic castration-resistant prostate cancer (nmCRPC) was based on PROSPER, a double-blind, phase III study that randomly assigned patients with nmCRPC and a PSA doubling time of 10 months or less to ADT + placebo or ADT + enzalutamide 160 mg daily. Primary endpoint was metastasis-free survival (MFS).

Secondary endpoint consisted of overall survival, time to PSA progression, time to first use of a successive therapy, time to first use of cytotoxic chemotherapy, time to pain progression, and safety [14]. The trial showed improvements in metastasis-free survival(primary endpoint)36,6 months in enzalutamide vs 14,7 months in placebo. Enzalutamide also demonstrates its effectiveness in terms of secondary endpoints: PSA progression (HR 0.07; 95%CI 0.05–0.08; P<0.001) and use of successive therapy (HR 0.21; 95%CI 0.17–0.26); P<0.001.

After around 4 years, there were 288 deaths in the enzalutamide group and 178 deaths in the placebo group. Recent update showed that the median overall survival (OS) in the enzalutamide group was 67 months, compared with 56.3 months in the placebo group [15]. About safety, enzalutamide toxicity profile was similar to previous trials with the androgen receptor antagonists in the patients with mCRPC [14].

Adverse effect associated with enzalutamide were 87% and 31 compared to 77% and 23% in the placebo group.

Patients receiving enzalutamide discontinued treatment at a rate of 9% versus 6% for placebo. The common adverse events were hypertension (12% with enzalutamide vs. 5% with placebo), cardiovascular problems (5% with enzalutamide vs. 3% with placebo), falls and non-pathologic fractures (17% with enzalutamide vs. 8% with placebo), and mental impairment disorders (5% with enzalutamide vs. 2% with placebo) [14].

Darolutamide

The multinational, randomized, double-blind, placebo-controlled, phase III ARAMIS trial evaluated the efficacy and safety of darolutamide in men with nmCRPC. 1509 patients went under randomization, in a 2:1 ratio: 955 patients were assigned to the Darolutamide group, with ADT + Darolutamide at a dose of 600 mg tablets (2 x 300 mg), whereas 554 patients were given ADT + placebo. Primary endopoint of this trial was the median metastasis-free survival (MFS, defined as time between randomization and evidence of metastasis or death from any cause). Secondary endpoints were overall survival (OS), time to pain progression, time to first symptomatic skeletal event and time to first cytotoxic chemotherapy.

A first planned analysis was performed after 437 primary end-point events had occurred (with a median follow up of 17.9 months): the median MFS was 40.4 months with darolutamide, as compared with 18.4 months with placebo (HR 0.41; 95% confidence interval [CI], 0.34 to 0.50; P<0.001); this finding was associated with benefits in all of the secondary endpoints.

In terms of safety, 83.2% of the patients in the Darolutamide group and the 76.9% in the placebo group had an adverse event. 54.6% and 54.2%, respectively, of

these AEs were grade 1-2, whereas 24.7% and 19.5% were of grade 3-4. The most common adverse events in the Darolutamide group were fatigue (12.1%), arthralgia (8.8%) and diarrhea (6.9%), and the most common grade 3-4 AEs was hypertension (3.1%). After the publication of these results, the trial was unblinded and all 170 patients who were still receiving placebo crossed over to receive open-label darolutamide (crossover group).

In 2020, an update demonstrated that treatment with Darolutamide would also lead to an improvement in a key secondary endpoint, median overall survival (OS). The median follow-up time was 29.0 months for the overall trial population, 11.2 additional months after the primary analysis [16,17].

The final analysis of OS was performed after 254 total deaths (15% in the darolutamide group and 19% in the placebo group) had occurred. In the Darolutamide group the percentage of patients who were alive at 3 years was 83%, and 77% (95% CI, 72 to 81) in the placebo group. The final results show that the risk of death is 31% lower in the darolutamide group than in the placebo group (HR, 0.69). The treatment effect on OS consistently favored darolutamide over placebo also in prespecified subgroups, including those defined according to baseline PSADT ≤6 months or >6 months [18].

Apalutamide

Apalutamide is another competitive inhibitor of the androgen receptor (AR). Its efficacy in the nmCRPC has been evaluated in the randomized-controlled, double blinded phase III SPARTAN trial.

In this trial, 1.207 men with a nonmetastatic castration-resistant prostate cancer underwent randomization in a 2:1 ratio: 806 patients were enrolled in the sperimental arm (ADT + Apalutamide 240 mg per day) and 401 in the placebo arm (ADT + placebo).

Inclusion criteria were the presence of an nmCRPC with a PSADT≤10 months under continuous ADT and without evidence of distant metastases on CT or bone scan. Interestingly, patients were required to have no evidence of disease in the regional nodes (N0) or at least malignant pelvic nodes that were <2 cm in the short axis (N1). Important stratification criteria were PSADT (≤6 months or >6 months) and local nodal disease (N0 or N1).

Patients in the sperimental arm were eligible to continue the aforementioned treatment until withdrawal of consent or evidence of progression or adverse events. After the detection of distant metastasis, patients were eligible to receive treatment with Abiraterone Acetate plus Prednisone.

Primary endpoint was MFS, defined as the time from randomization to the first detection of distant metastasis on imaging (as assessed by means of blinded independent central review) or death from any cause. Secondary endpoints were PFS, OS, time to metastasis, time to symptomatic progression and time to initiation fo cytotoxic chemotherapy.

In regards to the primary endpoint, the median MFS was 40.5 months in the sperimental arm (ADT + Apalutamide) and 16.2 months in the placebo arm (HR 0.28; 95% confidence interval [CI], 0.23 to 0.35; P<0.001). Following these results, in July 2017 the independent safety monitoring committee recommended the trial to be unblinded, thus providing patients in the placebo group to receive Apalutamide (crossover group).

Even if data were not conclusive, Apalutamide was associated with better result regarding all secondary endopoints. Notably, of the patients who had progression of disease (PD), 52.5% in the sperimental group and 77.8% in the placebo group received Abiraterone Acetate + Prednisone. Even so, data from the second-progression free survival (PFS2) was significantly in favor of patients in the Apalutamide Group (HR 0.49).

Regarding AEs, 10.6% of the patients in the sperimental group and 7.0% in the placebo group developed adverse events that led to the discontinuation of the trial regimen. Grade 3 to 4 AEs were observed in 45.1% of patients treated with apalutamide vs. 34.2% treated with placebo. AEs related to apalutamide were fatigue (30.4%), rash (23.8%), hypothyroidism (8.1%), and seizure (0.2% vs. 0%) [19].

In 2020, the final update of this trial showed that data coming from OS evaluation were consistent with what has been showed in 2018: at a follow up of 52 months, median OS was significantly longer in the Apalutamide arm that in the placebo arm: 73.9 months vs 59.9 months (HR 0.784; p=0.0161) [20].

Comparison Between the Studies

Several comparative evaluation have been made, but at the time present an head-to-head comparison between all these new molecules is not available: nevertheless, as demonstrated by Di Nunno et al. (Figure 1), a mild advantage can be observed for Enzalutamide and Apalutamide for MFS, while Darolutamide seems to be more effective on long term mOS. Probably, these differences can be explained by the different data maturity of the three trials.

All three studies met their primary endpoint MFS [21-23]. The three studies have the same inclusion criteria except for some minor differences (which are summarized

in Table 1), in the Prosper the patients were without nodal involvement (N0) while in the SPARTAN and ARAMIS were included patients with nodes involvement up to 2 cm (N1) below aortic bifurcation.

	Apalutamide (SPARTAN)	Darolutamide (ARAMIS)	Enzalutamide (PROSPER)
Inclusion criteria	M0 N0-N1 CRPC	M0 N0-N1 CRPC	M0 N0 CRPC
	PSADT <10 months	PSADT <10months	PSADT <10 months
		PSA >2 ng/ml	PSA >2 ng/ml
Number of patients	1,207	1,509	1,401
Median age (range)	74 (48–94) vs. 74 (52–97)	74 (48–95) vs. 74 (50–92)	74 (50–95) vs. 73 (53–92)
Randomization	2 (apalutamide): 1 (placebo)	2 (darolutamide): 1 (placebo)	2 (enzalutamide): 1 (placebo)
Dosage	240 mg	600 mg	160 mg
ADT	Yes	Yes	Yes
Diagnostic evaluation	CT (pelvis, abdomen, chest, head)	CT or MRI (pelvis, abdomen, chest)	CT or MRI
	Technetium-99m bone scan	Technetium-99m bone scan	Technetium-99m bone scan
N1 patients	16.5% vs. 16.2%	17% vs. 29%	0% vs. 0%
Metastasis-free survival (months)	40.5 vs. 16.2	40.4 vs. 18.4	36.6 vs. 14.7
	HR 0.28; 95%CI 0.23–0.35; P<0.0001	HR 0.41; 95%CI 0.34–0.5; P<0.001	HR 0.29; 95%CI 0.24–0.35; P<0.001
Overall survival (months)	73.9 vs. 59.9 vs.	83 vs. 77	67 vs. 56.3
	HR 0.784; 95%CI; 0.65-0.96;	HR 0.69; 95%CI; 0.53–0.88;	HR 0.73; 95%CI; 0.61–0.89;
	P = 0.0161	P = 0.003	P = 0.001
Secondary PFS (months)	55.6 vs. 41.2	N/A	N/A
	HR 0.55; 95%CI 0.46–0.66		
	P<0.0001		
Adverse events (any, %)	97 vs. 94	85.7 vs. 79.2	94 vs. 82
Adverse events (Grade 3-4, %)	56% vs. 36%	24.7 vs. 19.5	48% vs. 27%
Adverse events (Grade 5, %)	3% vs. 0.5%	3.9% vs. 3.2%	5% vs. 1%
Discontinuation rate	15% vs. 7.3%	8.9% vs. 8.7%	17% vs. 9%
Median follow up (months)	52	29	48

Table 1: Comparison between SPARTAN trial, ARAMIS trial, PROSPER trial (29,30; updated 2020)

Adverse events are similar between the 3 molecules, however there are specific characteristics of the molecules that can favor the use of one substance over another, when accounting for patient's comorbidities. Most common adverse events were: fatigue, hypertension, arthralgia, nausea, and diarrhea. The molecular structure of darolutamide determines a lower ability to cross the blood-brain barrier, this can explain why darolutamide has fewer cerebral side effects when compared to enzalutamide and apalutamide, as seen in preclinical studies [24,25].

A high percentage of patients with prostate cancer are considered "elderly" (i.e. >75 years), therefore it is common the use of polypharmacological therapies. For this reason it is necessary to pay attention to the use of these new molecules for their ability to induce or inhibit the metabolism of other drugs through the cytochrome P450 system: in particular enzalutamide and apalutamide are strong CYP3A4 inducers [26].

Conclusions

nmCRPC pivotal trials provided a clear evidence that early administration of one ARTA produced not only a MFS

but also an OS advantage. Nonetheless, it's important to address the issue of staging and classification of this set of patients: Wolfgang P. Fendler, et al. demonstrated that patients considered nmCRPC when studied with CT and bone scan actually resulted in an early metastatic stage when stadiated with more accurate techniques (e.g. PSMA-PET). Therefore it is probable that, with the improvement and diffusion of more sensitive imaging techniques, this setting of patients is destined to downsize in the future.

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