Review Article

The past, present, and future of non-metastatic castration-resistant prostate cancer (nmCRPC): a narrative review

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Background and Objective: Non-metastatic castration-resistant prostate cancer (nmCRPC) is a diverse disease state defined as the absence of radiographic evidence of metastatic disease by conventional imaging with a castrate level of testosterone and a confirmed rising prostate-specific androgen (PSA) level. Until recently, no treatment strategies had shown an improvement in the overall survival (OS) of these patients. In this narrative review, we aim to describe nmCRPC and the treatment options before 2018 and thoroughly analyze the phase 3 trials that have led to the approval of the first three drugs for this condition.

Methods: We performed a PubMed search using the keywords 'non-metastatic castration-resistant prostate cancer' (nmCRPC) in English and Spanish from 2005 through 2021. We reviewed and summarized the current literature on the definition, diagnosis, and treatment of nmCRPC. We examined the design of the SPARTAN, PROSPER, and ARAMIS trials and the efficacy and safety profile results. Finally, we examined the possible impact of novel imaging techniques on the applicability of these results and the potential role of prognostic biomarkers to guide treatment decisions.

Key Content and Findings: Enzalutamide, apalutamide, and darolutamide were tested in three phase 3 trials in a high-risk population of patients with nmCRPC, selected by a PSA doubling time (PSA-DT) ≤10 months. Enzalutamide, apalutamide, and darolutamide are the first drugs that have shown an improvement in metastasis free survival (MFS) and overall survival (OS) in a selected high-risk population (PSA-DT ≤10 months).

Conclusions: Given these results, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved enzalutamide, apalutamide, and darolutamide for the treatment of nmCRPC with a PSA-DT ≤10 months. No direct comparisons have been made between the three agents. The role of new imaging techniques in these patients is yet to be defined, and there is a need to identify prognostic biomarkers to guide the treatment of nmCRPC.

Keywords: Castration-resistant prostate cancer (CRPC); androgen deprivation therapy (ADT); non-metastatic castration-resistant prostate cancer (nmCRPC)

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Introduction

Background

Prostate cancer (PCa) is the second most common malignancy in men worldwide, with an estimated 1,414,259 new cases diagnosed and 375,304 deaths in 2020 (1). The National Comprehensive Cancer Network (NCCN) guidelines recommend the use of serum prostate-specific

androgen (PSA) levels for the early detection of PCa, although there is no consensus on when to start and stop screening (2). As a result of this opportunistic screening, the incidence of PCa has increased dramatically since the early 1990s (3). The 5-year relative survival of patients diagnosed in the period 2000–2007 was 84.6%, the highest after testicular tumor (4). This explains why the most prevalent cancer in men is prostate, with an estimated prevalence worldwide of 1,193,715 (1).

As a result of the dissemination of screening programs using PSA, the number of early-stage PCa diagnoses has increased, allowing local treatment with surgery or radiotherapy. However, after 10 years of follow-up, 27–53% of patients present biochemical recurrence (BCR). The most accepted definition for BCR is a PSA higher or equal to 0.2 ng/mL confirmed on a second determination after radical prostatectomy or a PSA rise of 2 ng/mL or more above de nadir PSA after radiotherapy, without evidence of metastasis on conventional imaging (5-7).

The best treatment for BCR depends on multiple factors like PSA level, PSA doubling time (PSA-DT), patient preferences, and comorbidities. Androgen deprivation therapy (ADT) has been widely used and is still an option in selected patients. However, the benefits of early ADT are unclear, and prolonged ADT could reduce cardiorespiratory fitness and increase the risk of cardiovascular mortality. Many physicians reserve ADT for high-risk patients with BCR, especially those with a PSA-DT <6 months (7,8). A retrospective review explored the outcomes of deferring ADT until the appearance of metastasis in 806 men with BCR and a PSA-DT <10 months after radical prostatectomy. A median metastasis-free survival (MFS) of 192 months and an overall survival (OS) of 204 months were observed. This study further argues for the need to discuss with the patient the lack of meaningful evidence for the use of ADT in this circumstance (9). Other systemic treatments are being explored in this situation, including immunotherapy, chemotherapy, new hormonal agents, and poly(ADP-ribose) polymerase (PARP) inhibitors. The TAX3503 trial is a phase 3 trial that randomized patients with high-risk BCR after radical treatment to receive ADT or ADT plus docetaxel. It is the first trial to have shown results in this setting. No significant benefit in progression-free survival (PFS) [hazard ratio (HR) 0.8, 95% confidence interval (CI): 0.61–1.04] or OS (HR 0.51; 95% CI: 0.23–1.10) was observed in the docetaxel arm (7,10).

Around 10–20% of PCas acquire resistance to ADT and become castration-resistant prostate cancer (CRPC) within 5 years of follow-up. The median survival of metastatic castration-resistant prostate cancer (mCRPC) is less than 3 years despite the use of historical standard therapies (11). The European Association of Urology (EAU) guidelines define CRPC as castrate serum testosterone <50 ng/dL or 1.7 nmol/L plus one of the following types of progression: biochemical progression (defined as three consecutive increases in PSA at least one week apart, resulting in two 50% rises over the nadir, and a PSA level >2 ng/mL), or radiological progression [the presence of two or more bone lesions identified by bone scan or a soft tissue lesion using the Response Evaluation Criteria in Solid Tumors (RECIST)]. Most patients have already developed metastases when they reach this state (mCRPC), and their therapeutic landscape has rapidly evolved in recent years. However, some patients do not present signs of metastases on conventional imaging (bone scan and cross-sectional imaging of chest, abdomen, and pelvis). These patients are known as non-metastatic CRPC (nmCRPC), and around 30% of them will develop distant metastases within 2 years. Despite this risk, prior to 2018, there were no treatment options that demonstrated an increase in OS for these patients (12-14).

For asymptomatic men with nmCRPC, the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group guidelines recommended PSA testing every 3 months and evaluation by conventional imaging when PSA reaches 2 ng/mL, again when PSA reaches 5 ng/mL, and again every time the PSA doubles (15).

However, not all patients will have the same progression. nmCRPC is a heterogeneous disease that varies from an indolent state to a disease with rapid development of metastases. A study that evaluated MFS in 201 patients with nmCRPC identified the baseline PSA level (higher than 10 ng/mL) and PSA velocity as independent risk factors for shorter time to first bone metastasis, MFS, and OS. Also, a large phase 3 randomized trial of denosumab in nmCRPC confirmed that a PSA-DT of ≤10 months predicted a shorter OS and bone metastasis-free survival (BMFS). These results support the use of PSA-DT to select high-risk patients in this setting (16,17).

Our goal with this review is to conduct a useful analysis of nmCRPC. We aim to describe nmCRPC and the treatment options before 2018 and thoroughly analyze the phase 3 trials that have led to the approval of the first three drugs for this condition. We will also discuss the emerging status of this disease in light of novel imaging techniques and molecular biomarkers.

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	July 1st 2021
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters)	Non-metastatic castration-resistant prostate cancer (nmCRPC)
Timeframe	January 1st 2005–July 1st 2021
Inclusion and exclusion criteria (study type, language restrictions, etc.)	We only included studies published in English or Spanish
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	The selection process was conducted by the authors
Any additional considerations, if applicable	Most of the studies reviewed in the article are phase 3 clinical trials

Objective

This review aims to outline the definition of nmCRPC and summarize the treatment options before 2018. We also analyze the three phase 3 trials that have led to approval of the first three therapies that have shown an impact in OS for patients with nmCRPC. Furthermore, we discuss the potential impact of novel imaging techniques in the diagnosis and treatment of nmCRPC and the possibility of guiding treatment options based on molecular subtypes. We present the following article in accordance with the Narrative Review reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-34/rc).

Methods

This is a narrative review. The PubMed database was searched using the keywords "non-metastatic castration-resistant prostate cancer" (nmCRPC) from 2005 through 2021. We reviewed and summarized the current literature regarding the definition, diagnosis, and treatment of nmCRPC (*Table 1*). We excluded articles not published in English and clinical trials that were not phase 2 or 3.

Discussion

We reviewed all articles and summarized the key findings. There were limitations in the search of treatments available before 2018 since most treatments were not tested in randomized clinical trials. We highlight the results of three recent phase 3 trials that showed significant impact in the management of nmCRPC. We also summarized the most important indirect comparisons of the three trials. However, direct comparisons are needed to identify the best treatment for individual patients.

Treatment options before 2018

Prior to 2018 and based on the above studies, nmCRPC was managed with either observation or different approaches, such as removing or adding first-generation androgen receptor (AR) inhibitors, the use of ketoconazole, or corticosteroids. Since these treatments had only shown PSA responses without any impact on OS, the NCCN guidelines prior to 2019 recommended continuing observation in patients with PSA-DT >10 months and, for patients with PSA-DT ≤10 months, enrolling them in a clinical trial given the high risk of progression (18,19).

Additional hormonal manipulations

The most common physiopathology for CRPC is a reactivation of AR transcriptions in an environment with low serum testosterone, which translates to a PSA elevation. For a long time, physicians have tried to extend the duration of hormone responsiveness in nmCRPC by modulating the timing and modalities of hormone therapy (18). Although nmCRPC is mainly driven by AR reactivation, additional hormonal manipulations have shown a modest PSA response in the short-term in phase 2 trials without further benefit (20) (*Table 2*).

Bone-targeted therapy

The skeleton is by far the most frequent site of metastasis in PCa. Thus, numerous studies have evaluated the role of

Table 2 Additional hormonal manipulations

Type of therapy	% PSA response (50% decrease)	Duration (months)
Anti-androgens withdrawal syndrome	15–50%	3–6
Anti-androgens	4–50%	4–18
Adrenal synthesis inhibitors	27–63%	4–20
Steroids	14–61%	2–7

PSA, prostate-specific androgen.

bone-targeted therapy in delaying the appearance of bone metastases in men with nmCRPC (20).

In a phase 3 randomized, double-blind trial, 508 men with nmCRPC were randomized to clodronate (a first-generation bisphosphonate) or placebo. With a median follow-up of nearly 10 years, no benefit was observed in terms of BMFS or OS (21). Another phase 3 trial randomized 201 men with nmCRPC in an unselected population to receive zoledronic acid, a second-generation bisphosphonate, or placebo. The trial was terminated prior to completing accrual due to an interim analysis that showed an event rate of bone metastases lower than anticipated (22).

Endothelin-1 (ET-1) and the endothelin-A (ETA) receptor are implicated in PCa progression. Atrasentan and zibotentan are strong ETA receptor antagonists. Two phase 3 randomized, double-blind, placebo-controlled trials have evaluated their ability to delay the appearance of bone metastases in nmCRPC. The role of atrasentan in nmCRPC was studied in a trial with 941 patients. There was a 93-day delay in the median time to progression (TTP) with atrasentan, but the difference was not statistically significant (P=0.288). There was also no difference in OS (22). In a placebo-controlled trial, 1,421 patients with nmCRPC were randomized to receive zibotentan or placebo. At the interim analysis, no significant difference was found in OS (HR 1.13; 95% CI: 0.73–1.76; P=0.589) or PFS (HR 0.89; 95% CI: 0.71–1.12; P=0.330). Given these results, the trial was concluded early (23).

The RANK ligand (RANKL) appears to influence the survival and function of osteoclasts and seems to be upregulated by tumor cells in the bone microenvironment. Denosumab is a RANKL inhibitor that was studied in a phase 3 randomized trial. A total of 1,432 men with nmCRPC were randomized to denosumab or placebo. It is important to highlight that this was the first study to use PSA-DT to select a population with a higher risk of developing metastases. Denosumab significantly increased BMFS with a median of 29.5 against 25.2 months (HR 0.85; 95% CI: 0.73–0.98; P=0.028). Nonetheless, OS did not differ between the groups, with a median of 43.9 months with denosumab and 44.8 months with placebo (HR 1.01; 95% CI: 0.85–1.20; P=0·91) (24). Despite the modest increase in BMFS, the regulatory agencies denied the approval of denosumab for the treatment of nmCRPC due to the lack of benefit in OS (18).

Immunotherapy

PSA-TRICOM is a novel vector-based PSA vaccine. In a phase 2 trial, 42 men with nmCRPC were randomized to receive PSA-TRICOM *vs.* nilutamide monotherapy. There was a trend toward improvement in OS in the vaccine group (5.1 *vs.* 3.4 years) that was not statistically significant (P=0.13) (25).

Sipuleucel-T is a type of vaccine that activates T-cells against the antigen prostatic acid phosphatase in PCa. It is approved by the Food and Drug Administration (FDA) for asymptomatic mCRPC without visceral metastases. Its efficacy in nmCRPC has been evaluated in a small study with 18 patients. Around 70% of patients had a longer PSA-DT after the treatment (7.9 *vs.* 4.9 months, P=0.09). However, no patients achieved a PSA decline ≥50%. No randomized trials have been carried out (26).

Second-generation antiandrogens

Second-generation AR antagonists are more potent than first-generation AR antagonists and do not act as partial agonists if AR is overexpressed unless there are some specific AR point mutations (27,28).

Due to the prolonged survival in nmCRPC, identifying a surrogate endpoint for OS is vital. An Oncologic Drugs Advisory Committee (ODAC) meeting in 2011 discussed possible clinical trial endpoints for this setting. MFS was identified as a reasonable endpoint. MFS is understood as the time from randomization until the discovery of distant metastasis on conventional imaging or death from any

cause, whichever occurred first (19). MFS has been shown to correlate with OS and quality of life in PCa (29-31). The FDA approved MFS as an acceptable clinical trial endpoint in nmCRPC due to the clinical benefit of delaying the appearance of symptoms (27).

Enzalutamide

Enzalutamide binds with high affinity (5–8-fold greater than bicalutamide) to the ligand-binding domain of the AR, inhibiting the binding of androgens. It also inhibits AR translocation to the nucleus and its binding to the DNA. In contrast with bicalutamide, enzalutamide did not show agonist activity in a castration-resistant setting in xenograft models (27).

Enzalutamide is approved by the FDA and the European Medicines Agency (EMA) for the treatment of mCRPC before or after docetaxel, based on two phase 3 trials in which enzalutamide significantly prolonged OS (32,33). The STRIVE trial was a phase 2, double-blind, randomized trial comparing enzalutamide *vs.* bicalutamide in 396 men with nmCRPC or mCRPC. Enzalutamide increased PFS with a median of 19.4 *vs.* 5.7 months with bicalutamide (HR 0.24; 95% CI: 0.18–0.32; P<0.001). All prespecified subgroups benefited from the treatment with enzalutamide, including non-metastatic patients (34). While the study was not powered for OS, these findings laid the groundwork for investigating second-generation AR antagonists in the earlier stages of the disease (35).

The PROSPER trial is a phase 3, randomized, double-blind, placebo-controlled trial. A total of 1,401 patients with high-risk nmCRPC (defined as PSA-DT ≤10 months and PSA level ≥2 ng/mL) were included. After randomization, 933 patients received enzalutamide (160 mg once daily), and 468 received placebo while continuing ADT. Stratification was made according to PSA-DT (≥6 or <6 months) and the use of bone-targeted agents (yes or no). This trial included men who had BCR after local therapy as well as men who had not received local treatment (36).

The two arms had similar baseline characteristics. The median baseline PSA level at study entry was 11.1 ng/mL in the enzalutamide arm and 10.2 ng/mL in the placebo arm. The PSA-DT was 3.8 and 3.6 months, respectively. MFS was the primary outcome. The secondary endpoints evaluated were time to first use of subsequent antineoplastic therapy, time to PSA progression, quality-of-life assessments, OS, and safety (36).

With a median follow-up of 22 months, the median MFS was 36.6 months in the enzalutamide group *vs.* 14.7 months in the placebo group (HR 0.29; 95% CI: 0.24–0.35; P<0.001). The improvement in MFS was consistent in all patient subgroups, including PSA-DT (<6 or ≥6 months). The time to the first use of a subsequent antineoplastic therapy was 39.6 months in the enzalutamide group *vs.* 17.7 months in the placebo group (HR 0.21; 95% CI: 0.17–0.26; P<0.001). Enzalutamide prolonged the time to PSA progression *vs.* placebo (37.2 *vs.* 3.9 months, HR 0.07, P<0.001) (36).

Patients received enzalutamide for a median time of 18.4 months and placebo for 11.1 months. Adverse events (AEs) of grade 3 or higher were reported in a higher percentage of patients in the enzalutamide group than in the placebo group. The most common was fatigue. AEs of special interest that occurred more frequently in the enzalutamide group were hypertension (12% *vs.* 5%), major adverse cardiovascular events (5% *vs.* 3%), mental impairment disorders (5% *vs.* 2%), and falls with non-pathological fractures (17% *vs.* 8%) (36). Nevertheless, enzalutamide did not worsen health-related quality of life (HRQOL). In fact, it showed a significant reduction in the risk of clinically meaningful deterioration of HRQOL in several domains, probably due to the benefit observed in MFS (37).

At the first interim analysis, all primary and secondary endpoints met the criteria for significance except for OS, which had not reached the median in either arm. Therefore, the analysis was considered final for all these endpoints, and the trial was unblinded. Patients in the placebo group were allowed to receive enzalutamide (87 patients initially assigned to placebo received enzalutamide). Based on this study, the FDA and the EMA approved enzalutamide for the treatment of high-risk nmCRPC in 2018 and 2019, respectively (36,38).

The final analysis showed a statistically significant benefit in OS (HR 0.73; 95% CI: 0.61–0.89; P=0.001). The median OS was 67 months in the enzalutamide group compared to 56.3 months in the placebo group. With a median treatment duration of 33.9 months with enzalutamide and 14.2 months with placebo, no new AEs were reported. When adjusted for exposure, there were no significant differences in the frequency of grade 3 or higher AEs (17 per 100 patient-years in the enzalutamide group *vs.* 20 per 100 patient-years in the placebo group) (38).

In a *post-hoc* analysis of OS and safety in subgroups by age and region, the OS benefit with enzalutamide was similar across geographic regions and all ages (HR 0.73; 95% CI: 0.58–0.9; for patients aged ≥70 years) (HR 0.72; 95% CI: 0.5–1.04; for those aged <70 years). Safety was

consistent across age groups and geographic regions. In this multivariate analysis, three factors emerged that significantly impacted OS: Eastern Cooperative Oncology Group (ECOG) performance status (1 *vs.* 0; HR 1.7; 95% CI: 1.4–2.1; P<0.0001), log of PSA (HR 1.2; 95% CI: 1.1–1.3; P<0.0001), and the use of subsequent therapy (yes *vs.* no; HR 2.5; 95% CI: 2.1–3.1; P<0.0001) (39).

Apalutamide

Apalutamide is a nonsteroidal antiandrogen agent that acts as a competitive binder to the androgen-binding domain of the AR inhibitor. It also inhibits AR translocation to the nucleus, AR binding to DNA, and transcription of AR-related genes. Apalutamide has been shown to antagonize AR-mediated signaling even in CRPC cell lines with overexpressed AR. In CRPC mice xenografts, apalutamide induced tumor regressions that were superior to those achieved by bicalutamide or enzalutamide. In a phase 2 study, patients with high-risk nmCRPC (defined as a PSA level of ≥8 ng/mL or PSA-DT ≤10 months) received apalutamide (240 mg once daily) while continuing ADT. The 12-week PSA response rate (defined as ≥50% decline in PSA after baseline) was 89% (40).

These results led to the design of the SPARTAN phase 3 double-blind, randomized, placebo-controlled trial involving men with nmCRPC and a PSA-DT ≤10 months. Patients could have pathologic pelvic lymph nodes if they were <2 cm in the short axis and located below the aortic bifurcation (N1). A total of 1,207 men were randomized at a 2:1 ratio to receive apalutamide (240 mg per day) combined with ADT (806 patients) or placebo (401 patients). At radiographic progression, patients in either arm could receive abiraterone acetate plus prednisone provided by the sponsor. Stratification was made according to PSA-DT (>6 *vs.* ≤6 months), the use of bone-sparing agents, and the presence of malignant lymph nodes (N0 *vs.* N1) (41).

Baseline characteristics were well balanced between both groups. Most patients had N0 disease (83.5% of patients assigned to apalutamide and 83.8% of patients assigned to placebo). In both arms, 76.6% of patients had received prior local treatment, and 71% had a PSA-DT ≤6 months. In the apalutamide and placebo groups, the median PSA-DT was 4.4 *vs.* 4.5 months, and the median PSA level was 7.78 *vs.* 7.96 ng/mL, respectively (42).

The primary endpoint was MFS, assessed by central review. The median MFS was 40.5 months in the apalutamide group compared with 16.2 months in the placebo group (HR 0.28; 95% CI: 0.23–0.35; P<0.001). The benefit of apalutamide was consistently favorable in all prespecified subgroups. In a *post-hoc* analysis, patients in all age subgroups had a significant improvement in MFS with apalutamide, with a similar incidence of treatment-related AEs. Patients aged 75 years or older had an MFS HR of 0.41 (95% CI: 0.31–0.56; P<0.0001), those aged 65 to 75 years had an HR of 0.24 (95% CI: 0.18–0.34; P<0.0001), and patients younger than 65 years had an HR of 0.14 (95% CI: 0.07–0.27; P<0.0001) (41,42).

Apalutamide also demonstrated a significant improvement at the first interim analysis in secondary endpoints such as time to metastasis (HR 0.28; 95% CI: 0.23–0.34; P<0.0001), PFS (HR 0.30; 95% CI: 0.25–0.36; P<0. 0001), and time to symptomatic progression (HR 0.45; 95% CI: 0.32–0.63; P<0.0001). Based on these outcomes, the independent data and safety monitoring committee unanimously recommended unblinding the study. As a result, 76 patients (19%) who were initially assigned to receive placebo then received apalutamide (41,43).

The first interim analysis of OS with a median follow-up of 20.3 months showed favorable results that did not reach statistical significance (HR 0.70; 95% CI: 0.47–1.04; P=0.0742) (36). At the second interim analysis, with a median follow-up of 41 months, 155 patients (19.3%) had treatment withdrawn due to progression in the apalutamide arm *vs.* 210 patients (52.8%) in the placebo arm. AEs led to treatment interruption for 85 patients (10.6%) in the apalutamide arm *vs.* 28 patients (7%) in the placebo arm. The rate of serious AEs was comparable between apalutamide and placebo (24.8% *vs.* 23.1%), with ten deaths *vs.* one, respectively. The most frequent AEs were fatigue (30.4% *vs.* 21.1%), skin rash (23.8% *vs.* 5.5%), falls (15.6% *vs.* 9%), fractures (11.7% *vs.* 6.5%), hypothyroidism (8.1% *vs.* 2%) and seizures (0.2% *vs.* 0%) (43). Apalutamide did not show a detrimental effect on HRQOL (44).

Second PFS (PFS2) was an exploratory endpoint in this trial, defined as the time from randomization to investigator-assessed disease progression (by PSA, imaging, or the appearance of symptoms) after the following treatment or death from any cause. In the first analysis, PFS2 was significantly longer in the apalutamide group than in the placebo group (HR 0.49; 95% CI: 0.36–0.66) (41). After 1 year of additional follow-up, PFS2 and safety were re-evaluated. With a median follow-up of 32 months, 51.3% of patients in the apalutamide group, 8% of patients who crossed over from placebo to apalutamide, and 99.7% of patients in the placebo group had discontinued the study treatment. Of these patients, 60% in the apalutamide

group and 79% in the placebo group initiated a subsequent systemic treatment for mCRPC. The most frequent subsequent systemic therapies were abiraterone (44% of patients in the apalutamide group and 58% in the placebo group), enzalutamide (6.6% and 10%, respectively), and docetaxel (4.9% and 5.6%, respectively). Patients randomized to apalutamide kept showing a significant increase in PFS2 with a median not reached *vs.* 39.3 months in the placebo group (HR 0.5; 95% CI: 0.39–0.63; P<0.0001). No substantial change in the incidence of treatment-related adverse events (TRAE) in the apalutamide group was observed (45).

Since the primary endpoint was met at the first analysis, apalutamide was approved by the FDA and the EMA in 2019. In the final OS analysis, with a median follow-up of 52 months, the median OS in the apalutamide group was significantly longer compared to the placebo group (73.9 *vs.* 59.9 months), reaching the prespecified statistical significance (HR 0.78; 95% CI: 0.64–0.96; P=0.016) (46).

Darolutamide

The last AR antagonist studied and approved by the FDA and the EMA for patients with nmCRPC was darolutamide. Darolutamide is a third-generation AR antagonist that inhibits androgen binding and androgen-induced translocation in overexpressing AR cells. It has been shown to act as an AR antagonist even in cells with AR mutations that confer resistance to antiandrogen therapies, including AR(F876L) that plays a role in enzalutamide and apalutamide resistance. Darolutamide has a distinct structure with lower penetration of the blood-brain barrier and low binding affinity for γ-aminobutyric acid type A receptors. Therefore, it has the potential for fewer and milder AEs. Darolutamide has shown significant antitumor activity and a good side-effect profile in patients with mCRPC in phase 1 and 2 studies (47,48).

Given these results, a randomized, double-blind, placebo-controlled, phase 3 trial was conducted. The Androgen Receptor Antagonizing Agent for Metastasis-free Survival (ARAMIS) trial was designed to evaluate the efficacy and safety of darolutamide in men with nmCRPC and a PSA-DT ≤10 months, including patients with malignant regional lymph nodes (N1 disease). A total of 1,509 patients were randomly assigned in a 2:1 ratio to receive darolutamide 1,200 mg per day (two 300-mg tablets given twice daily) (64% of patients) or placebo (36%) while continuing ADT. This study included patients with BCR after local treatment as well as patients who had never received local treatment. Furthermore, it is the only one of the three trials that did not exclude patients with a history of seizure or conditions predisposing to seizure. Stratification was made based on PSA-DT (>6 *vs.* ≤6 months) and the use of bone-sparing agents (49).

Baseline characteristics were well balanced. Most patients had N0 disease (83% in the darolutamide arm and 71% in the placebo arm). The median PSA-DT was 4.4 months in the darolutamide arm and 4.7 months in the placebo arm. The median PSA level was 9 and 9.7 ng/mL, respectively (49).

In the planned primary analysis, with a median follow-up of 17.9 months, the median MFS was 40.4 months with darolutamide *vs.* 18.4 months with placebo (HR 0.41; 95% CI: 0.34–0.5; P<0.001). In the first interim analysis of OS with 136 deaths, darolutamide presented a tendency to increase OS compared with placebo, although it did not reach statistical significance (HR 0.71; 95% CI: 0.5–0.99; P=0.045) (49).

Other secondary end points such as time to pain progression (median 40.3 *vs.* 25.4 months; HR 0.65; 95% CI: 0.53–0.79; P<0.001), time to first cytostatic chemotherapy (HR 0.43; 95% CI: 0.31–0.60; P<0.001), time to first symptomatic skeletal event (HR 0.43; 95% CI: 0.22–0.84; P<0.001), PFS (HR 0.38; 95% CI: 0.32–0.45; P<0.001), or time to PSA progression (HR 0.13; 95% CI: 0.11–0.16; P<0.001) were significantly longer with darolutamide compared to placebo (49).

Regarding safety, 83.2% of patients reported AEs of any grade in the darolutamide group, compared with 76.9% in the placebo group. In the darolutamide group, 24.7% had grade 3–4 AEs *vs.* 19.5% in the placebo group. Grade 5 AEs were comparable in both groups (3.9% and 3.2%, respectively). No significant difference was observed between groups in the treatment discontinuation rate due to AEs (8.9% *vs.* 8.7%, respectively). AEs that appeared more often with darolutamide than placebo were hypertension (6.6% *vs.* 5.2%), heart failure (1.9% *vs.* 0.9%), fractures (4.2% *vs.* 3.6%), and fatigue/asthenia (15.8% *vs.* 11.4%) (50). AEs related to the central nervous and coronary systems were similar with both treatments. Darolutamide maintained HRQOL and delayed the appearance of PCa-related symptoms and deterioration of HRQOL (50).

After the first interim analysis results were published, the study was unblinded and crossover was permitted. Therefore, the 170 patients that remained in the placebo group received darolutamide. With a median follow-up of 29 months, darolutamide showed a statistically significant benefit in OS with 83% of patients alive at 3 years compared

Table 3 Comparisons between the three second-generation antiandrogens

	PROSPER (37,39)	SPARTAN (42,44,46,47)	ARAMIS (50,52)
Agent tested	Enzalutamide	Apalutamide	Darolutamide
	cM0 cN0 CRPC	cM0 cN0-1 CRPC	cM0 cN0-1 CRPC
Inclusion criteria	PSA-DT ≤10 months	PSA-DT ≤10 months	PSA-DT ≤10 months
	PSA ≥2 ng/mL	–	PSA ≥2 ng/mL
Study population			
Median age	74 *vs.* 73 years	74 years both groups	74 *vs.* 74 years
Median PSA at entry	11.1 *vs.* 10.2 ng/mL	7.78 *vs.* 7.96 ng/mL	9.0 *vs.* 9.7 ng/mL
Median PSA-DT	3.8 vs. 3.6 months	4.40 *vs.* 4.50 months	4.4 *vs.* 4.7 months
PSA-DT <6 months	77% in both groups	71.5% *vs.* 70.8%	70% *vs.* 67%
Total number of patients	1,401	1,207	1,509
MFS	36.6 *vs.* 14.7 months; HR 0.29; P<0.0001	40.5 *vs.* 16.2 months; HR 0.29; P<0.0001	40.4 *vs.* 18.4 months; HR 0.41; P<0.0001
OS	67 *vs.* 56.3 months; HR 0.73; P=0.001	73.9 *vs.* 59.9 months; HR 0.78; P=0.016	3-year OS 83% *vs.* 77%; HR 0.69; P=0.003
Serious adverse events	24% *vs.* 18%	25% *vs.* 23%	24% *vs.* 15%

CRPC, castration-resistant prostate cancer; PSA, prostate-specific androgen; PSA-DT, prostate-specific androgen doubling time; MFS, median metastasis-free survival; OS, overall survival; HR, hazard ratio.

with 77% of those who received placebo (HR 0.69; 95% CI: 0.53–0.88; P=0.003) (51).

Comparisons between the three drugs (*Table 3*)

While these three trials have revolutionized the treatment of nmCRPC, there is no direct comparative data between the three agents. Thus, many indirect meta-analyses have been designed to help guide treatment decisions.

Mori *et al*. designed a meta-analysis of the three phase 3 trials mentioned above (SPARTAN, PROSPER, and ARAMIS) to indirectly compare the efficacy and safety of the three agents. This meta-analysis was performed with immature OS data. For MFS, all three agents were significantly better than placebo, and apalutamide emerged as the most effective (P=0.8809). Compared with darolutamide, apalutamide (HR 0.85; 95% CI: 0.77–0.94) and enzalutamide (HR 0.86; 95% CI: 0.78–0.95) showed a significantly improved MFS. Grade 3 or 4 AEs were more frequent with all three agents than placebo. However, darolutamide and placebo had a similar frequency of grade 5 AEs and a similar rate of treatment withdrawal due to AEs (OR 1.20 *vs.* OR 1.03). By contrast, apalutamide (OR 5.01 *vs.* OR 1.56) and enzalutamide (OR 5.49 *vs.* OR 1.61) had a higher frequency of grade 5 AEs and toxicity leading to treatment withdrawal. Based on this meta-analysis, apalutamide and enzalutamide appear to be the most effective drugs for the treatment of nmCRPC. Nevertheless, darolutamide emerges as the agent with the more tolerable profile. These findings may help guide individualized treatment strategies and inform future direct comparative trials (52).

Another meta-analysis between the three trials confirmed these results. In this meta-analysis, apalutamide and enzalutamide showed a significantly higher MFS compared to darolutamide with an HR of 0.73 (95% CI: 0.55–0.97) and HR of 0.71 (95% CI: 0.54–0.93), respectively, with no differences in OS. Although no significant differences were shown regarding AEs, darolutamide had the highest probability of being the best tolerated (53).

A third meta-analysis using individual patient-level data from the SPARTAN and ARAMIS trials has been published. This study made an anchored matching-adjusted indirect comparison (MAIC), adjusting the patients included in the SPARTAN trial to match the baseline characteristics of the patients included in the PROSPER trial. Then, MFS and OS were reanalyzed for the new SPARTAN population.

MAIC-based HRs for apalutamide *vs.* enzalutamide were 0.91 (95% CI: 0.68–1.22) for MFS and 0.77 (95% CI: 0.46–1.30) for OS. Given these results, apalutamide appears to improve MFS and OS more than enzalutamide (54).

A meta-analysis published in 2019 included the aggregated data from the interim analyses of the three phase 3 randomized trials (PROSPER, SPARTAN, and ARAMIS). This meta-analysis concluded that these drugs improve MFS with a statistically significant difference (HR 0.32; 95% CI: 0.25–0.41; P<0.001). Nonetheless, the administration of these hormonal agents was significantly associated with an increased risk of treatment-related death with a relative risk (RR) of 2.41 (95% CI: 1.37–4.24; P=0.002). They also increased the risk of cardiovascular events (RR 2.44), fractures (RR 2.24), falls (RR 2), and hypertension (RR 1.38). The risk of fatigue, diarrhea, skin rash, or seizures was not increased with the three agents *vs.* placebo. However, enzalutamide showed a higher risk of death, cardiovascular toxicity, and fatigue. Apalutamide showed an increased risk of falls, fractures, and skin rash. Darolutamide was associated with an increased risk of cardiovascular toxicity (55).

Finally, an exploratory analysis with pooled data from the three trials mentioned above studied the safety and efficacy of the three agents according to age in patients with nmCRPC. In the three trials, a total of 4,117 men were included; 2,694 men received a second-generation AR inhibitor (apalutamide, enzalutamide, or daralutamide), and 1,423 received placebo. A total of 1,023 men included in these trials were aged 80 years or older, and 3,094 were younger. The median MFS for the subgroup of men ≥80 years old was 40 months in patients allocated to the second-generation AR inhibitor groups and 22 months in the placebo groups, with an adjusted HR of 0.37 (95% CI: 0.28–0.47). For patients <80 years old, the median MFS was 41 and 16 months, respectively (HR 0.31; 95% CI: 0.27–0.35). Regarding OS, men ≥80 years old had a median OS of 54 months in patients allocated to the second-generation AR inhibitor groups and 49 months in the placebo groups. Men <80 years old had a median OS of 74 months compared to 61 months in the placebo groups, with an adjusted HR of 0.69 (95% CI: 0.60–0.80). Concerning toxicity, grade ≥3 AEs were slightly more common in men > 80 years old treated with second-generation AR inhibitors (55% *vs.* 41% with placebo). On the other hand, only 44% of men <80 years old treated with second-generation AR inhibitors presented with grade ≥3 AEs compared to 30% with placebo. The most frequent grade 3–4 AEs were hypertension (8% with AR inhibitor in both age groups *vs.* 5% of men <80 years old and 6% of men ≥80 years old with placebo) and fracture (3% and 5% with AR inhibitors compared to 1% and 3% with placebo, respectively). These results support the use of these three agents in patients with nmCRPC regardless of age (56).

Although no direct comparisons between the three agents have been made, these meta-analyses may help guide treatment decisions and lay the groundwork for the design of direct comparative trials in the future (52-55).

Future directions

nmCRPC in the prostate-specific membrane antigen ligand positron emission tomography (PSMA-PET) era

The approval of three second-generation AR inhibitors for the treatment of nmCRPC brings non-metastatic and metastatic CRPC closer together. Nonetheless, the three phase 3 trials that led to the approval of these drugs included patients categorized as non-metastatic based on the absence of distant metastasis by standard imaging (bone scan and CT). We now know that these conventional imaging modalities do not have enough sensitivity to identify the presence of metastasis in a large proportion of patients. The sensitivity of CT scans in detecting malignant lymph nodes is 42%. Meanwhile, bone scans have a 79% sensitivity and an 82% specificity for identifying bone metastasis. New imaging techniques based on the use of several PET tracers are being studied, and some have been established in clinical practice. These PET tracers include, among others, 18F-fluciclovine, ^{68}Ga-PSMA, and ^{18}F-sodium fluoride (NaF). A study with 30 patients with nmCRPC showed a 100% detection of metastasis with ^{68}Ga-PSMA-PET/CT in patients with a PSA level higher than 2 ng/mL (20/20) and 70% in patients with a lower PSA (7/10). A meta-analysis compared bone scans to PSMA-PET/CT, and a higher sensitivity was observed for PSMA-PET/CT (0.97 *vs.* 0.86 with bone scans) with comparable specificity (0.95 for bone scans and 1.00 for PSMA-PET/CT). ^{68}Ga-PSMA-PET/CT has also shown a significant decrease in the maximum standardized uptake value (SUVmax) of the primary tumor and metastatic lymph nodes that correlates with PSA response after ADT. As novel imaging techniques become broadly used, the number of patients diagnosed with nmCRPC will likely decrease (13,18,57-60).

The role of PSMA-PET in nmCRPC is still mostly unknown. Given the higher sensitivity of PSMA-PET, metastases may be detected earlier, which would lead to a reclassification of the disease stage and could consequently

affect the management of the disease. A retrospective study was conducted to estimate the PSMA-PET sensitivity for pelvic and distant metastasis. This study included 200 patients with high-risk nmCRPC (defined as PSA >2 ng/mL, a PSA-DT ≤10 months, or a Gleason score of 8, using conventional imaging). The population included in this analysis was similar to the one described in the phase 3 trials mentioned above. A total of 98% of patients had local recurrence or metastasis using PSMA-PET imaging: 24% had only local recurrence, and 55% had M1 disease. N1 or M1 disease was oligometastatic (1–3 lesions) in 29% of patients and polymetastatic (≥4 lesions) in 46%. This retrospective trial suggests that a large proportion of men included in the PROSPER, SPARTAN, and ARAMIS trials would have been categorized as mCRPC if molecular imaging techniques had been done at screening (13).

The definition of nmCRPC depends entirely on radiological findings and does not describe the biology of the tumor. With the implementation of molecular imaging techniques, fewer men are expected to be categorized as nmCRPC patients. Moreover, enzalutamide, apalutamide, and darolutamide have shown important clinical improvement in all patients with high-risk nmCRPC (defined by PSA-DT ≤10 months) irrespective of the detection of metastasis by more sensitive imaging techniques. Given the benefit seen in MFS and OS in the PROSPER, SPARTAN, and ARAMIS trials, a more intensive treatment approach starting sooner would probably be the best strategy for men with high-risk nmCRPC, independent of the presence or absence of metastasis identified by novel imaging techniques (57).

Molecular subtypes

Individualized management of patients with nmCRPC could improve their OS and quality of life. Molecular biomarkers could help identify patients at a higher risk of metastases. A cohort study was designed to assess if molecular subtypes are predictive of response to apalutamide. In this study, the gene expressions from 233 nmCRPC tumors included in the SPARTAN trial were analyzed (61).

Stratification was carried out according to the genomic classifier (GC) scores (high risk >0.6; low risk ≤0.6) and basal or luminal types. The Decipher prostate test is a gene expression classifier that reports a GC score. This score has been validated as a predictor of the risk of metastasis in localized PCa. On the other hand, the luminal and basal molecular classification identifies a more indolent disease with high AR signaling (luminal type PCa) and a more aggressive subtype (basal type PCa) (61).

A total of 116 patients (50% of the patients analyzed) had a high-risk GC score. While it is important to highlight that all patients benefited from adding apalutamide to ADT, patients with a high risk of metastasis according to the GC score benefited the most from the addition of apalutamide to ADT, with an HR for MFS of 0.21 (95% CI: 0.11–0.4; P<0.001) compared with placebo plus ADT. Consistent with these results, OS (HR 0.52; 95% CI: 0.29–0.94; P=0.03) and PFS2 (HR 0.39; 95% CI: 0.23–0.67; P=0.001) also showed a significant improvement with the addition of apalutamide to ADT in patients with a GC score >0.6. Meanwhile, patients with a low-risk GC score had a borderline benefit with the addition of apalutamide to ADT (HR 0.46; 95% CI: 0.23–0.95; P=0.04). However, there was no statistically significant interaction between the effect of apalutamide and the GC score on MFS, OS, or PFS2 (61).

Concerning the prognostic value of the GC score, a significantly shorter MFS was observed in patients with high-risk compared to low-risk GC scores when analyzing patients who received ADT plus placebo (median MFS 14.5 *vs.* 22.1 months; HR 0.43; 95% CI: 0.22–0.85; P=0.01). Inversely, no difference was observed in the GC score when analyzing patients who received apalutamide plus ADT (HR 1.11; 95% CI: 0.58–2.13; P=0.75). A similar trend was observed for OS and PFS2. Given these results, apalutamide added to ADT appears to overcome the worse prognosis observed in patients with a high-risk GC score (61).

Regarding luminal and basal subtypes, 65% of patients were classified with the basal molecular subtype. The addition of apalutamide to ADT showed a significant increase in MFS in both subtypes, with an HR of 0.22 for the luminal subtype (95% CI: 0.08–0.56; P=0.002) and 0.34 for the basal subtype (95% CI: 0.20–0.58; P<0.001). In patients who received ADT plus placebo, no differences were observed between the luminal and basal subtypes. Nonetheless, in the apalutamide plus ADT arm, men with luminal subtype tumors showed an increased benefit in MFS than men with basal subtype tumors, with an HR of 0.4 (95% CI: 0.18–0.91; P=0.03). Comparable tendencies were observed for OS and PFS2. As mentioned before, all patients seem to benefit from adding apalutamide. Nonetheless, these findings indicate that men with luminal subtype tumors may benefit the most from this treatment (61).

Given these results, the GC score and the molecular subtype (basal or luminal) may be good predictors of response when adding apalutamide to ADT for patients with nmCRPC. Apalutamide benefited all patients, but the patients who benefited most from this treatment were

Table 4 Ongoing clinical trials

Trial	Phase	Intervention	N	Description
NCT01046916	Phase II, one arm	TAK-700 (CYP17 inhibitor)	38	Designed to evaluate the safety and efficacy of TAK-700 in nmCRPC with a PSA-DT ≤8 months or PSA level ≥8 ng/mL
NCT04567875 (apa-CARDIO1)	Prospective observational study	No intervention	54	The primary objective of the study is to evaluate the arterial hypertension in patients with nmCRPC treated with apalutamide
NCT03569280	Phase 1, open-label	KPG-121 (immunomodulator) in combination with enzalutamide or abiraterone or apalutamide	36	The primary objective is to determine the MTD in patients with mCRPC or nmCRPC
NCT03800784	Single group assignment	18F-DCFPyL PET/CT	48	The primary outcome of the study is the sensitivity of 18F-DCFPyL PET/CT imaging to detect progression in patients with metastastatic or nmCRPC receiving standard AR inhibitors

nmCRPC, non-metastatic castration-resistant prostate cancer; PSA-DT, prostate-specific androgen doubling time; MTD, maximum tolerated dose; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific androgen; AR, androgen receptor.

patients with a high-risk GC score and luminal subtype tumors. The GC score may help identify the best candidates for second-generation hormonal therapy. Basal-luminal subtyping may help select patients with basal-subtype tumors for further treatment intensification in combination with second-generation hormonal therapy (61).

Ongoing trials

We summarize the ongoing trials for patients with nmCRPC in *Table 4*.

Conclusions

nmCRPC is a heterogeneous disease state that varies from an indolent to a rapidly progressive disease. Nowadays, PSA-DT is the best tool to select patients at a high risk of developing metastases. Over the years, several pharmacological strategies have been studied to delay the appearance of metastatic disease in an unselected population with nmCRPC. However, until 2018, none of them had shown an improvement in OS.

Recently, the FDA and EMA have approved the first three agents for the treatment of nmCRPC. Enzalutamide, apalutamide, and darolutamide have shown an improvement in MFS and OS with a reasonable safety profile in a selected high-risk population (PSA-DT ≤10 months). Given these results, every patient with nmCRPC and a PSA-DT ≤10 months should be treated with one of these agents unless they present significant comorbidity that limits OS more than the PCa.

While no direct comparison between the three agents has been made, three meta-analyses with indirect comparisons suggest that apalutamide and enzalutamide may be more effective, whereas darolutamide seems to have the best tolerability.

With the advent of novel imaging techniques, the future status of nmCRPC as a distinct disease is put into question. Nevertheless, given the benefit seen in MFS and OS in these trials, the early treatment intensification with a second-generation AR antagonist is probably the best option in nmCRPC, irrespective of the detection of metastasis by molecular imaging techniques.

Finally, biomarkers would be helpful to individualize the management of patients with nmCRPC and better identify those who could benefit from the addition of a second-generation AR antagonist. The GC score and basal-luminal subtype may act as biomarkers predictive of response, although more data is needed to confirm their predictive value.

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