**Name of Journal:** *World Journal of Clinical Oncology*

**Manuscript NO:** 59435

**Manuscript Type:** EDITORIAL

**Nonmetastatic castration-resistant prostate cancer: Novel agents to treat a lethal disease**

Henriquez I *et al*. nmCRPC: A lethal disease

Ivan Henriquez, Daniel Spratt, Alfonso Gómez-Iturriaga, Oscar Abuchaibe, Felipe Couñago

**Ivan Henriquez,** Department of Radiation Oncology, Hospital Universitario Sant Joan, Instituto Investigación Pere i Virgili, Reus 43204, Tarragona, Spain

**Daniel Spratt,** Department of Radiation Oncology, Ann Arbor, University of Michigan, Michigan, MI 48109, United States

**Alfonso Gómez-Iturriaga,** Department of Radiation Oncology, Hospital Universitario Cruces/Biocruces Health Research Institute, Barakaldo 48903, Bizcaia, Spain

**Oscar Abuchaibe,** Department of Radiation Oncology, Virgilio Galvis Ramirez Cancer Centre, Bucaramanga s/n, Santander, Colombia

**Felipe Couñago,** Department of Radiation Oncology, Hospital Universitario Quirónsalud Madrid, Pozuelo de Alarcón, Hospital La Luz, Clinical Department, Faculty of Biomedicine, Universidad Europea, Madrid 28223, Spain

**Author contributions:** Henriquez I, Spratt D, Gómez-Iturriaga A, Abuchaibe O, and Couñago F contributed equally to this work.

**Corresponding author: Ivan Henriquez, MD, PhD, Academic Research, Doctor, Medical Assistant,** Department of Radiation Oncology, Hospital Universitario Sant Joan, Instituto Investigación Pere i Virgili, Av. Josep Laporte 2, Reus 43204, Tarragona, Spain. ivanhenriquezlopez@me.com

**Received:** September 10, 2020

**Revised:** December 1, 2020

**Accepted:** December 13, 2020

**Published online:** January 24, 2021

**Abstract**

Nonmetastatic castration-resistant prostate cancer (nmCRPC) - defined as prostate-specific antigen (PSA) > 2 ng/mL, testosterone castration levels < 1.7 nm/L, and the absence of metastatic lesions on conventional imaging (computed tomography or bone scan) - has been defined as a lethal disease by the Prostate Cancer Work Group. One-third of patients with prostate cancer who receive androgen deprivation therapy for biochemical recurrence after local treatment will develop CRPC, with death occurring an average of 2.5 years after diagnosis of castration resistance. Most patients diagnosed with nmCRPC are asymptomatic or minimally symptomatic at diagnosis due to local treatment. In patients with short PSA doubling times (< 10 mo) and high baseline PSA levels, there is a high risk of bone metastases followed by prostate cancer-related mortality. These patients also present significant morbidity that negatively impacts quality of life (QoL). Recently, the results of three randomized trials (PROSPER, SPARTAN, and ARAMIS) were published. Those trials evaluated the efficacy of three different androgen receptor inhibitors - enzalutamide, apalutamide, and darolutamide - in patients with nmCRPC. In all three trials, the study drugs improved both metastasis-free survival and overall survival compared to placebo, plus on-going androgen deprivation therapy without a negative impact on QoL. In patients with nmCRPC, the most important clinical objective is early detection and treatment to maintain a low tumor burden and to prolong the symptom-free interval. For patients with nmCRPC, these novel drugs offer new hope for better QoL and survival outcomes.

**Key Words:** Nonmetastatic castration-resistant prostate cancer; Prostate cancer; Apaluta-mide; Enzalutamide; Darolutamide; Toxicity

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Henriquez I, Spratt D, Gómez-Iturriaga A, Abuchaibe O, Couñago F. Nonmetastatic castration-resistant prostate cancer: Novel agents to treat a lethal disease. *World J Clin Oncol* 2021; 12(1): 6-12

**URL:** https://www.wjgnet.com/2218-4333/full/v12/i1/6.htm

**DOI:** https://dx.doi.org/10.5306/wjco.v12.i1.6

**Core Tip:** The main focus of this editorial is to review novel treatments for nonmetas-tatic castration-resistant prostate cancer (nmCRPC). The three-practice changing pivotal randomized controlled trials - PROSPER, SPARTAN, and ARAMIS - are reviewed. We discuss the findings of these trials, emphasizing the strengths of the studies and critically examining controversies related to the diagnosis of nmCRPC and the role of advanced imaging techniques and molecular determinants.

**INTRODUCTION**

Nonmetastatic castration-resistant prostate cancer (nmCRPC) - defined by the Prostate Cancer Working Group[1] as a prostate-specific antigen (PSA) level > 2 ng/mL and testosterone castration level < 1.7 nm/L, without evidence of metastasis on conventional radiographic imaging techniques [computed tomography (CT) or bone scans] - is considered lethal in the absence of effective treatments to extend overall survival (OS). It is estimated that 30% of patients who receive androgen deprivation therapy (ADT) for biochemical recurrence after local treatment will develop CRPC, and most of these patients will die from the disease, on average, 2.5 years from diagnosis of castration resistance.

Due to local treatment of the primary tumor, most cases of nmCRPC are asymptomatic or minimally symptomatic at diagnosis, even though most of these patients are considered “high risk” due to rapid (< 10 mo) PSA doubling time (PSADT) and high baseline PSA values. Consequently, the risk of developing bone metastases (M1) and/or prostate cancer-related mortality is high. For this reason, early identification of patients with castration resistance should be prioritized to offer effective treatments. In this regard, it is crucial to keep in mind that patients with M1 bone involvement will present substantial morbidity with a significant loss of quality of life (QoL)[2,3].

Recently, the results of three randomized trials (SPARTAN, PROSPER, and ARAMIS)[4-6] were published in high-impact scientific journals. These trials were performed to evaluate second-generation antiandrogens (enzalutamide, apalutamide, and darolutamide), known as androgen receptor inhibitors (ARIs). These agents significantly increased both metastasis-free survival (MFS) - the primary objective - and OS - the secondary objective - *vs* placebo, plus on-going ADT in patients with nmCRPC. In all three trials, adverse effects (AEs) were minimal, and QoL was excellent. These results were achieved mainly through early diagnosis and treatment, which helped to maintain a low tumor burden and to minimize symptoms in these patients for a prolonged period of time.

The emergence of these new novel agents offers new expectative to patients with nmCRPC, providing them with a remarkable opportunity for better survival outcomes (MFS and OS) while maintaining excellent QoL. In the present editorial, we review and discuss the most relevant clinical, biological, and radiographic aspects related to the diagnosis and treatment of nmCRPC.

**Why should we treat nmCRPC?**

***Clinical evidence***

The results of the aforementioned pivotal clinical trials SPARTAN, PROSPER, and ARAMIS were published between February 2018 and February 2019. The study design of these trials was quite similar, involving patients diagnosed with high-risk nmCRPC, with a rapid PSADT (≤ 10 mo) and an Eastern Cooperative Oncology Group performance status of 0-1. The patients were randomized (2:1 ratio) to receive the study drug (apalutamide, enzalutamide, or darolutamide) or placebo, plus on-going ADT. These potent ARIs prevent androgen-receptor translocation, DNA binding, and receptor-mediated transcription. Structurally, the drugs are quite similar, although with several differentiating characteristics. For example, darolutamide has less capacity to penetrate the central nervous system (blood-brain barrier) and low affinity for the γ-aminobutyric acid type A receptor, which theoretically confers a lower risk of AEs in the brain compared to enzalutamide and apalutamide[6].

The primary endpoint in all three trials was MFS. Secondary endpoints included OS, time to bone-related events, time to initiation of chemotherapy, progression-free survival (PFS), time to PSA progression, and time to pain progression, among others. The enrolment in each study ranged from 1200 to 1500 patients. Today, is it clear that MFS is an “intermediate event” (surrogate) that can predict OS. In this regard, the Food and Drug Administration has recognized that a substantial delay in the onset of metastasis is a clinically-relevant endpoint[7,8].

Although the trials are not directly comparable, they do share many characteristics: More than 70% of patients had Eastern Cooperative Oncology Group status 0, more than 70% had a PSADT < 6 mo, and only 3%-11% received bone-targeted therapies from the beginning diagnosis of nmCRPC. In addition, both the SPARTAN and ARAMIS trials - but not PROSPER - included patients with N1 disease. Only the SPARTAN study assessed PFS2 as a secondary endpoint. Treatment-related toxicity was assessed every 4 wk in the SPARTAN trial *vs* every 16 wk in the ARAMIS and PROSPER studies.

All three trials achieved the main endpoint (MFS): SPARTAN [hazard ratio (HR) 0.28; 95% confidence interval (CI): 0.23-0.35; *P* < 0.0001), PROSPER (HR 0.29; 95%CI: 0.24-0.35; *P* < 0.0001), and ARAMIS (HR 0.41; 95%CI: 0.34-0.50, *P* < 0.001). The low HR in these trials is noteworthy, as it is unusual in the field of oncology to observe such low values in three consecutive trials. These findings show that distant metastases or death decreased by 59%-72% in patients treated with the study drugs *vs* placebo. Moreover, administration of these novel agents in patients with nmCRPC extended MFS by approximately 2 years (Table 1).

The OS rates for these trials - a highly anticipated secondary objective - were recently published, showing a significant reduction in mortality risk in the treatment arms, as follows: SPARTAN, 22%; PROSPER, 27%; and ARAMIS, 31%. Median OS in patients treated with apalutamide was 73.9 mo *vs* 59.9 mo in the placebo group. The corresponding OS values for enzalutamide were 67 mo *vs* 56.3 mo. OS values have not reached for darolutamide. These findings indicate that treatment with ARIs extended OS by approximately 1 year.

***Should we assess molecular determinants in nmCRPC?***

In a *post hoc* analysis of the SPARTAN study, Saad*et al*[9]used the DECIPHER® platform (Decipher Biosciences Inc., San Diego, CA, United States) to evaluate the molecular subtypes associated with a decrease in PSA values and with survival outcomes. Those authors stratified patients into risk groups according to their genomic classifier (GC) scores - GC > 0.6 (high risk) *vs* GC ≤ 0.6 (low-to-average risk) and also stratified patients according to the molecular subtype (basal or luminal A/B). The biomarker characteristics of these patients revealed the presence of aggressive disease. A total of 116 patients (50%) had a GC > 0.6 (high risk), 151 patients (65%) had a basal subtype *vs* 8 patients with the luminal A subtype. Importantly, apalutamide improved survival outcomes in all patients, regardless of the specific molecular subtype. Patients treated with apalutamide plus ADT presented a rapid and constant decrease in PSA levels, regardless of the specific molecular characteristics (high or low-average GC, basal/luminal subtype). The patients who presented the largest decrease in PSA levels were those with a low-risk GC profile and those with the luminal subtype. Treatment with apalutamide plus ADT improved both MFS and OS compared to placebo in all molecular subtypes, although the greatest benefits were observed in those with high-risk GC and the luminal subtype.

Although there is not strong evidence to support that earlier initiation of ARIs in patients with nmCRPC may result in a more aggressive molecular subtype or clinical stage, it is a controversial issue.

Smith *et al*[10] evaluated the frequency of AR anomalies, including AR-V7 expression, AR mutations, and AR amplification, before and after treatment with apalutamide plus ADT. In addition, they examined the impact on the exploratory endpoint PFS2 and time on subsequent therapy in patients with nmCRPC who were enrolled in the phase 3 SPARTAN study. Frequency of total AR anomalies was higher in patients at end of treatment than at baseline for both the apalutamide and placebo groups (apalutamide *vs* placebo at baseline: 16% *vs* 13% and at end of treatment: 20% *vs* 30%). Most patients with AR anomalies in the apalutamide group achieved a PSA response at 12 wk. Following the end of apalutamide or placebo treatment, individual AR anomalies did not have a substantial effect on PFS2.

There is a clear need to determine molecular subtypes in prostate cancer to identify better the clinical subgroups likely to benefit from specific therapies[11].

***Do apalutamide, enzalutamide, and darolutamide have different toxicity profiles?***

To date, no head-to-head randomized studies have been performed to compare these three agents, although the available evidence clearly shows that all three have a relatively safe toxicity profile. The overall rate of grade 3/4 AEs in the three trials was approximately 24%, with the most common AEs being hypertension, fatigue, erythema, falls, fractures, and cognitive alterations. The rates of AEs reported seem to be lower in the darolutamide study. Apalutamide has a unique rash reported in 23.8% of patients (grade 3-4 4.2%). Most of them were solved, allowing to continue treatment. The discontinuation rate due to treatment-emergent AEs was quite low, ranging from 8.9% to 15% (apalutamide 15%, enzalutamide 9.8%, darolutamide 8.9%), and few treatment-related deaths have been reported.

Selection of the most appropriate first-line drug will depend on the clinical, biological, and logistical factors at the individual treatment center as well as on availability and cost of the agent, among other factors. In other words, selection will be personalized according to the specific needs of each patient.

***Have any meta-analyses been performed for nmCRPC?***

Two study level meta-analyses of the three randomized trials have been performed to date[12,13], the most recent being the meta-analysis conducted by the Toronto group, presented at the American Society of Clinical Oncology 2020 meeting[12]. In that meta-analysis, the authors evaluated survival outcomes and treatment-related toxicity in the three trials, finding a clear benefit for all three agents *vs* placebo for MFS (HR 0.32; 95%CI: 0.25-0.41), PFS (HR 0.08; 95%CI: 0.05-0.13), and OS (HR 0.74; 95%CI: 0.61-0.90). In terms of grade 3-4 toxicity, treatment with these agents was associated with significantly more AEs than placebo (HR 1.47; 95%CI: 1.27-1.71).

***Does local treatment provide any benefit in nmCRPC?***

There is no solid evidence that treatment (radiotherapy or surgery) of the primary tumor has any benefit in patients with PCa who subsequently develop nonmetastatic castration-resistance, although the findings of the STAMPEDE trial[14] demonstrated that hormone-sensitive metastatic patients with a low tumor burden who received radiotherapy presented better OS outcomes than untreated patients.

A *post hoc* analysis of the SPARTAN trial[15] assessed the impact of initial radical local treatment on OS. In patients who received local treatment, the hazard ratio for OS was better in the apalutamide group (HR 0.67; 95%CI: 0.45-0.98), with a clear and consistent separation between the apalutamide and placebo groups on the Kaplan-Meier OS curves after 15 mo. In the subset of patients who did not receive radical local treatment, although the HR was still favorable for the apalutamide group (HR, 0.82), it was not statistically significant.

The mechanism by which local treatment impacts survival in patients with metastatic PCa is unknown. A plausible mechanism is that eradication (or debulking) of the local tumor may prevent future metastases from the primary tumor. Although this hypothesis should be interpreted cautiously, there is enormous interest in determining the value of definitive local treatment in patients with nmCRPC, an approach that warrants investigation in prospective studies.

***What role do new imaging techniques play in patients with nmCRPC?***

Conventional imaging tests - CT, bone scans, and pelvic magnetic resonance imaging - were performed in all three trials, and the overall evidence suggests that conventional imaging techniques are adequate. However, newer imaging modalities such as choline 68Ga-prostate-specific membrane antigen positron emission tomography (PSMA-PET)/CT have greater sensitivity and specificity than conventional imaging tests[16,17] and are capable of detecting metastatic lesions that are not visible on conventional imaging. These more advanced imaging techniques could potentially provide important data to improve decision-making. In fact, the RADAR III group[18] recently concluded that next-generation imaging techniques should be used in patients with nmCRPC who present a rapid (< 6 mo) PSADT, provided that there is an appropriate treatment available to treat the metastases and alter the course of disease.

The most relevant data published to date were reported by Fendler *et al*[19], who retrospectively evaluated 200 patients with high-risk nmCRPC. In that study, the authors centrally reviewed data obtained by PSMA-PET imaging to determine the detection rate for pelvic disease and distant metastases, which was positive in 196 of the 200 patients evaluated. Overall, despite negative conventional imaging studies, PSMA-PET imaging revealed pelvic involvement in 44% of the sample (24% with local prostate bed recurrence) and M1 disease in 55%.

***QoL in nmCRPC***

All three trials evaluated treatment-related QoL. Overall, the findings from these three trials indicate that, in asymptomatic patients with high-risk nmCRPC, treatment with ARIs does not appear to impact negatively health-related QoL[20]. In recent years, the association between second-generation antiandrogens and health-related QoL has been assessed not only in nmCRPC but also in hormone-sensitive metastatic prostate cancer. The available data strongly support the use of these drugs, which have proven efficacious with acceptable treatment-related toxicity that does not negatively impact QoL. In short, the introduction of these new agents has generated a revolutionary impact in the treatment of patients with nmCRPC.

**CONCLUSION**

To conclude, nonmetastatic CRPC is a heterogeneous, aggressive, and lethal clinical disease. If left untreated, most high-risk nmCRPC patients develop significant symptoms with a substantial deterioration in QoL, leading to a rapid death. However, the published data from clinical trials have shown that treatment with these novel ARIs (enzalutamide, apalutamide, and darolutamide) significantly improves MFS, OS, and QoL. Moreover, all of these agents have a low toxicity profile and can therefore be used safely.

**REFERENCES**

1 **Scher HI**, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, Antonarakis ES, Beer TM, Carducci MA, Chi KN, Corn PG, de Bono JS, Dreicer R, George DJ, Heath EI, Hussain M, Kelly WK, Liu G, Logothetis C, Nanus D, Stein MN, Rathkopf DE, Slovin SF, Ryan CJ, Sartor O, Small EJ, Smith MR, Sternberg CN, Taplin ME, Wilding G, Nelson PS, Schwartz LH, Halabi S, Kantoff PW, Armstrong AJ; Prostate Cancer Clinical Trials Working Group 3. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol* 2016; **34**: 1402-1418 [PMID: 26903579 DOI: 10.1200/JCO.2015.64.2702]

2 **Smith MR**, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, Miller K, Sieber P, Karsh L, Damião R, Tammela TL, Egerdie B, Van Poppel H, Chin J, Morote J, Gómez-Veiga F, Borkowski T, Ye Z, Kupic A, Dansey R, Goessl C. 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 [PMID: 22093187 DOI: 10.1016/S0140-6736(11)61226-9]

3 **Smith MR**, Kabbinavar F, Saad F, Hussain A, Gittelman MC, Bilhartz DL, Wynne C, Murray R, Zinner NR, Schulman C, Linnartz R, Zheng M, Goessl C, Hei YJ, Small EJ, Cook R, Higano CS. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol* 2005; **23**: 2918-2925 [PMID: 15860850 DOI: 10.1200/JCO.2005.01.529]

4 **Smith MR**, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, Olmos D, Mainwaring PN, Lee JY, Uemura H, Lopez-Gitlitz A, Trudel GC, Espina BM, Shu Y, Park YC, Rackoff WR, Yu MK, Small EJ; SPARTAN Investigators. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med* 2018; **378**: 1408-1418 [PMID: 29420164 DOI: 10.1056/NEJMoa1715546]

5 **Hussain M**, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, Ivashchenko P, Demirhan E, Modelska K, Phung, Krivoshik A, Sternberg CN. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med* 2018; **378**: 2465-2474 [PMID: 29949494 DOI: 10.1056/NEJMoa1800536]

6 **Fizazi K**, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, Jievaltas M, Luz M, Alekseev B, Kuss I, Kappeler C, Snapir A, Sarapohja T, Smith MR; ARAMIS Investigators. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med* 2019; **380**: 1235-1246 [PMID: 30763142 DOI: 10.1056/NEJMoa1815671]

7 **Xie W**, Regan MM, Buyse M, Halabi S, Kantoff PW, Sartor O, Soule H, Clarke NW, Collette L, Dignam JJ, Fizazi K, Paruleker WR, Sandler HM, Sydes MR, Tombal B, Williams SG, Sweeney CJ; ICECaP Working Group. Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer. *J Clin Oncol* 2017; **35**: 3097-3104 [PMID: 28796587 DOI: 10.1200/JCO.2017.73.9987]

8 **Beaver JA**, Kluetz PG, Pazdur R. Metastasis-free Survival - A New End Point in Prostate Cancer Trials. *N Engl J Med* 2018; **378**: 2458-2460 [PMID: 29949489 DOI: 10.1056/NEJMp1805966]

9 **Saad F**, Graff JN, Hadaschik B, Oudard S, Mainwaring P, Bhaumilk A, Gormley M, Londhe A, Thomas S, Lopez-Gitlitz A, Mundle S, Davicioni E, Small EJ, Smith MR, Feng FY. Molecular determinants of prostate specific antigen (PSA) kinetics and clinical response to apalutamide (APA) in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC) in SPARTAN. *J Clin Oncol* 2020; **38**: 5521-552 [DOI: 10.1200/JCO.2020.38.15\_suppl.5521]

10 **Smith MR**, Thomas S, Chowdhury S. Androgen receptor anomalies and efficacy of apalutamide in patients with nonmetastatic castration-resistant prostate cancer from the phase 3 SPARTAN study. *Cancer Res* 2018 [DOI: 10.1158/1538-7445.AM2018-2605]

11 **Zhao SG**, Chang SL, Erho N, Yu M, Lehrer J, Alshalalfa M, Speers C, Cooperberg MR, Kim W, Ryan CJ, Den RB, Freedland SJ, Posadas E, Sandler H, Klein EA, Black P, Seiler R, Tomlins SA, Chinnaiyan AM, Jenkins RB, Davicioni E, Ross AE, Schaeffer EM, Nguyen PL, Carroll PR, Karnes RJ, Spratt DE, Feng FY. Associations of Luminal and Basal Subtyping of Prostate Cancer With Prognosis and Response to Androgen Deprivation Therapy. *JAMA Oncol* 2017; **3**: 1663-1672 [PMID: 28494073 DOI: 10.1001/jamaoncol.2017.0751]

12 **Roviello G**, Gatta Michelet MR, D'Angelo A, Nobili S, Mini E. Role of novel hormonal therapies in the management of non-metastatic castration-resistant prostate cancer: a literature-based meta-analysis of randomized trials. *Clin Transl Oncol* 2020; **22**: 1033-1039 [PMID: 31617061 DOI: 10.1007/s12094-019-02228-2]

13 **Hird AE**, Magee DE, Bhindi B, Ye XY, Chandrasekar T, Goldberg H, Klotz L, Fleshner N, Satkunasivam R, Klaassen Z, Wallis CJD. A Systematic Review and Network Meta-analysis of Novel Androgen Receptor Inhibitors in Non-metastatic Castration-resistant Prostate Cancer. *Clin Genitourin Cancer* 2020; **18**: 343-350 [DOI: 10.1016/j.clgc.2020.02.005]

14 **Parker CC**, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, Ritchie AWS, Attard G, Chowdhury S, Cross W, Dearnaley DP, Gillessen S, Gilson C, Jones RJ, Langley RE, Malik ZI, Mason MD, Matheson D, Millman R, Russell JM, Thalmann GN, Amos CL, Alonzi R, Bahl A, Birtle A, Din O, Douis H, Eswar C, Gale J, Gannon MR, Jonnada S, Khaksar S, Lester JF, O'Sullivan JM, Parikh OA, Pedley ID, Pudney DM, Sheehan DJ, Srihari NN, Tran ATH, Parmar MKB, Sydes MR; Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* 2018; **392**: 2353-2366 [PMID: 30355464 DOI: 10.1016/S0140-6736(18)32486-3]

15 **Small EJ**, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, Olmos D, Mainwaring PN, Lee JY, Uemura H, De Porre P, Smith AA, Zhang K, Lopez-Gitlitz A, Smith MR. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. *Ann Oncol* 2019; **30**: 1813-1820 [PMID: 31560066 DOI: 10.1093/annonc/mdz397]

16 **Afshar-Oromieh A**, Holland-Letz T, Giesel FL, Kratochwil C, Mier W, Haufe S, Debus N, Eder M, Eisenhut M, Schäfer M, Neels O, Hohenfellner M, Kopka K, Kauczor HU, Debus J, Haberkorn U. Diagnostic performance of 68Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. *Eur J Nucl Med Mol Imaging* 2017; **44**: 1258-1268 [PMID: 28497198 DOI: 10.1007/s00259-017-3711-7]

17 **Meller B**, Bremmer F, Sahlmann CO, Hijazi S, Bouter C, Trojan L, Meller J, Thelen P. Alterations in androgen deprivation enhanced prostate-specific membrane antigen (PSMA) expression in prostate cancer cells as a target for diagnostics and therapy. *EJNMMI Res* 2015; **5**: 66 [PMID: 26576996 DOI: 10.1186/s13550-015-0145-8]

18 **Crawford ED**, Koo PJ, Shore N, Slovin SF, Concepcion RS, Freedland SJ, Gomella LG, Karsh L, Keane TE, Maroni P, Penson D, Petrylak DP, Ross A, Mouraviev V, Reiter RE, Divgi C, Yu EY; RADAR III Group. A Clinician's Guide to Next Generation Imaging in Patients With Advanced Prostate Cancer (RADAR III). *J Urol* 2019; **201**: 682-692 [PMID: 30077557 DOI: 10.1016/j.juro.2018.05.164]

19 **Fendler WP**, Weber M, Iravani A, Hofman MS, Calais J, Czernin J, Ilhan H, Saad F, Small EJ, Smith MR, Perez PM, Hope TA, Rauscher I, Londhe A, Lopez-Gitlitz A, Cheng S, Maurer T, Herrmann K, Eiber M, Hadaschik B. Prostate-Specific Membrane Antigen Ligand Positron Emission Tomography in Men with Nonmetastatic Castration-Resistant Prostate Cancer. *Clin Cancer Res* 2019; **25**: 7448-7454 [PMID: 31511295 DOI: 10.1158/1078-0432.CCR-19-1050]

20 **Seymour Z**, Hamstra D. Quality of life is not compromised with intensification of androgen therapy in recurrent prostate cancer. *Lancet Oncol* 2018; **19**: 1275-1276 [PMID: 30213450 DOI: 10.1016/S1470-2045(18)30567-9]

**Footnotes**

**Conflict-of-interest statement:** The authors have no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** September 10, 2020

**First decision:** November 16, 2020

**Article in press:** December 13, 2020

**Specialty type:** Oncology

**Country/Territory of origin:** Spain

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A, A

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Schlaepfer IR **S-Editor:** Huang P **L-Editor:** Filipodia **P-Editor:** Wang LL

**Table 1 Metastasis-free survival in patients with nonmetastatic castration-resistant prostate cancer in the SPARTAN, PROSPER, and ARAMIS randomized controlled trials**

|  |  |  |  |
| --- | --- | --- | --- |
| **Objective: MFS** | ***n*** | **HR** **for MFS** | **95%CI; *P* value** |
| Apalutamide *vs* placebo (SPARTAN) | 1207 | 0.28 | 0.23-0.35; < 0.0001 |
| Enzalutamide *vs* placebo (PROSPER) | 1401 | 0.29 | 0.24-0.35; < 0.0001 |
| Darolutamide *vs* placebo (ARAMIS) | 1509 | 0.41 | 0.34-0.50; < 0.001 |

CI: Confidence interval; HR: Hazard ratio; MFS: Metastasis-free survival.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**