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nmCRPC, a look in the continuous care of prostate cancer patients: state of art and future perspectives

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ABSTRACT

Non-metastatic castration resistant prostate cancer (nmCRPC) is a clinical setting defined as confirmed rising levels of PSA in patients treated with ADT but without detectable metastases on conventional imaging with computerized tomography (CT) and technetium-99 m scintigraphy. Men with nmCRPC and a PSA doubling time (PSADT) $\leq$ 10 months are considered at high risk of rapidly developing metastases with a consequent possible impact on survival. Three recent phase III trials have demonstrated, in this setting, the efficacy of adding a next-generation androgen receptor targeted agent (ARTA) to ADT in respect to ADT only, in delaying the development of metastases (metastasis-free survival, MFS) and prolong overall survival. The magnitude of clinical benefit of these agents was even more meaningful if considering the low incidence of drug related adverse events. Our review described the latest advances in the management of nmCRPC, deriving from the pivotal clinical trials, SPARTAN, PROSPER and ARAMIS, in order to support clinicians to optimally manage these patients. Of note, the emergence of novel, more accurate, next-generation imaging techniques (including Ga PSMA-PET/CT), as well as eventual future tumor biomarkers, is modifying the entity and definition of the nmCRPC setting, with a consequent impact on patient's diagnosis and management.

Introduction

Prostate cancer (PC) is one of the most frequently diagnosed cancers and the second-leading cause of cancer death in adult males, globally [1]. Most PC related deaths are associated with metastatic widespread, a condition which can occur either at diagnosis (about 5–10 % of cases) or after disease relapse following local treatments (radical prostatectomy and/or radiation therapy). PC may relapse as biochemical recurrence in absence of distant metastases, a condition also known as "biochemical failure", mainly treated with salvage radiotherapy. However, also salvage treatment can be ineffective, leading to a further disease progression. Of note, two different patterns of PC recurrence can be observed, either with the evidence or the absence of metastases on conventional imaging. In case of biochemical recurrence without the

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evidence of distant metastases, being PC an androgen-dependent tumor, androgen deprivation therapy (ADT), via surgical or chemical castration with gonadotropin-releasing hormone agonists or antagonists, is the backbone of therapy. However, these patients, after an initial PSA response, which is often long-lasting, may develop a further biochemical relapse despite castrate levels of serum testosterone (≤50 ng/dL), defining a condition called castration-resistant prostate cancer (CRPC) [2]. According to PCWG3 criteria, this condition is defined as a 25 % increase of PSA from the nadir (considering a starting value of ≥1.0 ng/ml), with a minimum rise of 2 ng/ml, in the context of castrate levels of testosterone [3]. The European Association of Urology considers suggestive of biochemical progression the evidence of two consecutive PSA rises of >0.2 ng/ml [4].

Of note, CRPC remains dependent on the AR signaling, which plays a key role in driving PC cells proliferation [5]. Rising levels of PSA associated with the lack of detectable metastases on conventional imaging with computerized tomography (CT) and technetium-99 m scintigraphy during ADT treatment define a condition known as non-metastatic CRPC (nmCRPC) [6]. The annual incidence of nmCRPC in the United States has been estimated at roughly 60,000 cases in 2020, with 34 % of annual progression rate to metastatic disease and 16 % of annual overall mortality [7].

Clinically, nmCRPC encompasses heterogeneous conditions, ranging from indolent disease to aggressive forms that rapidly progress to radiologically evident metastases, a condition often associated with the onset of cancer-related symptoms and higher morbidity and mortality rates compared to the previously asymptomatic population [8].

A significant percentage of patients with biochemical disease progression will develop a metastatic disease detectable on CT scan and by 99mTc bone scan, but it is expected that only one-third of patients with nmCRPC would develop metastases within 2 years from the diagnosis [9,10]. Baseline PSA level, PSA velocity, and PSA doubling time (PSADT) have been associated with time to first, mainly bone, metastasis, metastasis-free survival (MFS) and overall survival (OS) [9]. In particular, PSADT is considered the most relevant predictive factor of disease progression with a PSADT ≤10 months as an indicator of high risk of developing metastases and of a higher therapeutic need. Therefore, these parameters are commonly used for monitoring nmCRPC patients, and guiding clinicians towards the most appropriate timing for disease radiologic re-assessment and for treatment modification. Indeed, recently novel drugs have been approved for nmCRPC given the demonstrated ability of next-generation androgen receptor targeted agents (ARTAs) to delay the development of visible metastases and prolong patient' survival.

The purpose of this paper is to review advances in the management of nmCRPC, including emerging data from clinical trials and development of novel imaging techniques. In particular, to evaluate the clinical benefit of these options and whether this outweighs the potential risks of treatment intensification in asymptomatic nmCRPC patients, one of the most debated issues. Moreover, the rapidly evolving field of imaging techniques must be considered for the reinterpretation of the available clinical data in this setting in favor of the best patient management in daily clinical practice.

Identification of nmCRPC patients: conventional or next-generation imaging

The definition (and standardization) of the optimal radiological disease assessment of PC patients has become one of the main problems in their management. This issue becomes even more important when considering the setting of nmCRPC patients, where the accuracy of the new imaging techniques has significantly modified the possibility of establishing the real extent of disease (local relapse or distant metastases), therefore impacting critically on the definition of a true nmCRPC disease condition. Conventional imaging includes CT scan and bone scan. Of note, the sensitivity of CT scan for the detection of metastatic lymph nodes is poor, reaching only the 42 % in a pooled analysis of 18 clinical studies [10]. Similarly, the bone scan has limited accuracy in detecting bone metastases, with a positive scan in nmCRPC patients up to 67 % [11]. The proper timing for conventional imaging assessment has been suggested by a consensus statement of the PCA Radiographic Assessment for Detection of Advanced Recurrence (RADAR) group, which supports a bone scan and a CT scan when the PSA reaches 2 ng/mL; and if this is negative, it should be repeated when the PSA reaches 5 ng/mL, and again after every doubling time of the PSA based on PSA testing every three months for asymptomatic men. Symptomatic patients should undergo relevant investigation regardless of PSA level [12].

Recently, three phase III trials have demonstrated the efficacy of adding a next-generation ARTA to ADT in prolonging the metastasis free survival (MFS) of nmCRPC patients, as it will be discussed extensively later [13–15]. Patients enrolled in these nmCRPC pivotal trials (SPARTAN, PROSPER and ARAMIS studies) had a biochemical recurrence with a PSADT shorter than 10 months, PSA >2 ng/ml and no evidence of macroscopic disease according to the standard imaging (CT + bone scan). However, from the start of these trials to their publication, next generation imaging (NGI) techniques, such as positron emission tomography-computed tomography (PET-TC) with ^{68}Ga-labelled prostate specific membrane antigen (PSMA), C-11 choline, and fluciclovine showed an improved accuracy of diagnosis compared to conventional techniques and strongly reduced the cohort of nmCRPC [16–18]. In the setting of biochemical recurrence after primary treatment, ^{68}Ga-PSMA-11 PET shows a major change (53 %) in management of patients [19]. Moreover, studies conducted in a patient population similar to that of the SPARTAN study showed that PSMA-PET led to identification of 55 % with M1 disease despite negative conventional imaging [20]. Therefore, with these more sensitive imaging techniques, more patients are expected to be diagnosed with early mCRPC. We need to carefully evaluate these data for daily clinical practice combining sensibility with specificity. Moreover, the adoption of PSMA PET-CT should be of value in a prospective of changes in patients' management and eventually survival [21]. However, at the moment, there are no definitive data showing a survival benefit with focal therapy (for example, stereotactic body radiotherapy – SBRT) at the time of castration resistant oligometastatic disease, and the clinical benefit of detecting metastases at an earlier time-point remains partially unclear [22].

As aforementioned, up to 55 % of nmCRPC patients like those enrolled in the ARTAs pivotal trials could have been a positive PSMA PET/CT in this setting, where ARTAs provides a clinically meaningful benefit in terms of OS. Therefore, the adoption of NGI plus an eventual focal therapy should be carefully evaluated in daily clinical practice mainly in the case of symptomatic oligodisease. In particular, PSMA PET-CT could be of utmost importance for those patients with a less aggressive disease (i.e. PSADT >10 months, PSA value <2 ng/dL), which could benefit from a loco-regional therapy directed against oligometastases.

The role of next-generation androgen receptor targeted agents in nmCRPC. Efficacy data from clinical trials

Prior to the recent introduction of ARTAs, it was expected that one in three nmCRPC patients would develop metastasis within 2 years of diagnosis (especially if associated with high baseline PSA and PSA rise kinetics, known as independent predictors of risk of developing detectable metastasis) [9,23].

Three recent randomized controlled phase III trials investigated the role of ARTAs in the setting of nmCRPC (Table 1). Indeed, SPARTAN, PROSPER and ARAMIS evaluated the efficacy of apalutamide, enzalutamide and darolutamide, respectively, compared to placebo in prolonging the metastasis free survival (MFS) of nmCRPC patients treated with maintained ADT [13–15]. All the patients continued to receive androgen-deprivation therapy. Heated debates have animated the

Table 1
Main efficacy data across pivotal trials.

Trial	mMFS	mPFS	mTTSP	mOS	TTChemo	PSA50	mTTPP	PFS2
SPARTAN [apalutamide + ADT vs placebo + ADT]	40.5 vs 16.2 mo (HR 0.28, 95 %CI 0.23–0.35; p < 0.001)	40.5 vs 14.7 mo (HR 0.29, 95 %CI 0.24–0.36; p < 0.001)	NR vs NR HR 0.57 (0.44–0.73; p < 0.0001)	73.9 vs 59.9 mo (HR 0.78, 0.64 – 0.96; p = 0.016)	NR vs NR (HR 0.63, 0.49 – 0.81; p = 0.0002)	93 % vs 3.5 %	NR vs 3.7 mo (HR 0.06, 95 %CI 0.05 – 0.08)	55.6 vs 41.2 mo (HR 0.55, 95 %CI 0.46 – 0.66; p < 0.0001)
PROSPER [enzalutamide + ADT vs placebo + ADT]	36.6 vs 14.7 mo (HR 0.29, 95 %CI 0.24–0.35; p < 0.001)	NR	NR	67.0 vs 56.3 mo (HR 0.73, 0.61 – 0.89; p = 0.001)	66.7 vs 19.1 mo (HR 0.29, 0.25 – 0.35; p = 0.0002)*	76 % vs 2 %	32.2 vs 3.9 mo (HR 0.07, 95 %CI 0.05 – 0.08; p < 0.001)	NR
ARAMIS [darolutamide + ADT vs placebo + ADT]	40.4 vs 18.4 mo (HR 0.41, 95 %CI 0.34 – 0.50; p < 0.001)	36.8 vs 14.8 mo (HR 0.38, 95 %CI 0.32 – 0.45; p < 0.001)	40.3 vs 25.4 mo (HR 0.65, 0.53 – 0.79; p < 0.001)**	3-yOS 83 vs 77 % (HR 0.69, 0.53 – 0.88; p = 0.003)	HR 0.58, 0.44 – 0.76; p < 0.001	NR	33.2 vs 7.3 mo (HR 0.13, 95 %CI 0.11 – 0.16; p < 0.001)	NR

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; mo = months; mMFS = median metastasis free survival; mOS = median overall survival; mPFS2 = median progression on or after first subsequent therapy or death; NR = not reported; PSA50 = PSA decline from baseline > 50 %; mTTChemo = median time to cytotoxic chemotherapy initiation; mTTPP = median time to PSA progression; mTTSP = median time to symptomatic progression; vs = versus.
* = time to use of a new subsequent antineoplastic therapy; **= time to pain progression.

scientific community about the appropriateness of the primary endpoint, and the possibility of considering MFS as a valid surrogate for OS in patients with nmCRPC. Assessing the magnitude of clinical benefit in this peculiar disease setting of asymptomatic patients with no evidence at conventional imaging of metastasis has been a major challenge for nmCRPC. Indeed, MFS represents a measure of the delayed appearance of a greater burden of metastatic disease visible [23,24]. Only patients considered at high risk for development of metastases (those with a PSA doubling time of 10 months or less during continuous ADT and PSA >2 ng/ml) were included. The M0 condition was evaluated by conventional imaging (bone scan and CT scan). Of note, the SPARTAN and ARAMIS trials additionally included also patients presenting pelvic lymph nodes that measured <2 cm in the short axis (classified as N1). All three studies reached the primary endpoint, significantly improving MFS and more recently, with a longer follow up, also prolonging OS (a secondary endpoint), leading to the FDA and EMA approval of the three ARTAs as strongly recommended in the American, European and Italian clinical practice guidelines [25–27]. Apalutamide was the first drug approved by FDA and EMA for nmCRPC patients with PSADT ≤ 10 months. Subsequently, enzalutamide and darolutamide also received FDA and EMA approval.

Analyzing in detail the three pivotal studies, the SPARTAN trial enrolled 1207 nmCRPC men with PSADT of 10 months or less, randomized in a 2:1 ratio to receive apalutamide (a nonsteroidal antiandrogen agent that binds directly to the ligand-binding domain of the androgen receptor thus preventing androgen-receptor translocation, DNA binding, and androgen-receptor–mediated transcription) or placebo in addition to ADT. It is noteworthy that 70 % of patients in both arms had a PSADT <6 months with a median of 4.5 months, suggesting that the majority of patients enrolled in the SPARTAN trial were at particularly high risk. The primary endpoint was MFS while secondary endpoints were progression free survival (PFS), second progression free survival (PFS2), time to symptomatic progression, OS and time to initiation of cytotoxic chemotherapy. The study demonstrated the superiority of apalutamide in terms of MFS (40.5 months versus 16.2 months; HR 0.28, 95 % confidence interval [CI] 0.23 to 0.35; P < 0.001) as well as in all prespecified secondary endpoints (p < 0.001 for all comparisons) [13]. Notably, apalutamide significantly also prolonged the PFS2 endpoint, defined as the time elapsed from the start of the study treatment until the date of progression to the eventual next line of therapy following the study treatment. This endpoint, which is infrequently used in the evaluation of treatment efficacy in prostate cancer, acquires particular importance in this setting, since little is known on the impact of subsequent treatments in relation to first-line treatment in CRPC patients. At final analysis, apalutamide extended PFS2 by 14.4 months versus placebo (mPFS2 55.6 months compared to 41.2 months) and reduced the hazard of second progression or death by 45 % versus placebo (HR 0.55; 95 % CI 0.45 – 0.68) [28]. Among patients who received a second-line treatment, 83 % in the apalutamide arm were treated with further anti-hormonal therapies (73 % abiraterone acetate + prednisone or 9.6 % enzalutamide). It is important to underline that starting earlier a second anti-androgen agent could increase cross-resistance with the others, as already demonstrated in the metastatic setting (mCRPC) [29–31]. This aspect seems at least partially denied in this study by both the documented PFS2 and OS advantage. An exploratory analysis involving 247 patients of the SPARTAN study showed that the onset of AR-V7, one of the most common splice variants of the androgen receptor mRNA resulting in the truncation of the ligand-binding domain, seems not increased by the previous treatment with apalutamide (9.4 % of patients at the end of treatment) compared to placebo (12.5 % of patients at the end of treatment) [32].

Final results of the SPARTAN trial, with a follow-up of 52.0 months,

stated an OS benefit of apalutamide over placebo (mOS 73.9 vs 59.9 months, with an absolute gain of 14 months), corresponding to a relative reduction of 21.6 % in the risk of death (HR 0.78, 95 % CI 0.64-0.96; p = 0.016). Of note, this benefit of apalutamide was observed despite a 19 % crossover from placebo. Indeed, censoring crossover patients at the date of crossover, translates into a higher OS benefit (mOS 73.9 vs 52.8 months, with an absolute gain of 21.1 months, HR 0.69, 95 % CI, 0.56–0.84: p = 0.0003) [25].

Together with the SPARTAN data, both PROSPER and ARAMIS studies results showed a significant benefit in terms of OS with enzalutamide and darolutamide (two other ARTAs with the same mechanism of action previously detailed), respectively, compared to placebo. The PROSPER trial randomized 1401 men with prostate adenocarcinoma, an increasing PSA despite castrate levels of testosterone, a baseline PSA level of 2 ng/mL or greater, a PSA doubling time of 10 months or less, and no previous or current evidence of metastatic disease at conventional imaging, to enzalutamide or placebo in combination to ADT. Enzalutamide plus ADT significantly lowered the risk of metastasis or death without radiographic progression compared to ADT alone (mMFS 36.6 versus 14.7 months; HR 0.29, 95 % CI 0.24 to 0.35; p < 0.001) [15]. Moreover, enzalutamide, reduced risk of PSA progression (HR 0.07; 95 % CI 0.05 to 0.08; p < 0.001), and prolonged time to use of subsequent antineoplastic therapy (HR 0.21; 95 % CI 0.17 to 0.26; p < 0.001) [14]. The final analysis of OS with a median follow-up of about 48 months, showed that enzalutamide significantly prolonged OS compared with placebo (mOS 67.0 months versus 56.3 months; HR 0.73, 95 % CI 0.61–0.89; p = 0.001) [26]. It is important to notice that the PROSPER trial did not collect data about the time to progression while receiving a next subsequent therapy, making therefore impossible to evaluate whether treatment with enzalutamide also determined differences in treatment effects of subsequent therapies.

Similar results were reported with darolutamide, another androgen receptor antagonist, which was compared to placebo in the ARAMIS study. Inclusion criteria of the ARAMIS trial were basically the same as the other two pivotal studies (CRPC men with PSA level of at least 2 ng per milliliter, a PSADT of 10 months or less, no detectable metastases at conventional imaging), except for the allowed presence of pelvic lymph nodes <2 cm in diameter in the short axis below the aortic bifurcation [15]. Darolutamide significantly prolonged MFS (40.4 compared with 18.4 months; HR 0.41, 95 % CI 0.34–0.50; p < 0.001); this benefit was consistent across all pre-specified subgroups including patients with PSA doubling times<6 months. Moreover, with a median follow-up of 29.1 months, darolutamide showed a statistically significant OS benefit corresponding to a 31 % reduction in the risk of death compared with placebo (median OS not reached vs not reached, HR 0.69, 95 % CI 0.53 – 0.88; p = 0.003) [27]. As secondary endpoints darolutamide prolonged the time to first use of cytotoxic chemotherapy, the time to first symptomatic skeletal event, and the time to pain progression [27].

A *meta*-analysis of these three pivotal trials confirmed the OS advantage with a pooled hazard ratio of 0.72 (95 % CI, 0.64–0.82) [33]. Therefore, the MFS advantage translated into a significant OS benefit, confirming the value of MFS as a potential surrogate endpoint for OS [34].

Despite the statistically significant and undoubted clinically relevant advantage of ARTAs in the nmCRPC setting, caution should be taken into account when interpreting these data. Moreover, no universal criteria for the selection of the best ARTA can be defined from the pivotal clinical trials, but this remains an important issue. No head-to-head studies comparing these novel front-line strategies have been conducted so far. Cross-trial comparisons are not advised. Moreover, median follow-up variations within these three randomized clinical trials further complicate this scenario (a median follow-up of the ARAMIS study of 29.1 months versus 52 months and 48 months of the SPARTAN and PROSPER trials, respectively). Moreover, at the present time, obviously, there are fewer subsequent therapies given in the ARAMIS trial compared to SPARTAN and PROSPER trials, as well as a much lower impact of cross-over patients as evidenced by median treatment duration of 11 months (compared to 26 months of the SPARTAN study). Once again, it is important to notice that these are not formal comparisons.

Several network *meta*-analyses have been performed in order to clearly state the OS benefit and indirectly compare the three different treatment alternatives [35,36]. Besides the results suggested the highest OS efficacy and lowest high-grade toxicity for darolutamide and the highest efficacy of enzalutamide in the subgroup of patients with PSA-DT ≤6 months [35], it is noteworthy to interpret these data with caution considering clear differences among the studies regarding statistical study design, number of patients, different study population, and follow-up duration. In addition, the lack of access to raw data represents a major limit of these analyses.

Safety and toxicities

Crucial in this setting is that the benefits of treatment intensification in asymptomatic nmCRPC patients should outweigh the early and long-term toxicities of long-lasting drug administration, as well as the associated economic implications [23].

Delaying the appearance of metastatic sites is linked to the delay of the appearance of symptoms. QoL was a secondary endpoint of the PROSPER trial and an exploratory analysis of the ARAMIS and SPARTAN trials. All three experimental agents were associated with a maintained health related QoL (HRQoL) despite the longer treatment period, due to a longer time to symptomatic progression, as shown in a pre-specified exploratory analysis of the SPARTAN study evaluating the patient-reported outcomes (PROs) of HRQoL of apalutamide compared to placebo. Moreover, no differences were observed between treatment groups in perceived burden of side effects [37]. Similar results were demonstrated in the ARAMIS trial, highlighting the ability of darolutamide to maintain HRQoL by significantly delaying time to deterioration of cancer-specific QoL compared to placebo [38]. Analogously, enzalutamide compared to placebo significantly delayed pain progression and symptoms worsening in the PROSPER study [39] (Table 2).

All three ARTAs have a generally tolerable safety profile, and do not significantly increase the burden of toxicity due to ADT alone (Table 3). Phase IV studies in real world clinical practice are needed to evaluate the long-term toxicity of these drugs in unselected populations, also taking into account different potential comorbidities and concomitant polypharmacotherapies.

Based on drugs' pharmacological profile, enzalutamide, apalutamide, and darolutamide show similarities for selected toxicities. Since androgens promote glucose and energy homeostasis via actions on the AR axis in skeletal muscle, liver, pancreatic beta-cells, and metabolic centers in the hypothalamus, AR antagonists can be responsible for fatigue, hot flashes, cognitive disorders, seizures, falls and fractures, arthralgia as peculiar adverse events [13–15]. Despite they share a same mechanism of action and similar study design, caution should be used when comparing adverse events of different molecules in different studies. Indeed, despite receiving the same ADT treatment, patients in the control arms experienced a different prevalence of adverse events across the 3 pivotal trials, with a higher frequency of AEs in both arms in the SPARTAN trial. (Table 3). Of note, the schedule for AE reporting was every 4 weeks in the SPARTAN and every 16 weeks in the PROSPER and ARAMIS trials, possibly affecting cross-trials comparisons, such as the longer follow-up for apalutamide and enzalutamide (about 52 and 48 months, respectively) with respect to darolutamide (29 months) and a consequent difference in treatment exposure (8 months shorter for darolutamide compared to apalutamide or enzalutamide) and treatment duration.

Commonly, ADT is associated with greater risk for clinical bone fractures due to a decreased bone mineral density and bone quality and extending the time in which patients are exposed to antiandrogen increases the risk of incurring fractures. Recent data focus on the importance of body composition in maintaining and preserving bone health.

Table 2
Patients reported outcomes (PROs) in nmCRPC men across pivotal trials.

Trial	Type of questionnaire	Compliance rate	Median time to deterioration in FACT-P scores	Median time to deterioration in EORTC-QLQ-PR25
SPARTAN [apalutamide + ADT vs placebo + ADT]	FACT-P EQ-5D-3L	≥92.9 % (on treatment) ≥61.5 % (during follow-up)	6.6 vs 8.4 months (p = 0.60) Pain-related subscale 6.4 vs 4.3 months (p = 0.16)	NR
PROSPER [enzalutamide + ADT vs placebo + ADT]	BPI-SF EORTC-QLQ-PR25 FACT-P EQ-5D-5L EQ-VAS	85 % (from baseline until week 97)	22.11 vs 14.7 months (HR 0.75, p = 0.0013)	Time to deterioration of hormonal treatment-related symptoms: 33.15 vs 36.83 (HR 1.29, p = 0.035)
ARAMIS [darolutamide + ADT vs placebo + ADT]	EORTC-QLQ-PR25 FACT-P PCS	82 % EORTC-QLQ-PR25 86 % FACT-P PCS (day 1, week 16, end of treatment)	11.1 vs 7.9 months (HR 0.80; p = 0.0005)	25.8 vs 14.8 months (HR 0.64; p < 0.0001) Time to deterioration of hormonal treatment-related symptoms: 18.9 vs 18.4 months, HR 1.06; p = 0.52)

ADT = androgen deprivation therapy; BPI-SF = Brief Pain Inventory short-form; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version; EORTC-QLQ-PR25 = European Organization for Research and Treatment of Cancer health-related quality of life questionnaire of prostate cancer; FACT-P = Functional Assessment of Cancer Therapy-Prostate; NR = not reported; PCS = Prostate Cancer Subscale; VAS = visual analogue scale.

Table 3
Safety profile of ARTAs in nmCRPC men across pivotal trials.

Trial	Median treatment duration	Any AEs, %	AEs of Grade 3–4	AEs of Grade 5	SAEs, %	AEs of any Grade leading to drug discontinuation, %	AEs of G3-4 leading to drug discontinuation, %
SPARTAN [apalutamide + ADT vs placebo + ADT]	32.9 vs 11.5 mo	97 vs 94 %	56 vs 36 %	3.0 vs 0.5 %	36 vs 25 %	15 vs 7.3 %	NR
PROSPER [enzalutamide + ADT vs placebo + ADT]	33.9 vs14.2 mo	94 vs 82 %	48 vs 27 %	5.0 vs 1.0 %	40 vs 22 %	17 vs 9 %	NR
ARAMIS [darolutamide + ADT vs placebo + ADT]	18.5 mo (25.8 mo double-blind + open-label periods vs 11 mo)	85.7 vs 79.2 %	26.3 vs 21.7 %	4.0 vs 3.4 %	26.1 vs 21.8 %	8.9 vs 8.7 %	0.5 % vs 1.6 %

ADT = androgen deprivation therapy; AEs = adverse events; SEAs = serious adverse events.

As ADT treatment places patients at risk of sarcopenic obesity, this condition should be countered due to its potential impact on bone health in addition to the negative effect on metabolic and cardiovascular diseases [40,41]. Major contributors for fractures in this setting are the duration of ADT in the hormone sensitive stage and the bone management received, comprehensive of antiresorptive agents (also considering the starting time of this therapy – concurrent to the start of ARSI or delayed at the diagnosis of osteoporosis), exercise, and diet. The relevance of an optimal management is even higher with effective treatments prolonging life and consequently the exposure to ADT. It is therefore of utmost importance a multidisciplinary management of patients, with a particular attention to bone health.

The undoubted benefit in disease control of ARTAs is associated with a marginal rate of serious adverse events, including toxic deaths, which require close clinical monitoring especially of patients with cardiovascular comorbidities. Certainly, the high incidence of comorbidities in this patient population (also considering a median age of 74 years in the three trials), including cardiovascular disorders, obesity, hyperlipidemia and diabetes, has to be taken into account in the patients' management. Treating physicians should be aware of the increased cardiovascular risk of nmCRPC patients also when determining whether a patient with preexisting cardiovascular disease should receive an ARTA and eventually which one.

Regarding some elective toxicities, in SPARTAN trial the onset of skin rash occurred at a median of 82 days of treatment and resolved within two months for most patients. This side effect led to treatment discontinuation in 2.4 % of patients, dose reduction in 2.7 % of patients, and dose interruption in 6.8 % of patients in the apalutamide group. Treatment options for patients with a skin rash, include topical and systemic corticosteroids, oral antihistamines and drug interruption or dose reduction. Despite being initially unexpected in this drug class, the same event was also observed in some cases treated with enzalutamide (rash events in 4 % of cases, compared to 3 % in the control arm) and darolutamide (3.1 % of cases). Another side effect reported in the SPARTAN study was asymptomatic hypothyroidism (grades 1–2), reported in 8.1 % of patients in the apalutamide arm.

As concerns the impact of ARTAs therapy on the central nervous system (CNS) and cognitive function, several data suggest a potential risk of treatment-related CNS effects due to the ability of ARTAs to penetrate the blood–brain barrier (BBB) [42]. Preclinical data demonstrated that enzalutamide crosses the BBB, leading to the inhibition of

Table DDI1
Metabolic profile of enzalutamide, apalutamide and darolutamide.

ADT	Substrate - metabolism	Induction/inhibition
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19

Table DDI2
Drug-drug interactions.

Cardiovascular

ADT	Substrate - metabolism	Induction/ inhibition	DDI effect	Concomitant drug	Substrate - metabolism	DDI effect
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✓	Dabigatran	CES1, CES2, UGT1A9, 2B7, 2B15, PgP	✓
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✗ Victim			✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✓			✓
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	Perpetrator	Apixaban	CYP3A4/5, 1A2, 2C8, 2C9, 2C19, 2J2, PgP, BCRP	✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	Perpetrator			✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	Perpetrator			✗ Victim
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	Perpetrator	Rivaroxaban	CYP3A4, 3A5, CYP2J2, PgP, BCRP	✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	Perpetrator			✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	Perpetrator			✗ Victim

Diabetes

ADT	Substrate - metabolism	Induction/ inhibition	DDI effect	Concomitant drug	Substrate/ metabolism	DDI effect
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✗ Victim	**Metformin**	CYP3A4 down-regulation	Perpetrator
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✗ Victim			Perpetrator
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✓			✓
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✓	**Phenformin**	CYP2D6	✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✓			✓
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✓			✗ Victim
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✓	**Gliben-clamide**	CYP3A4, 2C9, 2C8	✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✓			✓
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✓			✗ Victim

Hypertension

(*continued on next page*)

the gamma-aminobutyric acid-gated chloride channel, finally resulting in a lowered seizure threshold. Data from animal models suggested a moderate BBB penetration for apalutamide, 4-fold lower than those observed for enzalutamide [43]. On the contrary, in preclinical studies darolutamide displayed >25-fold lower BBB penetration and a low binding affinity for γ-aminobutyric acid type A receptors, suggesting that this drug may be less likely to induce CNS-related AEs [44–45]. These findings should be verified in treated nmCRPC patients, also considering the very limited incidence of AEs related to the central nervous system (i.e. seizures, cognitive impairment, falls). Certainly, the lack of cognitive function evaluation by patients-reported outcomes (PROs) in the nmCRPC pivotal trials represents a strong limitation, especially considering the long duration of treatment in this setting of disease [46].

As concerns treatment-related deaths in both the arms of the studies, a rare event, not exceeding 5 % across the three pivotal trials, in the PROSPER trial 5 % of patients in the enzalutamide arm and 1 % in the placebo arm presented AEs leading to death (mainly cardiovascular events, n = 14); in the ARAMIS trial darolutamide was responsible for grade 5 adverse events in 3.9 % of cases (n = 37) compared to 3.2 % in the placebo group (n = 18); in the SPARTAN trial, apalutamide adverse events leading to death accounted for 2.1 % in the experimental arm and 0.5 % in the control arm.

Globally, patients treated with ARTAs for nmCRPC have an increased relative risk (RR) of adverse events of high-grade compared to controls (RR = 1.53; $p < 0.01$) [33]. A matching-adjusted indirect comparison of the tolerability of ADT + apalutamide and ADT + darolutamide showed similar safety profile between the two drugs, with a roughly identical overall rate of adverse events of any grade (1.02; 95 % CI 0.50–2.04) [47]. Data from large real-world series with long follow-up are highly warranted to confirm the safety profiles of these molecules in the nmCRPC setting.

Table DDI2 (*continued*)

ADT	Substrate - metabolism	Induction/ inhibition	DDI effect	Concomitant drug	Substrate/ metabolism	DDI effect
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✗ Victim	**Losartan**	CYP2C9, 3A4,2C8, UGT1A1	✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✗ Victim		Inhibitor of CYP2C8 and 3A4	✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✗ Victim			✗ Victim
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✗ Victim	**Amlodipine**	CYP3A4, 1A1, 2B6, 2C8, 2D6, UGT, PgP	✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✗ Victim			✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✗ Victim		Inhibitor of CYP1A1, 3A4, 2B6, 2C9, 2C8	✗ Victim
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✓	**Hydrochloro thiazide**	No metabolism	✓
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✓			✓
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✓			✓

https://go.drugbank.com/drugs/

Drug-drug interactions

Recently, particular attention is growing concerning the risk of drug-drug interactions (DDI) between anti-cancer therapies and concomitant treatments administered to patients. DDIs are linked to the metabolic profile of a drug, and its ability of being an inducer or an inhibitor of enzymes involved in the metabolism of other drugs. Therefore, DDIs may impair the absorption, distribution, metabolism and/or elimination of a drug. However, not all the DDIs may be clinically relevant, and particular attention should be paid to DDIs at risk of reducing the safety of drugs with narrow therapeutic index (i.e., anticancer, immunosuppressants, analgesic opioids, selected cardiovascular medications, anticoagulants). From a pharmacological point of view, enzalutamide, apalutamide and darolutamide show different pharmacokinetic and pharmacodynamic (PK/PD) profiles. Considering the metabolic profile of the new antiandrogen agents, enzalutamide and apalutamide show a similar PK profile, being enzalutamide metabolized by CYP2C8, and apalutamide by CYP2C8 and 3A4 (https://go.drugbank.com/drugs/) (Table DDI1). Differently, darolutamide is mainly metabolized by CYP3A4 and UGT1A9, 1A1, 1A3 and 2B10 (https://go.drugbank.com/drugs/) (Table DDI1). On the other side, the profile of enzymes induced or inhibited by the three drugs is quite peculiar: enzalutamide and apalutamide are inducers of the CYP450 isoforms 3A4, 2D6, 2C9, 2C19, therefore their concomitant use with drugs metabolized by these same enzymes could reduce drugs exposure. Darolutamide is instead an inhibitor of the BCRP, PgP, OATP1B1, OATP1B3 transporters, which may be responsible for an intracellular accumulation of BCRP substrate drugs, and consequently of an increased drug exposure (https://go.drugbank.com/drugs/) (Table DDI1). While enzalutamide bioavailability is not influenced by food, bioavailability of darolutamide was enhanced by 2.0- to 2.5-fold when administered with food (https://www.ema.europa.eu/en/documents/product-information/xtandi-epar-product-information_it.pdf; https://www.ema.europa.eu/en/documents/product-information/nubeqa-epar-product-information_it.pdf). Apalutamide Cmax and AUC does not vary in case of administration with fatty food, while tmax resulted in 2 h delayed if apalutamide was administered with food (https://www.ema.europa.eu/en/documents/product-information/erleada-epar-product-information_it.pdf). Induction or inhibition of drug transporters involved in cellular uptake and efflux of drugs also represent another important mechanism of DDIs. Since transporters of the small intestine, liver and kidney are major determinants of plasmatic concentration of drugs, they can significantly modify the pharmacokinetics and the clinical effects of treatments.

Therefore, due to the different induction and inhibition profile of CYPs and transporters, a different DDI profile is expected for enzalutamide, apalutamide and darolutamide (Table DDI1). Table DDI2 represent the effect of DDIs considering different concomitant therapies, which may be administered in cancer patients.

In conclusion, interactions between drugs with narrow therapeutic index should be carefully evaluated and, whenever a drug substitution is not possible, therapeutic drug monitoring should be performed.

Conclusions

The diagnostic and treatment landscape of nmCRPC is rapidly evolving. Apalutamide, enzalutamide and darolutamide are currently all available therapeutic options for the management of nmCRPC. All the three drugs significantly improve MFS and prolong OS in high-risk nmCRPC patients. The magnitude of the clinical benefit of these agents is even more meaningful if considering the low incidence of drug related adverse events, which must be carefully managed considering the particular setting of asymptomatic, nonmetastatic patients, candidates to a long expectancy of life and treatment. A multidimensional evaluation, including patients' comorbidities, polypharmacy assessment and an accurate management of the specific side effects of these therapies should be performed in order to offer the greatest benefit to these patients, also considering that the availability of novel and more accurate next-generation imaging techniques (including PSMA-PET/CT) will change the entity, and possibly also the definition, of nmCRPC.

CRediT authorship contribution statement

Alfredo Berruti: Conceptualization, Writing – review & editing. **Sergio Bracarda:** Conceptualization, Writing – review & editing. **Orazio Caffo:** Conceptualization, Writing – review & editing. **Enrico Cortesi:** Conceptualization, Writing – review & editing. **Rolando D'Angelillo:** Conceptualization, Writing – review & editing. **Marzia Del Re:** Conceptualization, Writing – review & editing. **Gaetano Facchini:** Conceptualization, Writing – review & editing. **Giovanni Pappagallo:** Conceptualization, Writing – review & editing. **Giuseppe Procopio:**

Conceptualization, Writing – review & editing. **Roberto Sabbatini:** Conceptualization, Writing – review & editing. **Daniele Santini:** Conceptualization, Writing – review & editing.

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