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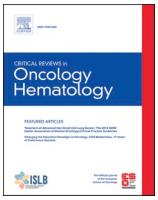

Pharmacological treatment landscape of non-metastatic hormone-sensitive prostate cancer: A narrative review on behalf of the meet-URO Group

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ABSTRACT

The definition of "non-metastatic hormone-sensitive prostate cancer" (nmHSPC) can be applied to patients with prostate cancer (PC) who are androgen-deprivation therapy-naïve and without evidence of metastatic disease. This definition includes heterogeneous situations; however, PC patients at high risk of metastatic spread – and who have not started a hormonal treatment – constitute a unique category with unmet clinical needs. This narrative review critically discusses the advances that characterize the rapidly evolving diagnostic and therapeutic scenario in the nmHSPC setting. We found that nmHSPC represents a grey zone in the context of PC. New clinical trials are trying to redefine the therapeutic algorithm of these patients, but escalating treatment seems not to be the right choice for the overall population. Biomarkers able to stratify patients – including molecular ones – are urgently needed, and biomarker-based clinical trials could clarify their prognostic and predictive role in the nmHSPC scenario.

1. Introduction

Prostate cancer (PC) is the most frequently diagnosed cancer in men worldwide, being the leading cause of cancer death in one out of four countries (Bergengren et al., 2023). Nearly 75 % of PC cases are diagnosed in a localized stage (Canadian Cancer Statistics Advisory Committee, 2019), meaning that a curative intent is pursuable in a high proportion of patients. Patients with localized PC are treated with curative-intent treatment, such as surgery, radical prostatectomy (RP) or radiation therapy (RT), with or without androgen-deprivation therapy (ADT) (Parker et al., 2020). Biochemical recurrence (BCR) is defined as a prostatic-specific antigen (PSA) rise after radical therapies for localized PC; the currently adopted PSA threshold values for BCR are 0.2 ng/mL after RP and 2 ng/mL above the nadir PSA value after RT, according to American Urological Association (AUA) guidelines and Phoenix definition, respectively (Biochemical Recurrence 2023). BCR can occur in up to 50 % of radically treated PC patients within 10 years from diagnosis (Paller et al., 2013).

The definition of "non-metastatic hormone-sensitive prostate cancer" (nmHSPC) can be virtually applied to all PC patients who are ADT-naïve and without evidence of metastatic disease; however, there are two specific situations in which this definition has been used so far in clinical trials: 1) PC patients with treatment-naïve high-risk locally advanced disease, defined as node-positive (N+) or, in the absence of nodal involvement, having at least two of the following: tumor stage cT3/cT4, Gleason score (GS) of 8–10, and PSA level ≥40 ng/mL, according to the STAMPEDE trial criteria (Attard et al., 2022); 2) PC patients experiencing BCR but deemed to be at high risk for developing metastases; in the EMBARK trial, the high-risk population was defined as having a PSA doubling time (PSADT) ≤9 months after radical treatment for PC, with a screening PSA ≥1 ng/mL after RP (with or without postoperative RT) or ≥2 ng/mL above nadir after RT alone, without suppression of serum testosterone at the time of enrollment (Freedland 2021). In the STAMPEDE trial, the high-risk features for relapse were: PSA ≥20 ng/mL; nodal relapse; PSA ≥4 with PSADT ≤6 months ng/mL (but in patients who received ≤12 months of total ADT with an interval of ≥12 months

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without treatment) (Attard et al., 2022). Even if this definition includes heterogeneous situations, PC patients at high risk of metastatic spread – and who have not started a hormonal treatment – constitute a unique category with unmet clinical needs; in detail, the current clinical practice is lacking valid options for these patients, being ADT alone the widely adopted approach. The possibility of over- or under-treatment must be considered, and the consequent need for better risk stratification is mandatory in this field.

This narrative review focuses on nmHSPC, as defined above, to present and critically discuss the advances that characterize the rapidly evolving diagnostic and therapeutic scenario in this patient setting.

2. Methods

A literature search was conducted by using articles published in the English language in the last 15 years (up to August 2024). All types of clinical study designs were included to expand the scope of this narrative review. Search terms used on PubMed/MEDLINE and EMBASE included "non-metastatic hormone-sensitive prostate cancer", "biochemical recurrent prostate cancer" and "treatment-naïve prostate cancer" (Table S1). A search of conference abstracts reported at ESMO OncologyPRO and ASCO library was also conducted in order to identify relevant unpublished data. References of the articles were screened by title and abstracts to identify relevant information on these topics. Further full-text screening was done for previously published review articles to identify gaps in the selected literature and elaborate on the importance of this topic comprehensively.

We, therefore, identified the main clinical trials focusing on nmHSPC patients, which were specifically designed to elucidate the role of pharmacological treatment in this scenario and divided accordingly to the previous radical treatments received by the patients.

3. Results

3.1. Therapy of nmHSPC

3.1.1. Treatment naïve

In patients diagnosed with high-risk nmHSPC, the standard treatment involves ADT, often supplemented by radiotherapy (Choi et al., 2022). While combining ADT with docetaxel or second-generation androgen receptor signaling inhibitors (ARSIs) – i.e., abiraterone, enzalutamide, or apalutamide – has shown improved outcomes in metastatic PC (Achard et al., 2022), these drugs have not yet exhibited consistent enhancements in the survival rates of patients undergoing long-term ADT for nmHSPC (Choi et al., 2022).

In detail, the STAMPEDE multi-arm multistage platform was designed to compare treatments against standard of care (SOC), and, intriguingly, nmHSPC patients were enrolled to receive either chemotherapy or ARSI in addition to ADT (Attard et al., 2022) (James et al., 2022). Six cycles of docetaxel were administered, together with SOC (ADT), in patients with newly diagnosed localized prostate cancer or patients showing features for high-risk relapse after previous radical treatments and naïve to long-term ADT (James et al., 2022). The long-term analysis for the non-metastatic cohort from this STAMPEDE trial (690 patients, of which 460 were in the control group and 230 in the docetaxel group) showed no statistically significant improvement on progression-free survival (PFS) from the addition of docetaxel to ADT (hazard ratio [HR]: 0.89, 95 % CI: 0.66–1.19; p=0.43); with 5-year median PFS (mPFS) 82 % vs 77 %, respectively (James et al., 2022). Among secondary endpoints of this trial, the addition of docetaxel improved failure-free survival (FFS) – time to biochemical progression, lymph node progression, distant metastatic progression, or prostate cancer death – (HR: 0.70, 95 % CI: 0.55–0.88; p=0.002), however, without overall survival (OS) benefit (HR: 0.88, 95 % CI: 0.64–1.21; p=0.44). Concerning safety, the adverse event (AE) rate after the first year of follow-up was similar between the two arms, even if the safety outcomes were assessed only in the population who had not already progressed (James et al., 2022).

In the context of the STAMPEDE project, two randomized controlled phase 3 trials evaluated the effectiveness of incorporating abiraterone acetate + prednisolone (AAP), alone or in combination with enzalutamide, alongside ADT for high-risk nmHSPC patients (Attard et al., 2022); the high-risk features for relapse are reported in the Introduction chapter. This extensive investigation involved 1974 patients randomly assigned to either receive ADT alone (control group) or oral AAP with or without enzalutamide, according to the two protocols; a meta-analysis has recently reported the primary results from these two trials, which are listed below (Attard et al., 2022). The primary endpoint was metastasis-free survival (MFS), while secondary endpoints encompassed OS, prostate cancer-specific survival, biochemical failure-free survival, and treatment-related adverse events (TRAEs). Results from these trials indicated that the combination therapy significantly prolonged MFS compared to ADT alone, with a median not reached (NR) for the combination therapy groups versus a median NR for ADT alone (HR: 0.53, 95 % CI 0.44–0.64; p<0.0001) (Attard et al., 2022). The 6-year MFS rate was higher in the combination therapy group compared to the control group (82 % and 69 %, respectively) (Attard 2022). Subgroup analyses further reinforced the efficacy of combination therapy in both trials separately (AAP trial, HR: 0.54, 95 % CI: 0.43–0.68; p<0.0001; AAP+enzalutamide trial, HR: 0.53, 95 % CI: 0.39–0.71; p<0.0001), with no observable disparity in treatment effects between the two (interaction HR: 1.02, 95 % CI: 0.70–1.50; p=0.91) (Attard et al., 2022). Moreover, both OS and PC-specific survival were markedly extended in the combination therapy groups. Median OS duration was NR in both the combination-therapy group; however, it was higher as compared to the control groups (HR: 0.60, 95 % CI: 0.48–0.73; p<0.0001); notably, the 6-year survival escalated from 77 % in the control groups to 86 % in the combination-therapy groups (Attard et al., 2022). Moreover, PC-specific survival also exhibited a significant improvement in the combination-therapy cohorts compared to the control cohorts (HR: 0.49, 95 % CI: 0.37–0.65; p<0.0001); the 6-year PC-specific survival increased to 93 % in the combination-therapy groups, surpassing the 85 % observed in the control groups. Nevertheless, AEs of grade 3 or higher, notably hypertension, fatigue, and an increase in alanine aminotransferase, were more prevalent in the combination therapy cohorts (Attard et al., 2022).

In summary, the incorporation of AAP, with or without enzalutamide, exhibited significantly improved rates of MFS in comparison to ADT alone among men with high-risk nmHSPC, suggesting AAP as a potential new standard treatment for this patient. However, while the survival benefits of adding enzalutamide to AAP are evident, the augmented toxicity and costs associated with enzalutamide might not be justifiable for this specific population. Therefore, the adoption of two years of AAP added to ADT and (potentially) RT could be contemplated as a novel standard treatment for nmHSPC patients showing high-risk features.

3.1.2. BCR

Treatment strategies for systemic management of biochemically recurrent PC involve a range of approaches, encompassing different forms of ADT, both initial and subsequent, in combination with external beam RT.

ADT works by impeding the release of hormones, such as luteinizing hormone-releasing hormone (LHRH), thereby reducing testicular androgen synthesis rates and levels of circulating androgens (Harris et al., 2009). However, the efficacy of salvage ADT following BCR lacks consensus, requiring careful consideration of associated AEs before decision-making. A systematic review evaluating ADT specifically for BCR identified its potential suitability for patients at high risk of disease progression (PSADT <6–12 months; GS >7) with a significant life expectancy (vandenBergh et al., 2016); this review is in line with European and NCCN Guidelines (NCCN, 2022, Motten et al., 2023).

AUA/ASTRO/SUO guidelines recommend intermittent ADT (iADT) solely for high-risk BCR cases without evidence of metastasis (Lowrance 2021); the authors also suggest clinical trial participation or observation for these patients.

Despite its potential survival benefit, ADT presents significant AEs that could adversely affect the quality of life (QoL), including symptoms, such as depression, fatigue, hot flashes and sexual dysfunction (Storey et al., 2012). Long-term ADT use is associated with increased risks of cardiovascular disease, diabetes and osteoporosis (Lapi et al., 2013, Brawer, 2006, Keating et al., 2010).

Regarding the timing of ADT, the TOAD trial investigated the impact on OS of immediate versus delayed ADT treatment in 293 men, 261 of whom experienced PSA relapse after curative therapy (Duchesne et al., 2016). The study found a slight increase in 5-year OS in the immediate therapy group compared to the delayed therapy group (91 % *vs.* 86 %; p=0.047): immediate therapy was linked to a reduced incidence of local progression (13 % *vs.* 20 %) and significantly prolonged time to local progression (adjusted HR 0.51; 95 % CI 0.34–0.76; p=0.001) as compared to delayed therapy; however, no significant difference in time to distant progression was observed between immediate and delayed therapy at 1-year or 6-year follow-up. Immediate therapy showed minimal reduction in QoL but had more patients experiencing serious AEs compared to delayed therapy (41 % *vs.* 32 %) (Duchesne 2016). Nevertheless, the study did not report subgroup analysis for BCR with shorter (<10 months) versus longer (≥10 months) PSADT, limiting the applicability of these findings for managing high-risk BCR cases (Duchesne 2016). Given the modest clinical benefit in OS observed so far and considering the side effects of chronic ADT therapy, early ADT is suggested only for high-risk patients as per NCCN and European guidelines (NCCN, 2022, Motten et al., 2023).

Intermittent ADT (iADT) emerges as an option that might delay disease progression while offering relief from AEs and complications associated with continuous dosing (Shore et al., 2020). In detail, a study demonstrated comparable effectiveness of iADT compared to continuous ADT (cADT) in terms of OS in patients experiencing BCR after RT (≥3 ng/mL increase over nadir PSA), alongside QoL improvements in the iADT group (Crook 2012); it must be noted that a significant number of deaths (59 %) was unrelated to PC. However, after adjusting for stratification and confounding factors, prostate cancer-specific survival did not differ between iADT and cADT groups (p=0.13) (Crook 2012). A meta-analysis of 15 clinical trials involving 6856 patients with PC who received iADT or cADT showed improvements in physical and sexual functions if treated with iADT. Nevertheless, there were no significant differences in OS, time to castration resistance, QoL, or AEs between the two groups, despite a tendency toward lower estimates for iADT (Magnan et al., 2015). NCCN Guidelines recommend iADT for non-metastatic BCR patients without specifying patient selection criteria (NCCN, 2022). In contrast, a panel of US-based uro-oncologists recommends iADT solely for high-risk patients (PSADT ≤9 months and GS ≥8) with early BCR (<3 years); low- and intermediate-risk patients with BCR cancer should undergo observation (Shore et al., 2020). ASCO guidelines suggest iADT for high-risk BCR cases after RP (PSADT ≤1 year or a pathologic GS 8–10) or RT (interval to BCR cancer ≤18 months or a clinical GS 8–10). In contrast, active surveillance may be considered for low-risk BCR cases after RP (PSADT >1 year and GS <8) or RT (interval to BCR cancer >18 months and GS <8) (Virgo et al., 2021).

The HERO trial aimed to compare the efficacy and safety of relugolix, an oral gonadotropin-releasing hormone antagonist, with the standard injectable luteinizing hormone-releasing hormone agonist (LHRHa), leuprolide, in achieving androgen deprivation for PC (Shore et al., 2020 HERO). Patients were eligible for treatment if they had one of three clinical disease presentations: signs of biochemical (PSA) or clinical relapse following a local primary intervention aimed at a cure, newly diagnosed with hormone-sensitive metastatic disease, or advanced localized disease that was unlikely to be cured by the initial local intervention intended for a cure (Shore et al., 2020 HERO). In this trial, patients were randomly assigned to receive either relugolix (120 mg orally once daily) or leuprolide (injections every 3 months) over 48 weeks: the primary endpoint was maintaining testosterone suppression to castrate levels (<50 ng/dL) throughout this period, with secondary endpoints including non-inferiority in testosterone suppression, specific testosterone levels on days 4 and 15, and testosterone recovery in a subset of patients. Results from 622 patients receiving relugolix and 308 receiving leuprolide showed that 96.7 % and 88.8 % of them, respectively, maintained castration through 48 weeks, indicating a 7.9 %-point difference favoring relugolix (p<0.001 for superiority) (Shore 2020 HERO). Among 467 patients with evidence of biochemical or clinical relapse after local primary intervention with curative intent (50.3 % of the overall enrolled population), 309 received relugolix (49.7 % of the relugolix cohort) and 158 received leuprolide (51.3 % of the leuprolide cohort). The outcomes regarding the main goal and the assessments for non-inferiority remained steady and uniform across a wide spectrum of subcategories (Shore et al., 2020 HERO). Other secondary endpoints also favored relugolix over leuprolide (p<0.001). Notably, testosterone suppression on day 4 was higher with relugolix (6 versus 0 % with leuprolide). Among 184 patients monitored for testosterone recovery, mean levels 90 days after treatment cessation were considerably higher in the relugolix group than in the leuprolide group (288.4 *vs.* 58.6 ng/dL, respectively) (Shore et al., 2020 HERO). The overall incidence of AEs was consistent across treatment groups, with hot flashes as the most common AEs reported in both groups (54.3 and 51.6 % in the relugolix and leuprolide groups, respectively). Diarrhea was observed in a higher percentage of patients who received relugolix than in those who received leuprolide (12.2 vs 6.8 %, respectively). The incidence of major adverse cardiovascular events was lower in the relugolix group compared to the leuprolide group (2.9 vs 6.2 %, respectively), indicating a 54 % reduced risk of such events with relugolix (HR: 0.46; 95 % CI: 0.24–0.88) (Shore et al.,2020 HERO). Based on the results of the HERO trial, we believe that relugolix could definitely become a valid alternative to injectable LHRHa, even if some concerns - especially about polypharmacy, which is common in PCa patients – could arise (Cordes et al., 2023). Moreover, longer follow-up is needed to assess the long-term efficacy of this therapeutic approach.

Enzalutamide, which is an oral ARSI firstly already approved for non-metastatic (m0) castration-resistant prostate cancer (m0CRPC) and metastatic castration-resistant prostate cancer (m1CRPC) and mHSPC patients (Scott, 2018) (FDA approved drugs), showed clinical efficacy when administered without luteinizing hormone-releasing hormone agonist (LHRHa)/antagonist in the mHSPC setting (Tombal et al.,2014); anticipating this drug in high-risk BCR patients and evaluating its efficacy – with or without LHRHa – versus LHRHa alone is the main purpose of the phase III EMBARK trial (Freedland et al., 2021). In this study, the high-risk population was defined as having a PSADT ≤9 months after radical treatment for PC, with a screening PSA of ≥1 ng/mL after RP (with or without postoperative RT) or ≥2 ng/mL above nadir after RT alone, without suppression of serum testosterone at the time of enrollment. The current standard of care for this setting is starting continuous or intermittent LHRHa, being the administration of enzalutamide in this trial de facto a treatment intensification. Among baseline patient characteristics, the median PSADT was approximately 5 months, and one out of five patients had a PSADT ≤3 months (Freedland et al., 2023). At a median follow-up of 5 years, the metastasis-free survival (MFS), which is the primary endpoint of this trial, was significantly improved for the combination of enzalutamide + LHRHa versus LHRHa alone (HR: 0.42, 95 % CI: 0.30–0.61; p<0.001); this benefit was also confirmed at the subgroup analysis – in detail when patients are stratified for PSADT, baseline age, PSA, geographic region, receipt of prior hormonal therapy, or prior RP. OS was also improved with the addition of enzalutamide (HR: 0.59, 95 % CI: 0.38–0.91; p=0.02), even if the pre-specified efficacy boundary (p<0.0001) was not met (Freedland et al., 2023). Similarly, enzalutamide versus LHRHa demonstrated an improved metastasis-free survival (MFS) but no significant OS improvement at

the time of this first analysis (Freedland et al., 2023). In the case of undetectable PSA (<0.2 ng/mL) at week 36, the study treatment was suspended; on the contrary, in case of detectable values at the same time point, the study treatment was continued; interestingly, 90.9 % and 85.9 % of patients in the enzalutamide + LHRHa and enzalutamide monotherapy arms, respectively, reached an undetectable PSA value, whilst only 67.8 % in the single-agent LHRHa arm (Freedland et al., 2023). No new safety signals were observed with the combination of enzalutamide and LHRHa (Freedland 2023) (Freedland et al., 2023b).

Apalutamide and the aforementioned abiraterone acetate are two ARSIs already approved for PC, even if in different settings (Boukovala et al., 2020) (Caffo et al., 2018). The association of these two molecules, which is justified by their different mechanism of action, has already been tested in mCRPC patients in the phase III ACIS trial, demonstrating an improvement in radiographic progression-free survival (rPFS) (Saad et al., 2021). In the phase III PRESTO trial, patients with BCR prostate cancer and a PSADT ≤9 months without distant metastases on conventional imaging were randomly assigned to receive a finite 52-week treatment course with ADT alone, ADT + apalutamide, or ADT + apalutamide + AAP (Aggarwal et al., 2024). The primary endpoint was biochemical PFS, with secondary endpoints including safety, patient-reported QoL, time to testosterone recovery, MFS, and time to castration resistance. A total of 503 patients were randomized across the three treatment arms. At the first planned interim analysis with a median follow-up of 21.5 months, both experimental arms significantly prolonged biochemical PFS compared to the control arm: ADT + apalutamide (median 24.9 months) and ADT + apalutamide + AAP (median 26.0 months) compared to ADT alone (median 20.3 months and 20.0 months, respectively) (Aggarwal et al., 2024). PSA-PFS also exhibited consistent results, and the median time to testosterone recovery varied slightly among the treatment arms (Aggarwal et al., 2024). The most common grade ≥3 AE reported was hypertension, being more frequent in the triple combination arm; only 2 % and 3 % of patients stopped treatment due to AEs in the ADT + apalutamide and ADT + apalutamide + AAP arms, respectively (Aggarwal et al., 2024).

The main features of trials in nmHSPC patients are summarized in Table 1.

3.2. The role of imaging for the diagnosis of nmHSPC

Newly diagnosed PC patients potentially having metastatic disease – based on PSA levels and histological characteristics (ultimately, according to the risk category) – or, in the case of BCR, require disease staging. The role of imaging is to identify the possible metastatic site(s) of the disease, given its prognostic and therapeutic implications (Perez-Lopez et al., 2019), and the absence of metastasis is necessary for diagnosing nmHSPC. "Conventional" imaging, which includes computed tomography (CT) and bone scan, has been adopted in the main clinical trials enrolling nmHSPC patients (Kane et al., 2003); however, in the latest years, imaging has improved, leading to a dramatic change in the disease assessment for PC patients (Tangel et al., 2018). Prostate-specific membrane antigen (PSMA) PET is a diagnostic nuclear medicine imaging that is gaining ground in PC management (Farolfi et al., 2021); to date, two main radiolabeled ligands, 68Ga-PSMA-11 and 18F-PSMA-1007, are used for PET imaging in PC patients: it is noteworthy that the main difference between them is that 68Ga-PSMA-11 is eliminated in the urine, potentially leading to false negatives in case of local relapses, therefore being 18F-PSMA-1007 the preferred radiotracer for restaging in case of BCR (Giesel et al., 2017). PSMA PET is currently indicated by international guidelines in case of high-risk PC staging and also in case of BCR onset (Mottet et al., 2021, Fanti et al., 2022); given its high sensitivity, PSMA PET can detect lesions – either as local relapses or metastatic ones – in more than 60 % of PC patients experiencing BCR (Caroli et al., 2018)(Pozdnyakov 2023)(Armstrong et al., 2023), thus potentially translating in therapeutic changes. For example, the adoption of 68Ga-PSMA-11 PET imaging in a prospective multicenter trial enrolling PC patients with BCR led to management changes in more than half of them (Fendler et al., 2020). In a post-hoc subgroup analysis of a prospective clinical trial in which PC patients experiencing BCR were enrolled, baseline PSMA PET was shown to be informative for the risk of biochemical progression. In detail, a higher risk for progression was observed in case of a higher number of detected lesions and when metastatic sites were found (versus local and/or pelvic nodal relapses) (Harsini et al., 2023). To date, the use of more sensitive imaging techniques has not been demonstrated to improve survival outcomes, especially in the initial staging phase (Varatharajan et al., 2023). Given the possibility of discordant results, consensus papers and guidelines do not recommend denying radical local treatment in case of positive PSMA PET and negative conventional imaging results (Fanti et al., 2022; Parker et al., 2020). We believe that PSMA PET should be widely adopted as a standard imaging technique in these patients, given the

Table 1
Trials in nmHSPC patients.

Trial name	Inclusion criteria	Drug (arms)	Main endpoints
STAMPEDE (Attard et al., 2022)	Treatment-naïve PC, node-positive (N+) or, in the absence of nodal involvement, having at least two of the following: tumor stage cT3/cT4, Gleason score (GS) of 8–10, and PSA level ≥40 ng/mL	• ADT + Docetaxel • ADT + AAP • ADT + AAP + enzalutamide • ADT (control arm)	• MFS • OS • PCSS • BFFS • Safety
TOAD (BCR cohort) (Duchesne et al., 2016)	BCR after previous attempted curative therapy (radiotherapy or surgery, with or without postoperative radiotherapy)	• Immediate ADT • Delayed ADT	• OS • PCSS • Time to clinical progression • Time to first androgen independence • Safety and QoL
HERO (BCR cohort) (Shore et al. 2020)	BCR following a local primary intervention aimed at a cure	• Relugolix • ADT (control arm)	• Sustained testosterone • Suppression to castrate levels through 48 weeks • Castrate levels of testosterone on days 4 and 15
EMBARK (Freedland et al., 2023)	BCR, PSADT ≤9 months after radical treatment for PC, PSA ≥1 ng/mL after RP (with or without postoperative RT) or ≥2 ng/mL above nadir after RT alone, without suppression of serum testosterone	• Enzalutamide • Enzalutamide + ADT • ADT (control arm)	• MFS • OS • TTCR • PSA-PFS • Proportion of patients per group with undetectable PSA at 36 weeks on study drug • Time to resumption of any hormonal therapy following suspension at week 37 due to undetectable PSA • Safety
PRESTO (Aggarwal et al., 2024)	BCR, PSADT ≤9 months, PSA >0.5 ng/mL after RP	• ADT + apalutamide • ADT + apalutamide + AAP • ADT (control arm)	• PSA-PFS • Time to testosterone recovery • TTCR • MFS • Safety and QoL

ADT, androgen-deprivation therapy; BCR, biochemical recurrence; BFFS, biochemical failure-free survival; MFS, metastasis-free survival; OS, overall survival; PC, prostate cancer; PCSS, prostate cancer-specific survival; PFS, progression-free survival; RP, radical prostatectomy; TTCR, time to castration resistance.

potential to upstage them, potentially offering them tailored therapies; however, the risk of false-positive lesions should be kept in mind, and multidisciplinary team (MDT) discussion should always be recommended in doubtful cases. This is why we should wait for further studies to validate the role of PSMA PET imaging in this specific setting and its use for treatment guidance.

4. Future perspective of nmHSPC management

The current clinical practice of adopting ADT alone for nmHSPC should be considered outdated, given the data discussed before, and a more personalized approach should be adopted in this setting. In our review, we show that a trend toward treatment intensification in the nmHSPC setting has been established in recent years. ARSIs have rapidly become the drug family of interest, given these new hormonal agents' acknowledged efficacy and tolerability in different moments of PC clinical history, especially in the nmCRPC setting (Berruti et al., 2023).

Concerning BCR, the results from the EMBARK trial have already been received and integrated into the latest guidelines, thus modifying the future clinical management of nmHSPC patients; moreover, the possibility of administering an ARSI without ADT should be seen as a game changer in this field, paving the way for a wider adoption of this approach in the future.

Apart from EMBARK and PRESTO, other clinical trials are evaluating the role of ARSI in this scenario.

In the ongoing ARASTEP trial (NCT05794906), patients with high-risk BCR – defined as having a PSADT <12 months – and no evidence of metastasis – with both conventional imaging and PET PSMA – are randomized to receive ADT with or without darolutamide. Radiographic PFS is the primary endpoint.

In the ongoing INDICATE (ECOG-ACRIN EA8191, NCT04423211) phase III trial, PET – with 18F-fluciclovine or PSMA, if available – is used to divide patients experiencing BCR after RP, and who are candidates for salvage RT, in two cohorts: cohort 1 (PET-negative for distant metastases) or cohort 2 (PET-positive for distant metastases); in cohort 1, patients are randomized to salvage RT with or without apalutamide for 6 months, whilst in cohort 2 salvage RT and apalutamide are given to all patients, but they are randomized to receive or not metastasis-directed RT to PET-positive lesion(s) (Vapiwala 2021). PFS is the primary endpoint of this trial, and results are awaited.

Delaying the onset of metastases and stopping the increase in PSA are certainly two of the main goals to be pursued in nmHSPC patients, especially in those experiencing BCR, and in fact, they were chosen as primary endpoints in the EMBARK and PRESTO trials, respectively. Despite encouraging results, several questions remain unanswered.

MFS is considered a surrogate of OS: a meta-analysis of 12,712 patients from 19 trials confirmed this hypothesis in high-risk localized PC (Xie et al., 2017); however, these results could not be directly translated in the ARSI era since they refer to a different setting of patients. Delaying ARSIs at the time of metastatic onset versus anticipating them at the time of biochemical recurrence has not been investigated yet, so it is impossible to assess, at the moment, the proper role of ARSIs in improving OS despite the clear MFS advantage observed in the EMBARK trial (Freedland et al., 2023).

In patients with localized PC, the biochemical recurrence-free survival, calculated as the time from random assignment to BCR or any death, was not a surrogate for OS, as recently shown by an individual patient data meta-analysis (Roy et al., 2023); these findings could, therefore, question the usefulness of including the solely PSA increase among the primary endpoints of clinical trials in the nmHSPC setting.

Molecular characterization is currently a hot topic in PC, but much of the research so far has been conducted on metastatic disease (Giunta et al., 2021). Germline *BRCA* mutations, which occur in less than 5 % of PC patients (Pritchard et al., 2016) (Casadei et al., 2024), confer poor prognosis to localized disease in patients harboring them, not only for cancer-specific survival but also for MFS (Castro et al., 2015): therefore, PARP inhibitors would be an intriguing therapeutic strategy for *BRCA*-mutant nmHSPC patients (Congregado et al., 2022). In the first stage of a phase II trial (NCT03047135), molecularly unselected BCR patients (after RP, with a PSADT <6 months) received olaparib without ADT: the PARP inhibitor demonstrated clinical activity, especially in *BRCA2*-mutant patients (Antonarakis et al., 2019). Results from the second stage of this trial have been recently presented, confirming that the clinical efficacy is limited to the biomarker-positive population – and mostly in *BRCA2*-mutant patients (Marshall et al., 2023). The ongoing phase II single-arm ROAR trial (NCT03533946) is testing rucaparib in *BRCA*-mutant BCR patients.

Androgen receptor (AR) status could be tested through liquid biopsy in blood samples from metastatic PC patients (Conteduca et al., 2019). AR has been studied for its possible informative role in ARSI resistance (Salvi et al., 2016); however, *ad hoc* biomarker-driven trials are needed to validate its use.

Other molecular biomarkers are currently under investigation in high-risk PC patients (Alarcón-Zendejas et al., 2022). *TMPRSS2–ERG* is a gene fusion that is common in PC (Wang et al., 2017), whose predictive role in PC patients treated with hormonal and radiation treatment after BCR will be elucidated in two ongoing trials (NCT02588404, NCT02573636); interestingly, the second trial will focus on patients with coexisting TMPRSS2-ERG fusion and PTEN deletion. MicroRNAs (miRNAs) are small single-stranded non-coding RNA molecules that are currently being studied in PC (Gujrati 2023); intriguingly, some of them have already been associated with a higher probability of BCR after radical treatment (Rana et al., 2022). Unfortunately, to date, none of these molecular biomarkers could be incorporated into clinical practice.

Lastly, the use of more sensitive and specific imaging, such as PSMA PET, has limited the cases of nmHSPC and has also increased the number of patients with oligo-recurrent PC amenable to localized approaches such as stereotactic body RT (SBRT); several clinical trials have been designed with this purpose (NCT05053152, NCT04641078, NCT04619069). It is noteworthy that the EMBARK and PRESTO trials adopted "conventional imaging" for enrollment, thus including PSMA-positive patients who would currently receive different treatments and ultimately overestimating the effect of ARSI in the enrolled population.

5. Conclusions

The nmHSPC setting is a grey zone in the scenario of PC. To date, clinical guidelines have been already updated based on the results of both EMBARK and STAMPEDE trials. In detail, the latest NCCN guidelines® suggest the adoption of enzalutamide + leuprolide only in certain circumstances (NCCN Guidelines 2024), whilst the latest EAU guidelines strongly recommend the use of enzalutamide – with or without androgen deprivation – in all eligible patients with the EMBARK criteria (EAU Prostate Cancer Guidelines, 2024). Moreover, the NCCN guidelines® suggest also the use of AAP in combination with ADT and RT in nmHSPC patients with the STAMPEDE criteria for the high-risk locally advanced disease (NCCN Guidelines 2024). To date, the HERO trial results have not led to guidelines modifications; the NCCN guidelines® panel reports that relugolix could be an acceptable option, but additional studies are needed to better define its role in the nmHSPC setting (NCCN Guidelines 2024).

New clinical trials are trying to redefine the therapeutic algorithm for these patients, but the escalating treatment seems not to be the right choice for the overall population; selecting patients is, therefore, fundamental to avoid unnecessary therapies – and related adverse events – in those who have a low probability of developing distant metastases. Biomarkers able to stratify patients – including molecular ones – are urgently needed, and biomarker-based clinical trials could clarify their prognostic and predictive role in the nmHSPC context.

Critical view section

- Prostate cancer (PC) patients at high risk of metastatic spread, androgen deprivation therapy (ADT)-naïve, constitute a unique category with unmet clinical needs.
- Androgen receptor signaling inhibitors have rapidly become the drug family of interest, given their acknowledged efficacy and tolerability, especially in the "non-metastatic hormone-sensitive PC" (nmHSPC) setting.
- Germline BRCA mutations confer poor prognosis to patients with localized PC. Therefore, PARP inhibitors would be an intriguing therapeutic strategy for *BRCA* mutant nmHSPC patients.
- Androgen receptor (AR) has been studied for its possible informative role in androgen receptor signaling inhibitor resistance; however, *ad hoc* biomarker-driven trials are needed to validate its use.
- The use of prostate-specific membrane antigen positron emission tomography has limited the cases of nmHSPC and has increased the number of patients with oligo-recurrent PC amenable to localized approaches.

Ethics approval

Not required.

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Declaration of Competing Interest

Emilio Francesco Giunta received personal fees from Novartis and travel accommodation from Janssen and Bayer.

Giandomenico Roviello received honoraria for advisory boards or invited speaker fees from BMS, Astellas, Bayer, Ipsen, Novartis, Roche, and AstraZeneca.

Vincenza Conteduca: received honoraria for advisory boards or speaker fees from Janssen, Astellas, Merck, AstraZeneca, 'Ipsen, Bayer, Novartis, Recordati, BMS, MSD, GSK.

Elena Verzoni received honoraria for advisory boards or speaker fees from MSD, Pfizer, Astellas, BMS, AstraZeneca, Ipsen and Janssen.

Giuseppe Procopio services advisory boards/consulting for Astellas, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Brystol Myers, BMS, Janssen, EISAI, Ely Lilly, Janssen, IPSEN, Menarini, Merk, MSD, Novartis, Roche, Pfizer.

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Authors' contributions

Study design: Vincenza Conteduca, Elena Verzoni, Giuseppe Procopio, Ugo De Giorgi; data collection and interpretation: All; manuscript writing: Emilio Francesco Giunta, Giandomenico Roviello; manuscript editing: All; approval to submit: All.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2024.104534.

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