Hormonal Agents in Localized and Advanced Prostate Cancer: Current Use and Future Perspectives

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Abstract

Prostate cancer (PC) is generally a hormone-dependent tumor. Androgen deprivation therapy (has been the standard of care in metastatic disease for more than 80 years. Subsequent studies have highlighted the efficacy of ADT even in earlier disease settings such as in localized disease or in the case of biochemical recurrence (BCR). Improved knowledge of PC biology and ADT resistance mechanisms have led to the development of novel generation androgen receptor pathway inhibitors (ARPI). Initially used only in patients who became resistant to ADT, ARPI have subsequently shown to be effective when used in patients with metastatic hormone-naive disease and in recent years their effectiveness has also been evaluated in localized disease and in case of BCR. The objective of this review is to describe the current role of agents interfering with the androgen receptor in different stages of PC and to point out future perspectives.

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Introduction

Based on the biologically significant androgen dependence, since 1940 androgen deprivation therapy (ADT) has represented the cornerstone of prostate cancer (PC) treatment.[1,2] Several approaches to suppress androgens have been used, including bilateral orchiectomy or medical castration.[3] After castration, the incorporation of androgens into the cell nucleus continues, because of the synthesis by the adrenal glands. This can be counteracted by adding an androgen receptor (AR) inhibitor to ADT.[4] First generation AR inhibitors (eg, bicalutamide) compete with circulating androgens for binding sites on the AR within the prostate cells.[4] ADT and the first-generation AR inhibitors can be therefore called "classic hormone therapy (HT)."

A better understanding of AR functioning and ADT resistance mechanisms has led to the development of novel generation androgen receptor pathway inhibitors (ARPI) such as abiraterone, enzalutamide, apalutamide, and darolutamide.[5]

Abiraterone is a selective, irreversible inhibitor of CYP17, a critical enzyme in the androgen synthesis while apalutamide, enzalutamide, and darolutamide are AR inhibitors that bind directly to the ligand-binding domain of AR and prevent AR translocation and DNA binding, and AR–mediated transcription.[6-9]

The objective of this narrative review is to describe the role of the classic HT as well as ARPIs, both in localized and in the metastatic PC setting and moreover to elaborate possible future perspectives of these therapies.

Hormonal Agents in Localized PC

Radical prostatectomy (RP) or external beam radiotherapy (EBRT) represent the standard of care (SOC) for the treatment

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of localized PC.[10,11] However, biochemical recurrence (BCR) at 10 years post-treatment occurs in 21% to 47% for RP and 16% to 52% for EBRT. Up to 34% of men who develop BCR may eventually develop clinical recurrence.[12] To improve the oncological outcomes for patients with localized PC, multimodality treatments have been investigated, combining surgery or EBRT with ADT and lately with ARPIs.[10,11]

The Role of Hormonal Agents as Neoadjuvant Therapy Before RP

Evidence From the Literature. The rationale of ADT use as neoadjuvant treatment before RP is dual: it might lower the risk of positive surgical margins (PSM) by decreasing the local tumor volume and it might eradicate micro metastases.[13] A meta-analysis of randomized trials testing neoadjuvant ADT showed that a short neoadjuvant approach (about 3 months) reduces the risk of PSM (relative risk, RR 0.49, 95% CI, 0.42-0.56, $P < .00001$) as well as the rate of lymph node involvement (LNI) (RR 0.66, 95% CI, 0.47-0.94, $P = .02$), though without obtaining an improvement in disease-free survival (DFS) or overall survival (OS).[14] A longer duration of neoadjuvant ADT ($\geq$ 8 months) resulted in a lower risk of positive margins, extra-prostatic extension and LNI. However, even with a longer duration of neoadjuvant ADT there was no improvement in DFS and OS.[15,16]

Although the hormonal dependence of PC is well documented, preclinical models suggest that castrate-resistant cellular clones can appear at an early disease stage therefore this could explain the poor results of neoadjuvant ADT.[17] The combination of chemotherapy and ADT has the potential to eradicate castrate-resistant clones inhibiting the growth of both AR dependent and independent cells.[18] Preliminary results of this therapeutic combination are conflicting.[19,20] While the study by Pan et al., showed that the neoadjuvant combination of docetaxel and ADT induces a lower BCR rate compared to the neoadjuvant ADT alone or to the immediate RP (14% vs. 47% and 81%, $P < .01$), the study by Eastham et al., testing the same combination could not show an improvement in 3-year biochemical progression-free survival (PFS) compared to neoadjuvant ADT alone.[19,20]

Clinical Considerations and Future Perspectives. In the absenceof studies having shown a significant advantage in OS for neoadjuvant ADT or chemo-hormonal therapy, to date these therapeutic strategies are not recommended by international guidelines.[10,11]

The lack of neoadjuvant ADT efficacy could be explained by the fact that these studies used "classic HT," leading to incomplete androgen suppression and the residual androgens levels could be still sufficient for PC growth.[21] With the introduction of ARPIs in the treatment of PC, neoadjuvant hormone-therapy has regained interest. The neoadjuvant ARPI use was discussed in a systematic review by Davos et al., total 431 patients with intermediate or high-risk localized PC were included, receiving a neoadjuvant ARPI and ADT.[13] Despite the complete androgen blockade, a pCR was rarely obtained (4%-13%). However, ADT + ARPI seems to be more effective than ADT alone. In the ARNEO study neoadjuvant ADT plus apalutamide prior to RP resulted in a significantly improved minimal residual disease compared to ADT alone (38% vs. 9.1%, $P = .002$).[22] This trial was done in only 90 patients and thus is only hypothesis generating. It remains unclear if the better pathological outcome will translate into a better oncological outcome.

There are several ongoing studies that are evaluating neoadjuvant ARPI both in monotherapy and in combination with other treatments (Table 1).

Finally, the lack of efficacy of neoadjuvant HT could explained both by either the use of classic HT or the presence of cells intrinsically resistant to HT. Hence giving even more rationale to use a combination of ADT+ARPI+chemotherapy prior to prostatectomy. This therapeutic strategy was evaluated in a phase II study (ACDC Trial) that randomized 76 high-risk PC patients to receive neoadjuvant treatment comprising 6 months of ADT + abiraterone plus 6 cycles of cabazitaxel or to 6 months of ADT + abiraterone. Early findings show a significant tumor response with 44% of patients experiencing a complete response (CR)/ minimal residual disease (MRD).[23]

In general, these neoadjuvant studies above mentioned are small trials with few patients enrolled, therefore the results described are only hypothesis generating. Therefore, these approaches remain experimental.

The Role of Hormonal Agents as Adjuvant Therapy After RP

Evidence From the Literature. Up to 15% of patients with clinically localized PC harbor LNI after RP and pelvic lymph node dissection.[24] The presence of LNI represents one of the most important risk factors for recurrence and cancer-specific mortality (CSM).[24] Studies were conducted evaluating the efficacy of adjuvant ADT in these patients. Messing et al., randomized 98 lymph node positive PC patients to immediate lifelong ADT or to start ADT only after the appearance of disease progression.[25] At a median follow-up of 11.9 years patients treated with immediate ADT had a significant improvement in OS (HR 1.84, 95% CI, 1.01-3.35, $P = .04$) and cancer-specific survival (CSS) (HR 4.09, 1.76-9.49, $P = .0004$).[25]

Even though all patients with LNI according to the TNM classification are categorized as pathological N1 (pN1), regardless of the number of positive nodes, the long-term prognosis of this group is very heterogeneous.[10,11] Schumacher et al., showed that CSS correlated with the number of nodes involved: patients with 1 or 2 positive nodes had CSS rates at 10 years of 72% and 79%, respectively, while in patients with $\geq$ 3 positive nodes it was only 33%.[26]

Adjuvant ADT has also been evaluated in patients with locally advanced PC in the absence of LNI without showing an improvement in OS.[27]

Finally, the combination of ADT and chemotherapy after surgery was investigated in the SWOG S9921 trial.[28] This phase III trial evaluated ADT alone or in combination with mitoxantrone after RP in 983 patients with high-risk PC. The study was terminated due to an increased incidence of leukemia in the mitoxantrone arm. No improvement was observed in OS or recurrence- free survival.[28]

Clinical Considerations and Future Perspectives. According to the current EAU guidelines, adjuvant ADT should only be evaluated for pN1 patients. The authors recommend observation in patients with

Table 1 Ongoing Trials With Classic Hormonal Therapy and ARPI in Localized Prostate Cancer

NCT Number (Name)	Phase	Setting	Treatment Arms	Primary Endpoints	Estimated Study Completion Date
NCT00430183	3	Neoadjuvant before prostatectomy	Docetaxel + ADT followed by prostatectomy vs. immediate prostatectomy	bPFS at 3 y	October, 2030
NCT04569461 (TALON)	2	Perioperative	Pembrolizumab + RT + ADT	bPFS at 2 y	December 1, 2026
NCT04812366 (GUNS)	2	Neoadjuvant before prostatectomy	-Group 1 (no targetable aberration,TMPRSS2-ERG fusion,CHD1 loss or SPOP mutations): ADT + apalutamide vs. ADT + apalutamide + abiraterone -Group 2 (PTEN,TP53 or TMB loss): ADT + abiraterone vs. ADT + abiraterone + docetaxel -Group 3(DDR mutations): ADT + abiraterone + niraparib -Group 4 (MSI,hypermutation,Lynch syndrome or CDK12): ADT + apalutamide + atezolizumab	pCR and pMRD	April 1, 2026
NCT05249712	2	Neoadjuvant before prostatectomy	Darolutamide + ADT	pCR	December 1, 2025
NCT04736108	2	Neoadjuvant before prostatectomy	Abiraterone + ADT	pCR	December, 2024
NCT03436654	2	Neoadjuvant before prostatectomy	ADT + apalutamide vs. ADT + apalutamide + abiraterone vs. apalutamide + RT	pMRD and pCR	February 14, 2025
NCT03767244 (PROTEUS)	3	Perioperative	Apalutamide + ADT vs. placebo + ADT	pCR and MFS	July 19, 2029
NCT05009290	3	Perioperative	SHR3680 + ADT vs. placebo + ADT	pCR and MFS	October 30, 2031
NCT02903368	2	Perioperative	Apalutamide + abiraterone + ADT + prostatectomy vs. abiraterone + ADT + prostatectomy vs. apalutamide + abiraterone + ADT	pCR or pMRD and bPFS	June, 2024
NCT02799706 (PEGASUS)	3	Peri-RT	ADT + RT vs. ADT + antiandrogen + RT	PFS	June 2024
NCT03070886	2/3	Peri-RT	ADT + RT + docetaxel vs. ADT + RT	MFS	May 2031

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Table 1 (*continued*)

NCT Number (Name)	Phase	Setting	Treatment Arms	Primary Endpoints	Estimated Study Completion Date
NCT02446444 (ENZARAD)	3	Peri-RT	Enzalutamide + ADT + RT vs. antiandrogen + RT	MFS	December 2025
NCT02531516 (ATLAS)	3	Peri-RT	Apalutamide + ADT vs. Placebo + ADT + RT	MFS	December 12, 2028
NCT04947254	2	Peri-RT	RT + apalutamide + ADT vs. RT + apalutamide + abiraterone + ADT + niraparib	rPFS and bPFS	June 7, 2026
NCT05050084 (GUIDANCE)	3	Peri-RT	Genomic-low risk: RT vs. RT + ADT Genomic-high risk: RT + ADT + Darolutamide vs. RT + ADT	De-intensification and intensification therapy according to genomic risk	April 30, 2037
NCT04513717 (PREDICT-RT)	3	Peri-RT	Genomic-low risk: RT + 12months ADT vs. RT+ 24 mo ADT Genomic-high risk: RT + 24 mo ADT + apalutamide vs. RT + 24 mo ADT	MFS	December 31, 2033
NCT04136353 (DASL-HiCaP)	3	Peri-RT or salvage RT	Darolutamide + ADT + RT (definitive or salvage) vs. Placebo + ADT+ RT(definitive or salvage)	MFS	July 31, 2028
NCT03541850	2	Adjuvant after prostatectomy	RT + ADT	bPFS	November 1, 2025
NCT00667069	3	Adjuvant after prostatectomy	Immediate RT +ADT vs. salvage RT + ADT	PFS	April 2025
NCT04295447 (ADAM)	2	Adjuvant after prostatectomy	Apalutamide + ADT + RT vs. ADT + RT	PFS	May 31, 2027
NCT04242017 (LOBSTER)	2/3	BCR after prostatectomy	RT+6 mo ADT vs. RT + 12 mo ADT	MFS	February 1, 2031
NCT04423211 (INDICATE)	3	BCR after prostatectomy	Apalutamide + ADT + RT vs. ADT + RT	PFS	December 31, 2032

Abbreviations: ADT = androgen deprivation therapy;ARPI = androgen receptir pathway inhibitor; BCR: = biochemical recurrence; bPFS = biochemical progression-free survival; MFS = metastasis free survival; MSI = microsatellite instability; N = number of patients; OS = overall survival; pCR = pathological complete response; PFS = progression free survival; pMRD = pathological minimal residual disease; rPFS = radiological progression-free survival; RT = radiotherapy; TMB = tumor mutational burden.

≤ 2 positive lymph nodes, while they recommend adjuvant ADT +/− adjuvant radiotherapy in patients with more lymph nodes involved.[10]

In the adjuvant setting after RP, no early validated endpoints have been identified and therefore there is a need for longer follow-up to capture meaningful endpoints. This could be one of the reasons why only a few trials are ongoing in this setting (Table 1).

To date, the only characteristic that guides us to offer adjuvant treatment is represented by the number of positive pathological lymph nodes. Results of studies evaluating molecular or genomic biomarkers predicting response to adjuvant treatments are therefore needed.

The Role of Hormonal Agents in Association With Definitive Radiotherapy

Evidence From the Literature. The role of ADT in combination with definitive RT has been investigated since the 1960s.[29] AR controls transcription of DNA repair genes crucial in mediating PC radio resistance. Indeed, AR inhibition increases DNA damage which improves radiosensitivity and decreases PC cells survival.[30,31] In addition, concomitant ADT can eliminate subclinical metastases outside the planned target RT volume not detected by radiological imaging and therefore could reduce both local and distant recurrence.[30]

The study by Bolla et al., was the first to show an OS advantage of the combination of ADT and RT. In 415 patients 3 years of adjuvant ADT with RT showed an improvement in 5 year- OS and DFS compared to RT alone (79% vs. 62%, $P = .001$ and 85% vs. 48%, $P = .001$ respectively)[32] These results were confirmed by several meta-analyses.[33,34]

To reduce side effects of ADT, subsequent studies have evaluated a shorter duration of ADT when combined with RT.[34] A phase III trial by Nabid et al., showed that ADT can be safely reduced from 36 to 18 months without compromising the outcome in high-risk PC patients.[35] The meta-analysis by Kishan and colleagues demonstrated that 18 to 36 months of adjuvant ADT significantly improves MFS compared to 4 to 6 months (HR 0.84, 95% CI, 0.78-0.91, $P < .0001$) in high-risk PC patients.[34]

A possible explanation for disease recurrence after combined RT and ADT is the existence of primary androgen-resistant tumor clones in primary tumor. Therefore, integrating systemic chemotherapy with RT and ADT in high-risk PC is one potential approach to improve treatment outcomes.[36-38] In the GETUG-12 trial patients with high-risk PC were randomized to 4 cycles of docetaxel plus estramustine and 3 years of ADT or 3 years of ADT alone. In this study recurrence-free survival (RFS) was superior in the experimental arm (HR 0.71, 95% CI, 0.54-0.94; $P = .017$).[36] In the RTOG 0521 trial, the addition of 6 cycles of docetaxel to 2 years of ADT and prostate RT improved OS from 89% to 93% at 4 years when compared with prostate RT + ADT.[37] In the randomized Scandinavian Prostate Cancer Group trial, 6 cycles of docetaxel did not improve biochemical disease-free survival after radical RT+ADT even if there was a trend toward a treatment benefit from docetaxel in patients with high-risk disease (GS 9-10). MFS and OS data are not yet mature.[38] In arm C of the STAMPEDE platform, RFS among patients with high-risk localized or cN1 disease was improved by adding docetaxel to long-term ADT.[39] A meta-analysis supported RFS improvement with docetaxel in patients with high-risk localized disease (HR 0.70; 95% CI, 0.61-0.81; $P < .0001$), but OS data were immature.[40] Based on these results, ESMO guidelines suggest to evaluate the possibility of adding docetaxel to RT + ADT in selected patients with high risk PC.[41] EAU and NCCN guidelines do not recommend the use of docetaxel in this setting.[10,11]

Several ongoing studies are evaluating the effectiveness of different RT+ADT+ARPI combination (Table 1). The first evidence for this therapeutic strategy comes from one of the analyses from the STAMPEDE platform.[42] In the STAMPEDE arm G and J the combination of ADT (3 years) + abiraterone +/− enzalutamide (2 years) was evaluated in node positive patients and in high-risk node negative patients (defined as having at least 2 of the following: ≥ cT3, GS ≥ 8, PSA ≥ 40 ng/mL). The experimental arm showed to improve MFS and OS compared to the control arm (HR 0.54, 95% CI, 0.43-0.68 and HR 0.6, 95% CI, 0.48-0.73, respectively). There was no difference in MFS and OS when enzalutamide and abiraterone were administered concurrently compared to abiraterone alone, but adverse events ≥ grade 3 were greater in patients who received both ARPIs (58% vs. 38%).[42]

Clinical Considerations and Future Perspectives. Based on the EAU risk group classification the EAU guidelines provide the indication for RT alone or in combination with ADT based on the risk classification.[10] In low-risk patients, only RT without ADT is recommended. In intermediate-risk patients it is recommended to use RT in combination with short-term ADT (4-6 months). In high-risk patients, the combination of RT with long-term (2-3 years) ADT is the standard treatment.[10] According to the results of STAMPEDE analysis NCCN and EAU guidelines recommend using 2 years of abiraterone when offering RT to the prostate in combination with long-term ADT for cN1 PC patients or in in cN0 high-risk patients according to the STAMPEDE definition.[10,11]

In patients treated with RT + ADT we currently do not have valid biomarkers predicting the individual benefit most from the addition of ADT+/− ARPI. Soon the use of artificial intelligence (AI) or molecular classifiers such as Decipher® may guide the therapeutic choice in these patients by selecting those for whom hormonal treatment can be omitted. Spratt et al., used digital pathology images from pretreatment prostate tissue and clinical data from patients enrolled in 5 phase 3 randomized trials, in which treatment was RT +/− ADT to develop and validate an AI-derived predictive patient-specific model that would determine which patients would develop distant metastasis. This model provides a binary output that could help to select which patient benefits from adding ADT to RT. In the NRG/RTOG 9408 validation cohort in patients with model positive adding ADT significantly reduced the risk of distant metastasis compared with radiotherapy alone while in patients with model negative, ADT did not provide benefit.[43] In another study Spratt et al., assessed the performance of the Decipher® genomic classifier (GC) in patients with intermediate-risk disease enrolled in NRG Oncology/RTOG 01-26. In this analysis GC was independently prognostic for disease progression, biochemical failure, distant metastasis and prostate

cancer-specific mortality.[44] Ten-year distant metastasis in GC low-risk patients was 4% compared to 16% for GC high-risk patients. In patients with a lower GC score, the 10-year difference in MFS rate between arms was 7%, compared with 21% for higher GC patients. Therefore, Decipher® GC improves risk stratification and can help in treatment decision-making in patients with intermediate-risk disease.[44]

The Role of Hormonal Agents in BCR After RP or RT

Evidence From the Literature. The definition of BCR depends on the local curative treatment previously performed. In patients undergoing RT +/− ADT, BCR is defined according to the Phoenix definition: any PSA increase > 2 ng/mL over the PSA nadir (defined as the lowest PSA achieved after curative treatment).[45]

BCR after RP is historically defined as the presence of PSA ≥ 0.2 ng/mL measured 6 to 13 weeks after RP followed by a confirmatory test showing a persistent PSA ≥ 0.2 ng/mL.[46] In patients with BCR after RP the use of salvage radiotherapy (SRT) showed a decrease in the risk for distant metastasis of 75%.[47] However, less than 50% of patients are deemed to be free of biochemical relapse 5 years after SRT.[48] These suboptimal results have raised the question whether the efficacy of SRT may be enhanced by combining it with HT.

In a phase III trial Carie et al., showed in 743 PC patients with BCR following RP that the addition of 6 months of ADT to SRT is associated with an improved 12-year PFS compared to SRT alone (64% vs. 49% HR 0.54, 95% CI, 0.43-0.68; $P < .0001$).[48]

In the study by Shipley et al., the addition of 24 months of bicalutamide (150 mg/day) to SRT resulted in significantly higher rates of 12-year OS (76.3% vs. 71.3%, HR 0.77; 95% CI, 0.59 to 0.99; $P = .04$) and lower death rates from PC (5.8% vs. 13.4%, $P < .001$) than SRT plus placebo.[49]

In 2018, EAU commissioned a systematic review to find clinical factors that could identify BCR patients who could benefit most from salvage treatments.[50] According to the results of this analysis BCR patients should be classified in "EAU low-risk BCR" (PSA-DT> 1 year and a GS of < 8 for RP, or an interval to biochemical failure of > 18 months and a GS of < 8 for RT) and "EAU high-risk BCR" (PSA-DT of < 1 year or a GS of 8-10 for RP, or an interval to biochemical failure of < 18 m or a GS of 8-10 for RT). This classification should select patients to be referred to salvage treatments in case of BCR.[51] The use of this classification was validated by a subsequent analysis in 1125 post-RP BCR patients conducted by Tilki et al.[52]

There is less evidence on the management of BCR after RT. Therapeutic options in these patients are ADT or salvage local interventions such as salvage prostatectomy, brachytherapy, high-intensity focused ultrasound, or cryosurgical ablation.[11,50,53]

Clinical Considerations and Future Perspectives. The treatment of BCR varies according to the previously performed local curative treatment and the risk class according to the EAU criteria.[50] In EAU low-risk BCR patients after RT or after RP, EAU guidelines suggest monitoring PSA values. In EAU high-risk BCR patients after RT though, the guidelines suggest salvage local procedures or alternatively start of ADT. In EAU high-risk BCR patients after RP guidelines endorse SRT with a strong strength rating. In these patients, hormonal therapy (24 months of bicalutamide 150 mg/die or ADT for 6 months) could be evaluated in addition to salvage RT (weak strength rating).[50] The "historical" definitions of BCR are very likely to be changed in the near future. Hence, the NCCN and EAU guidelines have already eliminated the PSA cut-off > 0.2 ng/mL to define BCR after RP that is currently defined as the evidence of PSA increase on 2 or more determinations after a PSA value undetectable.[11,50] The Phoenix definition to define BCR after RT is still valid in the guidelines thus likely to be modified to a lower PSA value cut-off, due to the increasing use and availability of modern imaging techniques such as PET-PSMA.

It is also unclear in what scenarios HT should be combined with SRT and for how long HT should be administered. According to the results of RADICALS-HD TRIAL short course ADT (6 months) did not meaningfully improve MFS (HR 0.89, 95% CI, 0.69-1.14) compared to no ADT while long course ADT (24 months), compared with short course ADT, improved MFS (HR 0.77, 95% CI, 0.61-0.97).[54]

Also, in the BCR setting there are studies ongoing that are evaluating whether the ADT + ARPI combination is more effective than ADT alone (Table 1).

Recently the results of the randomized phase III trial EMBARK were published.[55] This trial enrolled patients with high-risk BCR defined as PSA doubling time of ≤ 9 months and a PSA level of ≥ 2 ng/mL above nadir after RT or ≥ 1 ng/mL after radical prostatectomy with or without postoperative RT. These patients were randomized to ADT alone, enzalutamide alone or ADT + enzalutamide. Regarding MFS both combination therapy and enzalutamide alone was superior to ADT alone (HR 0.42 95% CI, 0.30-0.61 $P < .001$; HR0.63 95% CI, 0.46-0.87 $P = .005$, respectively). Both combination therapy and enzalutamide alone demonstrated an improvement of other key outcomes such as PSA progression, first use of new antineoplastic therapy, distant metastasis and symptomatic progression while data on OS impact were immature. Interestingly in this trial treatment was suspended at week 37 in case of PSA < 0.2 ng/mL and was restarted when the PSA level > 5.0 ng/mL (if the patient had not had previous RP) or at least 2.0 ng per milliliter (if the patient had previously had RP).[55] Based on these results ADT + enzalutamide should be now considered in patients with high-risk BCR according to the EMBARK definition.

Hormonal Agents in Advanced PC

ADT represents the basis of systemic treatment in patients with advanced PC in both the hormone-sensitive and the castration-resistant setting.[2] Over the past decade, several ARPIs have demonstrated to be effective when used in combination with ADT in metastatic hormone-sensitive prostate cancer (mHSPC),[6-8,56,57] in nonmetastatic castration resistant prostate cancer (nmCRPC)[9,58,59] and in metastatic castration resistant prostate cancer (mCRPC) setting.[60-63]

The Role of Hormonal Agents in the mHSPC Setting

Evidence From the Literature. In recent years the anticipation of ARPI and/or docetaxel in combination with ADT into the mHSPC

setting (upfront therapy) has shown superiority compared to ADT alone.[11,50]

The rationale for upfront therapies is based on the understanding of the mechanisms that lead to the transformation into the castration resistant phase of the disease.[64] PC should be considered a heterogeneous disease, characterized by the coexistence of both AR-positive and AR-negative tumor cells. In this biologic context, patients with mHSPC may benefit from a treatment able to act on AR independent mechanisms of neoplastic progression as chemotherapy in addition to ADT. Three randomized controlled trials and 2 subsequent meta-analyses showed that ADT + docetaxel improves OS compared to ADT alone, particularly in patients with high-volume disease according to the CHAARTED criteria.[39,40,65-67]

Resistance to ADT could also be induced by the reactivation of AR signaling through persistent adrenal androgen production, upregulation of intratumoral testosterone production and modification of the AR biologic structure. Based on this rationale, several randomized controlled trials were conducted evaluating the combination of ARPIs and ADT versus ADT alone. These studies have shown that the combination of abiraterone, enzalutamide or apalutamide with ADT results in a reduced risk of death compared to ADT alone.[6-8,56,57]

In patients with low-burden disease also the addition of the RT to the primary showed to improve OS compared to ADT monotherapy.[68-70] The rationale for this combination derived from the hypothesis that the primary prostatic tumor may play a fundamental role in metastatic expansion and that effective local therapy might disrupt the complex dynamics between primary tumor, the microenvironment of secondary organs, and metastatic disease.[71]

There is a strong biological rationale for the association of both an ARPI and chemotherapy with ADT in patients with mHSPC. The presence of cellular clones intrinsically hormone resistant (potentially sensitive to chemotherapy) and the persistence of low testosterone levels during ADT however sufficient for PC growth (which could be decreased by ARPI) represent mechanisms that lead to the development of castration resistant phase. Blocking both mechanisms could delay the development of castration resistant disease and consequently improve OS. The results of 2 phase 3 studies that evaluated triplet therapy (ADT + docetaxel + ARPI) in mHSPC setting were recently published.[72,73] In the PEACE-1 trial ADT + docetaxel + abiraterone demonstrated to improve OS compared to ADT + docetaxel (0.82, 95% CI, 0.69-0.98; $P = .030$.[72] Similarly, the ARASENS trial showed the superiority of ADT + docetaxel + darolutamide in terms of OS versus ADT + docetaxel (HR 0.68; 95% CI, 0.57-0.80; $P < .001$).[73]

Clinical Considerations and Future Perspectives. According to current guidelines, ADT monotherapy is no longer SOC for mHSPC patients.[11,50] Therefore, all patients with an adequate life expectancy (≥ 1 year) and no contra-indications for a combination therapy should be treated according to this strategy (ADT + ARPI +/− docetaxel). However, several open questions remain, for example which patients would benefit most from triplet therapy and whether triplet therapy is better than doublet therapy with ADT + ARPI.[74] Therefore, there is no clear evidence on how to choose best upfront treatment. Future studies investigating response to the individual treatments upfront should implement predictive biomarkers. Finally, all combination studies in the mHSPC setting used continuous therapies. Therefore, the guidelines do not recommend intermittent therapy in this setting. However, in the precombination therapy era some studies showed that intermittent therapy was not inferior to continuous therapy and that intermittent therapy also resulted in a better quality of life.[75,76] Based on these previous data future studies like the EORTC GUCG 2238 De-escalate trial evaluating the role of intermittent therapies are necessary in order to try to improve patients' quality of life and reduce the financial toxicity that these treatments cause.[77]

Several studies are ongoing that are evaluating different combinations with ARPI in the mHSPC setting (Table 2).

The Role of Hormonal Agents in the CRPC Setting

Evidence From the Literature. Although ADT can initially induce a response in more than 90% of patients, after a median of about 12 to 14 months, despite the persistence of suppressed testosterone levels, disease progresses in the majority of cases and therefore becomes castration resistant.[11,50]

Enzalutamide, apalutamide, and darolutamide in combination with ADT showed to improve MFS and OS in nmCRPC (on conventional imaging) with a PSA doubling time (PSAdt) < 10 months compared to ADT alone.[9,58,59]

In mCRPC patients, chemotherapeutic drugs (docetaxel, cabazitaxel),[78-81] ARPIs (enzalutamide and abiraterone),[60-63] radiopharmaceutical therapy (radium 223, 177- Lutetium- PSMA-617)[82-84] and the PARP-inhibitor (PARPi) olaparib[85] have proven an OS benefit in combination with ADT in randomized phase II to III trials.

Clinical Considerations and Future Perspectives. In the nmCRPC setting, guidelines recommend the use of enzalutamide, apalutamide, or darolutamide in combination with ADT in patients with a PSAdt < 10 months.[11,50] In patients with nmCRPC and PSA-DT > 10 months we have no evidence for efficacy of adding an ARPI or other therapies to ADT. Therefore, the SOC in these patients is surveillance with regular PSA testing plus continuous ADT.

International guidelines have few recommendations on therapeutic sequencing in this setting and they are based especially on the characteristics of the pivotal studies or restrictions by regulatory authorities. Enzalutamide and abiraterone can be used in chemonaïve patients or after docetaxel treatment. Docetaxel can be recommended in first line mCRPC and is commonly used also in second line in patients with progression to a previous ARPI, although there is no evidence of its use in this setting. Cabazitaxel should only be used in patients who have previously received docetaxel. According to EMA restrictions radium-223 can only be given to patients who have previously received docetaxel and an ARPI. Based on the results of the CARD study, guidelines recommend the use of cabazitaxel in patients previously treated with docetaxel and abiraterone or enzalutamide.[81] Based on the design of the pivotal studies, olaparib should only be considered in patients who have previously received an ARPI who have an alteration in the DNA repair genes, whereas 177-Lutetium - PSMA-617 only in patients previously treated with docetaxel and one ARPI who have a PET

Table 2 Ongoing Trials With Classic Hormonal Therapy And ARPI In Advanced Prostate Cancer

NCT Number (Name)	Phase	Setting	Treatment Arms	Primary Endpoints	Estimated Study Completion Date
NCT04720157 (PSMAddition)	3	mHSPC	^{177}Lu-PSMA-617 + ADT vs. ADT	rPFS	February 11, 2026
NCT03879122	3	mHSPC	Docetaxel + ADT vs. docetaxel +ADT + nivolumab vs. docetaxel + ADT + ipilimumab + nivolumab	OS	December 31, 2024
NCT04736199 (ARANOTE)	3	mHSPC	Darolutamide + ADT vs. placebo + ADT	rPFS	September 26, 2025
NCT04191096 (KEYNOTE-991)	3	mHSPC	Pembrolizumab + enzalutamide + ADT vs. placebo + enzalutamide + ADT	rPFS and OS	February 2, 2026
NCT04497844 (AMPLITUDE)	3	mHSPC	Niraparib + abiraterone + ADT vs. abiraterone + ADT	rPFS	May 27, 2027
NCT04821622 (TALAPRO-3)	3	mHSPC	Talazoparib + enzalutamide + ADT vs. placebo + enzalutamide + ADT	rPFS	August 7, 2027
NCT04493853 (CAPItello-281)	3	mHSPC	Capivasertib + abirateron + ADT vs. placebo + abiraterone + ADT	rPFS	March 26, 2027
NCT02257736	3	mCRPC I line	Apalutamide + abiraterone + ADT vs. placebo + abiraterone + ADT	rPFS	December 2025
NCT01949337	3	mCRPC I line	Enzalutamide + abiraterone + ADT vs. enzalutamide + ADT	OS	August 31, 2024
NCT04691804	3	mCRPC I line	Fuzuloparib + abiraterone + ADT vs. placebo + abiraterone + ADT	rPFS	December 31, 2026
NCT04455750 (CASPAR)	3	mCRPC I line	Rucaparib + enzalutamide + ADT vs. placebo + enzalutamide + ADT	rPFS and OS	September 2026
NCT03395197 (TALAPRO-2)	3	mCRPC I line	Talazoparib + enzalutamide + ADT vs. placebo + enzalutamide + ADT	rPFS	December 31, 2025
NCT03834493 (KEYNOTE-641)	3	mCRPC I line	Pembrolizumab + enzalutamide + ADT vs. placebo + enzalutamide + ADT	rPFS and OS	May 31, 2024
NCT02194842 (PEACE III)	3	mCRPC I line	Radium-223 + enzalutamide + ADT vs. enzalutamide + ADT	rPFS	December 2025
NCT04100018 (CheckMate-7DX)	3	mCRPC II line after ARPI	Nivolumab + docetaxel + ADT vs. Placebo + docetaxel + ADT	rPFS and OS	August 30, 2028
NCT03574571	3	mCRPC	Radium-223 + docetaxel + ADT vs. docetaxel + ADT	OS	June 1, 2026
NCT04689828 (PSMAfore)	3	mCRPC II line after ARPI	^{177}Lu-PSMA-617 + ADT vs. ARPI + ADT	rPFS	September 30, 2025
NCT05204927	3	mCRPC II line after ARPI	^{177}Lu-PSMA + ADT vs. ADT abiraterone or enzalutamide	rPFS	June 2029

Abbreviations: ^{177}Lu-PSMA-617 = Lutetium-177 – PSMA-617; ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; mCRPC = metastatic castration-resustant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; N = number of patients; OS = overall survival; rPFS = radiographic progression-free survival; SSE-FS symptomatic skeletal related events-free survival.

PSMA positive disease.[83,85] The use of sequential ARPIs in mCRPC showed limited benefit in retrospective series as well as in one prospective trial. Therefore, this sequence should be avoided because of known cross resistance and the availability of other effective therapies.[86-90]

Considering the current therapeutic landscape in the mCRPC setting, studies are needed to identify predictive biomarkers for response, helping to identify the best therapeutic sequence for each individual patient. To date, in fact, only the search for homologous repair deficiencies (HRD) is useful for selecting patients to be candidates for a treatment with olaparib.[11,50]

Several studies are ongoing that are evaluating different combinations with ARPIs in the mCRPC setting (table 2). In particular different studies evaluated the efficacy of ARPI + PARPi as first-line treatment in mCRPC setting.[91-93] In the PROpel trial abiraterone + olaparib demonstrated to improve radiographic PFS in patients with mCRPC regardless of homologous recombination repair (HRR) pathway mutation status.[91] However, OS was not significantly different between treatment groups at the final prespecified analysis. Patients in the BRCA-subgroup seem to have the greatest benefit from this combination (HR 0.29, 95% CI, 0.14-0.56), while patients without HRR mutations seem not to have a significant OS benefit with the combination (HR 0.89, 95% CI, 0.7-1.14). In the MAGNITUDE trial abiraterone plus niraparib showed to improve rPFS in patients with mCRPC with HRR mutations compared to abiraterone plus placebo but not in patients

without HRR mutations.[92] Finally TALAPRO-2 study showed that enzalutamide plus talazoparib resulted in longer PFS than enzalutamide plus placebo regardless of HRR pathway mutation status.[93] Based on these results, the Food and Drug Administration (FDA) approved the use of abiraterone + olaprib, abiraterone + niraparib and enzalutamide + talazoparib as first line treatment in mCRPC setting only in patients with BRCA1-2 mutations.[94]

Another group of drugs with interesting preliminary results in the mCRPC setting is the novel CYP11A1 inhibitors. ODM-208 is a first-in-class, nonsteroidal small molecule that selectively and completely inhibits CYP11A1 enzyme, the first and rate limiting step in steroidogenesis leading to deficiency of endogenous steroid hormones.[95] In the phase I/II CYPIDES ongoing trial ODM-208 showed anticancer activity in extensively pretreated patients with mCRPC and AR mutations with a 50% PSA response > 50%.[95] Therefore, since some late-stage mCRPC remain androgen receptor pathway-dependent despite prior ADT and ARPI, ODM-208 is a promising future treatment option.

Conclusions

Since the 1940s, ADT has been the cornerstone of medical treatment for PC.[2] Initially used only in metastatic disease, it has subsequently proved its efficacy even in the earliest disease settings such as adjuvant therapy after RP, concomitant therapy with curative intent radiotherapy and in the BCR setting both after RP or RT.[10,11,50] The improved knowledge on the biology of PC has led to the development of ARPIs which have been shown to be effective in the castration resistant setting and subsequently also in the earliest stages of advanced PC such as in nmCRPC, mHSPC and in the treatment of cN1 or high-risk PC patients according to the STAMPEDE criteria and in high-risk BCR.[10,11,50]

The anticipation of hormonal agents will put the patient at greater risk for meaningful side effects, which could compromise quality of life, compliance with treatment, but even patients' outcome. The correct prevention and management of ADT associated toxicity, such as cardiovascular risk and bone health, can therefore improve survival and quality of life of patients as well as the efficacy if their anticancer treatments.[96] Therefore, physicians need to gain an adequate knowledge of potential side effects, their management and their prevention. Future research should focus on personalizing the use of these hormonal therapies in PC patients by identifying biomarkers that are able to predict response to hormonal agents. A correct use of these therapies would determine not only an improvement of the general health status of PC patient but also a considerable economic saving for national health care services considering their high costs.

To date, unfortunately, the only biomarker useful from a therapeutic point of view is the search for HRDs, which helps to select in ARPI pretreated patients, the use of the PARP-inhibitor olaparib, or in patients ARPI naïve patients, the combination of an ARPI + PARPi as first line treatment in mCRPC.[11,50] Several ongoing studies are evaluating new predictive biomarkers that could be potentially used in clinical practice. Their results are urgently awaited.

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CRediT authorship contribution statement

Fabio Turco: Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Consuelo Buttigliero:** Writing – review & editing, Writing – original draft, Validation, Supervision, Data curation, Conceptualization. **Marco Donatello Delcuratolo:** Data curation. **Silke Gillessen:** Data curation. **Ursula Maria Vogl:** Data curation. **Thomas Zilli:** Data curation. **Nicola Fossati:** Data curation. **Andrea Gallina:** Data curation. **Giovanni Farinea:** Data curation. **Rosario Francesco Di Stefano:** Data curation. **Mariangela Calabrese:** Data curation. **Isabella Saporita:** Data curation. **Veronica Crespi:** Data curation. **Stefano Poletto:** Data curation. **Erica Palesandro:** Data curation. **Massimo Di Maio:** Data curation. **Giorgio Vittorio Scagliotti:** Data curation. **Marcello Tucci:** Writing – review & editing, Writing – original draft, Data curation.

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