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Review – Prostate Cancer – Editor's choice

# Combination Therapies in Locally Advanced and Metastatic Hormone-sensitive Prostate Cancer

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**Abstract**

***Background and objective:*** The treatment landscape for advanced prostate cancer has evolved significantly over the past decade. The introduction of docetaxel, androgen receptor pathway inhibitors (ARPIs), poly(ADP-ribose) polymerase inhibitors, and targeted radionuclides has redefined the treatment paradigm, with a focus now on early treatment intensification through combination therapies. This narrative collaborative review summarises the current evidence of combination therapies in locally advanced and metastatic hormone-sensitive prostate cancer (mHSPC).
***Methods:*** We conducted a literature search up to November 2024. Search terms included "metastatic hormone-sensitive prostate cancer", "metastatic castration-sensitive prostate cancer", "locally advanced prostate cancer", "combination", "intensification", and "de-escalation". Articles were selected by the authors based on their scientific merit, clinical impact, and relevance to provide a summary of the evidence surrounding combination therapy in locally advanced prostate cancer and mHSPC.
***Key findings and limitations:*** A doublet approach with an androgen deprivation therapy (ADT) backbone and an ARPI is now considered the standard treatment for mHSPC, with a triplet regimen incorporating docetaxel considered in select subgroups. Similar efforts to improve survival in the high-risk localised and locally advanced disease setting have led to several trials evaluating the benefit of combination therapy in addition to standard-of-care surgery or radiotherapy with ADT. Continued improvements in survival have turned the focus to optimising patient selection for treatment intensification and, in some cases, de-escalation, with the goal of reducing unnecessary overtreatment and

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minimising harm from long-term treatment toxicity. This is particularly important with the integration of prostate-specific membrane antigen positron emission tomography, which has led to the earlier detection of metastatic disease.

***Conclusions and clinical implications:*** In select subgroups, early treatment intensification with combination therapy leads to improved survival, though it can be associated with long-term toxicity.



**ADVANCING PRACTICE**

**What does this study add?**

The treatment landscape for prostate cancer has evolved significantly over the past decade, with a focus now on early treatment intensification. This review summarises the key data evaluating combination therapy in locally advanced as well as metastatic hormone-sensitive prostate cancer. It aims to synthesise and provide the most up-to-date contemporary evidence to provide a concise resource for clinicians.

**Clinical Relevance**

The therapeutic landscape for advanced prostate cancer has undergone rapid and significant advancements over the past decade. This review brings together some of the leading trialists in prostate cancer research to provide a succinct yet comprehensive overview of pivotal studies shaping the current standard of care for locally advanced and metastatic hormone-sensitive prostate cancer. Notably, many trials have demonstrated survival benefits with specific combination therapies. However, increasing emphasis is being placed on refining patient selection and exploring de-escalation strategies to maximize therapeutic benefits while minimizing potential harms. This approach requires a comprehensive evaluation of existing data and a focus on ongoing trials that integrate biomarker assessments and precision molecular imaging. Associate Editor: Gianluca Giannarini, MD.

**Patient Summary**

We summarise the evidence for combination therapy for both locally advanced and metastatic hormone-sensitive prostate cancer. In select patient groups, intensification of treatment with multimodal or combination systemic therapy leads to improved outcomes. The benefits need to be balanced against the potential for increased long-term side effects and impact on quality of life.

## 1. Introduction

Prostate cancer is the second most common cancer diagnosed in men globally, with the incidence predicted to increase over the next decade [1]. Since the discovery of testosterone dependency in prostate cancer made by Huggins et al [2] in 1941, androgen deprivation therapy (ADT) has formed the mainstay of treatment for advanced disease. In some patients, ADT alone can lead to rapid and durable disease control. This can be long-lasting for some, but in others, a transition to metastatic castration-resistant prostate cancer (mCRPC) occurs, with a correspondingly poorer prognosis [3,4]. Addition of agents such as taxane chemotherapy, androgen receptor pathway inhibitors (ARPIs), poly(ADP-ribose) polymerase inhibitors (PARPi), and targeted radionuclides have improved overall survival (OS) in mCRPC [5]. Efforts have recently focussed on integrating these agents earlier in the prostate cancer disease course to enhance outcomes. A combination treatment approach is now considered standard for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC); however, questions remain regarding which patients benefit most from treatment intensification or, in some cases, de-escalation. Likewise, intensification strategies are being evaluated in locally advanced disease, underscoring the need to optimise patient selection for additional treatments that may lead to improved survival at the cost of potentially increased long-term toxicity. This narrative collaborative review summarises the data behind combination treatment approaches for locally advanced prostate cancer (LAPC) and mHSPC, and discusses on-going challenges and clinical considerations.

## 2. Methods

We searched, up to November 2024, annual proceedings of the online registries PubMed, EMBASE, Cochrane Library, ClinicalTrials.gov, European Society of Medical Oncology, and the American Society of Clinical Oncology for the following terms: ‘‘metastatic hormone-sensitive prostate cancer’’, ‘‘metastatic castration-sensitive prostate cancer’’, ‘‘locally advanced prostate cancer’’, ‘‘combination’’,

"intensification", and "de-escalation". Suitable articles for inclusion in this review were in English language and comprised meta-analyses, randomised controlled trials, retrospective studies, abstracts, and on-going clinical trials. Articles were selected by the co-first authors (A.A.A. and L. K.) and a senior author (K.F.) based on their scientific merit, clinical impact, and relevance to the title topic. The objectives of this review were to firstly summarise the data supporting combination therapies in both LAPC and mHSPC, while also highlighting limitations and relevant negative studies, clinical challenges, and on-going clinical trials. The remaining coauthors then reviewed the manuscript and provided their expert opinion.

## 3. Results

### 3.1. *Metastatic hormone-sensitive prostate cancer*

Management of mHSPC has been transformed over the past decade as the armamentarium of available therapies has grown steadily. Prior to 2014, ADT (via luteinising hormone-releasing hormone analogues or bilateral orchiectomy)—either alone or in combination with earlier generations of androgen receptor (AR) antagonists—was the only systemic treatment offered to patients with mHSPC outside of clinical trials [6]. The treatment of metastatic prostate cancer has since undergone a paradigm shift, with enhanced risk stratification based on volume and timing of metastatic disease and an emphasis on intensifying treatment earlier in the disease course. As such, several novel agents initially approved for use in mCRPC now have demonstrable survival benefits in mHSPC [5].

#### 3.1.1. *ADT + docetaxel*

Docetaxel was the first systemic therapy utilised in addition to ADT that improved survival in patients with mHSPC (Table 1). The GETUG-AFU15 trial evaluated 385 patients who received ADT ± up to nine cycles of docetaxel (75 mg/m$^2$ every 3 wk) for mHSPC. In a post hoc analysis (median follow-up 83.9 mo) [7], there was a 13.5 mo improvement in the point estimate of median OS in the docetaxel arm, although this was not statistically significant (62.1 vs 48.6 mo, hazard ratio [HR] 0.88 [95% confidence interval {CI} 0.68–1.14], $p$ = 0.3). The CHAARTED (E3805) trial similarly evaluated whether the addition of docetaxel (75 mg/m$^2$ every 3 wk for six cycles) to ADT resulted in improved survival in 790 patients with mHSPC. This study prospectively defined disease volume criteria (with high volume defined as the presence of visceral metastases, or four or more bone metastases, with at least one being outside the axial skeleton) and stratified patients by high and low volume. Improved OS was demonstrated in the overall combination arm (57.6 vs 47.2 mo, HR 0.72, [95% CI 0.59–0.89], $p$ = 0.0018) and was more pronounced in patients with high-volume disease (51.2 vs 34.4 mo, HR 0.63 [95% CI 0.50–0.79], $p$ = 0.001). While there was a modest but not significant OS benefit in synchronous low-volume disease (HR 0.86 [95% CI 0.52–1.42], $p$ = 0.56), no benefit was observed for those with metachronous low-volume disease (HR 1.26 [95% CI 0.60–2.6], $p$ = 0.86) [8].

Arm C of the multiarm, multistage platform STAMPEDE protocol further confirmed a survival benefit with the early addition of docetaxel to ADT for patients with mHSPC (median OS 59.1 vs 43.1 mo [arm A], HR 0.81 [95% CI 0.69–0.95], $p$ = 0.009) [9]. In contrast to CHAARTED, there was no differential effect on survival when considering the volume of metastatic disease at diagnosis (high-volume disease: HR 0.81 [95% CI 0.64–1.02], $p$ = 0.064; low-volume disease: HR 0.76 [95% CI 0.54–1.07], $p$ = 0.107). A subsequent individual patient meta-analysis of the three above studies found that a meaningful OS benefit of adding early docetaxel to ADT was seen only in patients with synchronous high-volume mHSPC (HR 0.72 [95% CI 0.62–0.84]) [10]. Consequently, docetaxel in combination with ADT became the standard of care (SOC) for patients with high-volume synchronous mHSPC who are fit for chemotherapy. Patient fitness for chemotherapy, however, should be assessed individually, considering age, performance status, comorbidities, and nutritional status.

#### 3.1.2. *ADT + ARPI—the new standard for mHSPC*

ARPIs are now considered the SOC in combination with ADT for mHSPC (Fig. 1). Two pivotal phase 3 trials (LATITUDE and STAMPEDE [arm G]) demonstrated an OS benefit when adding abiraterone acetate (hereafter referred to as "abiraterone"), a CYP17 inhibitor, in combination with prednisolone, to ADT in patients with mHSPC (HR for median OS 0.66 and 0.62, respectively) [11,12]. These studies, however, enrolled differing patient populations. The LATITUDE trial evaluated the addition of abiraterone to ADT in patients with high-risk (defined as having at least two out of three risk factors: three or more bone lesions on bone scan, visceral metastases, and a Gleason score of $\geq$8) synchronous mHSPC. In contrast, arm G of the STAMPEDE trial included all mHSPC patients and reported a high degree of overlap using the LATITUDE high-risk inclusion criteria or high-volume status [13].

Similar survival improvements have been demonstrated with enzalutamide and apalutamide in mHSPC (Table 1). The ENZAMET trial was an international phase 3 study evaluating the addition of enzalutamide 160 mg daily to the SOC for patients with mHSPC. Notably, this was compared with a more active control arm of ADT plus a first-generation nonsteroidal AR antagonist (NSAA) such as bicalutamide, rather than ADT plus placebo as used in preceding studies [14]. Patients were also allowed to receive concurrent docetaxel given at the investigator's discretion following a protocol amendment after the CHAARTED results were presented. After a median follow-up of 68 mo, OS was longer in the enzalutamide arm in the intention-to-treat (ITT) cohort (5-yr OS 67% vs 57%, HR 0.70 [95% CI 0.58–0.84], $p \leq 0.0001$), with a survival benefit persisting on subgroup analysis for patients with low-volume (HR 0.54 [95% CI 0.39–0.74]), high-volume (HR 0.79 [95% CI 0.63–0.98]), synchronous (HR 0.70 [95% CI 0.56–0.87]), and metachronous (HR 0.71 [95% CI 0.52–0.98]) metastatic disease. Similar findings were also demonstrated in the ARCHES trial (4-yr OS 71% vs 57%, HR 0.66 [95% CI 0.53–0.81], $p \leq 0.001$), including a consistent benefit with enzalutamide regardless of disease volume [15,16]. In this study, however, patients

**Table 1 – Pivotal trials evaluating doublet therapy in metastatic hormone-sensitive prostate cancer**

| | GETUG-AFU15 [6,7] | CHAARTED [8] | STAMPEDE (arm C) [9] | LATITUDE [11] | STAMPEDE (arm G) [12] | ENZAMET [16] | ARCHES [17] | TITAN [19] | ARANOTE [29] | STAMPEDE (arm H) [24] |
|---|---|---|---|---|---|---|---|---|---|---|
| Intervention arm | ADT + docetaxel (75 mg/m$^2$ Q3W × up to 9 cycles) | ADT + docetaxel (75 mg/m$^2$ Q3W × 6 cycles) | ADT + docetaxel (75 mg/m$^2$ Q3W × 6 cycles) | ADT + abiraterone 1000 mg daily + prednisolone 5 mg daily | ADT + abiraterone 1000 mg daily + prednisolone 5 mg daily | ADT + enzalutamide 160 mg daily | ADT + enzalutamide 160 mg daily | ADT + apalutamide 240 mg daily | ADT + darolutamide 600 mg twice daily | ADT + prostate radiotherapy |
| Control arm | ADT | ADT | ADT (arm A) | ADT + placebo | A (arm A) | ADT + NSAA | ADT + placebo | ADT + placebo | ADT + placebo | ADT |
| Patients enrolled | 385 | 790 | 1776 | 1199 | 1917 (1002 with mHSPC) | 1125 | 1150 | 1052 | 669 | 2061 (1939 analysed for efficacy) |
| Synchronous metastatic disease (%) | 71 | 73 | 58 | 100 | 49 | 61 | 67 | 81 | 72 | 100 |
| Metachronous metastatic disease (%) | 28 | 27 | 3 | 0 | 2 | 28 | 15 | 14 | 22 | 0 |
| Docetaxel allowed | NA | NA | NA | No | No | Yes—concurrent | Yes—prior | Yes—prior | No | Yes |
| Median follow-up (mo) | 83.9 | 53.7 | 78.2 | 51.8 | 96 | 68 | 44.6 | 44 | 25 | 37 |
| ITT cohort (interventional arm vs control arm): median OS (mo) | 62.1 vs 48.6 | 57.6 vs 47.2 | 59.1 vs 43.1 | 53.3 vs 36.5 | 76.6 vs 45.7 | NR vs NR<br>60-mo OS: 67% vs 57% | NR vs NR<br>48-mo OS: 71% vs 57% | NR–52.2<br>48-mo OS: 65.1% vs 51.8% | NR vs NR<br>24-mo OS: 79.8% vs 75.5% | 48 vs 46<br>36-mo OS: 65% vs 62% |
| ITT cohort: median OS, HR (95% CI), *p* value | 0.88 (95% CI 0.68–1.14), $p = 0.3$ | 0.72 (95% CI 0.59–0.89), $p = 0.0018$ | 0.81 (95% CI 0.69–0.95), $p = 0.009$ | 0.66 (95% CI 0.56–0.78), $p \leq 0.0001$ | 0.62 (95% CI 0.53–0.74), $p \leq 0.0001$ | 0.70 (95% CI 0.58–0.84), $p \leq 0.0001$ | 0.66 (95% CI 0.53–0.81), $p \leq 0.001$ | 0.65 (95% CI 0.52–0.79), $p \leq 0.0001$ | 0.81 (95% CI 0.59–1.12) | 0.92 (95% CI 0.80–1.06), $p = 0.266$ |
| High-volume disease: median OS, HR | 0.78 (95% CI 0.56–1.09), $p = 0.14$ | 0.63 (95% CI 0.50–0.79), $p < 0.001$ | 0.81 (95% CI 0.64–1.02), $p = 0.064$ | 0.62 (95% CI 0.52–0.74), $p \leq 0.0001$ | 0.66 (95% CI 0.54–0.81) | 0.79 (95% CI 0.63–0.98) | 0.66 (95% CI 0.52–0.83) | 0.70 (95% CI 0.56–0.88) | 0.80 (95% CI 0.57–1.13) | 1.07 (95% CI 0.90–1.28), $p = 0.420$ |
| Low-volume disease: median OS, HR | 1.02 (95% CI 0.67–1.55), $p = 0.9$ | 1.04 (95% CI 0.70–1.55), $p = 0.68$ | 0.76 (95% CI 0.54–1.07), $p = 0.107$ | 0.72 (95% CI 0.47–1.10), $p = 0.1242$ | 0.58 (95% CI 0.44–0.75) | 0.54 (95% CI 0.39–0.74) | 0.66 (95% CI 0.43–1.03) | 0.52 (95% CI 0.35–0.79) | 0.90 (95% CI 0.38–2.13) | 0.68 (95% CI 0.52–0.90), $p = 0.007$ |

ITT= intention-to-treat; ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; mHSPC = metastatic hormone-sensitive prostate cancer; NR = not reached; NSAA = nonsteroidal androgen receptor antagonist; OS = overall survival; Q3W = 3 weekly; NA = not applicable.

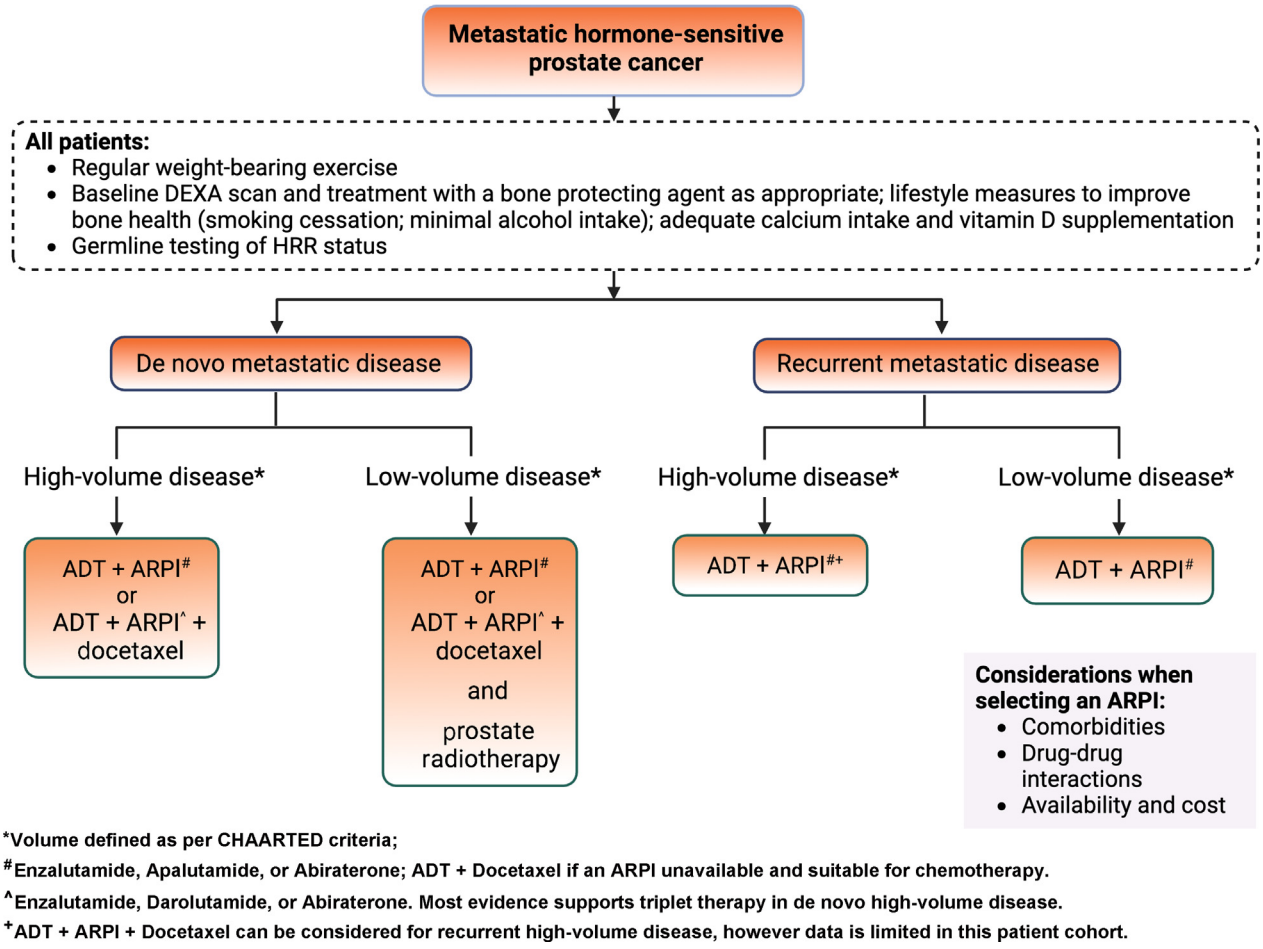


**Fig. 1 – Recommended treatment algorithm for the treatment of metastatic hormone-sensitive prostate cancer. ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; DEXA = dual-energy x-ray absorptiometry; HRR = homologous recombination repair. Created with BioRender.com.**

could have received docetaxel prior to commencing enzalutamide, but not concurrently. The TITAN study evaluated the combination of apalutamide 240 mg daily to ADT for patients with mHSPC and reported similar findings [17]. Importantly, despite additive androgen blockade, overall health-related quality of life was maintained in the combination arm across these studies [18–20]. The ARANOTE trial demonstrated significantly longer radiographic progression-free survival (rPFS) with the addition of darolutamide to ADT in patients with mHSPC (HR 0.54 [95% CI 0.41–0.71], $p < 0.0001$), though no improvement in OS has so far been observed [21]. Importantly, rPFS is the solitary primary endpoint of the ARANOTE study and is not a validated surrogate endpoint for OS in advanced prostate cancer [22]. Following these studies, docetaxel and various ARPIs have been approved for use in mHSPC (Fig. 1).

### 3.1.3. *Which ARPI to select?*

Which ARPI to use depends on a patient's current symptoms, comorbidities, and concurrent medications. For example, abiraterone should be avoided in a patient with significant cardiovascular disease or poorly controlled diabetes, given the risk of mineralocorticoid excess and the need for concurrent prednisolone. Similarly, in patients with a history of seizures, enzalutamide or apalutamide is contraindicated. Darolutamide has the least drug-drug interactions, with some statins as the main considerations, although it requires twice daily dosing and has not yet demonstrated an OS benefit over ADT monotherapy in the ARANOTE trial.

### 3.1.4. *ADT + ARPI + docetaxel—who benefits from triplet therapy?*

Triplet therapy incorporating ADT with docetaxel and an ARPI has also been evaluated in several trials (Table 2). The PEACE-1 trial utilised a 2 × 2 factorial design to evaluate the combination of the SOC (ADT ± docetaxel) with abiraterone with prednisolone ± prostate radiotherapy in patients with synchronous mHSPC. This study enrolled a population of patients associated with poor prognostic features, with 63% of patients having high-volume disease and 11% having visceral metastases. The primary endpoint of rPFS was prolonged by 2.5 yr with the addition of abiraterone to ADT + docetaxel when compared with ADT + docetaxel alone (median rPFS 4.5 vs 2 yr, HR 0.50 [95% CI 0.40–0.62], $p \leq 0.0001$), and the benefit was maintained irrespective of disease volume. Improved OS was observed in the ITT cohort (median OS not reached [NR] vs 4.5 yr, HR 0.75 [95%

**Table 2 – Pivotal trials evaluating triplet therapy in metastatic hormone-sensitive prostate cancer**

| | ENZAMET [16] | PEACE-1 [25] | ARASENS [26] |
|---|---|---|---|
| Intervention arm | ADT ± docetaxel (75 mg/m$^2$ Q3W) + enzalutamide 160 mg daily | ADT ± docetaxel (75 mg/m$^2$ Q3W) + abiraterone 1000 mg daily and prednisolone 5 mg daily | ADT + docetaxel (75 mg/m$^2$ Q3W) + darolutamide 600 mg BD |
| Control arm | ADT ± docetaxel (75 mg/m$^2$ Q3W) | ADT ± docetaxel (75 mg/m$^2$ Q3W) | ADT + docetaxel (75 mg/m$^2$ Q3W) |
| Patients enrolled | 1125 | 1173 | 1306 |
| Patients treated with docetaxel (%) | 43 | 60.5 | 100 |
| Synchronous metastatic disease (%) | 61 | 100 | 86.1 |
| High-volume disease (%) | 52 | 64.2 | 77 |
| Median follow-up (mo) | 68 | 52.9 (for OS) | 43.7 |
| Primary endpoint | OS | OS, rPFS | OS |
| ITT cohort (ADT + docetaxel only; interventional arm vs control arm): median OS (mo) | Median NR (>60 mo for both arms) | NR vs 53.2 | NR vs 48.9 |
| | Synchronous: NR vs 62.0 mo | | |
| | Metachronous: NR vs NR | | |
| ITT cohort (ADT + docetaxel only): HR (OS; 95% CI), *p* value | Overall: 0.82 (0.63–1.06) | 0.75 (0.59–0.95), $p = 0.017$ | Overall: 0.68 (0.57–0.80), $p \leq 0.001$ |
| | Synchronous: 0.73 (0.55–0.99) | | Synchronous: 0.70 (0.57–0.85) |
| | Metachronous: 1.10 (0.65–1.86) | | Metachronous: 0.70 (0.39–1.24) |
| High-volume disease (ADT + docetaxel only): HR (OS) | 0.87 (0.66–1.17) | 0.72 (0.55–0.95), $p = 0.019$ | 0.68 (0.57–0.82) |
| Low-volume disease (ADT + docetaxel only): HR (OS) | 0.61 (0.33–1.10) | 0.83 (0.50–1.39), $p = 0.66$ | 0.68 (0.41–1.13) |

ADT = androgen deprivation therapy; BD = twice daily; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; NR = not reached; OS = overall survival; Q3W = 3 weekly; rPFS = radiographic progression-free survival.

CI 0.59–0.95], $p = 0.017$), though remained statistically significant only for patients with high-volume disease (median OS 5.1 vs 3.5 yr, HR 0.72 [95% CI 0.55–0.95], $p = 0.019$) on a subgroup analysis. There was no clear significant OS benefit for patients with low-volume disease at the first analysis, with longer follow-up awaited to further elucidate the magnitude of benefit in this cohort [23]. The phase 3 ARASENS trial evaluated the addition of darolutamide to ADT and docetaxel, compared with ADT and docetaxel alone, in patients with mHSPC. A majority (86%) of the patients had synchronous metastatic disease, 17.5% had visceral metastases, and 77% had high-volume disease. A significant improvement in OS was observed with the addition of darolutamide (median OS NR vs 48.9 mo, HR 0.68 [95% CI 0.57–0.80], $p \leq 0.001$) [24]. A clear benefit was seen in the high-volume disease subgroup (HR 0.69 [95% CI 0.57–0.82]), while median OS remains immature in the low-volume subgroup (HR 0.68 [95% CI 0.41–1.13]). Of note, the survival analysis based on disease volume was performed retrospectively in a secondary analysis. Of the 43% of patients who received docetaxel in addition to either enzalutamide or an NSAA with ADT in the ENZAMET trial, 61% had high-volume disease and 72% had synchronous metastatic disease [25]. There was no statistically significant OS improvement in the entire subgroup (both synchronous and metachronous, high- and low-volume) of patients who received docetaxel (HR 0.82 [95% CI 0.63–1.06]). However, when the analysis is restricted to patients with synchronous disease, the HR for OS was consistent with the PEACE-1 and ARASENS trials (0.73 [95% CI 0.55–0.99]) [14]. Overall, while the PEACE-1, ARASENS, and ENZAMET trials show a benefit for triplet treatment over ADT + docetaxel doublet in patients with synchronous mHSPC, there are no data comparing this approach with an ADT + ARPI doublet. As such, the role of triplet therapy remains uncertain, with the benefit possibly apparent in select patients with synchronous, high-volume metastatic disease (Fig. 1).

Though recent data suggest that real-world utilisation of both doublet and triplet therapy for mHSPC has increased [26], many patients with mHSPC still receive ADT alone [27]. The primary reasons for underutilisation of intensified treatment identified include concerns about tolerance, efficacy, and affordability [28]. The PEACE-6 trial (NCT04916613) aims to address the question of tolerance by evaluating whether the addition of darolutamide to ADT in patients with synchronous mHSPC with limited functional ability still leads to improved survival. Geographic variation in uptake of combination therapy also occurs [27], with low uptake usually being a reflection of poor access to speciality care or financial limitations. Ongoing education of health care providers and improving access to treatment are vital steps towards optimising the implementation of intensified therapy.

#### 3.1.5. *Radiation to the prostate in the metastatic setting*

Radiotherapy to the prostate is recommended in select situations in mHSPC and is often combined with intensification of systemic therapies. The PEACE-1 trial demonstrated that the addition of prostate radiotherapy to SOC + abiraterone in the low-volume disease cohort was associated with improved rPFS (median rPFS 7.5 vs 4.4 yr, HR 0.65 [95% CI 0.36–1.19], $p = 0.02$). Though there was no improvement in OS so far in this cohort, significant improvements in the time to serious genitourinary events

were observed ($p$ = 0.0006). Arm H of the STAMPEDE trial prospectively compared the SOC treatment (ADT ± docetaxel) with and without prostate radiotherapy and did not demonstrate an OS benefit in the ITT population (HR 0.92 [95% CI 0.80–1.06, $p$ = 0.266]; Table 1) [29]. A survival benefit was seen, however, in the subgroup of patients with low-volume disease (HR 0.68 [95% CI 0.52–0.90]). Consistent findings were also demonstrated in the HORRAD trial, which compared ADT with and without concurrent radiotherapy to the prostate in patients with mHSPC. No significant OS benefit was observed in the ITT population (HR 0.90 [95% CI 0.70–1.14]); however, a trend towards improved survival was seen in those with fewer than five bone metastases (HR 0.68 [95% CI 0.42–1.10]) [30], though this low-volume group only made up 17% of the ITT cohort. In the STOPCAP meta-analysis, prostate irradiation in addition to ADT leads to an OS benefit in patients with synchronous low-volume disease [31]. The role of a cytoreductive prostatectomy in the metastatic setting on both survival and quality of life outcomes is being evaluated in the SWOG S1802 (NCT03678025) and SIMCAP (NCT03456843) trials.

### 3.2. Locally advanced prostate cancer

Given the high risk of disease recurrence and the emergence of multiple combination approaches in mHSPC, attention has turned to evaluating such approaches in high-risk, very-high-risk, and unfavourable intermediate-risk localised prostate cancer or LAPC. D'Amico et al [32] proposed the first risk stratification system for localised prostate cancer in 1998. This system considered the initial prostate-specific antigen (PSA) level, clinical T stage (based on the American Joint Committee on Cancer staging system, using digital rectal examination), and biopsy Gleason score to divide patients into those having low-, intermediate-, or high-risk non-metastatic prostate cancer with an associated risk of disease recurrence. The risk stratification system has since been developed and refined further [33], and further divides disease into localised prostate cancer (very–low-risk to very-high-risk cases) and LAPC (cT3-T4 or involved lymph nodes) [34]. Over 20% of patients with localised prostate cancer have high-risk or very-high-risk disease [35], and a further 10–15% of patients have LAPC with involved regional lymph nodes [36]. High-risk and very-high-risk disease has a significant recurrence rate after curative-intent local therapy, accounting for two-thirds of prostate cancer–specific mortality at 10 yr from diagnosis [37]. High-dose radiotherapy to the prostate ± regional lymph nodes with a course of adjuvant ADT is considered the SOC for patients with unfavourable intermediate-risk disease (4–6 mo of ADT) to high-risk disease (2–3 yr of ADT) [38]. Salvage radiotherapy may be offered for biochemical recurrence following a radical prostatectomy, though the benefit of ADT in this setting remains unclear with mixed findings from trials regarding a metastasis-free survival (MFS) and OS benefit. Further studies should evaluate the role of ADT specifically in patients at a high risk of recurrence, noting that the RADICALS-HD trial did not risk stratify patients [39]. Importantly, current staging systems are based on conventional rather than more sensitive next-generation imaging modalities such as prostate-specific membrane antigen positron emission tomography (PSMA-PET) or whole-body diffusion-weight magnetic resonance imaging.

#### 3.2.1. Combination therapy for non-metastatic prostate cancer

Although some studies have demonstrated improvements in disease-free survival with the addition of docetaxel to standard treatment for high-risk non-metastatic prostate cancer, this has not translated into an OS benefit, and therefore, docetaxel is not recommended in this setting [40,41].

Conversely, there is growing evidence to support the use of an ARPI in addition to ADT and standard local therapy in select high-risk patients categorised as having non-metastatic disease on conventional imaging. A meta-analysis of two arms of the platform STAMPEDE trial evaluated the addition of an ARPI to patients with very-high-risk non-metastatic prostate cancer who received ADT for 3 yr in addition to local radiotherapy for node-negative disease (mandated for node-negative disease, encouraged for node-positive disease) [42]. In the experimental arm of the first trial, abiraterone was given for 2 yr if radiotherapy was administered (71% of patients) and continued otherwise until disease progression. In the second trial, enzalutamide was given in addition to abiraterone. Patients in this analysis were at a very high risk of recurrence, with a median PSA at baseline between 30 and 40 ng/ml, and approximately 40% had involved lymph nodes. With a median follow-up of 72 mo, a significant improvement in MFS and OS was observed with the addition of abiraterone to local radiotherapy and ADT (MFS: HR 0.54 [95% CI 0.43–0.68]; OS: HR 0.63 [95% CI 0.48–0.82]). Trials evaluating other combinations with ARPIs, radiotherapy, and ADT are on-going (Table 3).

Baseline data across these studies are not directly comparable as these include patient populations of differing risks, particularly when compared with the higher-risk STAMPEDE cohort. For example, 28%, 13%, and 11% had cN1 stage disease across the DASL-HiCAP (darolutamide) [43,44], ATLAS (apalutamide) [45,46], and ENZARAD (enzalutamide) [47] trials, respectively. In DASL-HiCAP and ENZARAD, 23% and 25% of patients had a PSA value of >20 ng/ml, and the median PSA in the ATLAS trial was 6.3 ng/ml. These trials will importantly help refine which patients should be considered for intensified treatment with an ARPI beyond the STAMPEDE criteria.

The EMBARK trial has already established enzalutamide as a new SOC for patients with biochemical recurrence following radical prostatectomy [48]. Several on-going trials (Table 3) are evaluating whether the addition of an ARPI either before or after radical prostatectomy (±lymph node dissection) for high-risk prostate cancer improves outcomes. The phase 2 ARNEO trial compared neoadjuvant apalutamide (240 mg daily) plus degarelix with placebo for 3 mo prior to radical prostatectomy. The primary endpoint was the proportion of patients with minimal residual disease, defined as $\leq$0.25 $cm^3$ at final pathology, and was higher in the experimental arm (38% vs 9.1%, relative risk = 4.2, $p$ = 0.002).

**Table 3 – On-going combination trials in locally advanced prostate cancer**

| Intervention | Trial | Trial number | Phase | Intervention | Primary endpoint | Current status |
|---|---|---|---|---|---|---|
| ARPI + ADT + RT | DASL-HiCaP | NCT04136353 | 3 | Darolutamide 600 mg BD + ADT for 24 mo + RT (primary or salvage setting) vs Placebo + ADT for 24 mo + RT | MFS | Active, not recruiting |
| | ATLAS | NCT02531516 | 3 | Apalutamide 240 mg daily + ADT for 30 mo + bicalutamide-placebo for 4 mo + RT vs apalutamide-placebo + ADT for 30 mo + bicalutamide 50 mg daily for 4 mo + RT | MFS | Active, not recruiting |
| | ENZARAD | NCT02446444 | 3 | Enzalutamide 160 mg daily + ADT for 24 mo + RT vs NSAA for 6 mo + ADT for 24 mo + RT | MFS | Active, not recruiting |
| | PEACE7 | NCT06625970 | 3 | ADT + conventional RT to prostate + pelvis (SOC) vs SOC + prostate SBRT vs SOC + darolutamide vs SOC + prostate SBRT + darolutamide (2 × 2 design) | MFS | Not yet recruiting |
| Cabazitaxel + ADT + RT | PEACE2 | NCT01952223 | 3 | ADT for 3 yr + RT to prostate + pelvis vs ADT for 3 yr + cabazitaxel × 4 cycles + RT to prostate only vs ADT for 3 yr + cabazitaxel × 4 cycles + RT to prostate and pelvis vs ADT for 3 yr + RT to prostate only | PFS | Active, not recruiting |
| ARPI + ADT + RP | PROTEUS | NCT03767244 | 3 | Apalutamide 240 mg daily + ADT for 12 mo with RP + pLND performed after 6 mo vs placebo + ADT for 12 mo with RP + pLND performed after 6 mo | MFS<br>Percentage of patients with pCR | Active, not recruiting |
| | ARNEO | NCT03080116 | 2 | Apalutamide 240 mg daily + degarelix for 3 mo followed by RP + pLND vs placebo + degarelix for 3 mo followed by RP + pLND | MRD | Active, not recruiting |
| | INNOVATE | NCT04134260 | 3 | RP followed by apalutamide 240 mg daily + ADT for 24 mo + salvage RT to prostate bed and pelvis vs RP followed by ADT for 24 mo + salvage RT to prostate bed and pelvis | MFS | Recruiting |
| ARPI ± PARPi + RP | ASCERTAIN | NCT05938270 | 1 | Darolutamide 600 mg BD alone for 3 wk followed by RP vs darolutamide 600 mg BD + saruparib 60 mg daily for 3 wk followed by RP vs saruparib 60 mg daily alone for 3 wk followed by RP | Fold change in % γH2AX-positive cells from baseline value in tumour samples | Recruiting |
| [$^{177}$Lu]Lu-PSMA + RP | LuTectomy | NCT04430192 | 1/2 | [$^{177}$Lu]Lu-PSMA-617 5GBq × 1 or 2 cycles Q6W + RP | Absorbed radiation dose in the prostate and involved lymph nodes (Gy) | Active, not recruiting |

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; BD = twice daily; MRD = minimal residual disease; MFS = metastasis-free survival; NSAA = nonsteroidal androgen receptor antagonist; PARPi = poly(ADP-ribose) polymerase inhibitor; pCR = pathological complete response; PFS = progression-free survival; pLND = pelvic lymph node dissection; PSMA = prostate-specific membrane antigen; Q6W = 6 weekly; RP = radical prostatectomy; RT = radiotherapy; SBRT = stereotactic body radiotherapy; SOC = standard of care.

**Table 4 – Current combination phase 3 trials in metastatic hormone-sensitive prostate cancer (October 2024)**

| Intervention | Trial | Trial number | Treatment arms | Primary endpoint | Current status |
|---|---|---|---|---|---|
| PARPi + ARPI (+ADT) | AMPLITUDE | NCT04497844 | Niraparib + abiraterone 1000 mg daily + prednisolone 5 mg daily vs placebo + abiraterone 1000 mg daily + prednisolone 5 mg daily | rPFS | Active, not recruiting |
| | TALAPRO-3 | NCT04821622 | Talazoparib 0.5 mg daily + enzalutamide 160 mg daily vs placebo + enzalutamide 160 mg daily | rPFS | Active, not recruiting |
| | EvoPAR-Prostate01 | NCT06120491 | Saruparib 60 mg daily + ARPI (physician's choice) vs placebo + ARPI (physician's choice) (HRR selected) | rPFS | Recruiting |
| | STAMPEDE2 (treatment arm N) | NCT06320067 | Niraparib 200 mg daily and abiraterone 1000 mg daily with prednisolone 5 mg daily + SOC (ADT ± docetaxel ± prostate RT) vs SOC (ADT + apalutamide 240 mg daily ± docetaxel ± prostate RT) | rPFS, OS | Recruiting |
| AKTi + ARPI (+ADT) | CAPItello-281 | NCT04493853 | Capivasertib 400 mg BD (4 d on/3 d off) + abiraterone 1000 mg daily + prednisolone 5 mg daily vs placebo + abiraterone 1000 mg daily + prednisolone 5 mg daily | rPFS | Active, not recruiting |
| [$^{177}$Lu]Lu-PSMA + ARPI (+ ADT) | PSMAddition | NCT04720157 | Six cycles of [$^{177}$Lu]Lu-PSMA-617 7.4 GBq Q6W + SOC (ARPI + ADT) vs SOC alone | rPFS | Active, not recruiting |
| | STAMPEDE2 (treatment arm P) | NCT06320067 | [$^{177}$Lu]Lu-PSMA-617 7.4 GBq on day 1 and day 8 Q6W for up to 3 cycles + SOC (ADT + ARPI ± docetaxel ± prostate RT) vs SOC alone | rPFS, OS | Recruiting |
| SABR + other therapies | PSMA-DC | NCT05939414 | SABR followed by 4 cycles of [$^{177}$Lu]Lu-PSMA-617 vs SABR alone | MFS | Recruiting |
| | PEACE-6 (Oligo-PRESTO) | NCT04115007 | SABR + SOC (ADT ± ARPI ± docetaxel ± prostate RT) vs SOC alone | CRPC-free survival | Recruiting |
| | POPSTAR II | NCT05560659 | SABR + 2 cycles of [$^{177}$Lu]Lu-PSMA-617 vs SABR alone | bPFS | Recruiting |
| | STAMPEDE2 (treatment arm S) | NCT06320067 | SABR in oligometastatic prostate cancer + SOC (ADT + ARPI ± docetaxel ± prostate RT) vs SOC (ADT + ARPI ± docetaxel ± prostate RT) | rPFS, OS | Recruiting |

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; BD = twice daily; bPFS = biochemical progression-free survival; CRPC = castration-resistant prostate cancer; HRR = homologous recombination repair; MFS = metastasis-free survival; OS = overall survival; Q6W = 6 weekly; rPFS = radiographic progression-free survival; RT = radiotherapy; SABR = stereotactic ablative body radiotherapy; SOC = standard of care.

## 4. Discussion

The mHSPC landscape is set to evolve further in coming years (Table 4). Several studies are comparing an ADT + ARPI + PARPi combination with ADT + ARPI alone in mHSPC [49–52]. Preclinical data have demonstrated a synergistic effect with coinhibition of PARP and AR, and this has translated to improved progression-free survival (PFS) when evaluated in the mCRPC setting—primarily for patients with a germline or somatic *BRCA* mutation, but also in the overall homologous recombination repair–mutated cohort [53–55]. Other agents currently being evaluated include targeted radioligand therapy such as [$^{177}$Lu]Lu-PSMA-617. The phase 2 UpFrontPSMA trial demonstrated a higher rate of achieving an undetectable PSA level by 48 wk (41% vs 16%, odds ratio 3.88 [95% CI 1.61–9.38], $p$ = 0.002), improved rPFS (HR 0.58, [95% CI 0.32–1.05], $p$ = 0.067), and PSA-PFS (31 vs 20 mo; HR 0.60 [95% CI 0.37–0.98], $p$ = 0.039) with the addition of two cycles of [$^{177}$Lu]Lu-PSMA-617 to six cycles of upfront docetaxel and ADT for synchronous high-volume mHSPC [56]. The PSMAddition trial will further inform the role of [$^{177}$Lu]Lu-PSMA when combined with ADT + an ARPI in mHSPC. For oligometastatic mHSPC, several studies are exploring the concept of metastasis-directed therapy with stereotactic ablative body radiotherapy either in combination with ADT or as a means of delaying commencement of ADT, with or without concurrent [$^{177}$Lu]Lu-PSMA-617.

Ultimately, the choice of first-line therapy is arguably one of the most critical decisions in a patient's prostate cancer journey. Biomarkers are urgently needed to optimise the risk stratification of patients and better inform treatment decisions. Improved patient selection for a more intensified regimen will aid in reducing unnecessary treatment toxicity. In addition to clinicopathological factors, several emerging molecular biomarkers have been identified through transcriptomics, genomics, and artificial intelligence. Circulating tumour DNA fraction can be both predictive and prognostic in advanced prostate cancer [57,58], and an analysis of the genomic profile provides additional insights. A gene expression signature correlating with a luminal subtype is associated with a benefit from an ARPI [59], as is a mutation in the *SPOP* gene [60], and luminal B may be predictive of a survival benefit with docetaxel [61]. Conversely, a basal subtype is associated with worse survival and a diminished response to ARPIs [59]. Several other mutations have been evaluated and confer additional prognostic information; however, on-going research is needed to identify predictive biomarkers. Decipher is a 22-gene genomic test that is used to risk stratify newly diagnosed prostate cancer [62] and is currently being evaluated prospectively to inform treatment choice in several studies (PREDICT-RT, NCT04513717; GUIDANCE, NCT05050084).

A consequence of adopting an upfront combination approach for mHSPC is fewer treatment options upon disease progression. Further, the optimal treatment sequence following first-line therapy is not clear, with most trials in the mCRPC setting being conducted in ARPI-naïve patients. Additionally, the integration of next-generation imaging, such as the PSMA-PET scan, presents further questions about the optimal treatment approach. Patients with advanced disease identified on PSMA-PET but with normal conventional imaging were not evaluated in the majority of the pivotal trials described above. A discord exists between the best imaging modality to use to assess the prostate cancer disease burden, with uptake of PSMA-PET increasing in the real-world but conventional imaging being used for most pivotal clinical trials. More contemporary trials now allow patients to be assessed with PSMA-PET imaging, which will hopefully (with revised PET-based PFS endpoints) provide important evidence to support clinical decisions.

Finally, as the prognosis for most patients with mHSPC now extends beyond 5 yr, the prevention of long-term treatment-related toxicities and disease-related complications warrants closer attention. Long-term suppression of testosterone with ADT increases significantly the risk of metabolic syndrome, cognitive decline, bone deficiency, and fractures [63,64]. The risk of fractures, in particular, can be mitigated by ensuring adequate calcium and vitamin D supplementation, encouraging regular exercise, smoking cessation, and limiting alcohol intake. Bone mineral density should be monitored with regular dual-energy x-ray absorptiometry scans and bone-protecting agents commenced as indicated [5].

Balancing extended survival with long-term toxicity and quality of life is paramount, and as such treatment de-escalation may be appropriate in a subgroup of patients. Most trials continue treatment until disease progression, exposing patients, in some cases, to years of chronic side effects. Identification of prognostic or predictive biomarkers may also help identify patients suitable for a de-escalation approach to treatment. Multiple mHSPC trials have shown that achieving an undetectable PSA level (typically $\leq$0.2 ng/ml at 6 mo) is associated with improved OS outcomes [65–68]. Several on-going trials are currently evaluating de-escalation strategies for patients who are identified as exceptional responders based on PSA kinetics (De-escalate [NCT05974774] and LIBERTAS [NCT05884398]).

## 5. Conclusions

The treatment landscape for prostate cancer continues to evolve at a rapid pace with impressive survival gains achieved over the past decade. Earlier treatment intensification through combination therapies has led to improved survival in select patients, though it can be associated with long-term toxicity. As patients live longer, clinicians need to be aware of the long-term risks of androgen suppression and implement strategies to mitigate these where possible.

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