Oncol Ther
https://doi.org/10.1007/s40487-020-00119-z

REVIEW

Metastatic Hormone-Sensitive Prostate Cancer (mHSPC): Advances and Treatment Strategies in the First-Line Setting

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Received: May 5, 2020

ABSTRACT

The treatment landscape of metastatic hormone-sensitive prostate cancer (mHSPC) has changed radically in recent years. Androgen deprivation therapy (ADT) alone was for decades the standard of care for treating mHSPC. This changed when studies showed that the addition of docetaxel chemotherapy or abiraterone acetate to ADT significantly increases overall survival of patients with mHSPC, followed by more recent evidence showing the efficacy of androgen receptor antagonists, such as enzalutamide and apalutamide, in this setting. While this rapid therapeutic evolution is welcome, it presents clinicians with a crucial challenge: the choice of treatment selection and sequencing. In the first-line setting there are no comparative data currently available to guide treatment choice between the different available regimens, and no prospective data to guide clinical decision after progression. Decisions on treatment will now need to be personalised based on indirect comparison of the available efficacy data from multiple phase 3 studies, together with considerations of disease volume, comorbidities, treatment aims, toxicity profile and cost reimbursement within the healthcare setting. Here, we provide an overview of the clinical trial data to date and propose some biological and clinical insights which may be helpful in making decisions on treatment selection and sequencing.

Keywords: Androgen deprivation therapy; Antiandrogen drugs; Chemotherapy; mHSPC; Prostate cancer

Digital Features To view digital features for this article go to: https://doi.org/10.6084/m9.figshare.12416507.

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Published online: 15 June 2020

Key Summary Points

Why conduct this review?

In the past 5 years, several systemic therapies have been introduced for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC).

While androgen deprivation therapy (ADT) remains the mainstay of treatment of mHSPC, docetaxel chemotherapy and oral anti-androgens have demonstrated survival benefit when added to ADT. No prospective clinical trials have compared the different therapy options.

In this review, we discuss results of the key phase 3 trials and cover factors which influence treatment selection and sequencing, with the aim to ensure that the optimal treatment is delivered to the appropriate patient at the correct time.

What was learned from this review?

There is an increasing drive to focus on biologically-based disease taxonomy instead of the traditional paradigm of castrate-sensitive and castrate-resistant disease.

A treatment decision for mHSPC must take several factors into account, including patient and disease factors and, importantly, the circumstances surrounding drug licensing and cost reimbursements in their healthcare setting.

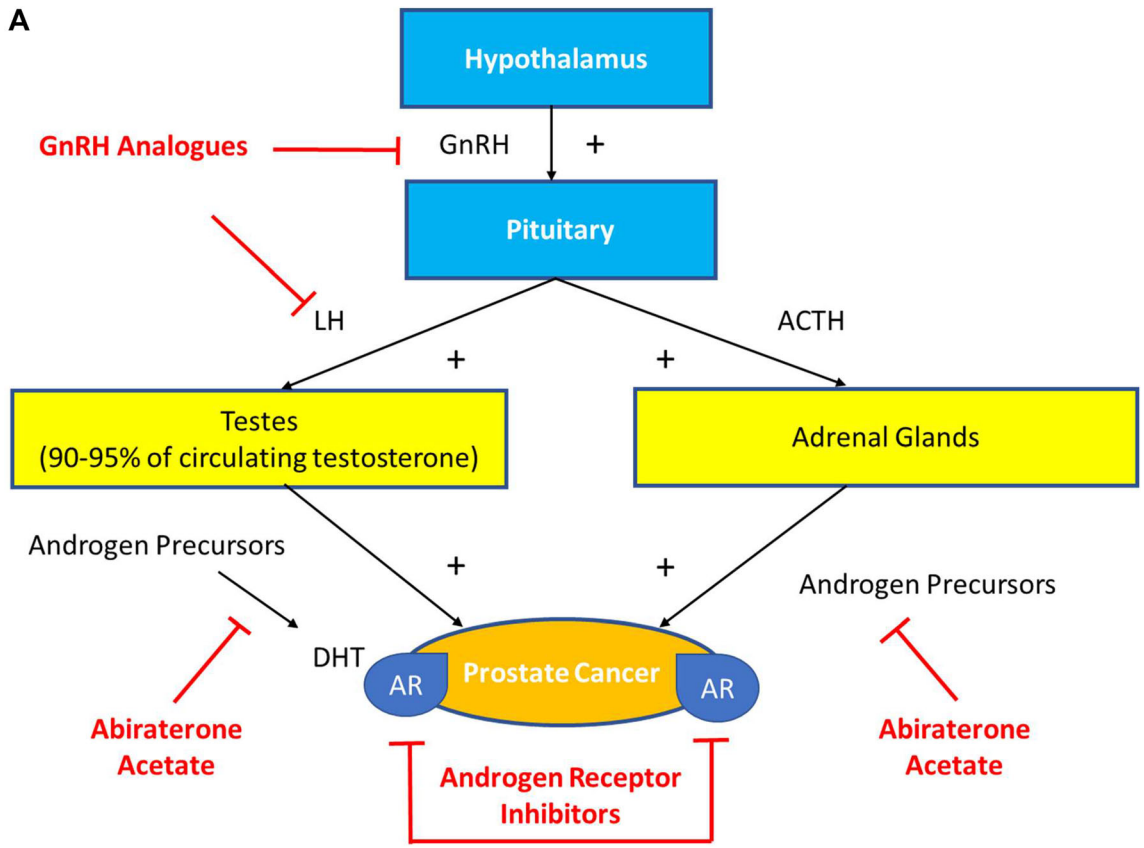
INTRODUCTION

Prostate cancer is the second most commonly diagnosed malignancy in men worldwide and accounted for 358,989 deaths in 2018 [1]. Most cases present at an early stage and often have an indolent course, requiring minimal or even no treatment. However, it has been estimated that up to one third of patients with prostate cancer will develop metastases at some point of their disease course [2]. While prostate cancer has an overall 5-year survival rate of 98.2%, patients with metastatic disease have a relatively dismal 30% 5-year survival rate [3].

In 1941, Charles Huggins and Clarence Hodges demonstrated that metastatic deposits from prostate cancer were hormonally sensitive [4]. The mainstay of treatment of metastatic hormone-sensitive prostate cancer (mHSPC) was to achieve castrate levels of testosterone by surgical means, such as bilateral orchidectomies, or by medical castration with androgen-deprivation therapy (ADT), such as gonadotropin-releasing hormone (GnRH) analogues. ADT decreases testicular production of testosterone (accounting for 90–95% of androgen production) by its effects on the hypothalamic–pituitary axis. The most widely employed strategy is continuous treatment with a GnRH agonist, which suppresses luteinising hormone production and therefore the synthesis of testicular androgens (Fig. 1a).

Unfortunately, mHSPC treated with ADT often transitions into a metastatic castrate-resistant state (mCRPC), defined by disease progression despite ADT with castrate testosterone levels (Fig. 1b). This may present in a variety of ways, including a continuous rise in serum prostate specific antigen (PSA) levels, progression of pre-existing disease and/or appearance of new metastatic deposits [5]. mCRPC is associated with a median survival of approximately 3 years [6]. Over the years, efforts were made to prolong the hormone-sensitive phase of treatment. The addition of first-generation antiandrogens, such as bicalutamide, to ADT was a commonly employed strategy to prolong the hormone-sensitive phase; this combination is often referred to as maximal androgen blockade. However, the benefit of this approach results in a low improvement rate of only 2–3% in 5-year survival alongside increased side effects [7].

In recent years, several systemic therapies have been introduced into the mHSPC space. While ADT remains the mainstay of treatment, docetaxel chemotherapy and second-generation antiandrogens, such as abiraterone,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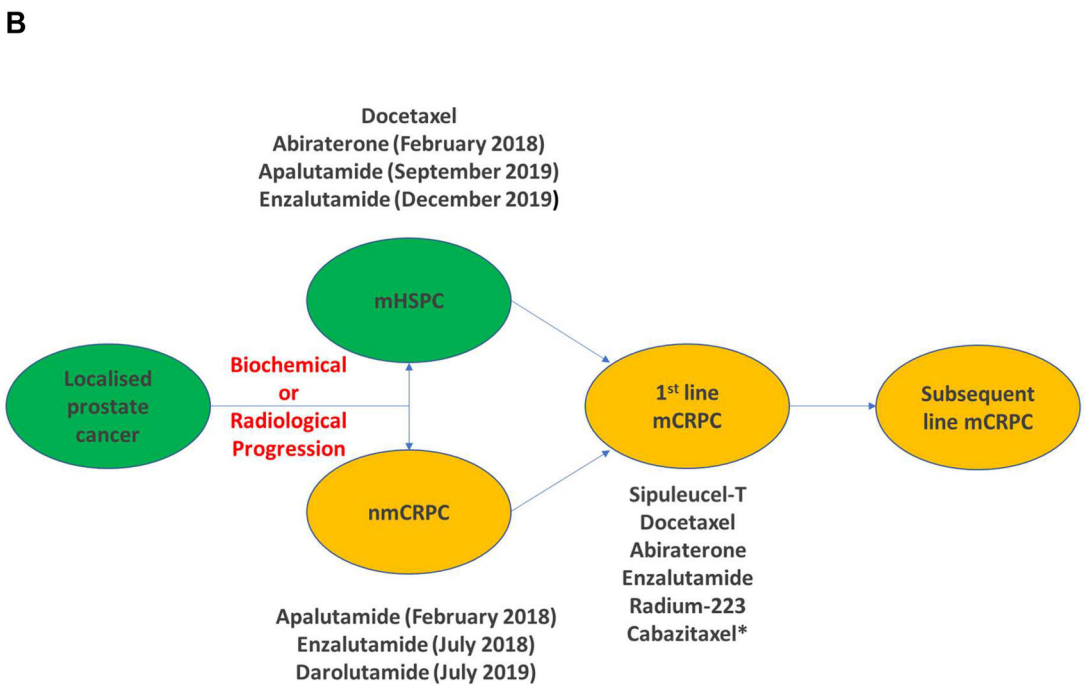
B
Docetaxel
Abiraterone (February 2018)
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Enzalutamide (December 2019)
mHSPC
Localised
prostate
cancer
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or
Radiological
Progression
nmCRPC
1st line
mCRPC
Subsequent
line mCRPC
Sipuleucel-T
Docetaxel
Abiraterone
Enzalutamide
Radium-223
Cabazitaxel*
Apalutamide (February 2018)
Enzalutamide (July 2018)
Darolutamide (July 2019)

◀**Fig. 1** **a** Mechanism of action of androgen deprivation therapy (ADT) and approved systemic therapies. The testes produce 90–95% of the total circulating testosterone, while the adrenal glands produce the remainder of the circulating androgens. Androgens, usually dihydrotestosterone (*DHT*), bind to the androgen receptor (*AR*), dissociating chaperone proteins. Ligand-bound AR molecules dimerise and translocate to the nucleus where they bind to androgen response elements and act as transcription factors to signal downstream targets. Apart from acting as AR antagonists, second-generation antiandrogens, such as enzalutamide, apalutamide and darolutamide, also prevent the translocation of AR to the nucleus. Abiraterone acetate, as a cytochrome P450 17A1 (CYP17) and α-hydroxylase inhibitor, largely prevents androgen biosynthesis. The detailed sites of action of abiraterone are not depicted in this diagram. *GnRH* Gonadotropin-releasing hormone, *ACTH* adrenocorticotrophic hormone, *LH* luteinising hormone. **b** Conventional treatment pathway of prostate cancer. *mHSPC* Metastatic hormone-sensitive prostate cancer, *nmCRPC* non-metastatic castration-resistant prostate cancer, *mCRPC* metastatic castration-resistant prostate cancer. *Cabazitaxel can be given in first-line treatment of mCRPC if docetaxel is given in the hormone-sensitive setting. Dates in parenthesis indicate month of US Food and Drug Administration approval; only drugs approved since 2018 have date of approval indicated

apalutamide and enzalutamide, have demonstrated survival benefit when added to ADT. The addition of these medications potential therapies has expanded the array of treatments available, but also presented the clinician with the conundrum of selecting the optimal agent for treatment intensification for the appropriate patient.

In the first part of this review we discuss results from the key trials which led to the approval of systemic treatments in the mHSPC setting. This is followed by an overview of the factors which may influence treatment selection, including disease factors, patient factors and toxicity profiles.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

DEFINITIONS AND TREATMENT LANDSCAPE

Men who present with mHSPC represent a heterogenous group of patients. Many patients will present with relapse after local treatment, while a minority (approximately 5% of all prostate cancer cases) present with de novo metastatic disease [8]. Metastatic sites and burden of disease will also vary between patients, as will their functional status and presence of cancer-related symptoms.

There are vastly different outcomes between patients, with some prognostic features established at diagnosis while others determined over the course of the treatment. Many of the clinical trials described in this review have attempted to develop prognostic systems for the different subtypes of mHSPC, and the results of individual trial results will need to be interpreted in the context of their study population. The key definitions used in this review are listed in Table 1.

DOCETAXEL: THE ROLE OF CHEMOTHERAPY IN MHSPC

Until 2004, chemotherapy played a peripheral role in the treatment of metastatic prostate cancer, with mitoxantrone and alkylating agents used for symptomatic benefit in the castrate-resistant setting [9]. Docetaxel was the first cytotoxic agent to demonstrate a survival benefit, as reported in the TAX 327 trial [10]. The question was then asked whether docetaxel would provide a similar, proportional benefit to survival if used earlier in the disease spectrum.

The benefit of adding docetaxel to lifelong ADT for mHSPC was established by three phase III trials: CHAARTED, STAMPEDE and GETUG-AFU 15. The key characteristics and results of these three trials are shown in Table 2.

In 2015, the US-led CHAARTED trial randomised 790 mHSPC patients to ADT with or without 6 cycles of docetaxel [11]. This was the first trial to demonstrate an overall survival (OS) benefit of adding docetaxel to ADT, with increased OS of 13.6-months (hazard ratio [HR]

Table 1 Definition of key terminology relating to metastatic hormone-sensitive prostate cancer

Terminology	Definition
Synchronous metastatic disease (de novo M1 disease)	The presence of metastases in the context of newly diagnosed prostate cancer
Metachronous metastatic disease	The presence of metastases after local treatment, usually radiotherapy and/or surgery to the prostate
High-volume disease	As defined by the CHAARTED trial. This is defined as visceral metastases and/or $\geq$ 4 bone lesions (with $\geq$ 1 beyond the vertebral bodies and pelvis)
High-risk disease (LATITUDE trial)	As defined by the LATITUDE trial, in the context of recruiting patients with de novo metastatic disease (M1). This is defined as the presence of $\geq$ 2 high-risk features, i.e. $\geq$ 3 bone metastases, visceral metastases and Gleason score $\geq$ 8
High-risk disease (STAMPEDE trial)	As defined by the STAMPEDE trial, in the context of recruiting patients with locally advanced prostate cancer (M0). This is defined by the presence of $\geq$ 2 of these features, i.e. T3/4 disease, Gleason score $\geq$ 8, and PSA > 40 ng/mL

M0 No distant metastases detectable, *M1* metastatic disease, *PSA* prostate specific antigen

0.61, 95% confidence interval [CI] 0.47–0.80). The trial was prospectively stratified by volume of disease according to a potentially controversial definition, which nevertheless has been shown to correlate with clinical outcome. Through a pre-planned subgroup analysis, only patients with high-volume metastatic disease, as defined by their 'CHAARTED criteria' (Table 1), demonstrated an OS benefit (HR 0.60, 95% CI 0.45–0.81). These findings were sustained in a longer-term follow-up report, with a median follow-up time of 53.7 months [12]. The OS benefit was maintained in the total cohort, but continued to be driven by patients with high-volume disease (HR 0.63, 95% CI 0.50 to 0.79), with no survival advantage observed in patients with low-volume disease (HR 1.04, 95% CI 0.7–1.55) and those who had prior local therapy (HR 0.97, 95% CI 0.58–1.56).

The STAMPEDE trial is a multi-arm, multi-stage platform design conducted primarily in the UK. In Arm C, the trial compared six cycles of docetaxel with ADT with standard ADT [13]. The STAMPEDE trial differs from the CHAARTED trial in at least two key areas. First, in the context of patient recruitment, patients with high-risk, locally advanced and node-positive disease were included together with patients with mHSPC disease, with M0 (= no distant metastases) patients constituting approximately 37% of the total STAMPEDE cohort. Secondly, maintenance prednisolone was administered at 5 mg twice daily in STAMPEDE along with docetaxel, mirroring the treatment protocol in the castrate-resistant setting [10]; maintenance prednisolone was not required in the CHAARTED or GETUG-AFU 15 studies. The addition of chemotherapy conferred a clear median OS benefit of 10 months (81 vs. 71 months; HR 0.78). The survival benefit attributable to docetaxel was evident in both the M0 and M1 (= metastatic disease) populations, with no evidence of heterogeneity, leading the authors to conclude that the addition of docetaxel to ADT should not only be the standard of care (SOC) for all men with mHSPC, but also considered for all men with high-risk nonmetastatic prostate cancer (M0).

The GETUG-AFU 15 French study [14] was the first phase III study to explore the use of docetaxel in the mHSPC setting and included 385 men with mHSPC randomised to receive ADT + docetaxel or ADT alone. This trial did not show an OS benefit (HR 1.01, 95% CI 0.75–1.36)—thus, a negative trial—although it demonstrated an improved PSA progression-free survival (PFS) and radiographic PFS. The reason for the divergence in results between GETUG-

Table 2 Summary of key aspects and results from the GETUG-AFU 15, CHAARTED and STAMPEDE (Arm C) phase III trials

Key aspects of the trials	SOC + docetaxel arm of study		
	STAMPEDE (*N* = 592)	**CHAARTED (*N* = 397)**	**GETUG-AFU15 (*N* = 192)**
Protocol	ADT + docetaxel at a dose of 75 mg/m^2; given every 3 weeks for up to 6 cycles		ADT + docetaxel at a dose of 75 mg/m^2; given every 3 weeks up to 9 cycles
	Prednisolone 5 mg twice daily; given for 21 days	Daily prednisolone not required Steroids only given as premedication	
	No recommendations were made on the use of GCSF	Use of GCSF was permitted	Prophylactic GCSF given on days 5–10
Age (years)			
Median	65	65	63
Range	40–81	36–88	57–68
Performance status (*n*)			
0	426 (72%)	277 (69.8)	181 (99%)
1–2	166 (28%)	120 (30.2)	2 (0.01%)
Study population	61% metastatic (M1) and 39% high-risk, locally advanced M0 disease	Metastatic (M1)	Metastatic (M1)
Volume of metastases (*n*)			
Low	For M1[a] patients only: 124 (46%)	34 (33.8%)	100 (52%)
High	148 (54%)	263 (66.2%)	92 (48%)
Visceral metastases	44 (7.4%)	57 (14.4%)	31 (16%)
Gleason score (*n*)			
≤ 7	110 (19%)	117 (29.5%)	84 (43%)
8–10	436 (74%)	241 (60.7%)	103 (54%)
Unknown	46 (8%)	39 (9.8%)	5 (2.6%)
PSA at start of ADT (ng/mL)			
Median	70	50.9	27
Range	1–9999	0.2–8540.1	IQR 5–106

Table 2 continued

Key aspects of the trials	SOC + docetaxel arm of study		
	STAMPEDE (*N* = 592)	**CHAARTED (*N* = 397)**	**GETUG-AFU15 (*N* = 192)**
HR for death in the docetaxel + SOC arm compared to the docetaxel alone	Entire population: HR 0.78 (95% CI 0.66–0.93)	Entire population: HR 0.72, 95% CI 0.59–0.89 High volume: HR 0.63, 95% CI 0.50–0.79 Low volume: HR: 1.04, 95% CI 0.70–1.55	Entire population: HR 0.88, 95% CI 0.68–1.14
	Metastatic subgroup (M1): HR 0.76 (95% CI 0.62–0.92)		Post hoc analysis: High volume: 0.78, 95% CI 0.56–1.09 Low volume: 1.02, 95% CI 0.67–1.55
	Post hoc analysis of M1 group: High volume: HR 0.81, 95% CI 0.64–1.02 Low volume: HR 0.76, 95% CI 0.54–1.0		
Febrile neutropenia	84 (15%)	24 (6.1%)	14 (7%)

ADT Androgen deprivation therapy, *CI* confidence interval, *GCSF* granulocyte colony-stimulating factor, *HR* hazard ratio, *IQR* interquartile range, *N* number treated with docetaxel in interventional arm, *n* number of patients, *SOC* standard of care

[a] In post hoc analysis of the STAMPEDE trial, 90 patients with M1 disease did not have bone scans

AFU 15 and the other two trials with positive results regarding the use of docetaxel is not entirely clear. Several reasons have been cited, the most common being that the GETUG-AFU 15 study was underpowered to study the effect of docetaxel and that that it included a higher proportion of patients with less aggressive disease (nearly half [43%] of the patients had Gleason scores ≤ 7). Post hoc analyses of data from this study, however, suggest a trend towards a survival benefit in men with 'CHAARTED high-burden' mHSPC although the lack of benefit in the low-volume disease group was sustained [15].

Following these trials, the addition of docetaxel to ADT became the SOC for mHSPC in men who are healthy enough to receive this therapy and especially in patients with a high burden of metastatic disease. However, there are concerns about the toxicity profile of this regimen and its effects on the quality of life (QoL), particularly in relation to the incidence of febrile neutropenia (FN). The CHAARTED trial reported FN rates of 6% whereas the STAMPEDE

trial demonstrated a FN rate of 15%, with both rates being considerably higher than the 3% rate seen if this regimen was administered in the mCRPC setting [10]. The tolerability of the treatment regimens and its influence on treatment choices are discussed later in the review.

ABIRATERONE AND PREDNISOLONE

Approximately 2 years after chemohormonal therapy was established as the SOC for patients with mHSPC, a series of positive trials involving the use of antiandrogens in combination with ADT emerged. The timeline of publication of these trials loosely mirrored historical developments in the castrate-resistant treatment setting, with positive results from abiraterone acetate and prednisolone being released first.

Two separate trials demonstrated the efficacy of abiraterone acetate in this disease setting. The multinational LATITUDE trial recruited 1199 patients and compared abiraterone and prednisolone (A + P) with ADT to double placebo and ADT (ADT only) in men with mHSPC. Importantly, all patients had de novo metastatic disease and met the definition of 'high risk', as defined in Table 1.

An interim analysis [16] performed at a median follow-up of 30.4 months demonstrated an OS advantage of 17% in the A + P arm compared to the ADT arm (66 vs. 49%). Because of these results, the trial was unblinded, and patients in the placebo arm were subsequently able to receive abiraterone.

The long-term results were reported recently after a median follow-up of 51.8 months. OS was significantly longer in the A + P and ADT group (53.3 vs. 36.5 months; HR 0.66) [17]. A post hoc analysis stratified patients based on disease volume defined in accordance with CHAARTED criteria. In patients with high-volume disease, abiraterone improved median OS by 16 months (49.7 vs 33.3 months; HR 0.62) and radiological PFS (33.1 vs 14.7 months; HR 0.46). In the low-volume subgroup, abiraterone showed an improvement in radiological PFS (49.8 vs 22.4 months; HR, 0.59) but not OS (not reached [NR] vs. NR; HR 0.72, $p = 0.1242$). However, the proportion of low-volume disease patients was relatively small (243/1198 patients) and, importantly, the study was not powered for subgroup analyses. In the context of toxicity and adverse events, approximately one-fifth of patients on the interventional arm had hypertension, with other side effects including hypokalaemia, hepatotoxicity and cardiac disorders.

Another trial which explored this treatment regimen was arm G of the STAMPEDE trial [18]. Over a median follow-up time of 40 months, A + P and ADT conferred an OS improvement when compared to ADT and placebo (HR 0.63, 95% CI 0.52–0.76). The interventional arm also showed a 71% improvement in failure-free survival (FFS) (HR 0.29, 95% CI 0.25–0.34).

Based on these results, abiraterone gained US Food and Drug Administration (FDA) approval in February 2018 for the treatment of high-risk mHSPC, expanding on its pre-existing approval in the metastatic castrate setting. The LATITUDE and STAMPEDE (Arm G) studies helped consolidate the notion that earlier intervention with a hormonally based approach leads to a more profound initial response and longer time to resistance and disease progression, with all these benefits leading to improved survival. This strategy was presented an alternative to docetaxel in the mHSPC setting, paving the way for discussion and debate about which combination is most effective, and for whom.

ENZALUTAMIDE IN MHSPC

In 2019, two other new-generation antiandrogen agents were added to the mHSPC treatment sphere. Enzalutamide, a potent androgen-receptor inhibitor had already been approved in the mCRPC setting. Unlike bicalutamide, enzalutamide does not promote translocation of the androgen receptor (AR) to the cell nucleus, thereby impairing binding of the AR to DNA [19].

ARCHES and ENZAMET were two multinational, randomised phase III trials that demonstrated clinically meaningful benefits in the first-line mHSPC setting. The multinational ARCHES trial studied 1150 men with mHSPC

randomised to receive ADT together with either enzalutamide or a placebo [20]. Patients were stratified by disease volume according to the CHAARTED criteria, as well as whether they had received prior docetaxel therapy. The risk of radiographic progression or death was significantly reduced in the interventional arm versus placebo + ADT (HR 0.39, 95% CI 0.30–0.50). The addition of enzalutamide to ADT was also beneficial to other parameters, such as a reduced risk of PSA progression, initiation of new anticancer therapy, first symptomatic skeletal-related event, castrate-resistant prostatic cancer and pain progression. As of the second half of 2019, the overall survival data was still immature. Overall, grade $\geq$ 3 adverse events were reported in 24.3% of patients in enzalutamide versus in 25.6% of patients in the placebo arm, indicating good tolerability. The most common grade 3 adverse event in the enzalutamide arm was hypertension, occurring in 3.3% of patients.

The second phase III trial published in 2019 was ENZAMET, in which 1125 men with mHSPC receiving ADT were randomised to treatment with open-label enzalutamide or a nonsteroidal antiandrogen [21] (e.g. bicalutamide, nilutamide or flutamide).This was the first trial to report survival data and outcomes of enzalutamide + ADT in patients who were also stratified to receive concurrent docetaxel. Randomisation was stratified by disease volume according to CHAARTED criteria, planned early docetaxel therapy, planned resorptive therapy, comorbidity scores and study site. At a median follow-up time of 34.2 months, OS was significantly prolonged in the enzalutamide arm compared to the nonsteroidal anti-androgen arm (HR 0.67, 95% CI 0.52–0.86), although median OS was not yet reached. In addition, time to PSA rise, clinical progression or death (HR 0.39, 95% CI 0.33–0.47) and time to clinical progression (HR 0.40, 95% CI 0.33–0.49) favoured the enzalutamide arm.

Interestingly in the prespecified subgroup analysis based on receipt of docetaxel, enzalutamide improved time to clinical progression significantly (HR 0.48 95% CI 0.37–0.62) but did not improve OS (HR 0.90, 95% CI 0.62–1.31) among men who received docetaxel. On the other hand, enzalutamide improved clinical progression (HR 0.34, 95% CI 0.26–0.44) and OS (HR 0.53, 95% CI 0.37–0.75) in the subgroup that did not receive docetaxel.

There are a few key differences between the ARCHES and ENZAMET trials. While the ARCHES trial employed radiological PFS as its primary endpoint, the ENZAMET trial used OS. The comparator also differed between both trials, with the comparator arm in ENZAMET being a nonsteroidal antiandrogen and that in ARCHES being ADT and placebo. Also, while both trials allowed the use of docetaxel, concurrent administration of docetaxel with enzalutamide and ADT was only allowed in ENZAMET, where ARCHES only allowed treatment with enzalutamide sequentially administered after the completion of docetaxel chemotherapy. A longer follow-up time may be required to analyse the full effect of chemotherapy in the docetaxel-treated mHSPC subset (concurrently or sequentially), particularly in the ENZAMET trial, although there is currently no justification for the use of triplet therapy. In December 2019, the FDA approved enzalutamide for patients in the mHSPC setting.

APALUTAMIDE

Apalutamide is a relative newcomer in the treatment of prostate cancer. This oral nonsteroidal antiandrogen, which binds directly to the ligand-binding domain of the AR and prevents AR translocation, was originally shown to have benefit over placebo in the non-metastatic CRPC setting in the SPARTAN phase III study originally published in 2018 [22]. Concurrently, the TITAN study explored the use of apalutamide in the mHSPC setting, randomising 1052 mHSPC patients to treatment with ADT with or without apalutamide [23]. Of these patients, 10.7% had received prior docetaxel treatment, and a majority had high-volume disease (62.7%) by CHAARTED criteria. At the first interim analysis at a median follow-up time of 22.7 months, the percentage of patients with radiological PFS at 24 months was higher in the apalutamide arm (HR 0.48, 95% CI 0.39–0.60);

OS was also greater in the apalutamide arm at 24 months (HR 0.67, 95% CI, 0.51 to 0.89). The frequency of grade ≥ 3 adverse events was 42.2% in the apalutamide group and 40.8% in the placebo group, with rash being more common among patients in the apalutamide arm. In September 2019, following the publication of these results in July 2019, the FDA approved apalutamide for the treatment of mHSPC patients.

RELEVANCE OF TRIAL DATA IN REAL-WORLD PRACTICE

After decades without significant progress in the treatment landscape of mHSPC, the results of the above-mentioned trials are welcome. Nevertheless, we need to cautiously interpret these results, taking into consideration the between-study heterogeneity in study populations, and how well they reflect our patient population (Table 3).

There are at least two areas where the trial populations diverge from real-world practice. These studies were highly enriched with patients with de novo metastatic disease, most notably in the LATITUDE (100% de novo) and STAMPEDE (97% de novo in M1 cohort) trials. Many patients seen in the mHSPC clinical setting are likely to have received radical treatment to the prostate prior to developing metachronous metastases. Despite the under-representation of patients with metachronous metastases, most oncologists would agree that treatment intensification benefits all patients with mHSPC. It remains unclear whether the margin of benefit of different treatments would differ based on the delivery of previous radical treatment.

More importantly, these results need to be interpreted against the background of an ageing, often less physically fit patient cohort in the clinical setting. Prostate cancer is predominantly a disease of the elderly, with peak incidence in men occurring at an age of just above 70 years. The median age of presentation of de novo metastatic prostate cancer based on registry data is 73–76 years [24–26], which is significantly higher than the age of the men recruited in all of the clinical trials. More than 90% of patients with prostate cancer are diagnosed with localised disease, at an average age of 66 years [27]. For the 3–8% of men who develop distant metachronous metastases after radical treatment, the median metastasis-free survival after radical treatment is 5–8 years [28–30].

Therefore, most men are in their seventies when they are referred to an Oncology clinic with mHSPC. A sizeable proportion will have comorbidities, some of which may be life limiting. These patients are under-represented in clinical trials, and their treatment decisions are complicated by competing risks of cancer, potential complications of treatment and individual comorbidities [31]. Rather than blindly extrapolating trial data, we need to understand how the diagnosis of mHSPC fits into the overall health picture of the patient—particularly in the context of the elderly patient.

In the following few sections we deliberate on the factors which may help distinguish between the four approved agents; however, the treatment goal for each patient must be the context in which all individualised treatments are considered.

POST HOC ANALYSES AND SYSTEMATIC REVIEWS

With at least four systemic treatment regimens showing benefit in the mHSPC setting, clinicians treating these patients are presented with the dilemma of choosing the best treatment for each patient. Despite the wealth of data available, no prospective trial has randomised patients to directly compare efficacy and tolerability between these treatments.

The multi-arm and multi-platform design of the STAMPEDE trial permits indirect comparison between the treatment options, benefitting from a period of contemporaneous recruitment in arm C (docetaxel) and arm G (abiraterone). In a post hoc analysis with a median follow-up of 4 years [32], there was no statistically significant difference in OS, metastasis-free survival, prostate cancer-specific survival and symptomatic skeletal events. However, abiraterone was associated with longer FFS.

Table 3 Characteristics of the study populations in the different trials

Study characteristics	CHAARTED	STAMPEDE (ARM C)	GETUG-AFU15	LATITUDE	STAMPEDE (ARM G)	ARCHES	ENZAMET	TITAN
Patients (*n*; experimental arm/placebo arm)[a]	397/393	592/1184	192/193	597/602	960/957	574/576	563/562	525/527
Patient characteristics								
Inclusion criteria	mHSPC	High-risk, locally advanced or mHSPC	mHSPC	De novo, high-risk mHSPC	High-risk, locally advanced or mHSPC	mHSPC	mHSPC	mHSPC
Age (years)	64/63	65/65	63/64	68/67	67/67	70/70	69/69	69/68
Disease characteristics								
Prior radical treatment (%)	27/27	3/3 in M1	33/24	0/0	4/3 in M1	25/28	42/42	18/15
Gleason score > 7 (%)	61/62	74/68	55/59	98/97	74/75	67/65	60/57	67/68
Median PSA (ng/mL)	51/52	70/67	27/26	NR	51/56	5/5	NR	6/4
M1 (%)	100/100	62/61	100/100	100/100	52/53	93/92	100/100	100/100

mHSPC Metastatic hormone-sensitive prostate cancer, *NR* not recorded

[a] All values for patient characteristics are presented as (value in the experimental arm)/(value in placebo arm)

A separate network meta-analysis indirectly compared ADT + docetaxel with ADT + abiraterone by using a common comparator arm of ADT alone [33]. This analysis used data from the GETUG-AFU15, CHAARTED, LATITUDE and STAMPEDE trials, including a total of 6067 patients. The pooled HR for OS was 0.75 (95% CI 0.63–0.91) for docetaxel + ADT and 0.63 (95% CI 0.55–0.72) for abiraterone + ADT. The indirect comparison of abiraterone + ADT to docetaxel + ADT demonstrated no statistically significant difference in OS between the two approaches (HR 0.84, 95% CI 0.67–1.06).

These post-hoc analyses suggest that as the efficacy data currently stands, both of these therapeutic options are acceptable in the mHSPC space. As of May 2020, there is still a relative paucity of meta-analyses of enzalutamide and apalutamide studies, as data from these trials await maturity. To our knowledge, the only systematic review in this area to date, published in March 2020, suggests that the combination therapy with any of the four available options provides an OS benefit compared to ADT alone, with no significant differences between the options [34].

DISEASE VOLUME

Disease volume is a key predictive factor in the selection criteria for treatment. Many trials highlighted in this review have stratified their trials based on the CHAARTED criteria of low- and high-volume disease, although notably most analyses were conducted in an unplanned, retrospective fashion. In addition, research is ongoing on definitive prostate-directed therapy, particularly in the context of low-volume, oligometastatic mHSPC with bone metastases, in addition to SOC.

Systemic Treatment Selection

In patients with high-volume disease, all four treatment options are reasonable. Many clinicians would reserve docetaxel for patients with high-volume disease because the initial results of CHAARTED did not demonstrate an effect in the low-volume disease cohort—a negative result sustained after longer-term follow-up (HR 1.04, $p = 0.86$). An updated analysis of GETUG-AFU 15 data suggested that docetaxel may have benefitted the cohort with high-volume disease but that low-volume disease patients derived no benefit from the addition of docetaxel to the therapeutic regimen (HR 1.02, $p = 0.9$). Similarly, the OS benefit in Arm C in STAMPEDE (docetaxel) was largely driven by the M1 subset. These data suggest that docetaxel + ADT should predominantly be reserved for patients with high-volume disease as defined by the CHAARTED criteria.

This opinion is by no means universal, and many clinicians would argue for docetaxel to be administered to patients with low-volume disease as well. An updated analysis of the STAMPEDE Arm C data published in December 2019 demonstrated a survival benefit regardless of the volume of metastatic disease [35]. There was no evidence of an OS difference in benefit associated with docetaxel with ADT over ADT alone when metastatic burden was taken into account (interaction $p = 0.827$). The STAMPEDE investigators argue that the discordance between their observation and those from previous trials was due to their larger sample size. STAMPEDE also recruited many more patients presenting with de novo low-volume metastatic disease, representing a different natural history of the disease and thereby possibly explaining the differential response to therapy.

For the abiraterone + ADT arm of the LATITUDE trial, the OS advantage did not reach statistical significance by post hoc analysis in the subset of patients who were defined as having low-volume disease (HR 0.72, $p = 0.12$) [17]. This result could potentially be explained by the relatively small numbers of patients with low-volume disease (20.2%, 243/1198) in the total study cohort. A post hoc subgroup analysis of the 2017 STAMPEDE "abiraterone comparison" cohort has been published that stratifies the analysis by the LATITUDE definition of high and low risk as well as by the CHAARTED disease volume criteria [36]. In this study, heterogeneity of effect was not seen between low- and high-risk groups for OS and FFS. The study recognised, however, that for OS benefit in the low-risk cohort, the number needed to treat was

fourfold greater than that in the high-risk cohort. Equally, no evidence of heterogeneity of effect was observed for OS (p interaction = 0.77) in an exploratory analysis stratified by CHAARTED 'volume'. In summary, the available evidence suggests that abiraterone is beneficial regardless of disease volume.

In the ENZAMET trial, 52% of the patients recruited were deemed to have high volume disease. The effects of enzalutamide on overall survival were smaller among the patients in the subgroup with high-volume disease. The p value for heterogeneity of the treatment effect of enzalutamide was insignificant ($p = 0.14$) for volume of disease after adjusting for multiple comparisons [21]. Considering the balanced recruitment of high- and low-volume disease patients in this trial, this suggests that enzalutamide demonstrates efficacy in both low- and high-volume disease. In the TITAN study, 62.7% of the total cohort had high-volume disease. Apalutamide demonstrated a benefit in all subgroups analysed including volume of disease—the HR was 0.68 (0.50–0.92) in the high-volume subgroup and 0.67 (0.34–1.32) in the low-volume subgroup [23].

In summary, none of the trials using antiandrogen agents have shown any evidence of heterogeneity of effect by metastatic burden. On the contrary, there is a moderate degree of uncertainty in the role of chemotherapy in low-volume disease patients. Stratifying treatment choice by disease volume continues to be one of the most disputed aspects of mHSPC treatment. In the recently published report of the Advanced Prostate Cancer Consensus Conference 2019, more than 85% of the panel voted for some form of additional treatment with ADT regardless of disease volume in the de novo metastatic setting, with a near-unanimous consensus that treatment intensification should be delivered in the high-volume M1 cohort. Beyond that, there continues to be much uncertainty as to which agent is preferred. While most panellists were equivocal between docetaxel and antiandrogens in high-volume disease, there was a preference for antiandrogens in low-volume disease, regardless of whether the metastatic disease was de novo or metachronous [37].

Prostate-Directed Therapy for Low-Volume mHSPC

Oligometastatic prostate cancer with bone-only metastasis warrants a separate discussion due to the possible role of definitive prostate-directed therapy. This is expected to be a rapidly expanding subset of the mHSPC disease spectrum due to the introduction of highly sensitive imaging modalities, such as the gallium-68 prostate specific membrane antigen scan [38]. The impact of concurrent local prostate radiotherapy (RT) in conjunction with ADT has been studied in two randomised trials. The phase III HORRAD trial randomly assigned 432 men with de novo metastatic prostate cancer with bone metastases and a serum PSA > 20 ng/mL to ADT with or without external beam RT to the prostate [39]. The addition of RT prolonged the median time to PSA progression (HR 0.78, 95% CI 0.63–0.97) although median OS was not improved by the addition of RT (HR 0.90, 95% CI 0.70–1.14). However, an unplanned subgroup analysis suggested that survival might be favourably impacted in the subgroup of men with < 5 metastases (HR 0.68, 95% CI 0.42–1.10).

Similarly, in the phase III STAMPEDE trial, 2061 men with de novo metastatic prostate cancer were randomly assigned to lifelong ADT ± docetaxel ± prostate RT [40]. Patients were stratified by disease volume according to the CHAARTED criteria. Overall survival at the 3-year timepoint was not improved in those receiving RT to the prostate (HR for death 0.92, 95% CI 0.80–1.06), but FFS was better (HR 0.76, 95% CI 0.68–0.84). In a prespecified subgroup analysis, OS was improved in the subgroup of patients with low-volume metastatic disease (HR 0.68, 95% CI 0.52–0.90). A pooled analysis of both trials found an approximately 7% improvement in survival in men with < 5 bone metastases and an overall improvement in biochemical PFS and FFS in the total cohort [41].

In summary, subgroup analyses of large phase III trials have suggested that RT to the prostate is beneficial for patients with oligometastatic bone deposits along with systemic therapy. Definitive therapy to the prostate remains an actively studied and debated area,

with phase III trials, such as Southwest Oncology Group (SWOG) 1802 in the USA (NCT03678025) and TRoMbone (ISRCTN15704862) in the UK, actively recruiting patients with oligometastatic prostate cancer and offering treatment to the prostate alongside SOC systemic treatment. In addition to consolidating previous results with a newer generation of first-line systemic therapies, the results from these trials will also inform us if either RT or surgical treatment to the prostate has value, particularly in patients with oligometastatic disease.

TOXICITY AND TOLERABILITY

The effects of the drugs on the QoL must be taken into consideration when treating patients with mHSPC. With a median OS of approximately 4 years from the time of diagnosis of mHSPC, it is important to balance efficacy of treatment with any treatment-related adverse events, particularly long-lasting effects which may compromise the patient's quality of life.

Docetaxel is an intravenous chemotherapy administered on a 3-weekly basis for up to six cycles. On the one hand, the treatment is delivered over a scheduled timeframe of 18 weeks (with only ADT continuing after completion of the 6 cycles) and, therefore, any reversible adverse effects and time away from social and professional commitments are condensed, in contrast to antiandrogens which are given up to the point of progression or intolerability. However, any patient considered for this treatment should be fit and eligible for chemotherapy. Relative contraindications, such as advanced age, poor performance status, significant comorbidities and patient preference, need to be taken into consideration. Importantly, patients receiving docetaxel are at a significantly higher risk of developing FN. While the three key trials demonstrate an FN risk of between 6 and 15% [11, 13], real-life studies have demonstrated a FN rate of up to 30%, and many large centres advise the concurrent use of granulocyte-colony stimulating factors or antibiotics alongside docetaxel [42, 43].

Overall, the second-generation antiandrogens are well tolerated with relatively few high-grade adverse effects. The STAMPEDE investigators compared QoL scores (using EORTC QLQ-C30 and -PR25 health-related quality of life questionnaires) of a contemporaneous cohort of patients recruited to receive docetaxel and abiraterone. The average global QoL over 2 years was higher in patients randomised to abiraterone, with a cross-sectional analysis showing clinically meaningful superior QoL in the abiraterone group at 3–6 months [44]. QoL was directly assessed by the FACT-P (a 12-item prostate cancer-specific scale) score in both the ARCHES and TITAN trials; the QoL scores did not differ between the intervention and control arms.

Despite the general tolerability of antiandrogen therapy, the time on treatment is likely to be significantly longer than that of patients on docetaxel as both are taken until disease progression or unacceptable toxicity. Tablet burden and duration of treatment should be discussed with each patient prior to initiating therapy.

Bearing in mind the heterogeneity of clinical trials and the limitations of cross-trial comparison, there is a remarkable similarity in the hazard ratios in OS benefit for abiraterone (HR 0.66 in LATITUDE), enzalutamide (HR 0.67 in ENZAMET) and apalutamide (HR 0.67 in TITAN). Hence the importance of selecting the appropriate antiandrogen based on individual comorbidity profile and preference cannot be over-emphasised. For example, enzalutamide is contraindicated in patients with seizures, as patients with pre-existing seizures were excluded in the phase III trial [21]. Abiraterone should ideally be avoided in patients with pre-existing cardiovascular or hepatic disorders, and patients who receive apalutamide should be counselled about the possibility of a serious rash. Inevitably, physician preference and experience of prescribing these medications in the mCRPC setting will influence individual prescribing patterns. Table 4 shows the grade ≥ 3 adverse events of the individual trials. In summary, treatments must be tailored according to the individual patient's profile, comorbidities and preferences.

Table 4 Summary of grade ≥ 3 adverse events across key clinical trials

Event	CHAARTED		STAMPEDE		LATITUDE		STAMPEDE		ARCHES		ENZAMET		TITAN	
	Doc	SOC	Doc	SOC	A + P	SOC	A + P	SOC	Enza	SOC	Enza	SOC	Apa	SOC
Any grade 3–5 AE	29.6%	Not recorded	52%	32%	63%	48%	47%	33%	24.3%	25.6%	57%	43%	42.2%	40.8%
Discontinuation (AE)	NA		NA	NA	12%	10%	NA	NA	7.2%	5.2%	33%	14%	8%	5.3%
Completed 6 cycles	86%		77%	NA	Not applicable						65%	76%	Not applicable	
Fatigue	4.1%		7%	4%	2%	2%	2%	2%	0.9%	1%	6%	1%	8.4%	9.1%
Neutropenia	12.1%		12%	0%	NA	NA	NA	NA	0.3%	0.3%	6%	3%	NA	NA
Febrile neutropenia	6.1%		15%	1%	NA	NA	NA	NA	NA	NA	7%	6%	NA	NA
Neuropathy	0.5%		3%	2%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hypertension	NA		NA	NA	20%	10%	5%	1%	3.3%	1.7%	8%	4%	8.4%	9.1%
Hypokalaemia	NA		NA	NA	11%	1%	1%	< 1%	NA	NA	NA	NA	NA	NA
Hyperglycaemia	NA		NA	NA	4%	3%	NA	NA	NA	NA	NA	NA	NA	NA
Endocrine disorders	NA		NA	NA	NA	NA	14%	4%	NA	NA	NA	NA	0%	0%
ALT increased	NA		NA	NA	5%	1%	6%	1%	NA	NA	NA	NA	NA	NA
AST increased	NA		NA	NA	4%	1%	1%	< 1%	NA	NA	NA	NA	NA	NA
ALP increased	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.4%	2.5%
Cardiac event	1.0%		NA	NA	4%	1%	10%	4%	1.5%	1.9%	3%	1.5%	NA	NA
Rash	NA		NA	NA	NA	NA	NA	NA	0%	0%	NA	NA	6.3%	0.6%
Seizure	NA		NA	NA	NA	NA	NA	NA	0.3%	0.3%	< 1%	0%	0.2%	0%
Fall/syncope	NA		NA	NA	NA	NA	NA	NA	0.3%	0.2%	4%	1%	0.8%	0.8%
Poor cognition	NA		NA	NA	NA	NA	NA	NA	0.7%	0.3%	< 1%	0%	NA	NA
Anaemia	1%		NA	NA	NA	NA	NA	NA	NA	NA	1%	1%	1.7%	3.2%

Grade 1–2 side effects are not listed

A + P Abiraterone and prednisolone, *AE* adverse events, *ALP* alkaline phosphatase, *ALT* alanine transaminase, *Apa* apalutamide, *AST* aspartate amino transferase, *Doc* docetaxel, *Enza* enzalutamide, *NA* not available,

CONCOMITANT STEROID ADMINISTRATION

The requirement for concomitant use of steroids alongside systemic therapy for mHSPC needs to be discussed with the patient. As an inhibitor of cytochrome P450 17A1 (CYP17) and 17α-hydroxylase, abiraterone blocks androgen synthesis and glucocorticoid production, leading to decreased cortisol levels [45]. Decreased cortisol levels can result in an increased release of adrenocorticotrophic hormone, which in turn can lead to excess mineralocorticoid levels. Consequently, prednisolone must be co-administered alongside abiraterone to provide adequate replacement of physiologic glucocorticoids. Long-term administration of prednisolone may cause Cushingoid syndromes, potentially limiting its use in patients with poorly controlled diabetes and chronic gastric ulcers [46]. In the context of mHSPC, the LATITUDE trial used prednisolone 5 mg once daily as opposed to the twice-daily prednisolone 5 mg twice-daily regimen used in the context of mCRPC in the COU-AA-301 trial [47]. This lower dosage of prednisolone has been cited as a reason for the relatively high proportion of mineralcorticoid-related adverse events, including fluid retention, hypertension and hypokalaemia, among participants in the LATITUDE trial. The co-administration of different glucorticoid regimens with abiraterone acetate in patients with mCRPC has been explored in a prospective clinical trial, with the results suggesting there is little scope for reducing prednisolone doses while still preventing mineralcorticoid excess [48].

The co-administration of prednisolone with docetaxel is another point of discussion. A key, but often overlooked, difference between the landmark mHSPC trials is the use of maintenance prednisolone. The STAMPEDE trial adopted the use of maintenance prednisolone 5 mg twice daily to mirror the protocol employed in the TAX-327 study in the castration-resistant setting, whereas the CHAARTED protocol did not adopt the routine use of maintenance steroids. The use of steroids has traditionally been associated with lymphopenia and arguably has a direct effect on lymphocyte function [49, 50], leading to an escalated degree of immunosuppression in any neutropenic patient. Some studies have suggested that the omission of maintenance prednisolone reduces the risk of FN while not compromising efficacy in the mHSPC setting [43]; however, this is an area which warrants further research.

TAILORING TREATMENT AIMS TO THE INDIVIDUAL GOAL

As alluded to earlier in the review, treatment of the mHSPC patient must take into context the overriding individual treatment aim. For most patients, metastatic prostate cancer is an incurable disease. The aim is to transform mHSPC into a manageable chronic illness so that the patient dies with the cancer, rather than of it.

For the young patient with few comorbidities presenting with mHSPC, the risk of dying from metastatic prostate cancer is significant. The likely treatment aim is to prolong OS with respect to the cancer. In the absence of a clearly superior agent and prospective sequencing data, the strategy is to maximise the lines of therapies that can be utilized in the patient's treatment course. The reasoning of the treating oncologist may be to administer docetaxel in the upfront setting, taking into account that the more tolerable oral antiandrogens can be added on more easily than docetaxel at a later point should the patient become increasingly frail from the disease and/or other underlying comorbidities.

More commonly, the average patient with mHSPC presenting to clinic will be in his mid-seventies. This elderly cohort of patients are likely to have a few comorbidities, some of which are likely to limit life expectancy more than prostate cancer, and therefore have competing risks of mortality. The treatment aim in these patients may be different, as the aim will be to balance symptomatic (and survival) benefit with the tolerability and toxicity of the treatment. With complex cases, oncologists may opt to make a joint decision about treatment goals together with another clinician, such as a geriatrician. A prospective clinical trial has recently shown that integration of a

comprehensive geriatric assessment improved QOL, unplanned hospital admissions and treatment discontinuation in older patients undergoing systemic treatment [51].

For some patients in this cohort, it would not be unreasonable to commence ADT as monotherapy. Initial predictive factors to response, such as starting PSA value, presence of symptoms and PSA nadir level, can guide further decision-making and prognostication [52]. Some oncologists argue that treatment intensification can be added later if the PSA is not adequately suppressed with initial ADT. While biologically this is not an unreasonable treatment strategy, it must be stressed that this was not the context in which the clinical trials were designed, and further research is needed to validate this as a treatment strategy.

We recognise that patients in the real-world range from the exceptionally healthy 80-year-old to the 55-year-old with end-stage renal failure on dialysis, and that no guidelines should be too prescriptive about treatment intensification. All treatment decisions and goals must be individualised in discussion with the patient about the potential benefits and risks of the different treatments, and no decisions should be made unilaterally based on chronological age and presence of comorbidities alone.

GENETIC AND BIOCHEMICAL BIOMARKERS

A variety of markers have been studied for their ability to prognosticate patients and even predict response to treatment in the mCRPC setting. The most extensive data have come from analyses of circulating tumour cells. The rapidly evolving treatment landscape has meant that drugs commonly used in the castrate-resistant setting are now used in the mHSPC setting, and previously identified genetic aberrations in the mCRPC setting may have prognostic and/or predictive value earlier in the treatment paradigm. While this topic warrants a brief discussion, there is currently insufficient evidence in this field to suggest that genetic markers should guide treatment in the mHSPC setting.

Circulating tumour cells (CTC) and AR splice variant 7 (AR-V7) have been proposed as prognostic and predictive biomarkers in patients with mCRPC treated with enzalutamide and abiraterone acetate [53, 54]. Theoretically, the poor response in AR-V7-positive patients in the castrate-resistant setting may indicate that docetaxel will be more beneficial than androgen targeting in these patients. Results from small studies have suggested support for this hypothesis [55], although larger randomised trials and improved isolation and analysis of CTC will be required to validate these results.

From a purely prognostic perspective, the role of PSA kinetics has been regarded as crucial in the non-metastatic CRPC setting [56]. The impact of early changes in serum biomarker levels, including PSA, haemoglobin and alkaline phosphatase, have been demonstrated as good prognostic markers for survival of patients with mHSPC as well [57], although further validation of the prognostic value of dynamic changes in laboratory markers is needed.

Selected genetic aberrations investigated in the mCRPC setting may warrant further research. For example, it has been suggested that mutations in *SPOP* predict response to abiraterone acetate [58], while loss of the retinoblastoma susceptibility gene (*RB1*) and mutations in tumor protein p53 (p53) are associated with a shorter time on treatment on abiraterone or enzalutamide [59, 60]. The PROREPAIR-B prospective study has confirmed *BRCA2* as an independent prognostic factor for survival in mCRPC, suggesting that mutations in BRCA2 might be a predictor of poor response to first-line chemotherapy [61]. While it is unclear in many of these studies whether these mutations are specific to aggressive or metastatic disease, rather than the result of selective pressure of treatments, they nevertheless provide an interesting area for future translational work.

DISCUSSION

The transition of multiple systemic treatments previously used in the mCRPC setting into the mHSPC space is both exciting and challenging.

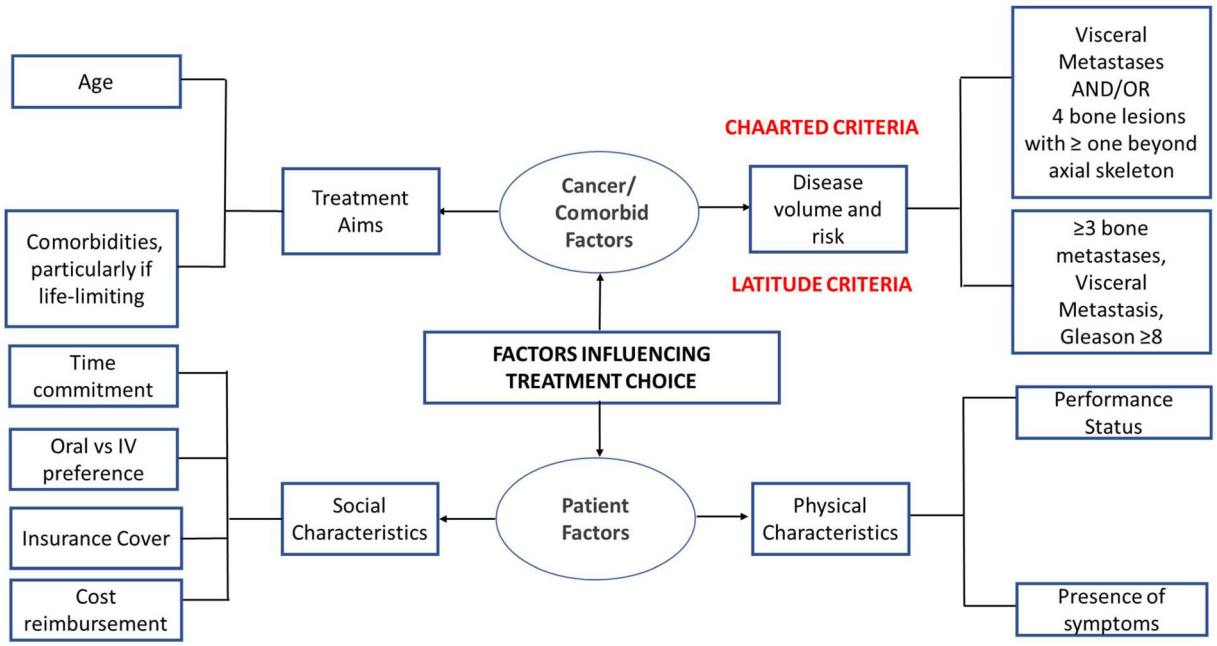

Fig. 2 Potential decision-making factors influencing choice of first line treatment for mHSPC. *IV* Intravenous

Apart from the obvious benefit of improving OS, the use of multiple antiandrogen agents in the mHSPC setting also challenges the paradigm of dividing prostate cancer treatment into the castrate-sensitive and castrate-resistant phases. There is an increasing drive to focus instead on biologically based disease taxonomy, which indicates a better understanding of the molecular heterogeneity of the disease, its associated biomarkers and therefore appropriate treatment sequencing.

The incorporation of concurrent and/or prior docetaxel treatment in the multivariate analyses of the ARCHES, ENZAMET and TITAN trials is welcome and highlights the importance of research into treatment sequencing. While most of these trials showed the benefit of oral antiandrogens regardless of prior docetaxel use, the concurrent administration of docetaxel did not add benefit to combined treatment with enzalutamide + ADT. A potential explanation for this is that the translocation of androgen AR to the nucleus may be blocked by docetaxel [62], hence the addition of a potent AR receptor antagonist may not confer additional advantage to tumours in which this pathway predominates. The results of the ARASENS study (NCT02799602), which is investigatings whether the addition of darolutamide to the docetaxel + ADT regimen improves survival, are expected in 2022, and these will help provide answers in this space. The combination of enzalutamide and abiraterone has also been studied in arm J of STAMPEDE, which has completed recruitment but whose results are yet to be published [63]. Moving forwards, an understanding of the scientific rationale of trialling combinatorial and sequential treatments—including retrospective translational studies of trials which have published negative results—will highlight more areas warranting research.

The treatment decision for patients presenting with mHSPC must account for several factors, including patient and disease factors, and importantly the circumstances surrounding drug licensing and cost reimbursements in their healthcare setting (Fig. 2). Both chemotherapy and new-generation antiandrogen agents demonstrate significant survival benefit when used in combination with ADT compared to ADT alone. In many developed countries, treatment intensification in mHSPC represents a new SOC, although ADT monotherapy

remains a reasonable alternative for a subset of patients with competing risks of mortality due to other comorbidities. For patients with oligometastatic disease, definitive radiotherapy to the primary tumour also constitutes a SOC. The treatment plan needs to be individualised to the patient's needs and considerations should also be made with regards to treatment sequencing. Whenever possible, biochemical markers and genetic aberrations should be used in a predictive or prognostic capacity to assist with decision making.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Kenrick Ng, Shievon Smith and Jonathan Shamash have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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