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REVIEW

Volume matters and intensification is needed: emerging trends in the management of advanced prostate cancer

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Abstract

Significant changes in the management of patients with de novo metastatic prostate cancer have led to the use of novel oral agents and docetaxel-based chemotherapy earlier in the natural history of their disease. Our main challenge is the lack of prospective randomized data comparing these regimens. It is clear that treatment intensification is needed. Yet, the heterogeneity of this patient population coupled with the lack of understanding of the specific biology for a given individual makes treatment selection challenging. The aim of this narrative review is to discuss the importance of defining advanced disease by volume, the necessity for treatment intensification, and the current and future landscape of metastatic hormone-sensitive prostate cancer management.

Keywords: de novo, metastatic prostate cancer, treatment intensification, trends, volume status.

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Introduction

Prostate cancer is the third most common cancer in the United States with 191,930 new cases in 2020.[1] While the number of localized prostate cancer cases has decreased over time given the changes in US Preventive Services Task Force screening guidelines, the number of de novo metastatic prostate cancer is increasing.[2–4] Additionally, unlike localized disease, the 5-year relative survival of de novo metastatic prostate cancer is dismal, dropping from the high 90s to 30.2%.[1] Thus, the focus over the past few years has shifted to improving the outcomes of metastatic prostate cancer through treatment intensification with novel therapies and the introduction of targeted agents as well the identification of high-risk populations based on volume of disease.

For this narrative review, we used all relevant articles found on PubMed from 1980 to 2020, with the aim to discuss the importance of defining advanced disease by volume, its role in clinical and research settings, the necessity for treatment intensification, the current landscape of metastatic hormone-naive/sensitive prostate cancer (mHSPC) management, including novel therapies on the horizon, and the potential predictive markers to help tailor therapies.

Definition of volume

Our modern definitions of volume have evolved since the Eisenberger trial in 1998,[5] which was among the first in prostate cancer to stratify its study participants by the existence of distant metastases. This early consideration of volume eventually became the basis for patient stratification by investigators in both the CHAARTED and LATITUDE phase III studies, which will be discussed further in this review.

While both LATITUDE and CHAARTED included the presence of visceral metastases in their criteria for high-volume disease, they differed in the number and location of metastases as well as in the importance of the Gleason score (GS). In LATITUDE, high-risk disease was defined by the presence of two out of three of the following features: GS >8, the presence of visceral disease and/or the presence of at least three bony lesions.[6] CHAARTED, on the contrary, did not include GS and high-volume disease was defined as the presence of at least four bone lesions, with at least one of those lesions being outside of the spinal column or pelvis.[7] Of note, these definitions were formed using computerized tomography and bone scans, not with newer modalities such as ^{18}F-fluciclovine or prostate-specific membrane antigen (PSMA) PET scans.

In general, the CHAARTED definitions are the most comprehensive and widely accepted guidelines to date.[8–12] The stratification of patients based on volume status enables clinicians to accurately determine who will receive the most benefit from certain treatments, while mitigating the unnecessary side-effects of other treatments.

Androgen deprivation therapy

Prostate cancer is dependent on androgen production for growth. The majority of a man's circulating testosterone is made in the testes (90–95%) and the rest is made by the adrenal gland.[13] Medical or surgical castration is defined as testosterone levels <50 ng/dL (with contemporary data favouring testosterone levels <20 ng/dL).[14,15] In the United States, medical castration is preferred, primarily to avoid surgical complications and psychological trauma as well as due to the convenience, efficacy and reversibility of the available treatments.[16]

The crux of medical castration is to control the hypothalamic–pituitary axis, the master regulator of endogenous androgen production. Gonadotropin-releasing hormone (GnRH) agonists are enhanced versions of GnRH that have an increased binding affinity for the GnRH receptor as well as resilience against degradation.[17] GnRH agonists work through a negative feedback loop, where overstimulation of the GnRH receptors leads to their downregulation. Ultimately, this decreases the production of testosterone; this process can take approximately a week to occur. In the meantime, the overactivation of the GnRH receptor can lead to a flare phenomenon, often requiring the use of antiandrogens for select patients at risk for complications derived from the transient testosterone elevation.

While the flare phenomenon is brief, the sequelae of an event can be catastrophic, including pain crisis, spinal cord compression and urinary outlet obstruction. Thus, GnRH antagonists, which bypass this process, were developed. A phase III trial of degarelix *versus* leuprolide showed that more patients treated with degarelix had castrate levels of testosterone at 3 days(95.5–96.1% *versus* 0) and lower median prostate-specific antigen (PSA) levels at 14 and 28 days ($p<0.0001$).[18] Degarelix was shown to be non-inferior to leuprolide at maintaining castrate levels of testosterone. Despite these findings, GnRH agonists remain the most commonly used agents for androgen deprivation therapy (ADT). Recently, the prospective phase III HERO trial demonstrated that relugolix, an oral GnRH antagonist, not only provided faster testosterone suppression at day 4 (56% *versus* 0) but also provided long-term testosterone suppression at 48 weeks (96.7% *versus* 88.8%).[19] Remarkably, relugolix was associated with less treatment-related adverse events (TRAEs) compared to leuprolide, most notably in cardiovascular events (2.6% *versus* 6.2%, HR 0.46, 95% CI 0.24–0.88). Given the superiority ($p<0.001$) shown in this trial, relugolix was granted priority review by the FDA.

In the contemporary setting, patients treated with ADT alone have a median failure-free survival of 11 months and median overall survival (OS) of 42 months.[20] While outcomes are inferior to the use of combination therapies, which will be discussed below, ADT alone remains a good choice for patients who are asymptomatic and have a life expectancy of ≤5 years. Unlike in the non-metastatic setting, intermittent ADT dosing is not recommended in those who can tolerate therapy. A phase III trial of intermittent *versus* continuous ADT in patients with mHSPC was unable to establish non-inferiority (HR 1.10, 90% CI: 0.99–1.23) and found only transient benefits (<3 months) in TRAEs such as erectile dysfunction or mental health.[21] Thus, intermittent ADT is considered for select cases with the focus of treatment is quality of life and not survival.

Treatment intensification

Historically, combined androgen blockade (CAB) was the mainstay of treatment intensification. Recently, the most notable change in the upfront management of de novo metastatic prostate cancer is the addition of docetaxel or novel hormonal therapies such as the adrenal biosynthesis inhibitor abiraterone acetate or androgen receptor inhibitors (apalutamide or enzalutamide) to traditional ADT.

Combined androgen blockade

CAB was initially used to combat the flare phenomenon seen with surgical or medical castration. However, the idea that patients may benefit from maximum androgen blockade is not new. Older studies evaluating the benefit of adding nilutamide to buserelin demonstrated not only a benefit in decreased bone pain ($p<0.05$) but also lower maximal PSA values with combination therapy compared to buserelin alone (550 µg/L *versus* 760 µg/L).[22] Likewise, a phase III study found that, when flutamide was added to leuprolide, patients had a longer progression-free survival (PFS; 16.5 *versus* 13.9 months; $p=0.039$) and OS (35.6 *versus* 28.3 months; $p=0.03$) compared to leuprolide alone.[23] CAB was associated with more TRAEs, specifically diarrhoea (13.6% *versus* 4.9%; $p<0.001$) and hot flashes (63.6% *versus* 60.8%). Additionally, a collaborative meta-analysis by the Prostate Cancer Trialists' Collaborative Group showed a 2.9% 5-year survival benefit of CAB (log-rank $p=0.005$).[24] Subsequent meta-analyses also showed similar survival benefits with CAB with the caveat of a potential increase in toxicity and decrease in quality of life.[24,25]

Docetaxel

The first wave of clinical trials to use combination therapies in mHSPC were GETUG, CHAARTED and STAMPEDE (Table 1). Although these randomized phase III studies differed, two of the three demonstrated OS improvement when docetaxel was added to ADT for men with mHSPC.

The initial analysis of the GETUG-AFU 15 trial did not find a survival benefit when docetaxel was added; 192 patients were randomized to receive either ADT with docetaxel 75 mg/m^2

Table 1. Pivotal trials for the treatment intensification in metastatic hormone-sensitive prostate cancer.

Trial	N	Treatment	Median follow-up (mo)	Median OS (mo)	Median time to mCRPC (mo)				
					Overall	bPFS	cPFS	rPFS	FFS
Docetaxel									
GETUG-AFU 15[26]	192	D + ADT *versus* ADT	50	58.9 *versus* 54.2 (HR 1.01, p=0.955)	NR	22.9 *versus* 12.9 (HR 0.72, p=0.005)	23.5 *versus* 15.4 (HR 0.75, p=0.015)	NR	NR
CHAARTED[7]	790	D + ADT *versus* ADT	29.8	57.6 *versus* 44.0 (HR 0.61; p<0.001)	20.2 *versus* 11.7 (HR 0.61, p<0.001)	NR	33.0 *versus* 19.8 (HR 0.61, p<0.001)	NR	NR
STAMPEDE[28] (Arms A, C, and E)	ITT= 2962 M1= 1817	ADT *versus* D + ADT *versus* D + ZA + ADT	43	ITT: 71 *versus* 81 (HR 0.78, p=0.006) *versus* 76 (HR 0.82, p=0.022) M1: 45 *versus* 60 (HR 0.76, p=0.005) *versus* 55 mo (HR 0.79, p=0.015)	NR	NR	NR	NR	ITT: 20 *versus* 37 (HR 0.62, p=0.413 × 10^{-13}) *versus* 36 (HR 0.62, p=0.134 × 10^{-12}) M1: HR 0.61, p=0.283 × 10^{-10}
Androgen receptor agonists									
LATITIUDE[6]	1199	AA/P + ADT *versus* ADT	30.4	NE *versus* 34.7 (HR 0.62, p<0.001)	NR	33.2 *versus* 7.4 (HR 0.30, p<0.001)	Pain: NR *versus* 16.6 (HR 0.70, p<0.001)	33.0 *versus* 14.8 (HR 0.47, p<0.001)	NR
STAMPEDE (Arm G)[30]	1917 M1=1002	AA/P + ADT *versus* ADT	40	At 3 years ITT: 83% *versus* 76% (HR 0.63, p<0.001) M1: HR 0.61 (95% CI 0.49–0.75)	ITT: 3-year PFS 80% *versus* 62% (HR 0.40, p<0.001)	(0.26–0.37)	ITT Symptomatic skeletal event: HR 0.46, p<0.001	NR	At 3 years ITT: 75% *versus* 45% (HR 0.29, p<0.001) M1: HR 0.31 (95%CI 0.26–0.37)

(Continued)

Table 1. (*Continued*)

Trial	N	Treatment	Median follow-up (mo)	Median OS (mo)	Median time to mCRPC (mo)				
					Overall	bPFS	cPFS	rPFS	FFS
ARCHES[10]	1150	Enza + ADT *versus* ADT	14.4	NE *versus* NE (HR 0.81, p=0.3361)	NE *versus* 13.8 (HR 0.28, p<0.001)	NE *versus* NE (HR 0.19, p<0.001)	Pain: HR 0.82, p=0.0322	NE *versus* 19.0 (HR 0.39, p<0.001)	NR
TITAN[11]	1052	Apa + ADT *versus* ADT	22.7	NE *versus* NE (HR 0.67, p=0.005)	NR	NE *versus* 12.9 HR 0.26 (95% CI 0.21–0.32)	Pain: HR 0.83, p=0.12	NE *versus* 22.1 (HR 0.48, p<0.001)	NR

AA/P, abiraterone acetate with prednisone; ADT, androgen deprivation therapy; Apa, apalutamide; bPFS, biochemical progression-free survival; cPFS, clinical progression-free survival; D, docetaxel; Enza, enzalutamide; FFS, failure-free survival; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; ITT, intent-to-treat population; M1, metastatic population; mo, months; NE, not estimable; NR, not reported; OS, overall survival; rPFS, radiographic progression-free survival; ZA, zolendronic acid.

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every 3 weeks for up to 9 cycles or ADT alone.[26] At a median follow-up of 50 months, while there were benefits in time to biochemical progression (22.9 *versus* 12.9, HR 0.72, 95% CI 0.57–0.91; p=0.005) and clinical progression (23.5 *versus* 15.4, HR 0.75, 95% CI 0.59–0.94; p=0.015), there was no benefit in OS (58.9 *versus* 54.2 months, HR 1.01, 95% CI 0.75–1.36; p=0.955). Of note, 62% of patients randomized to ADT alone were started on docetaxel at the time of progression. The post hoc analysis continued to show that, at a median follow-up of 83.9 months, there was a non-significant benefit of adding docetaxel to ADT (62.1 *versus* 48.6 months, HR 0.88, 95% CI 0.68–1.14; p=0.3).

In CHAARTED, 790 patients with mHSPC were randomized to receive ADT with docetaxel 75 mg/m^2 every 3 weeks for 6 cycles *versus* ADT alone.[7] The eligibility criteria included patients who had adjuvant ADT greater than 1 year prior to enrolment and patients who started ADT within 120 days of randomization. At a median follow-up time of 29.8 months, patients who received combination therapy had improved OS (57.6 *versus* 44.0 months, HR 0.61, 95% CI 0.47–0.80; p<0.001), prolonged time to castration-resistant disease (20.2 *versus* 11.7 months, HR 0.61, 95% CI 0.51–0.72; p<0.001) and a longer time to clinical progression (33.0 *versus* 19.8 months, HR 0.61, 95% CI 0.50–0.75; p<0.001). Interestingly, the OS benefit was most pronounced in patients with high-volume disease as opposed to low-volume disease (49.2 *versus* 32.2 months, HR 0.60, 95% CI 0.45–0.81; p<0.001). The most common grade 3 or higher TRAEs with combination therapy were febrile neutropenia (6.1%), neutropenia (12.1%) and fatigue (4.1%). The updated analysis of CHAARTED continues to show improvement in OS (57.6 *versus* 47.2, HR 0.72, 95% CI 0.59–0.89; p=0.0018) with the addition of docetaxel to ADT at a median follow-up of 53.7 months.[27] Like in the original analysis, there was only a benefit of adding docetaxel to patients with high-volume disease (51.2 *versus* 34.4 months, HR 0.63, 95% CI 0.50–0.79; p<0.001) and no benefit seen with low-volume disease (HR 1.04, 95% CI 0.70–1.55; p=0.86).

Simultaneously, the STAMPEDE trial is a large multiarm trial evaluating the ongoing response of patients with prostate cancer, of all stages, to various treatment arms.[28] In a preplanned subgroup analysis of 1817 patients with mHSPC (62% de novo) at randomization, a benefit was observed when docetaxel 75 mg/m^2 every 3 weeks for six cycles was added to ADT (60 *versus* 45 months, HR 0.76, 95% CI 0.62–0.92; p=0.005) and when docetaxel was added to ADT plus zoledronic acid (55 *versus* 45 months, HR 0.79, 95% CI 0.66–0.96; p=0.015) compared to ADT alone. Long-term follow-up (median follow-up 78.2 months) of STAMPEDE stratified by volume status showed an OS benefit of adding docetaxel to ADT in patients with high-volume disease (HR 0.81, 95% CI 0.64–1.02; p=0.064) and low-volume disease (HR 0.76, 95% CI 0.54–1.01; p=0.107).[29] There was no heterogeneity of treatment effect between low- and high-volume disease ($p_{interaction}$=0.827). Compared with CHAARTED, STAMPEDE had a large sample size, extended follow-up and more patients with de novo, low-volume mHSPC enrolled. Thus, STAMPEDE had a higher power to detect a difference.

Interestingly, as the GETUG-AFU 15 trial data matures, it increasingly resembles the findings of STAMPEDE and CHAARTED. The dissonance between these similar trials is explained by the shortcomings of GETUG's trial design, including an insufficient sample size to generate power (particularly for subgroups), underestimating OS of the ADT arm and a higher proportion of patients with low-volume disease. Additionally, the heterogeneity analysis from STAMPEDE found that patients across all subgroups, including volume status, nodal status, GS and performance status, had similar benefit with the combination of docetaxel and ADT.[29] Thus, while the addition of docetaxel to ADT is beneficial for patients with de novo metastatic disease, specifically for those with high-volume disease, it is less clear for patients with recurrent disease and those with low volume of disease. Further investigation with a larger low-volume subset may reveal a significant OS benefit.

Abiraterone acetate with prednisone

Abiraterone is a cytochrome P-450c17 inhibitor, which works synergistically with ADT to block gonadal and extragonadal androgenesis. The phase III LATITIUDE trial enrolled 1199 patients with newly diagnosed mHSPC with high-risk features to receive either ADT plus abiraterone acetate with prednisone (AA/P) 1000 mg oral daily *versus* ADT alone (Table 1).[6] High risk was defined as two of the three risk factors: GS ≥8, more than three bony lesions and/or visceral metastases. At a median follow-up of 30.4 months, there was not only a radiographic PFS (rPFS) benefit (33.0 *versus* 14.8 months, HR 0.47, 95% CI 0.39–0.55; p<0.001) but also an OS benefit (not estimable *versus* 34.7 months, HR 0.62, 95% CI 0.51–0.76; p<0.001) in those who received combination therapy compared to ADT alone. Most common grade 3 or greater TRAEs were hypertension (20%) and hypokalaemia (10%) with TRAE-related dose reductions in 32% of patients and TRAE-related discontinuation in 12% of patients in the ADT + AA/P arm. The final analysis of LATITUDE showed that, at a median follow-up of 51.8 months, OS was significantly longer in patients who received AA/P (53.3 *versus* 36.5 months, HR 0.66, 95% CI 0.56–0.78; p<0.0001).[8] Post hoc exploratory analysis based on CHAARTED-defined volume status showed that patients with high-volume disease had both an rPFS benefit (33.1 *versus* 14.7 months, HR 0.46, 95% CI 0.39–0.54; p<0.001) and an OS benefit (49.7 *versus* 33.3 months, HR 0.62, 95% CI 0.52–0.74; p<0.0001) compared to ADT alone. In low-volume disease, patients who received the combination had an rPFS benefit (49.8 *versus* 22.4 months, HR 0.59, 95% CI 0.40–0.85; p=0.0048) but OS data remains immature.

Likewise, the STAMPEDE trial also compared the use of AA/P with ADT *versus* ADT across all stages of prostate cancer, 52% of which had metastatic disease (Table 1).[30] At a median follow-up of 40 months, there was an almost significant decrease in mortality (HR 0.61, 95% CI 0.49–0.75) and failure-free survival (HR 0.31, 95% CI 0.26–0.37). While there were more grade 3 or higher TRAEs (47% *versus* 33%), there were no TRAE-related

treatment discontinuations. Long-term follow-up showed that patients with mHSPC treated with AA/P and standard of care (SOC) continued to have a survival benefit (HR 0.60, 95% CI 0.50–0.71; $p=0.31 \times 10^{-9}$) at a median follow-up of 6.1 years.[31] Additionally, the benefit of combination therapy was evident both in CHAARTED-defined low-volume (HR 0.53, 95% CI 0.38–0.74; $p=0.000058$) and high-volume disease (HR 0.59, 95% CI 0.47–0.74; $p=0.000011$) as well as in LATITUDE-defined low-risk (HR 0.66, 95% CI 0.44–0.98; $p=0.41$) and high-risk (HR 0.54, 95% CI 0.43–0.69; $p<0.0001$) groups. Thus, abiraterone acetate is considered front-line therapy for de novo, high-risk, high-volume mHSPC, with a potential increased benefit in those with low-volume disease.

Enzalutamide

Enzalutamide is a non-steroidal androgen receptor inhibitor. Two key trials, ENZAMET and ARCHES, evaluated the use of enzalutamide in combination with ADT, with ENZAMET assessing OS as its primary end point and ARCHES using rPFS to evaluate efficacy.

The phase III ENZAMET trial randomized 1125 men with mHSPC to receive either enzalutamide 160 mg daily with ADT or SOC non-steroidal androgen therapy (Table 1).[9] Early treatment with docetaxel prior to randomization was permitted and used to stratify each arm (65% *versus* 76%). Additionally, patients were divided into high-volume and low-volume disease groups based on the CHAARTED criteria. At a median follow-up of 34 months, there was an OS benefit in the combination therapy arm compared to SOC (HR 0.67, 95% CI 0.52–0.86; $p=0.002$), regardless of volume status ($p_{interaction}=0.04$) and prior docetaxel administration ($p_{interaction}=0.04$). Additionally, there was an improvement in both 3-year PSA PFS (HR 0.39, 95% CI 0.33–0.47; $p<0.001$) and 3-year clinical PFS (HR 0.40, 95% CI 0.33–0.49; $p<0.001$). The most common grade 3 or higher TRAEs were hypertension (8%), febrile neutropenia (7%) and fatigue (6%). Unlike SOC, the most notable TRAE with enzalutamide was seizures ($n=7$).

Results of ARCHES showed that, at a follow-up of 14.4 months, patients with mHSPC treated with enzalutamide + ADT had a significant improvement in rPFS (not reported *versus* 19.0 months, HR 0.39, 95% CI 0.30–0.50; $p<0.001$) compared to ADT alone (Table 1).[10] Based on the CHAARTED criteria, 63.2% of patients had high-volume disease. Like ENZAMET, there was no difference in outcomes based on high-volume (HR 0.43, 95% CI 0.33–0.57) or low-volume disease (HR 0.25, 95% CI 0.14–0.46). At the time of interim analysis, no significant OS benefit was seen with the addition of enzalutamide compared to ADT alone (HR 0.81, 95% CI 0.53–1.25; $p=0.3361$). The lack of benefit seen in OS might be due to a more heterogenous population in the ARCHES study. The inclusion criteria for ARCHES was more lenient than ENZAMET, allowing the enrolment of patients who had high-risk or low-risk disease, high-volume or low-volume disease, or prior docetaxel therapy. Based on its improvement on PFS, the FDA granted the use of enzalutamide as front-line therapy in mHSPC.

Apalutamide

The most recent front-line approval for mHSPC is apalutamide, a potent oral non-steroidal androgen receptor inhibitor. TITAN, an international phase III trial, enrolled 1052 patients with mHSPC (Table 1). Patients were randomized to receive either apalutamide 240 mg daily with ADT or ADT + placebo.[11] When compared to ADT + placebo, patients who received ADT + apalutamide had significantly longer OS (HR 0.67, 95% CI 0.51–0.89; $p=0.005$) and rPFS (HR 0.48, 95% CI 0.39–0.60; $p<0.001$) across all subgroups, including high-volume (HR 0.53, 95% CI 0.41–0.67) and low-volume (HR 0.36, 95% CI 0.22–0.57) disease. The most common grade 3 or higher TRAEs were hypertension (8.4%), rash (6.3%) and ischemic heart disease (4.4%). In addition to its benefit on survival, the addition of apalutamide did not negatively affect health-related quality of life compared to ADT alone, with similar Brief Pain Inventory-Short Form scores (1.14 *vs* 1.14, HR 0.89, 95% CI 0.75–1.06; $p=0.20$), Brief Fatigue Inventory scores (1.29 *vs* 1.43, HR 1.09, 95% CI 0.88–1.35; $p=0.4428$) and Functional Assessment of Cancer Therapy-Prostate total scores (8.87 *versus* 9.23 months, HR 1.02, 95% CI 0.85–1.22; $p=0.85$).[32]

Patients who can tolerate combination therapy have a longer PFS, time to skeletal-related event and OS without compromising quality of life compared to those on ADT alone.[6,7,9,10,22,23,28] However, not all patients are able to receive treatment intensification because of patient comorbidities, performance status or compliance. Additionally, for those who are healthy enough for intensification, it is still not clear which regimen or sequence they would benefit from the most. Given the toxicities and increased healthcare exposures associated with treatment intensification, the identification of patients who would benefit the most from which therapy is critical for the personalization of care.

Emerging therapies

Darolutamide

A new androgen receptor inhibitor already approved in the non-metastatic castration-resistant prostate cancer (CRPC) setting is also moving to the early setting. Unlike the earlier antiandrogen therapies, darolutamide has a higher affinity for the androgen receptor, less penetration of the blood–brain barrier and a lower affinity for GABA receptors.[33,34] The phase III trial, ARASENS, is currently recruiting 1300 patients with mHSPC to receive ADT and docetaxel for 6 cycles followed by darolutamide 600 mg oral bid *versus* placebo with the hopes that the addition of darolutamide will add survival benefit[35] (Table 2, NCT 02799602).

Triplet therapy

It is unclear how 'deep' androgen deprivation has to be to prevent disease progression. In the neoadjuvant setting, the combination of enzalutamide, AA/P and leuprolide for 6 months led to an improved pathologic complete response

Table 2. Ongoing trials for metastatic hormone-sensitive prostate cancer.

NCT	Phase	N	Treatment	Primary end point	Status
Androgen receptor inhibitor					
NCT02799602[35]	III	1300	Darolutamide + ADT + D *versus* ADT + D	OS	Recruiting
Triplet versus doublet therapy					
NCT03436654[41]	II	76	ADT + Apa *versus* ADT + Apa + AA/P	pCR and MRD	Recruiting
NCT02867020[42]	II	126	ADT+ Apa *versus* Apa *versus* Apa + AA/P	Number of patients with undetectable PSA at week 25	Recruiting
PSMA-directed therapy					
NCT04443062[46]	II	58	^{177}Lu-PSMA *versus* SOC	Fraction of patients with disease progression and EOT1 criteria within 6 months and overall	Recruiting
NCT04343885[47]	II	140	^{177}Lu-PSMA + D *versus* D	Undetectable PSA rate at 12 months	Recruiting
Prostate-directed therapy					
NCT01957436[52]	III	1173	ADT + D (arm A) *versus* ADT + AA/P + D (arm B) *versus* arm A + RT (arm C) *versus* arm B + RT (arm D)	OS and PFS	Active, not recruiting
NCT03678025[53]	III	1273	SOC + (RP or RT) *versus* SOC	OS	Recruiting
Metastasis-directed therapy					
NCT03298087[62]	II	28	RP *versus* SOC for 6 months *versus* SBRT *versus* postoperative fractionated RT	Percentage of patients with undetectable PSA 6 months after testosterone recovery	Recruiting
NCT03940235[63]	II	150	SBRT *versus* SBRT + ADT	PFS	Recruiting
NCT03796767[64]	II	40	RT *versus* oligometastasectomy *versus* oligometastasectomy + RT	PSA response rate	Recruiting
DNA damage repair gene mutations					
NCT 03413995[76]	II	30	Rucaparib	Response rate	Recruiting
NCT 04171700[77]	II	220	Rucaparib	ORR	Recruiting
NCT 03934840[79]	III	61	ADT + carboplatin + cabazitaxel × 6 cycles followed by ADT + AA/P	Percentage of patients with PSA or radiographic progression at 1 year	Recruiting

AA/P, abiraterone acetate with prednisone; ADT, androgen deprivation therapy; Apa, apalutamide; D, Docetaxel; EOT, end of treatment; ^{177}Lu-PSMA, ^{177}Lutetium prostate-specific membrane antigen; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; pCR, pathologic complete response; PSA, prostate surface antigen; RT, radiation therapy; RP, radical prostatectomy; SBRT, stereotactic body radiation therapy; SOC, standard of care.

(10%) and minimal residual disease (20%) compared to enzalutamide with leuprolide in patients with high-risk, localized prostate cancer (response difference 14%, 80% CI 3–30; p=0.263).[36] Similar to previous findings, triple therapy did not lead to any added safety concerns.[37]

In mHSPC, the first interim analysis of ENZAMET showed that patients who received early docetaxel therapy in addition to enzalutamide and ADT or ADT with SOC had a PSA PFS (HR 0.46, 95% CI 0.36–0.60) and clinical PFS benefit (HR 0.48, 95% CI 0.37–0.62). However, there was no survival benefit at 3 years (HR 0.90, 95% CI 0.62–1.31).[9] While these data continue to mature, there are three additional phase II studies that will try to answer this question. METACURE will enrol 76 patients with very high-risk localized and low-volume metastatic prostate adenocarcinoma to receive either apalutamide with AA/P and ADT *versus* apalutamide with ADT alone[38] (Table 2, NCT 03436654). All patients on the trial will undergo surgery

and receive radiation therapy to the prostate bed and sites of oligometastatic disease. Their primary end point is to evaluate pathological complete response and minimal residual disease (≤5 mm of morphologically identifiable carcinoma). A similar study will look at outcomes in patients with mHSPC being treated with apalutamide with AA/P and ADT, apalutamide monotherapy, or apalutamide with ADT[39] (Table 2, NCT 02867020). The primary end point of this study will be the number of patients who achieve undetectable PSA. CASCARA will be discussed below.

PSMA therapeutics

PSMA is a transmembrane protein overly expressed on most prostate epithelial cancer cells. When a ligand binds to the extracellular domain of PSMA, the PSMA–ligand complex is endocytosed via clathrin-coated pits.[40] Thus, PSMA is hypothesized to be an actionable target for anticancer treatment. There are multiple molecules being explored for PSMA radioligand therapy (RLT), including alpha- and beta-emitting radioisotopes, bispecific T cell engagers or docetaxel nanoparticles.[41]

The most developed PSMA RLT is ^{177}Lu-PSMA, which is a therapeutic isotope linked to a PSMA-specific antibody. It is currently in the late stages of development. One phase II trial will compare the use of ^{177}Lu-PSMA RLT against SOC in newly diagnosed mHSPC and the other will compare the addition of ^{177}Lu-PSMA RLT to upfront docetaxel treatment[42,43] (Table 2, NCT04443062 and NCT04343885, respectively).

Prostate-directed therapy

Typically, when patients develop asymptomatic metastatic disease, the focus of treatment becomes systemic. However, more studies on the effects of how the primary tumour primes the metastatic environment, through the expression of osteopontin and subsequent activation of bone marrow-derived cells,[44,45] have shined light on the potential benefit of treating the primary site.

A large analysis of the National Cancer Database looked at patients with metastatic prostate cancer treated with ADT with and without prostate-directed therapy from 2004 to 2012.[46] Patients who received ADT and radiation had improved OS (HR 0.624, 95% CI 0.551–0.706; $p<0.001$) and a specific analysis of survivors of ≥1, ≥3 and ≥5 years showed improved benefits (all $p<0.05$). Not surprisingly, secondary analysis showed that ADT with prostatectomy also had superior outcomes than ADT alone (HR 0.38, 95% CI 0.25–0.58; $p<0.001$). In fact, there was no difference in OS between those who received surgical *versus* radiation focal treatment ($p=0.453$).

Findings from retrospective reviews like the National Cancer Database analysis led to the prospective HORRAD trial looking at the benefits of adding prostate-directed external beam radiation therapy (EBRT) to ADT in patients with bone-only metastatic prostate cancer.[12] When comparing ADT with prostate-directed EBRT to ADT alone, there was no PSA recurrence-free survival (HR 0.86, 95% CI 0.69–1.08; $p=0.20$) or OS benefit (HR 0.90, 95% CI 0.70–1.14; $p=0.4$). One hypothesized reason that this was a negative study was that the majority of the patients included had high-volume bony metastases (>5 lesions) with a median PSA of 142 ng/mL. Thus, the STAMPEDE trial included a more balanced number distribution of low-volume and high-volume disease.[47] Once again, no PFS (HR 0.96, 95% CI 0.85–1.08; $p=0.468$) or OS benefits were observed (HR 0.92, 95% CI 0.80–1.06; $p=0.266$). Interestingly, patients with low-volume disease benefited from the addition of prostate-directed EBRT, specifically in failure-free survival (HR 0.60, 95% CI 0.50–0.72; $p=0.0024$) and PFS (HR 0.78, 95% CI 0.63–0.98; $p=0.033$). It is important to put into perspective that the majority of these patients with low-volume disease were on ADT alone, with only 16% of patients receiving concurrent docetaxel. Therefore, while prostate-directed EBRT could benefit those with low-volume disease on ADT, further conclusions about its benefits in those on intensified regimens cannot be drawn. There are currently two ongoing trials looking at prostate-directed therapy in mHSPC. The phase III PEACE-1 trial is a multiarmed trial with two arms comparing the addition of radiotherapy to ADT and docetaxel *versus* ADT with docetaxel and AA/P in mHSPC[48] (Table 2, NCT01957436). This trial has completed recruitment but the analysis has not yet been published. Likewise, the SWOG1802 trial will look at the outcomes of patients who will receive prostatectomy or radiation therapy to the primary tumour in addition to SOC treatment[49] (Table 2, NCT03678025).

Metastases-directed therapy for oligometastatic disease

The idea of oligometastatic disease (≤3 distant metastases) began with Weichselbaum and Hellman,[50–52] who believed that the process from localized to distant metastatic disease was a continuum. The ability to catch and treat cancer during this transition phase could spare patients from the early initiation of systemic therapies and the toxicities that accompany treatment. Prostate cancer with low-volume disease falls under this unique subset of patients. Given the increased sensitivity of ^{18}F-fluciclovine and ^{68}Ga-PSMA PET scans, the incidence of low-volume disease will only continue to increase.[53,54] Thus, it is imperative to devise a plan of how to treat these patients.

A prospective study of 33 patients with oligometastatic mHSPC (≤3 lesions) were treated with a single fraction of 20-Gy stereotactic ablative radiotherapy (SABR) to each lesion.[55] The 2-year ADT-free survival was 38%. Interestingly, there was no change in quality of life from baseline with SABR administration. There was one grade 3 TRAE (vertebral fracture) and no deaths. The larger phase II STOMP trial evaluated the benefits of metastasis-directed therapy in patients with asymptomatic, recurrent, low-volume prostate cancer (≤3 metastases) *versus*

surveillance.[56] At a median follow-up of 5 years, there was a higher percentage of patients who remained ADT free (HR 0.57, 80% CI 0.38–0.84; *p*=0.06) and CRPC free (HR 0.62, 80% CI 0.35–1.09; log-rank *p*=0.27) compared to those on surveillance. Similarly, the ORIOLE trial looked at men with recurrent mHSPC with 1–3 metastases and randomized them to either SABR *versus* observation.[57] Only 19% of patients who received SABR, compared to 61% of patients who underwent observation, had progression at 6 months (*p*=0.005). Interestingly, patients treated with SABR also had more T cell expansion (0.082 *versus* 0.26; *p*=0.03). Both these studies continue to reveal the complexity of low-volume disease and the need to identify patients who would benefit from local therapy *versus* those with higher metastatic potential. Patients treated with SABR also had more T cell expansion (0.082 *versus* 0.26; *p*=0.03). Both these studies continue to reveal the complexity of low-volume disease and the need to identify patients who would benefit from local therapy versus those with higher metastatic potential who would benefit from ADT. Currently, for mHSPC, there are two trials looking at the adjunctive role of metastasis-directed radiotherapy to SOC and one trial comparing outcomes in patients who have their oligometastatic disease treated by surgery, radiation or the combination of both[58–60] (Table 2, NCT03298087, NCT03940235 and NCT03796767).

Homologous recombination repair deficiencies

With the discovery of targeted therapies for patients with defective DNA repair genes in breast and ovarian cancer, investigations of the role of homologous recombination repair (HRR) deficiencies in prostate cancer have also begun. Under normal circumstances, when DNA is damaged, the body initiates PARylation to recruit DNA repair complexes. However, in those with HRR deficiencies, this process does not occur.[61–63] Therefore, treating these particular patients with cytotoxic therapies to initiate single-strand DNA injury along with poly(ADP-ribose) polymerase (PARP) inhibitors provides a 'synthetic lethality'.

Mutations in the HRR system with actionable targets can be found in 23–27% of patients with metastatic prostate cancer.[64,65] Patients with HRR mutations have aggressive tumour biology and have a poor prognosis compared to those without mutations when traditional therapies are given.[66,67] However, with the discovery of PARP inhibitors, outcomes have greatly improved in patients.[68–71] There are currently two phase II trials that will explore the use of rucaparib in patients with mHSPC. The TRIUMPH trial will explore the use of rucaparib in the mHSPC setting exclusively[72] (Table 2, NCT 03413995), whereas the phase II LODESTAR trial will enrol all stages of prostate cancer, including unresectable, locally advanced, metastatic and relapsed/progressive disease[73] (Table 2, NCT 04171700). Hopefully, both these trials will clarify the optimal timing for PARP inhibition for metastatic disease. Additionally, capitalizing on the concept of synthetic lethality, the idea of moving up platinum-based therapy from the castration-resistant space is also under way. Based on improved responses to platinum-based therapies in patients with ovarian cancer and HRR mutations,[74] the phase II study, CASCARA, will evaluate the use of carboplatin, cabazitaxel and abiraterone in high-volume mHSPC with and without DNA repair mutations[75] (Table 2, NCT 03934840).

Predictive markers

In the era of precision medicine, investigations looking into ways to personalize treatment are ongoing. Areas of interest include identifying molecular signatures to predict treatment response as well as sequencing and quantifying circulating mRNA to measure tumour burden.

Molecular signatures

Prostate cancer carcinogenesis originates from glandular luminal cells as well as basal cells. Like in breast and bladder cancer, where these cells are derived from can determine the characteristics of how prostate cancer behaves and responds to treatment.[76–79] Zhao et al. used PAM50 to classify 3872 radical prostatectomy samples into luminal A, luminal B or basal subtypes.[76] Patients with luminal B tumours had high preoperative PSA, GS and extra-prostatic extension. Not surprisingly, patients with luminal B subtype had the worst outcomes across all end points, including prostate cancer-specific survival (78% *versus* 89% *versus* 86%) and OS (69% *versus* 82% *versus* 80%) compared to luminal A or basal subtypes. Using matched cohorts, the response to postoperative ADT *versus* placebo based on luminal or basal subtypes was evaluated. Patients with the luminal B subtype had better 10-year distant metastasis-free survival when treated with ADT *versus* placebo (33% *versus* 55%), whereas patients with the non-luminal B subtype did better with placebo than with ADT (21% *versus* 37%).

The correlative study of CHAARTED showed that the predominant histopathologic phenotype of patients with metastatic disease was luminal B subtype (50%), compared to basal (46%) and luminal A (2%) subtypes.[79] There was no difference in distribution of each subtype based on low-volume or high-volume disease status. Similar to the previous study, patients with luminal B subtype prostate cancer had longer OS (52.1 *versus* 29.8 months, HR 0.45, 95% CI 0.25–0.81; *p*=0.007) when docetaxel was administered compared to no administration. Both these studies suggest that the type of prostate cancer progenitor cell can predict treatment response; thus, obtaining this knowledge is invaluable at the start of treatment.

Circulating tumour DNA and microRNA

Circulating tumour DNA (ctDNA) and cell-free DNA (cfDNA) are expelled from the primary tumour into the blood stream and can be used as biomarkers in prostate cancer. A prospective

study evaluating ctDNA fluctuations before, during and after ADT initiation showed that patients with mHSPC and cfDNA levels above the median (9.6 ng/mL) had shorter time to progression to CRPC compared to those who did not (HR 2.29, 95% CI 1.13–4.65; log-rank p=0.02).[80] When stratified by CHAARTED-defined volume status, a high-volume burden had higher levels of cfDNA yield compared to low-volume disease (median 5.82 ng/mL *versus* 3.96 ng/mL; p=0.04). Not surprisingly, it was found that a combination of CHAARTED-defined high-volume disease burden and increased ctDNA had the highest rate of ADT failure and worse OS (log-rank p=0.03 for both). Those with a mixed combination, high volume with low ctDNA levels and the reverse, had similar intermediate survival curves. This study suggests that ctDNA can serve as both a predictive and prognostic biomarker for mHSPC.

Similarly, microRNAs (miRNAs) are hypothesized to be released by similar mechanisms as circulating tumour cells; however, they are more readily detected in the blood.[81,82] Correlative studies of patients treated on the SWOG 0925 study explored the use of miRNA in patients with mHSPC treated with ADT with or without cituxumuab.[83] Of the five miRNAs evaluated (miR-200a, miR-200c, mirR-210 and miR-375), only miR-141 was correlated with circulating tumour cell counts at baseline (p=0.0006). Additionally, only baseline miR-375 (p=0.001) and miR-200b (p=0.005) levels correlated with treatment response. This study suggests that miR-375 elevations, along with other miRNA, can also be prognostic in the mHSPC setting.

HSD3B1 genetics and impact in treatment outcome

The *HSD3B1* gene encodes for an enzyme critical in extragonadal androgen synthesis. The presence of the adrenal permissive *HSD3B1*(1245C) allele is associated with increased dihydrotestosterone synthesis and early progression to castration resistance in prostate cancer.[84] A retrospective analysis obtained from the Cleveland Clinic and Mayo Clinic registries looked at outcomes of patients who were started on ADT for post-prostatectomy biochemical recurrence and *HSD3B1* genotyping. They found that patients with homozygous alleles have worse PFS (HR 2.4, 95% CI 1.1–5.3; p=0.029) and OS (HR 3.3, 95% CI 1.3–8.3; p=0.13) compared to those with wild type.[85] A validation study performed by Agarwal et al. showed that, in 102 patients with newly diagnosed mHSPC, approximately 31% of patients had a *HSD3B1*(1245C) variant.[86] Of those with homozygous *HSD3B1*(1245C) alleles, PFS, determined by PSA progression, was much shorter compared to homozygous wild type (11 *versus* 21 months, HR 2.16, 95% CI 1.01–4.58; p=0.046).

Whether *HSD3B1* genotyping can also predict outcomes with more intensified regiments is unclear. A retrospective analysis of CHAARTED found that patients with low-volume disease and the presence of at least one adrenal permissive *HSD3B1*(1245C) allele predicted worse 2-year CRPC-free survival (HR 1.89, 95% CI 1.13–3.14; p=0.02) and 5-year survival (HR 1.74, 95% CI 1.01–3.00; p=0.045).[85] There was no benefit of docetaxel based on genotype. Interestingly, there was also no association seen with high-volume disease and genotype. It is hypothesized that the disease biology behind those with high-volume disease is much more aggressive and less reliant on extragonadal androgen synthesis. Unlike with docetaxel, the *HSD3B1*(1245A>C) allele does affect management with androgen receptor antagonist. Patients with this variant have an increased metabolism of abiraterone.[87]

Taken together, the presence of an *HSD3B1*(1245C) allele suggests a more aggressive prostate cancer that is more resistant to systemic therapies. Thus, genotyping can be helpful for clinicians to help select appropriate treatment options as well as to increase surveillance for disease progression.

Conclusion

Options for the treatment of advanced prostate cancer are evolving at an ever-increasing rate. While numerous therapies have been approved for the castration-resistant and now castration-sensitive space, more clinical trials are needed to elucidate the efficacy, necessity and safety of these treatments for use in earlier disease settings.

Further stratification of patients based on their disease volume will increasingly change the way we treat advanced prostate cancer. Ultimately, the goal is to reach a point at which we are able to completely customize prostate cancer care in a manner that comprehensively considers patients' own molecular phenotype, their disease volume, treatment side-effects and impact on their overall quality of life.

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