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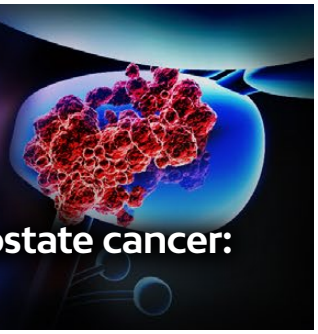
Enzalutamide in men with metastatic hormone-sensitive prostate cancer: focus on the ARCHES and ENZAMET trials



Making Education Easy 2021

Independent commentary by Professor Ian Davis

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Abbreviations used in this issue:

ADT = androgen deprivation therapy; **AR** = androgen receptor; **LHRH** = luteinising hormone-releasing hormone; **mCRPC** = metastatic castration-resistant prostate cancer; **mHSPC** = metastatic hormone-sensitive prostate cancer; **OS** = overall survival; **PFS** = progression-free survival.

This publication is intended as an educational resource for healthcare professionals involved in the management of patients with prostate cancer, focusing on patients with the metastatic hormone-sensitive stage of this disease (mHSPC). In particular, outcomes from two phase 3 trials (ENZAMET and ARCHES) in which enzalutamide was added to androgen deprivation therapy in patients with mHSPC will be discussed.

Introduction

Prostate cancer is a major cause of morbidity and mortality.[1] Worldwide, prostate cancer accounted for 3.8% of deaths in men in 2020.[2] In Australia, prostate cancer was the most commonly diagnosed cancer in men (16,741 cases) in 2020.[3] It resulted in the second highest number of cancer deaths in men (after lung cancer), with an age-standard rate of mortality of 21.3 deaths per 100,000 males.[3]

Most cases of prostate cancer run an indolent course, requiring minimal or no treatment.[4] However, up to one third of men with prostate cancer will develop metastases at some point in the course of the disease.[5, 6] Men with metastatic hormone-sensitive prostate cancer (mHSPC), have metastatic disease, but have not yet received, or are continuing to respond to, androgen deprivation therapy (ADT).[7, 8] Metastatic hormone-sensitive prostate cancer can occur due to recurrence after initial local therapy for localised prostate cancer or as the first presentation of prostate cancer (*de novo* metastatic disease).[7] In men with metastatic castration-resistant prostate cancer (mCRPC), the disease progresses despite the use of ADT.[8] The exact mechanism of transition from hormone-sensitive to castration-resistant prostate cancer is not yet fully understood, and some disease may be inherently resistant to inhibition of signalling through the androgen receptor (AR) axis at presentation.[8] The vast majority of men who die of prostate cancer will have mCRPC prior to death.

Treatment of metastatic hormone-sensitive prostate cancer

Since the discovery in 1941 by Huggins and Hodges that metastatic deposits from prostate cancer responded to endocrine manipulation,[9] reducing serum testosterone to castrate levels via ADT has been the standard of care for patients with metastatic prostate cancer.[10, 11] To this end, Australian guidelines recommend that patients with metastatic prostate cancer can be treated with either orchiectomy or a luteinising hormone-releasing hormone (LHRH) agonist, or antagonist, according to patient preference.[12]

More recently, a paradigm shift has come with the demonstration that the earlier introduction of drugs previously reserved for castrate-resistant disease can improve outcomes for men with hormone-sensitive prostate cancer when added to androgen deprivation at the commencement of therapy.[13-22] Improved outcomes were first shown with the combination of ADT and chemotherapy (docetaxel),[13-16] with survival benefits demonstrated when docetaxel was initiated early in the course of treatment, particularly in men with high-volume and de novo metastatic disease.[23, 24] Large phase 3 studies have since shown improvements in progression-free survival (PFS) and/or overall survival (OS) when newer androgen signaling-targeted inhibitors such as abiraterone,[17-19] apalutamide,[20] or enzalutamide[21, 22] are added to ADT in patients with mHSPC (**Table 1**).

Table 1. **Drugs used in patients with metastatic hormone-sensitive prostate cancer**

Drug	Mechanism of action	Common adverse effects	Relevant studies
Chemotherapy			
Docetaxel	Cytotoxicity	Hair loss, nausea/vomiting, cytopenias, neurotoxicity	GETUG-AF15 (2013)[13] STAMPEDE (2015)[16] CHAARTED (2017)[14]
Androgen signalling–targeted inhibitor			
Abiraterone	CYP17-A1 inhibitor	Peripheral oedema, hypokalaemia, hypertension, urinary tract infection, and liver function test abnormalities[25] (low-dose prednisolone is co-administered to reduce mineralocorticoid excess)	LATITUDE (2017)[18] STAMPEDE (2017)[17]
Apalutamide	Androgen receptor inhibitor	Fatigue, hypertension, rash, gastrointestinal upset, falls, arthralgia, weight loss, hot flush[26]	TITAN (2019)[20]
Enzalutamide	Androgen receptor inhibitor	Fatigue, nausea, hot flush, diarrhea, asthenia, and hypertension[27]	ARCHES (2019)[21] ENZAMET (2019)[22]

Consequently, recent American and European guidelines recommend that, in patients with mHSPC, ADT can be combined with docetaxel, abiraterone, apalutamide, or enzalutamide.[7, 28, 29] In Australia, the choice of agent added to ADT is usually determined according to the availability and reimbursement status of the agent. Patient factors such as disease volume, previous treatments, the ability to tolerate potential side effects associated

with a given drug, and the desire for convenience of an oral versus an intravenously administered drug (or conversely the shorter duration of treatment with docetaxel compared with oral therapy) are all relevant considerations when multiple agents become widely available. For medically fit patients, docetaxel in addition to ADT has usually been the choice of initial therapy for mHSPC in Australia, predominantly as a result of current funding and reimbursement issues.[30]

This education review will focus on the role of enzalutamide in the management of patients with mHSPC, particularly as highlighted in the ARCHES[21] and ENZAMET.[22]

Expert comment

All agents (docetaxel, abiraterone, apalutamide, enzalutamide) are registered in Australia. Only abiraterone, apalutamide, and enzalutamide have specific registration for mHSPC; docetaxel prescribing is unrestricted. The practical considerations of cost and reimbursement mean that docetaxel is the only agent widely available for use, and that patients for whom docetaxel is not thought appropriate will receive androgen deprivation therapy alone. Uptake of docetaxel use in Australia was rapid after the presentation of the CHAARTED data in 2014, including use in both low- and high-volume disease.[31] Use of docetaxel in low-volume disease is now less frequent, and mainly reserved for younger men with higher risk features, despite a relative lack of evidence. An additional point to consider is that all of the trials defined metastatic disease and disease burden based on conventional CT and ^{99m}Tc bone scans. It is not yet clear whether patients with low-volume disease by conventional imaging, but high-volume patterns of disease on novel imaging such as 68Ga-PSMA PET/CT, represent a distinct biological group that should be treated differently. Unfortunately, at present only imperfect clinical indicators are available to help direct choice of therapy; the results of predictive biomarker studies from the large phase III trials are awaited with interest. Clinicians must also take into account likely future treatment needs: will their choice of agent in the mHSPC setting affect their ability to use life-prolonging therapies in mCRPC when it develops?

Enzalutamide

Enzalutamide is an orally administered AR inhibitor that blocks several steps in the AR signaling pathway.[27] It blocks androgen binding to the AR receptors, thereby inhibiting nuclear translocation of the activated AR and the association of the activated AR with DNA.[27, 32] *In vitro*, enzalutamide decreased proliferation and induced prostate cancer cell death.[27]

In Australia, enzalutamide is indicated for the treatment of patients with:[26]

- non-metastatic CRPC (nmCRPC),
- mCRPC following failure of ADT in whom chemotherapy is not yet indicated,
- mCRPC who have previously received docetaxel,
- mHSPC.

The full Xtandi® (Enzalutamide) Product information should be referred to before prescribing this agent.

Enzalutamide is currently PBS listed (authority required) only for patients with CRPC who have:[33]

- failed treatment with docetaxel due to resistance or intolerance; or
- who are unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel.

Previous trials have shown that enzalutamide improved OS in nmCRPC (PROSPER study),[34] and in mCRPC, regardless of whether it was used before (PREVAIL study) or after docetaxel chemotherapy (AFFIRM study).[35, 36] Enzalutamide treatment was generally well tolerated in men with mCRPC, with common adverse reactions including fatigue, nausea, hot flush, diarrhea, asthenia, and hypertension.[27, 32] Enzalutamide should be used with caution in patients with a history of seizure due to rare incidence of this during therapy.[27]

The benefit of adding enzalutamide to ADT in patients with mHSPC has been established in two phase III trials (ARCHES[21] and ENZAMET[22]). The study design and outcomes from these trials will be discussed below.

ARCHES trial

Authors: Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al.[21]

Aim: To assess the efficacy and safety of enzalutamide plus ADT in men with mHSPC, regardless of prior docetaxel or disease volume.[21]

Study design: The multinational (202 centres in North and Latin America, Europe, and Asia), double-blind, phase 3 ARCHES trial randomised 1150 men, who were stratified by disease volume and prior docetaxel therapy, to receive ADT plus enzalutamide 160 mg daily, or ADT plus placebo.[21] Treatment continued until, radiographic disease progression (confirmed by independent central review), unacceptable toxicity, initiation of an investigational agent or new prostate cancer therapy, or treatment withdrawal.[21] Prior ADT and prior docetaxel (up to six cycles) were permitted.

Endpoints: The primary endpoint of the trial was radiographic progression-free survival (rPFS), defined as the time from randomisation to the first objective evidence of radiographic disease progression, as assessed by independent central review or death (defined as death from any cause within 24 weeks from study drug discontinuation).[21] For secondary endpoints see **Table 2.**

Eligibility criteria: Eligible patients had:[21]

- Pathologically-confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet-cell, or small-cell features,
- An Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1,
- Hormone-sensitive metastatic disease, either *de novo* or after recurrence after prior local therapy, documented by a positive bone scan, or metastatic lesions on computed tomography (CT) or magnetic resonance imaging (MRI).

Study outcomes: *Patients:* The median age of patients was 70 years.[21] The majority of patients were Whites; 13% were Asian, and 1.4% were of African American descent. Approximately two-thirds of the trial patients had high-volume disease; and 82% had not received prior docetaxel chemotherapy.[21]

Efficacy: After a median follow-up time of 14.4 months, enzalutamide plus ADT significantly reduced the risk of radiographic disease progression or death compared with placebo plus ADT by 61% (Hazard ratio [HR] 0.39; 95% CI 0.30, 0.50; p<0.001; **Figure 1**).[21]

Significant reductions in rPFS were observed across all pre-specified subgroups, including patients with low versus high disease volume, and patients treated with, or without, prior docetaxel therapy.

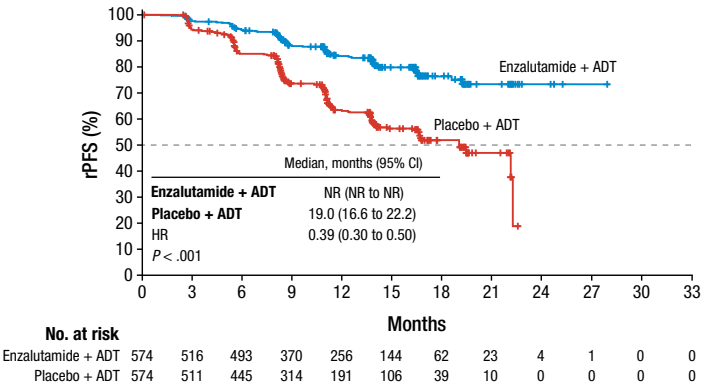


Figure 1. Radiographic progression-free survival in patients with metastatic hormone sensitive prostate cancer in the ARCHES trial[21]

OS data were not mature at the time of rPFS analysis, with 84 deaths (enzalutamide plus ADT, n=39; placebo plus ADT, n=45).[21]

Enzalutamide plus ADT significantly reduced the risk of prostate-specific antigen (PSA) progression, initiation of new antineoplastic therapy, first symptomatic skeletal event, castration resistance, and reduced risk of pain progression (**Table 1**).[21]

Treatment with enzalutamide plus ADT, compared with placebo plus ADT, was not associated with a statistically significant change in the time to deterioration in urinary symptoms (**Table 2**).[21]

Table 2. **Primary and key secondary endpoints in the phase III ARCHES trial**[21]

Endpoint (median values)	Enzalutamide plus ADT (n=574)	Placebo plus ADT (n=576)	Hazard ratio (95% CI)
Primary endpoint			
rPFS, months	NR	19.0	0.39 (0.30, 0.50)***
Secondary endpoints			
Time to PSA progression, months	NR	NR	0.19 (0.13, 0.26)***
Time to initiation of new antineoplastic therapy, months	30.2	NR	0.28 (0.20, 0.40)***
Time to deterioration of urinary symptoms, months	NR	16.8	0.88 (0.72, 1.08)
Overall survival, months	NR	NR	0.81 (0.53, 1.25)
Time to first SSE, months	NR	NR	0.52 (0.33, 0.80)**
Time to castration resistance, months	NR	13.8	0.28 (0.22, 0.36)***
Time to worst pain progression[a], months	14.1	11.1	0.82 (0.69, 0.98)*
Time to pain severity[a], months	19.4	16.8	0.79 (0.65, 0.97)*

[a]Pain progression defined as an increase of ≥2 points from baseline in the average Brief Pain Inventory–Short Form score.

ADT = androgen deprivation therapy; **HR** = hazard ratio; **NR** = not reached; **PSA** = prostate-specific antigen; **rPFS** = radiographic progression-free survival; **SSE** = symptomatic skeletal event.

*p<0.05, **p<0.01, p<0.001.

Safety: Grade 3 or greater adverse events (AEs), serious AEs, and AEs leading to treatment discontinuation were reported in similar proportions of patients in both treatment groups.[21] AEs of all grades were reported in 85.1% of enzalutamide plus ADT recipients and 85.9% of those treated with placebo plus ADT. The most frequently reported AE were hot flush (27.1%), fatigue (19.6%), and arthralgia (12.2%) in patients receiving enzalutamide plus ADT, and hot flush (22.3%), fatigue (15.3%), and back pain (10.8%) in patients treated with placebo plus ADT.

Expert comment

ARCHES was a well-designed, industry-sponsored study that formed the basis of US FDA approval of enzalutamide for mHSPC due to demonstrated benefits in PFS. OS was a secondary endpoint and the data were immature at the time of reporting of the primary endpoint of PFS, but it would be surprising if OS were not also positive with longer follow-up. Benefits were seen in both high- and low-volume disease, and a high proportion of participants (48%) had soft tissue metastases. Docetaxel use was permitted but not concurrently; it was given to only 18% of participants, and those participants did not commence enzalutamide until after docetaxel had finished, i.e. at least four months after commencing ADT and considerably later than patients not planned for docetaxel. The low use of docetaxel was somewhat surprising given that ARCHES commenced recruitment in 2016, well after the evidence for docetaxel from CHAARTED and STAMPEDE became available. That, together with the use of placebo control with ADT, suggests that the control arm might not have represented standard of care offered to the community at the time. However, the benefits of the experimental arm were substantial and convincing, and it was encouraging to see that health-related quality of life metrics were not significantly affected by treatment.

ENZAMET trial

Authors: Davis ID, Martin AJ, Stockler MR, et al.[22]

Aim: To determine the impact in patients with mHSPC of adding enzalutamide to first-line treatment that included testosterone suppression, with or without early docetaxel.[22]

Study design: The multinational (Australia, Canada, Ireland, United Kingdom, New Zealand, United States), open-label ENZAMET trial randomised 1125 men to receive ADT plus either enzalutamide (n=563) or standard nonsteroidal antiandrogen therapy with either bicalutamide, nilutamide, or flutamide (standard-care group; n=562).[22] Prior to randomisation, ADT up to 12 weeks and two cycles of docetaxel were allowed.

Randomisation was stratified according to the volume of disease (high/low), the planned use of early docetaxel (yes/no), the planned use of bone anti-resorptive therapy (yes/no), the score on the Adult Comorbidity Evaluation 27 (ACE-27, 0/1 or 2/3), and trial site.[22]

Endpoints: The primary end point was OS, measured as the interval from randomisation to death from any cause or to the date at which the patient was last known to be alive.[22] Secondary endpoints included PFS, as determined by the PSA level.[22] Clinical progression, another secondary endpoint, was defined as the earliest sign of radiographic progression according to the criteria of the Prostate Cancer Working Group 2 for bone lesions and the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) for soft-tissue lesions, the development of symptoms attributable to cancer progression, or the initiation of another anti-cancer treatment for prostate cancer.[22]

Eligibility criteria: Eligible patients had:[22]

- Prostatic adenocarcinoma with metastases on CT, bone scanning with technetium-99, or both;
- An ECOG performance status of 2 or less, and
- Adequate bone marrow, liver and renal function.

Study outcomes: *Patients:* The median age of the men was 69 years, and 58% were from Australia.[22] High-volume disease was present in 52% of the patients. Early docetaxel treatment was planned in 45% of the patients, although it was not administered to 22 patients (11 in each of randomised groups). Six cycles of docetaxel were given to 65% of patients in the enzalutamide group and 76% of those in the standard-care group.

Overall survival: After a median follow-up of 34 months, men who received ADT plus enzalutamide had a 33% reduced risk of death compared with those receiving ADT plus standard care.[22] A total of 102 deaths were reported in the enzalutamide group compared with 143 deaths in standard-care group (HR 0.67, 95% CI 0.52, 0.86, p=0.002; **Figure 2**). Kaplan–Meier estimates of OS at 3 years were 80% (based on 94 events) for men treated with enzalutamide and 72% (based on 130 events) for men treated with standard care. The results were unaffected by adjustments for geographical region, volume of disease, use of early docetaxel treatment, bone anti-resorptive therapy, and coexisting conditions.

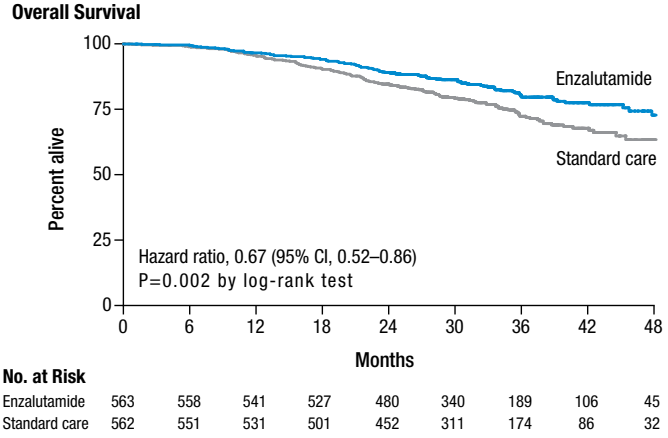
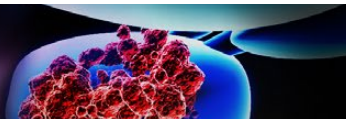


Figure 2. Overall survival in patients with metastatic hormone-sensitive prostate cancer in the ENZAMET trial[22]

Progression-free survival: Men in the enzalutamide group, compared with those receiving standard care, also had better PFS, as determined by PSA level (174 versus 333 events, respectively).[22] At 3 years, 67% of men in the enzalutamide group were alive without PSA progression of their disease, compared with 37% in the standard treatment group (HR 0.39, 95% CI 0.33, 0.47, p<0.001).[22] Clinical progression-free survival was also improved in those treated with enzalutamide, compared with standard care (167 versus 320 events, respectively).[22] At 3 years, 68% of men in the enzalutamide group were alive without clinical progression of their disease, compared with 41% in the standard treatment group (HR 0.40; 95% CI 0.33, 0.49, p<0.001). Access to at least one other life-prolonging therapies (including enzalutamide) occurred in 85% of men on the standard arm compared with 67% on enzalutamide; only 4% of men whose disease progressed on the control arm died without receiving further therapy for CRPC.



Safety: AEs, including serious AEs (42% vs 34%), were more common in men treated with enzalutamide than with standard care.[22] Fatigue was more common in the enzalutamide group (6% vs 1%); seizures occurred in seven patients in the enzalutamide group (1%) and in none of those receiving standard care.[22] Overall, more men treated with enzalutamide (n=33) than with standard care (n=14) discontinued treatment due to AEs, but more men remained on enzalutamide at the time of analysis.[22]

Expert comment

Four points distinguish ENZAMET from ARCHES: (1) it is an academic investigator-initiated study; (2) OS was the primary endpoint; (3) the control arm included active therapy (bicalutamide, nilutamide, or flutamide); (4) concurrent docetaxel was permitted and was used in 45% of participants. Visceral metastases were present in 11% of men. The protocol was amended after completion of recruitment and before analysis to allow additional interim analyses, due to the observation of activity of abiraterone in the LATITUDE and STAMPEDE trials. ENZAMET was positive at its first interim analysis, triggered by 50% of planned events at a median 34 months follow-up, and showed a strong benefit for all endpoints in favour of enzalutamide. The control arm was clearly appropriate, with outcomes similar to the experimental arm of CHAARTED, suggesting that the study represented "real world best practice." Enzalutamide did not show benefit at this interim analysis of additional OS benefit for patients who had been planned to receive docetaxel, to the surprise of many, although there is a strong signal (HR 0.40) for PFS benefit. This latter observation must be interpreted with caution: by definition, the patients contributing to the first interim analysis were those with the worst prognosis, and further follow-up might yet show benefit of the triplet. However, for now ENZAMET provides no evidence that triplet therapy should be used. Use of enzalutamide was associated with small decrements in health-related quality of life endpoints,[37] but these were outweighed by the clinical benefit; docetaxel had a greater adverse effect than enzalutamide. Further planned analyses will occur with more mature follow-up, together with health economic analyses and a large range of translational work. ENZAMET was not cited in the US FDA approval, probably due to uncertainty of the assessors of the effect of docetaxel, but it was used for regulatory approval in Europe, Japan, and Australia, and appears in multiple guideline documents including NCCN and ESMO. ENZAMET was a Plenary presentation at ASCO 2019; included in "ASCO Clinical Cancer Advances 2020: ASCO's Annual Report on Progress Against Cancer," published on World Cancer Day, February 4, 2020 in the Journal of Clinical Oncology at https://ascopubs.org/journal/jco and available online at https://asco.org/CCA; and won the Australian Clinical Trials Alliance 2020 Trial of the Year Award, STInG Award for Excellence in Trial Statistics, and Consumer Involvement Award.

Conclusions

- The ARCHES trial demonstrated that the addition of enzalutamide to ADT significantly reduced the risk of metastatic progression or death in men with mHSPC, including those with low-volume disease and/or prior docetaxel treatment.
- The ENZAMET trial demonstrated that the addition of enzalutamide to ADT was associated with significantly longer PFS and OS in men with mHSPC.
- The safety profile of enzalutamide in men with mHSPC was similar to that observed in previous clinical trials in men with mCRPC.
- Outcomes from the ARCHES and ENZAMET trials have shifted and expanded the treatment landscape for patients with advanced prostate cancer, providing patients with a further option for the management of mHSPC.

Expert concluding comments

One of the commonest questions asked after presentation of the ARCHES, ENZAMET, and TITAN (apalutamide) data was, "Which drug would you choose?" This implies there is a right answer, but the truth is that there is no wrong answer. Clinical factors and patient preference will determine whether a specific man with mHSPC should receive ADT combined with docetaxel, or enzalutamide, or abiraterone, or apalutamide, or ADT alone. We can state with confidence that all of these approaches have a place as best practice treatment in 2021, depending on their local availability.

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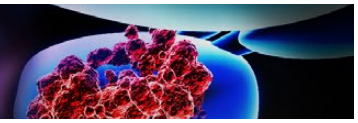

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