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ADIS DRUG EVALUATION

Enzalutamide: A Review of Its Use in Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer

Gillian M. Keating

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Abstract Enzalutamide (Xtandi®) is an androgen receptor inhibitor that blocks several steps in the androgen receptor signalling pathway. This article reviews the clinical efficacy and tolerability of oral enzalutamide in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (CRPC), as well as summarizing its pharmacological properties. In the randomized, double-blind, multinational PREVAIL trial, enzalutamide significantly improved both radiographic progression-free survival and overall survival versus placebo in chemotherapy-naïve men with metastatic CRPC who were asymptomatic or mildly symptomatic. In addition, enzalutamide significantly delayed the need for chemotherapy and the decline in health-related quality of life versus placebo. Enzalutamide was generally well tolerated in chemotherapy-naïve men with metastatic CRPC. In conclusion, enzalutamide is a convenient, effective and well tolerated treatment for chemotherapy-naïve men with metastatic CRPC who are asymptomatic or mildly symptomatic.

Enzalutamide in chemotherapy-naïve men with metastatic castration-resistant prostate cancer: a summary
Androgen receptor inhibitor that blocks several steps in the androgen receptor signalling pathway
Significantly improves radiographic progression-free survival and overall survival vs. placebo
Significantly delays the need for chemotherapy vs. placebo
Significantly delays the decline in health-related quality of life vs. placebo
Generally well tolerated

1 Introduction

Androgen-deprivation therapy [comprising orchiectomy or a luteinising hormone-releasing hormone (LHRH) agonist or antagonist, with or without an antiandrogen] is considered gold standard treatment for men with metastatic prostate cancer [1]. Despite treatment, most patients will eventually experience disease progression, leading to castration-resistant prostate cancer (CRPC) [2]. Androgen receptor signalling remains active in CRPC, indicating an ongoing role for antiandrogen treatment [2, 3].

Enzalutamide (Xtandi®) is a second-generation androgen receptor inhibitor. The use of enzalutamide in the treatment of metastatic CRPC that has progressed despite treatment with docetaxel has been reviewed previously [4]. This article reviews the clinical efficacy and tolerability of

The manuscript was reviewed by: ***J. Carles***, Department of Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; ***C. N. Sternberg***, Department of Medical Oncology, San Camillo and Forlanini Hospitals, Rome, Italy.

G. M. Keating (✉)
Springer, Private Bag 65901, Mairangi Bay 0754, Auckland, New Zealand
e-mail: demail@springer.com

enzalutamide in chemotherapy-naïve men with metastatic CRPC, as well as summarizing its pharmacological properties.

2 Pharmacodynamic Properties

Enzalutamide, a phenylthiohydantoin derivative, blocks several steps in the androgen receptor signalling pathway [3, 5]. Enzalutamide has high affinity for the ligand-binding domain of the androgen receptor (fivefold to eightfold greater affinity than bicalutamide) [3]. As well as competitively inhibiting binding of androgens to androgen receptors, enzalutamide inhibits translocation of activated androgen receptors to the cell nucleus, inhibits the recruitment of androgen receptor cofactors and inhibits androgen receptor binding to androgen response elements within DNA [3, 5, 6]. On positron emission tomography scans, uptake of the androgen receptor ligand 16β-^{18}F-fluoro-5α-dihydrotestosterone (FDHT) was reduced by 20–100 % in patients with CRPC who received enzalutamide 60–480 mg/day, indicating displaced FDHT binding [7].

In vitro, enzalutamide suppressed proliferation and induced apoptosis in human prostate cancer cell lines [3, 5]. The sensitivity of prostate cancer cells to T cell-mediated lysis via androgen receptor-dependent immunomodulation was enhanced by enzalutamide [8]. Enzalutamide lacked androgen receptor agonist activity in CRPC cell models and induced tumour regression in CRPC xenograft models [3, 5].

Several potential mechanisms of enzalutamide resistance in metastatic CRPC have been identified [9]. One possible resistance mechanism is the presence of androgen receptor splice variants (i.e. truncated androgen receptor proteins that lack the ligand-binding domain, but remain constitutively active), in particular, androgen receptor splice variant 7 (AR-V7) [6, 10–13]. For example, among men with metastatic CRPC who received enzalutamide ($n = 31$), clinical outcomes were significantly ($p < 0.01$) better in AR-V7-negative patients than in AR-V7-positive patients [12].

Other possible resistance mechanisms include mutations (e.g. F876L) in the ligand-binding domain of the androgen receptor that confer enzalutamide with agonist activity [14–16], alternative steroid receptors (e.g. glucocorticoid receptors) driving expression of androgen-regulated genes [17], activation of the phosphatidylinositol 3-kinase signalling pathway [18], overexpression of NF-κB2/p52 [19] and overexpression of programmed death ligand-1 [20].

Partial cross resistance between enzalutamide and the androgen synthesis inhibitor abiraterone acetate may occur when these agents are administered sequentially [21–29].

3 Pharmacokinetic Properties

The estimated oral absorption of enzalutamide is 84 % [30]. Enzalutamide pharmacokinetics were linear over the dose range of 30–480 mg/day in men with metastatic CRPC [7]. Maximum plasma concentrations (C_{max}) of enzalutamide were reached in a median of 1 h following oral administration of enzalutamide 160 mg/day (the approved dosage) to patients with metastatic CRPC [31]. Steady-state plasma concentrations were reached after 1 month of daily administration of enzalutamide [7]. At steady state, mean C_{max} values of enzalutamide and its major active metabolite *N*-desmethyl enzalutamide were 16.6 and 12.7 μg/mL, respectively, and mean trough plasma concentrations (C_{trough}) were 11.4 and 13.0 μg/mL, respectively [31]. In a phase I/II trial, the C_{trough} value in patients with metastatic CRPC receiving enzalutamide 150 mg/day (≈10 μg/mL) was reported to be similar to the effective enzalutamide concentration seen in xenograft models of CRPC [7]. Enzalutamide can be administered without regard to food [30, 31].

Following a single oral dose, enzalutamide had a mean apparent volume of distribution of 110 L [30, 31]. Plasma protein binding of enzalutamide and *N*-desmethyl enzalutamide was 97–98 % (primarily to albumin) and 95 %, respectively [30, 31].

Enzalutamide is metabolized by cytochrome P450 (CYP) 2C8 and CYP3A4, with CYP2C8 mainly responsible for the formation of *N*-desmethyl enzalutamide [31]. Following administration of radiolabelled enzalutamide 160 mg, the parent drug, *N*-desmethyl enzalutamide and a major inactive carboxylic metabolite accounted for 30, 49 and 10 % of radioactivity, respectively [31].

The primary route of elimination of enzalutamide is hepatic metabolism [31]. Following administration of radiolabelled enzalutamide 160 mg, 71 and 14 % of radioactivity was recovered in the urine and faeces, respectively [30, 31]. In patients receiving a single oral dose of enzalutamide, the mean apparent clearance was 0.56 L/h and the mean terminal elimination half-life ($t_{½}$) was 5.8 days. *N*-desmethyl enzalutamide had a mean $t_{½}$ of ≈7.8–8.6 days [31].

Dosage adjustment is not needed in patients with mild to moderate hepatic or renal impairment [30, 31], although the EU summary of product characteristics (SPC) recommends caution in patients with moderate hepatic impairment [30]. The pharmacokinetics of enzalutamide in patients with severe hepatic or renal impairment or end-stage renal disease have not been assessed; local prescribing information should be consulted for further information [30, 31].

Bodyweight and age did not alter the pharmacokinetics of enzalutamide to a clinically significant extent, and there

were no clinically relevant differences in enzalutamide pharmacokinetics between Caucasian and Japanese patients [30, 31].

There is potential for clinically relevant pharmacokinetic interactions between enzalutamide and strong CYP2C8 inhibitors (e.g. gemfibrozil), moderate or strong CYP2C8 inducers (e.g. rifampicin), moderate or strong CYP3A4 inducers (e.g. rifampicin, carbamazepine) or substrates of CYP3A4 (e.g. midazolam), CYP2C9 (warfarin) or CYP2C19 (e.g. omeprazole) [30, 31]. Local prescribing information should be consulted for further information [30, 31].

No clinically relevant pharmacokinetic interactions were seen between enzalutamide and the strong CYP3A4 inhibitor itraconazole or the CYP2C8 substrate pioglitazone [30, 31].

4 Therapeutic Efficacy

The potential of enzalutamide in the treatment of men with metastatic CRPC was shown in a phase I/II study [7]. Given the availability of the randomized, double-blind, multinational, phase III PREVAIL study [32], this phase I/II study [7] is not discussed further.

PREVAIL included men with histologically or cytologically confirmed adenocarcinoma of the prostate who had documented metastases and prostate specific antigen (PSA) and/or radiographic progression in bone or soft tissue despite treatment with an LHRH analogue or undergoing orchiectomy (serum testosterone level of $\leq$1.73 nmol/L) [32]. Additional inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and a score on question 3 of the Brief Pain Inventory Short Form (BPI-SF) of 0 or 1 (i.e. asymptomatic) or 2 or 3 (i.e. mildly symptomatic); patients had not received prior cytotoxic chemotherapy, ketoconazole or abiraterone acetate [32]. At baseline, an ECOG performance status of 0 or 1 was seen in 68 and 32 % of patients, respectively, and a BPI-SF question 3 score of 0–1, 2–3 or >3 was seen in 67, 32 and 2 % of patients, respectively [32].

Patients were randomized to receive oral enzalutamide 160 mg once daily or placebo [32]. The co-primary endpoints were radiographic progression-free survival (PFS) and overall survival (OS). After a prespecified interim OS analysis, the study was halted on the recommendation of the data and safety monitoring committee and eligible placebo recipients were offered treatment with enzalutamide. An updated OS analysis included an additional 116 deaths [32].

Enzalutamide improved both radiographic PFS and OS in chemotherapy-naïve men with metastatic CRPC [32]. There was a significant 81 % reduction in the risk of radiographic progression or death with enzalutamide versus placebo (Table 1). The median duration of radiographic

Table 1 Efficacy of oral enzalutamide 160 mg once daily in chemotherapy-naïve men with metastatic castration-resistant prostate cancer; co-primary endpoints in the PREVAIL trial [32]

	ENZ	PL
Radiographic PFS (final analysis)[a]		
Rate of radiographic PFS[b] (% of patients)	65	14
Median radiographic PFS duration (months)	NR	3.9
Hazard ratio for radiographic progression or death (95 % CI)	0.19 (0.15–0.23)*	
OS (prespecified interim analysis)[c]		
Mortality[d] (% of patients)	28	35
Estimated median OS duration (months)	32.4	30.2
Hazard ratio for mortality (95 % CI)	0.71 (0.60–0.84)*	
OS (updated analysis)[c]		
Mortality[d] (% of patients)	34	42
Estimated median OS duration (months)	NR	31.0
Hazard ratio for mortality (95 % CI)	0.73 (0.63–0.85)*	

ENZ enzalutamide, *NR* not yet reached, *OS* overall survival, *PFS* progression-free survival, *PL* placebo

* $p < 0.001$ vs. PL

[a] Radiographic PFS was evaluated in 832 ENZ recipients and 801 PL recipients

[b] Radiographic PFS rate after 12 months' follow-up

[c] OS was evaluated in the intent-to-treat population comprising 872 ENZ recipients and 845 PL recipients. The interim analysis had a data cut-off of September 16 2013 and the updated analysis had a data cut-off of January 15 2014

[d] Median duration of follow-up of $\approx$22 months at the interim analysis and $\approx$26 months at the updated analysis

PFS had not yet been reached in enzalutamide recipients and was 3.9 months in placebo recipients (Table 1) [32].

The risk of death was significantly reduced by 29 % with enzalutamide versus placebo at the prespecified interim OS analysis, with an estimated median OS duration of 32.4 months in enzalutamide recipients and 30.2 months in placebo recipients (Table 1) [32]. Consistent results were seen at the updated OS analysis, with a significant 27 % reduction in the risk of death. At this time point, the estimated median OS had not yet been reached in enzalutamide recipients and was 31.0 months in placebo recipients (Table 1) [32].

The radiographic PFS and OS benefit seen with enzalutamide versus placebo was generally consistent across prespecified subgroups (e.g. ECOG performance status 0 or 1, age <75 or ≥75 years, geographic region, total Gleason score at diagnosis of ≤7 or ≥8, type of progression, presence or absence of visceral disease, baseline PSA value, baseline lactate dehydrogenase value, baseline haemoglobin value) [32]. For example, in the subgroup of patients without visceral metastases ($n = 1{,}513$), the hazard ratio (HR) with enzalutamide versus placebo for radiographic PFS was 0.18 (95 % CI 0.14–0.22) and for OS was 0.69 (95 % CI 0.57–0.83) [analysis available as an abstract and slide presentation] [33]. In patients with visceral metastases (i.e. lung and/or liver metastases; $n = 204$), the HR with enzalutamide versus placebo for radiographic PFS was 0.28 (95 % CI 0.16–0.49) and for OS was 0.82 (95 % CI 0.55–1.23) [33].

The median time until initiation of cytotoxic chemotherapy (28.0 vs. 10.8 months) [HR 0.35; 95 % CI 0.30–0.40] and PSA progression (11.2 vs. 2.8 months) [HR 0.17; 95 % CI 0.15–0.20] was significantly ($p < 0.001$) longer with enzalutamide than with placebo [32]. A significant ($p < 0.001$) reduction in the risk of a first skeletal-related event was also seen with enzalutamide versus placebo (HR 0.72; 95 % CI 0.61–0.84), with 32 % of enzalutamide recipients and 37 % of placebo recipients experiencing a first skeletal-related event at a median of 31.1 and 31.3 months, respectively. In addition, significantly ($p < 0.001$) more enzalutamide than placebo recipients had a PSA decline from baseline of ≥50 % (78 vs. 3 %) or ≥90 % (47 vs. 1 %) [32].

The objective response rate (ORR) was significantly higher in enzalutamide recipients than in placebo recipients (59 vs. 5 %; $p < 0.001$); a complete response was seen in 20 versus 1 % and a partial response was seen in 39 versus 4 % [32]. Among evaluable patients with visceral metastases at baseline who received enzalutamide or placebo ($n = 120$), the ORR was 60 versus 0 % in those with lung metastases and 29 versus 0 % in those with liver metastases (analysis available as an abstract) [34].

In terms of health-related quality of life (HR-QOL), the median time until decline in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) global score (11.3 vs. 5.6 months) [HR 0.63; 95 % CI 0.54–0.72] was significantly ($p < 0.001$) longer with enzalutamide than with placebo [32]. Median times until decline in FACT-P scores for physical, functional, emotional and social well-being were also significantly ($p < 0.001$) longer with enzalutamide than with placebo (analysis available as an abstract) [35]. In addition, during the first 6 months of treatment, significantly ($p < 0.001$) fewer enzalutamide than placebo recipients experienced progression in pain severity (41 vs. 50 %) or pain interference (31 vs. 42 %) [35].

5 Tolerability

Oral enzalutamide was generally well tolerated in chemotherapy-naïve men with metastatic CRPC [32]. In PREVAIL, adverse events were reported in 97 % of enzalutamide recipients and 93 % of placebo recipients; it should be noted that the median duration of the safety reporting period was 17.1 and 5.4 months in the corresponding treatment groups. The most commonly reported adverse events were fatigue, back pain, constipation, arthralgia, decreased appetite, hot flushes, diarrhoea, hypertension, asthenia and falls (Fig. 1). After adjustment for the duration of exposure in enzalutamide and placebo recipients, incidence rates were 14 versus 12 events per 100 patient-years for hot flushes, 11 versus 7 events per 100 patient-years for hypertension and 11 versus 9 events per 100 patient-years for falls [32].

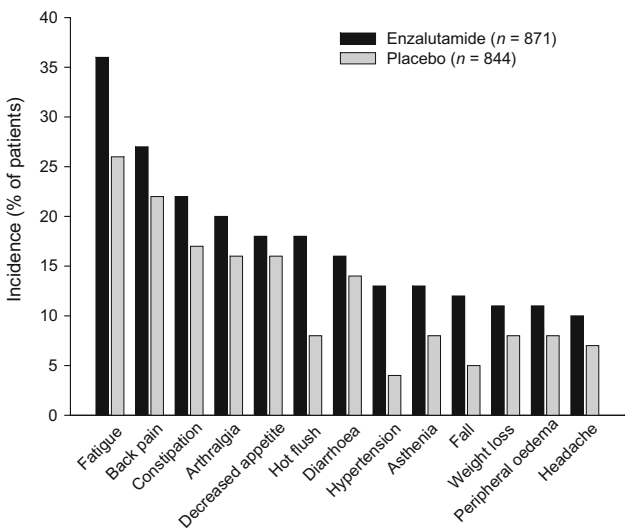

Fig. 1 Most commonly reported adverse events (incidence ≥10 %) in chemotherapy-naïve men with metastatic castration-resistant prostate cancer who received oral enzalutamide 160 mg once daily or placebo in the PREVAIL trial [32]. The median duration of the safety reporting period was 17.1 months in enzalutamide recipients and 5.4 months in placebo recipients

Adverse events of at least grade 3 severity occurred in 43 % of enzalutamide recipients and 37 % of placebo recipients, and included hypertension (7 vs. 2 % of patients), back pain (3 vs. 3 %), fatigue (2 vs. 2 %), arthralgia (1 vs. 1 %), asthenia (1 vs. 1 %), fall (1 vs. 1 %) and weight loss (1 vs. 0.2 %) [32]. The median time to an adverse event of at least grade 3 severity in enzalutamide and placebo recipients was 22.3 and 13.3 months, respectively [32].

Serious adverse events were reported in 32 % of enzalutamide recipients and 27 % of placebo recipients [32]. Adverse events leading to death (most commonly disease progression and a general deterioration in physical health) occurred in 4 % of patients in each treatment group [32]. Treatment discontinuation because of adverse events occurred in 6 % of enzalutamide recipients and 6 % of placebo recipients [32].

In terms of specific adverse events, cardiac adverse events were reported in 10 % of enzalutamide recipients and 8 % of placebo recipients, with atrial fibrillation reported in 2 and 1 % of patients and acute coronary syndromes reported in 1 and 0.5 % of patients [32]. Seizures were reported in one (0.1 %) enzalutamide recipient and one (0.1 %) placebo recipient; at the time of study enrolment, investigators were not aware that both these patients had a history of seizures. There was no evidence of hepatotoxicity in enzalutamide recipients; alanine aminotransferase levels increased in 1 % of enzalutamide recipients and 1 % of placebo recipients [32].

6 Dosage and Administration

Enzalutamide is approved in the USA for the treatment of patients with metastatic CRPC [31] and in the EU for the treatment of men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen-deprivation therapy in whom chemotherapy is not yet clinically indicated, and in men with metastatic CRPC whose disease has progressed on or after docetaxel therapy [30]. The recommended dosage of enzalutamide is 160 mg once daily [30, 31].

Local prescribing information should be consulted for contraindications, special warnings and precautions for use relating to enzalutamide.

7 Current Status of Enzalutamide in Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer

US National Comprehensive Cancer Network (NCCN) guidelines recommend various options in chemotherapy-naïve men with metastatic CRPC who are asymptomatic or mildly symptomatic, including enzalutamide, abiraterone acetate and immunotherapy with sipuleucel T [1]. Systemic chemotherapy should generally be reserved for men with metastatic CRPC who are symptomatic, although treatment with docetaxel may be considered in asymptomatic patients with signs of rapid progression or visceral disease [1]. Use of chemotherapy may be limited by the presence of pre-existing medical conditions and the development of adverse effects [32]. Thus, enzalutamide provides a convenient, less toxic treatment for chemotherapy-naïve metastatic CRPC.

The PREVAIL trial included chemotherapy-naïve men with metastatic CRPC who were asymptomatic or mildly symptomatic. As well as prolonging radiographic PFS and OS, enzalutamide also delayed the need for chemotherapy and the decline in HR-QOL in PREVAIL (Sect. 4). Patients with metastatic CRPC and visceral disease have a worse prognosis than those without visceral disease. Key trials of other agents (e.g. abiraretone acetate [36], sipuleucel T [37]) in chemotherapy-naïve patients with metastatic CRPC excluded those with visceral disease. As a result, abiraretone acetate has a category 2A recommendation for use in patients with visceral metastases in NCCN guidelines [1]. However, PREVAIL included patients with visceral disease (i.e. lung and/or liver metastases) and a significant improvement in radiographic PFS was seen with enzalutamide in this subgroup (Sect. 4), hence its category 1 recommendation in patients with visceral metastases [1].

Abiraterone acetate is administered in combination with prednisone in order to ameliorate symptoms of mineralocorticoid excess (e.g. hypertension, hypokalaemia, peripheral oedema) [38]. Abiraterone acetate recipients may also experience hepatotoxicity. Although hypertension was seen in numerically more enzalutamide than placebo recipients in PREVAIL (Sect. 5), it occurred more often in patients with a history of hypertension and symptoms of mineralocorticoid excess were not present [32]. In addition, enzalutamide was not associated with hepatotoxicity.

Indeed, enzalutamide was generally well tolerated in chemotherapy-naïve men with metastatic CRPC (Sect. 5). Witnessed seizures were reported in two patients receiving supratherapeutic dosages of enzalutamide (360 or 600 mg/day) in a phase I/II study [7]. In the PREVAIL trial, two patients reported a seizure event, one from the enzalutamide group and one from the placebo group; both patients had a prior history of seizures (Sect. 5). Seizures were also reported in 0.6 % of enzalutamide recipients versus 0 % of placebo recipients in the earlier AFFIRM study, which was conducted in men with metastatic CRPC progressing after docetaxel therapy [39]. Exclusion criteria in both PREVAIL [32] and AFFIRM [39] included patients with a history of seizures or any condition that may predispose to seizures. The EU SPC recommends that enzalutamide be

administered with caution to patients with a history of seizures or other predisposing factors (e.g. brain injury, stroke, primary brain tumours, brain metastases, alcoholism) [30]. A phase IV study designed to examine the risk of seizures in patients with metastatic CRPC who have at least one risk factor for seizures and who are receiving enzalutamide is currently underway (UPWARD; NCT01977651).

Currently, there are no biomarkers to identify patients with primary resistance to enzalutamide [40]; more data are needed regarding the potential of AR-V7 as a biomarker [12]. In addition, development of secondary resistance to enzalutamide is common and it appears there may be partial cross resistance between enzalutamide and abiraterone acetate (Sect. 2). It should be noted that patients who had received prior treatment with abiraterone acetate were excluded from the PREVAIL trial [32]. Results of a phase II trial suggest that combination therapy with enzalutamide and abiraterone acetate may help avoid potential escape mechanisms [41]. A phase III trial is currently underway comparing enzalutamide alone with enzalutamide plus abiraterone acetate and prednisone in chemotherapy-naïve patients with metastatic CRPC (NCT01949337).

Antiandrogen withdrawal syndrome (i.e. a decline in PSA levels after antiandrogen cessation) has been reported with antiandrogens such as flutamide and bicalutamide [42]. Enzalutamide may also be associated with antiandrogen withdrawal syndrome in a minority of patients, although more data are needed [43, 44].

In conclusion, enzalutamide is a convenient, effective and well tolerated treatment for chemotherapy-naïve men with metastatic CRPC who are asymptomatic or mildly symptomatic.

Data selection sources: Relevant medical literature (including published and unpublished data) on enzalutamide was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 9 February 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Enzalutamide, ASP?9785, MDV?3100, Xtandi.
Study selection: Studies in patients with metastatic castration-resistant prostate cancer who received enzalutamide. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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