

Enzalutamide: a new prostate cancer targeted therapy against the androgen receptor

Martín Lázaro Quintela^c, Luis León Mateos^d, Sergio Vázquez Estévez^a, Ovidio Fernández Calvo^f, Urbano Anido Herranz^e, Francisco Javier Afonso Afonso^g, Lucía Santomé^b, Luis Antón Aparicio^h

^a *Servicio de Oncología Médica, Hospital Universitario Lucus Augusti, C/Doutor Ulises Romero, s/n, 27003 Lugo, Spain*

^b *Servicio de Oncología Médica, Hospital Povisa, C/Salamanca 5, 36211 Vigo, Spain*

^c *Oncología Médica, Complejo Hospitalario Universitario de Vigo, C/Pizarro 22, 36204 Vigo, Spain*

^d *Servicio de Oncología Médica, Complejo Hospitalario Universitario de Pontevedra, Spain*

^e *Oncología Médica, Complejo Hospitalario Universitario de Santiago de Compostela, c/Choupana s/n, 15706 Santiago de Compostela, A Coruña, Spain*

^f *Servicio Oncología Médica, Complejo Hospitalario Universitario Ourense, C/Ramón Puga 54.32005, Spain*

^g *Oncología Médica, C.H.U.Ferrol, Ferrol, A Coruña, Spain*

^h *Medical Oncology Service, CHUA Coruña, Spain*

Abstract

Enzalutamide (MDV3100), an androgen receptor-signalling inhibitor, represents the most recent compound added to the therapeutic armamentarium for the treatment of metastatic castration-resistant prostate cancer (mCRPC) who progressed to docetaxel. The anti-tumour activity and safety of enzalutamide has been demonstrated in a phase III clinical trial, showing a benefit in overall survival, which was the primary endpoint. There are no head-to-head studies comparing the different treatment options in this subset of patients. In this article, most relevant data published in the literature have been reviewed, with special attention to the therapeutic alternatives currently available for postdocetaxel mCRPC patients, emphasising the mechanisms of action of the different drugs, efficacy and quality of life-related aspects.

Keywords

Enzalutamide; Metastatic castration-resistant prostate cancer; Abiraterone; Cabazitaxel; Docetaxel

Introduction

Docetaxel combined with prednisone is currently the treatment of choice in patients with disseminated castration-resistant prostate cancer (CRPC). The option of docetaxel plus prednisone in advanced CRPC was approved in 2004 after publication of two independent phase III randomised studies showing an improvement in overall survival and quality of life in this group of patients [1], [2]. Thereafter, a better knowledge of the mechanisms of resistance and androgen production-related signalling pathways made possible the synthesis of new drugs with different mechanisms of action, including chemotherapeutic agents (cabazitaxel) [3] and agents with anti-androgenic activity (abiraterone acetate and enzalutamide) [4], [5], [6], all of which have demonstrated an increase in survival after disease progression on docetaxel.

This article presents a review of the different mechanisms of action of these drugs, with a particular focus on enzalutamide (MDV3100) because of its pharmacological characteristics, toxicity profile and health-related quality of life benefits in patients with prostate adenocarcinoma who had been treated with docetaxel.

Comparative analysis of the mechanisms of action

The development of CRPC is characterised by progression of the disease despite serum testosterone levels in the range of castration. There is increasing evidence of CRPC dependence on the androgen-receptor (AR) signalling pathway and underlying mechanisms. Androgen receptor expression is maintained throughout prostate cancer progression. Adrenal and intra-tumour androgens are an important source of AR activation. Other mechanisms resulting in permanent activation of AR include amplification and overexpression of the AR gene, AR mutations reducing ligand-binding specificity, activation of alternative Ras/Raf/MEK/ERK or Src and Ack1 tyrosine kinase pathways, altered levels of proteins promoting co-activation of AR and constitutively active AR splice variants [7].

The taxanes are microtubule-stabilising agents. Microtubules, key components of the cytoskeleton, are crucial in the development and maintenance of cell shape, in the transport of vesicles, traffic of transcription factors, mitochondrial function, cell signalling and cell division and mitosis. Taxanes are known to have a role in the separation of chromosomes during mitosis preventing transition from metaphase to anaphase and promoting apoptosis [8], [9]. Also, taxanes inhibit anti-apoptotic function of the Bcl-2 family proteins [9], [10] and activate cyclin-dependent kinase inhibitor 1A (p21, Cip1) and p53 protein in cancer cells causing cell cycle arrest and apoptotic cell death [11]. Taxanes may also have a direct effect on androgenic signalling pathway in prostate cancer. The microtubule stabilising activity of taxanes leads to AR cytoplasmic sequestration and subsequent inhibition of transcription activity in response to androgens or other ligand-independent pathways [12], [13]. In addition, it has been shown that taxanes induce nuclear accumulation of FOXO1, which is a known AR suppressive nuclear factor [14]. It is possible that taxane inhibition of the AR signalling pathway may be more relevant than the anti-mitotic activity, which may explain why taxanes are the only chemotherapeutic agents with a beneficial effect on survival in prostate cancer. Cabazitaxel overcomes one of the mechanisms of resistance of other taxanes due to poor affinity for the p-glycoprotein drug efflux pump, a major mechanism of resistance to docetaxel [12].

Abiraterone, the active metabolite of abiraterone acetate, is an irreversible inhibitor of CYP17A1 [15], the 17α -hydroxylase and $C_{17,20}$ -lyase enzymatic activity of which is essential for androgen biosynthesis [16]. Pregnenolone and progesterone are converted to 17α -hydroxypregnenolone and 17α -hydroxypregesterone by the 17α -hydroxylase activity of CYP17A1, and then to dehydroepiandrosterone (DHEA) and androstenedione by $C_{17,20}$ -lyase activity. DHEA and androstenedione are precursors of testosterone [16]. CYP17A1 is expressed in testicular, adrenal and prostate tumour tissue. The expression of CYP17A1 in castration-resistant metastases has been reported to be 16.9 times higher than in the primary tumour [17]. Abiraterone requires the concurrent use of low-dose corticosteroids to inhibit ACTH stimulation and subsequent increase of

mineralocorticoids and prevent secondary effects, such as fluid retention, hypokalemia and hypertension.

Enzalutamide has a much higher affinity for the AR receptor than first-generation antiandrogens [7], with no agonist activity and demonstrates activity even in case of amplification and overexpression of the AR, which are well known mechanisms involved in androgenic castration resistance [18]. Enzalutamide inhibits the AR signalling pathway and is a competitor inhibitor of dihydrotestosterone (DHT), the active metabolite of testosterone. In contrast to first-generation antiandrogens, enzalutamide also inhibits nuclear translocation of DHT-AR complex, remaining a significant fraction of AR in the cytoplasm and interfering directly in AR-mediated DNA transcription [18]. This clear differentiating mechanism results in a reduction of prostate cancer cell proliferation and an increase in cell death. Enzalutamide has also shown activity in AR splice variants lacking the ligand binding domain, a further known mechanism of castrate resistance, although detection of AR-V7 in circulating tumour cells may be associated with resistance to enzalutamide and abiraterone [19]. Therefore, in contrast to the ligand-dependent activity of abiraterone (adrenal and intratumoral residual androgens) in CRPC, enzalutamide acts on ligand-dependent resistance mechanisms (AR amplification) as well as ligand-independent resistance mechanisms (AR splice variants) (Fig. 1).

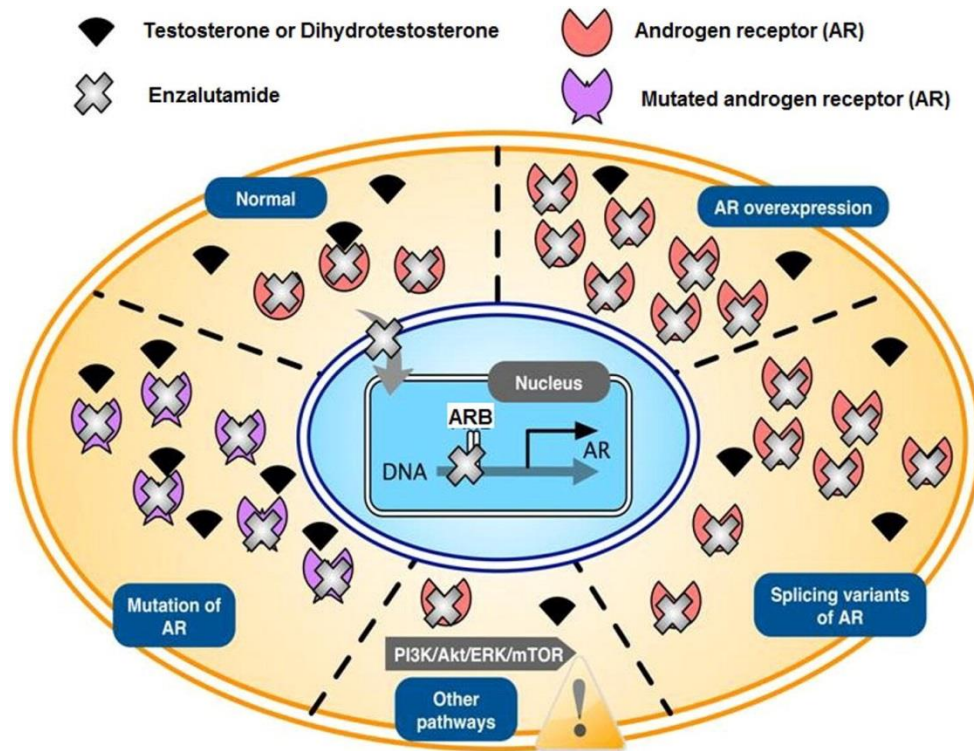


Fig. 1. Mechanism of action of enzalutamide (ARB: androgen receptor binding).

Unlike abiraterone, concomitant steroids are not needed because enzalutamide lacks the detrimental effects of mineralocorticoids excess.

Despite the different mechanisms of action of enzalutamide and abiraterone, there is some scientific evidence of a possible interaction between taxanes and hormonal therapy based on preclinical data suggesting that androgen ablation, although effective in the control of the prostate tumour size, may increase the possibility of metastases and castration resistance by promoting epithelial mesenchymal transition (EMT) [20]. Androgen deprivation also increases ZEB1 transcription factor levels, a direct regulator of EMT related to taxane resistance [21].

Clinical data mostly based on retrospective studies with a small number of patients also indicate that androgen-deprivation therapies may reduce the efficacy of subsequent treatments with taxanes [22], [23], [24]. Studies suggesting a possible cross resistance between enzalutamide and abiraterone are also retrospective with a limited number of patients [25], [26].

Clinical development of enzalutamide

Before the use of enzalutamide in phase I–II studies, the effect of this drug was studied on CRPC xenograft models. Enzalutamide showed the ability to inhibit AR signalling in the overexpression of AR cells with high binding affinity to the AR and lack of agonist activity [18], [27]. Enzalutamide bound to the AR in a castration-resistant LNCaP/AR human prostate cancer cell model showing an eight-fold greater affinity than bicalutamide. Also, enzalutamide induced regression of established LMCaP/AR xenograft tumour cells, which overexpress ARs growing in castrated male mice [18], [27]. These data demonstrated the activity of enzalutamide and allowed the development of subsequent clinical studies.

A phase I–II study was conducted by Scher et al. [28] to assess the antitumour activity and efficacy of enzalutamide in patients with progressive metastatic CRPC (mCRPC). In this study, 140 patients were enrolled in dose-escalation cohorts of 3–6 patients starting with 30 mg dose. The final doses studies were 30 mg ($n = 3$), 60 mg ($n = 27$), 150 mg ($n = 28$), 240 mg ($n = 29$), 360 mg ($n = 28$), 480 mg ($n = 22$) and 600 mg ($n = 3$). Decreases in prostate specific antigen (PSA) levels were seen at all doses, in both chemotherapy-naïve and chemotherapy-treated patients, with a PSA decline of 50% or more in 56% of patients. Partial responses were observed in 13 (22%) out of 59 patients with soft tissue metastases. The median time to radiological progression was 47 weeks. The maximum tolerated dose was 240 mg, with fatigue as the most frequent adverse event (grade 3–4 in 11% of patients). The subsequent lower level (150 mg) was established as the dose to be used in further studies, although the final commercialised dose was 160 mg. This study also assessed AR binding *in vivo* in 22 patients using 16 beta[18F]-fluoro-5 alpha-dihydrotestosterone (FDHT) positron emission tomography (PET) scans to measure change in FDHT uptake before and after starting treatment. All patients showed a clear reduction in FDHT uptake (range approximately ~20–100%).

In the landmark phase III, double-blind, placebo-controlled AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) trial [6], 1199 men with castration-resistant prostate cancer with ≤ 2 prior chemotherapy regimens, including ≥ 1 containing docetaxel, were randomly assigned in a 2:1 ratio, to receive oral enzalutamide at a dose of 160 mg per day (800 patients) or placebo (399 patients). Corticosteroids administration was optional in both arms. At a planned interim analysis after 520 death events, enzalutamide was superior to placebo in the primary endpoint, overall survival (hazard ratio [HR] for death 0.63, 95% confidence interval [CI] 0.53–0.75, $P < 0.001$). On the basis of these results, an independent data and safety monitoring committee recommended that the study be halted and unblinded, with eligible patients in the placebo group offered treatment with enzalutamide. An additional analysis has been done based on data cut-off of 29-June-2012, when 734 events had been reported (61.2% of the total study population). Again, results remain in the same line: HR 0.696 (95% CI: 0.599–0.809) and a difference of 4.9 months in median time to death was observed. Enzalutamide was also superior over placebo with respect to all secondary endpoints, including reduction in PSA level by 50% or more (54% vs. 2%, $P < 0.001$); the soft-tissue response rate (29% vs. 4%, $P < 0.001$); the quality of life response rate (43% vs. 18%, $P < 0.001$); the time to PSA progression (8.3 vs. 3.0 months, HR 0.25, $P < 0.001$); radiographic progression-free survival (8.3 vs.

2.9 months, HR 0.40, $P < 0.001$) and the time to the first skeletal-related event (16.7 vs. 13.3 months, HR 0.69, $P < 0.001$).

Enzalutamide has a good toxicity profile. The different target of enzalutamide and the lack of need to use concomitant steroids are likely to offer some potential advantages over abiraterone in terms of adverse events. In fact, a *post hoc* analysis of the AFFIRM trial found that on-study use of corticosteroids led to worse outcomes regardless of whether patients were randomly assigned to enzalutamide or placebo [29]. Median survival for on-study corticosteroid users was 12.8 months for the enzalutamide arm vs. 9.6 months for placebo ($P < 0.001$). For those not taking corticosteroids, the median survival was not yet reached in enzalutamide-treated patients vs. 18.8 months for placebo ($P < 0.001$). The benefit of enzalutamide compared to placebo was seen in both corticosteroid- and non-corticosteroid-treated patients. Median progression-free survival for enzalutamide and placebo was 5.6 vs. 2.9 months, respectively, in on-study corticosteroid users, and 11.1 vs. 3 months in patients who did not use corticosteroids ($P < 0.001$ for both comparisons). Median time to PSA progression in on-study corticosteroid users was 5.6 months for enzalutamide and 3.1 months for placebo ($P < 0.001$) and 8.6 vs. 2.9 months, respectively ($P < 0.001$) among non-users. Use of on-study corticosteroids was associated with higher rates of grade 3 and 4 adverse events, including anaemia, fatigue, spinal cord compression and back pain. These results should be interpreted with caution, since this was a retrospective analysis, groups were not well balanced and the inferior outcomes in corticosteroid-treated patients may be due to unmeasured confounders or the biological properties of corticosteroid use itself.

Abiraterone has also been tested in mCRPC patients with ECOG PS < 2 progression after docetaxel (phase III trial COU-AA-301) [4], [5]. Patients were randomized to either abiraterone plus prednisone or placebo plus prednisone. OS was increased with abiraterone treatment (15.8 months vs. 11.2 months; HR: 0.74; 95% CI: 0.64–0.86; $P < 0.0001$). Benefits were similar for all secondary endpoints. Several grade 3–4 toxicities were more frequent in patients treated with abiraterone, including fluid retention (4% vs. 1%), hypertension (1% vs. 0%) and cardiac disorders (4% vs. 2%).

In the phase III PREVAIL study [30], enzalutamide was compared to placebo in the pre-docetaxel setting. In a planned interim analysis, more than 1700 men with (mCRPC) that have progressed despite androgen deprivation therapy and chemotherapy naïve were analysed. Patients treated with enzalutamide demonstrated a statistically significant overall survival advantage compared with patients treated with placebo ($P < 0.0001$). Enzalutamide provided a 30% reduction in the risk of death compared with placebo (HR 0.70, 95% CI 0.59–0.83). Moreover, there was a statistically significant radiographic progression-free survival advantage compared with placebo-treated patients ($P < 0.0001$) [30]. Enzalutamide provided an 81% reduction in the risk of radiographic progression or death versus placebo (HR 0.19, 95% CI 0.15–0.23). Also, patients on treatment with enzalutamide showed a delay of 17 months in time to initiation of subsequent as compared to patients treated with placebo (28.0 vs. 10.8 months, HR 0.35, $P < 0.0001$). A total of 58.5% of enzalutamide-treated patients, most of them with soft tissue metastatic disease, showed complete or partial response as compared to 5% in placebo-treated patients. Before final database block, seizure events were not reported in the enzalutamide group as compared with one seizure event in the placebo group. A seizure event was notified in the enzalutamide group after database block and unblinding [30].

The efficacy of enzalutamide in three subsets of patients was assessed in subgroup analyses of the AFFIRM study, including elderly patients, patients with visceral metastases and long-term responders. In relation to elderly patients, older patients accounted for 25% (199/800) and 26% (104/399) of enzalutamide- and placebo-treated patients, respectively. Improved outcomes with enzalutamide treatment were observed in both elderly and younger patients, with similar safety profiles in each age group [31]. In patients ≥ 75 years of age, the median overall survival was 18.2 months in the enzalutamide arm as compared to 13.3 months in the placebo arm (HR 0.60, 95% CI 0.43–0.86, $P = 0.004$). In patients < 75 years, the median overall survival was not met (NM) for enzalutamide vs. 13.6 months for placebo (HR 0.63, 95% CI 0.52–0.78, $P < 0.0001$). Safety and tolerability data were comparable between the two age groups.

In patients with visceral metastases [32], including liver metastases (11.5% [92/800] in the enzalutamide group and 8.5% [34/399] in the placebo group) and lung metastases (15.3% [122/800] in the enzalutamide group and 14.8% [59/399] in the placebo group), the median overall survival in patients with liver and/or lung metastatic disease was 11.4 months (enzalutamide 13.4 months, placebo 9.5 months; HR 0.78 (95% CI 0.56–1.09). Improved outcomes with enzalutamide were observed in both liver and lung mCRPC patients.

A total of 35% (276/800) of patients treated with enzalutamide were on therapy for >12 months and 22% (174/800) for >18 months [33]. When the long-term responder (LTR) subgroup was compared to the whole group of enzalutamide-treated patients, the median survival was longer (7.9 vs. 5.9 years) and had lower disease burden at baseline. Also, 50% PSA response was 87% in the LTR subgroup and 54% in the whole enzalutamide group.

Small clinical series of patients have been reported in which the clinical activity of abiraterone acetate was evaluated in mCRPC progressing after enzalutamide [25], [26] as well as the activity of enzalutamide in patients pre-treated with docetaxel and abiraterone [34], [35], [36], [37]. Data of these studies are summarised in Table 1.

Table 1. Sequential treatment with enzalutamide and abiraterone in mCRPC.

Baseline characteristics and outcome	Abiraterone progressing after enzalutamide (reference #26)	Abiraterone progressing after docetaxel and enzalutamide (reference #25)	Enzalutamide progressing after docetaxel and abiraterone (reference #34)	Enzalutamide progressing after abiraterone (reference #35)	Enzalutamide progressing after docetaxel and abiraterone (reference #36)	Enzalutamide progressing after abiraterone (reference #37)
No. patients	30	38	35	20	39	23
Age, years, median (range)	70 (56–84)	71 (52–84)	70 (57–81)	76 (64–84)	70 (54–85)	76 (65–82)
Metastatic sites (>1)	26 (86.7)	37 (97.4)	NR	13 (65)	33 (84.6)	22 (95.6)
Bone	18 (60)	15 (39.5)	NR	8 (40)	21 (53.8)	NR
Lymph nodes	9 (30)	10 (26.3)	NR	4 (20)	6 (15.4)	4 (17.4)
Efficacy endpoints						
PSA response \geq 50%	1/27 (3.7) ^a	3/38 (7.9) ^a	10/35 (28.6) ^b	9/20 (45)	5/39 (12.8) ^a	9/23 (39.1)
Overall survival, months						
Median (range)	11.5 (6.5–16.6)	7.2 (5.0-NYR)	7.1 (6.2–8.1) ^c	NR	NR	NR
Progression-free survival, months						
Median (95% CI)	3.5 (2.5–4.6)	2.7 (2.3–4.1)	4.0 (2.0–6.0)	NR	2.8 (2.0–3.6)	NR
rProgression-free survival	0 (0)	1/12 (8.3)	1/17 (5.9)	NR	NR	0 (0) ^d

Abbreviations: NR: not reported; PSA: prostate-specific antigen; NYR: not yet reached; rProgression: radiographic progression.

^a PSA response defined as \geq 50% decline in PSA confirmed after \geq 4 weeks.

^b PSA response defined as >50% decline in PSA.

^c Overall survival calculated as mean.

^d A trend for improved radiographic progression-free survival in patients sensitive to abiraterone (15.7 vs. 11.4 weeks, $P = 0.40$).

Toxicity of enzalutamide

Enzalutamide has a favourable toxicity profile. In the phase I–II study [28], fatigue was the most common adverse effect, requiring dose reduction in 11% of patients treated with a daily dose of 240 mg or higher (grade 3). Fatigue usually appears after 30 days of treatment. Other grade 3–4 toxicities were anaemia (3%) and joint pain (2%). Nausea, constipation, diarrhoea and anorexia were mild adverse effects. The percentage of patients who discontinued enzalutamide treatment was 13% in those treated with doses of 360 mg/day or higher, and 1% when the dose administered was 240 mg/day or lower. Two of the 140 patients included in the study developed seizures at doses of 360 and 600 mg/day, respectively; another patient possibly had seizures at a dose of 480 mg/day. The two patients with seizures were also receiving concomitant medication that reduced the threshold for seizures. Other causes of treatment withdrawal were skin rash (2 patients) and a myocardial infarction in a patient with a metabolic syndrome.

In the phase III clinical trial [6], the rate of adverse events was similar in the enzalutamide and placebo arms, with a lower incidence of adverse events (grade < 3) in the enzalutamide group (45% vs. 53%) as compared with placebo. The time elapsed from starting treatment to the first adverse event was 12.6 months and 4.2 months in the enzalutamide and placebo groups, respectively. The incidence (any grade) of fatigue (34%), diarrhoea (21%), hot flashes (20%), musculoskeletal pain (14%) and headache (12%) was higher in the enzalutamide arm. Cardiac disorders were observed in 6% of patients and hypertension in 6.6% among enzalutamide-treated patients versus 8% and 3.3%, respectively, among placebo-treated patients. Patients remained on treatment for a median of 8.3 months in the enzalutamide group and 3 months in the placebo group.

Of the 800 patients assigned to treatment with enzalutamide, seizures were recorded in 6 patients (0.8%) (4 of the seizures were witnessed), whereas no seizures were reported in the placebo group. One of the five patients had a status epilepticus that required medical intervention; in the remaining cases, seizures events were self-limited and did not recur after discontinuation of treatment. However, potential predisposing factors were present in four patients (two patients had brain metastases, one patient had inadvertently been administered lidocaine intravenously immediately before seizure and one patient with brain atrophy had an unwitnessed event classified as a seizure). A mechanism of inhibition of the γ -aminobutyric acid (GABA) related to the ligand-gated ion channels of the GABA_A receptor complex, decreasing the threshold for seizures has been postulated [38]. For this reason, enzalutamide should be used with caution in patients with history of seizures or predisposing factors, such as brain injury, stroke, cerebral metastasis, alcoholism or patients concomitantly treated with medications that may reduce the threshold for seizures (such as droperidol, lidocaine, bupropion, insulin, lithium, etc.) and, in these cases, treatment should be stopped if seizures occur. There is an ongoing study to assess the safety of enzalutamide in patients at risk of seizure events.

In the PREVAIL trial, incidence of hypertension and cardiac disorder in any grade were higher than in the AFFIRM study (13 vs. 6.6% and 10 vs. 6% respectively) [30], whereas the incidence of seizures happened less frequently in the PREVAIL trial (5 of 800 patients in AFFIRM, 1 of 871 patients in PREVAIL).

The most common adverse event recorded in three randomized clinical trials with the use of enzalutamide [6], abiraterone [4] and cabazitaxel [3] are shown in Table 2.

Table 2. Adverse events recorded in three randomised studies of enzalutamide, abiraterone and cabazitaxel.

Adverse event	Enzalutamide (AFFIRM study, reference #6)		Abiraterone (COU.AA-301 study, reference #4)		Cabazitaxel (TROPIC study, reference #3)	
	Any grade	Grade \geq 3	Any grade	Grade \geq 3	Any grade	Grade \geq 3
Anaemia	NR	NR	23	7	97	11
Thrombocytopenia	NR	NR	4	1	47	4
Febrile neutropenia	NR	NR	0	0	0	8
Arthralgia	NR	NR	27	4	11	1
Fatigue	34	6	44	8	37	5
Headache	12	1	NR	NR	NR	NR
Diarrhoea	21	1	18	1	47	6
Cardiac disorder	6	1	13	4	NR	
Oedema/fluid retention	NR	NR	31	3	NR	NR
Hypertension	6.6		10	1	NR	NR
Nauseas	NR	NR	30	2	34	2
Liver dysfunction	1	<1	10	3	NR	NR
Seizures	<1	<1				
Urinary tract infection	NR	NR	12	2	7	1

NR: not reported.

Symptomatic benefit and enzalutamide

Secondary endpoints in the trials of enzalutamide included improvement in health-related quality of life, relief of pain and time to the first skeletal-related event. Improvement of the quality of life is a very relevant objective in the treatment of patients with mCRPC. The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire is a reliable self-administrated scale for assessing health-related quality of life in patients with prostate cancer [40]. The FACT-P is a 39-item questionnaire on which the score for each item can range from 0 to 4, with higher scores indicating a better quality of life.

In the pivotal randomised trial of enzalutamide [6], quality-of-life response (a secondary endpoint) was defined as a 10-point improvement in the global score on the FACT-P questionnaire, as compared with baseline, on two consecutive measurements obtained at least 3 weeks apart, and worsening as 10-point decrease. Patients with baseline and \geq 1 post-baseline evaluation were included in the analysis ($n = 938$) [41]. A greater percentage of patients on enzalutamide reported health-related quality of life improvement compared to placebo (42.2% vs. 14.5%, $P < 0.001$), with a median time to the first quality of life deterioration of 9.0 and 3.7 months for enzalutamide and placebo, respectively ($P < 0.001$). Overall, 46.8% of patients on enzalutamide and 59.3% on placebo experienced health-related quality of life deterioration at some point while on treatment ($P = 0.001$). The time to the first skeletal-related event (defined as pathological fracture, spinal cord compression or palliative radiation therapy or surgery to bone) was 16.7 vs. 13.3 months for the arms of enzalutamide and placebo, respectively (HR 0.69, $P < 0.001$).

In the AFFIRM trial [6], patients were stratified according to the baseline Eastern Cooperative Oncology Group (ECOG) performance status score and the Brief Pain Inventory-Short Form (BPI-SF) question 3 score addressing the average pain over the 7 days before randomisation (0–3 [no pain to mild pain] vs. 4–10 [moderate-to-severe pain]). At baseline, 28% had a BPI-SF score \geq 4. Palliation of pain was defined as a decrease of \geq 30% in the BPI-SF score on week 13 as compared

to baseline, without an increase $\geq 30\%$ in the use of analgesics. Palliation of pain was achieved by 45% of enzalutamide patients vs. 7% of placebo patients ($P = 0.0079$). Pain progression was recorded in 28% of patients treated with enzalutamide and in 39% of patients treated with placebo ($P = 0.0018$) [42].

In the COU-AA-301 randomised trial [39], secondary endpoints were pain control and skeletal-related events. Pain intensity defined as item 3 of the BPI-SF in the past 24 hours. Patients with BPI-SF score ≥ 4 at baseline were included in the analysis. Pain intensity palliation was defined according two consecutive follow-up visits (at least 4 weeks apart) at which the pain intensity score was at least 30% lower than that at baseline, without an increase in analgesic use (defined as a ≥ 1 point increase on the WHO analgesic scale). Abiraterone acetate plus prednisone resulted in significantly more pain palliation than prednisone (45% vs. 28.8%, $P = 0.0005$). The median time to occurrence of first skeletal-event was also longer with abiraterone (25 vs. 20.3 months, $P = 0.0001$). In a recent analysis [43], significant improvements in the FACT-P total score were observed in 48% of patients receiving abiraterone acetate plus prednisone vs. 32% of patients receiving prednisone ($P < 0.0001$).

In the prednisone plus cabazitaxel or mitoxantrone for mCRPC (TROPIC study) [3], pain and analgesic was assessed with the McGill-Melzack present pain intensity (PPI) scale and analgesic use was derived from consumption normalised to morphine equivalents. Pain response rates were similar in the two groups (7.7% mitoxantrone vs. 9.2% cabazitaxel, $P = 0.63$).

Future directions

New questions currently arise in the context of androgen deprivation therapy and AR-dependent tumours. Which is the best drug for starting treatment? Which drug combination improves efficacy or reverses resistance to other treatments? Is enzalutamide active in patients with other solid tumours? According to recent favourable results of enzalutamide obtained in the phase III PREVAIL study [30], enzalutamide is an option in the treatment of mCRPC before docetaxel. However, final analyses of the PREVAIL trial and data provided by other ongoing studies will contribute to define the better use of enzalutamide and other drugs in mCRPC.

At the present time, other studies of enzalutamide in the pre-chemotherapy setting have been registered, such as enzalutamide versus bicalutamide in castrate men with metastatic prostate cancer who have progressed while on while on luteinizing hormone receptor hormone (LHRH) agonist/antagonist or after receiving a bilateral orchiectomy (NCT01288911). This ongoing, head-to-head, phase 2 clinical trial (TERRAIN study) [44] is the first to prospectively determine whether enzalutamide can provide improved antitumour effects vs. bicalutamide in men with metastatic progressive CRPC (enrollment 375 patients). Enzalutamide vs. bicalutamide in men with prostate cancer who have failed after primary androgen deprivation therapy is also being evaluated in a phase II study (STRIVE), in which both metastatic and non-metastatic patients are eligible (enrollment 400 patients) (NCT01664923). Also, enzalutamide as neoadjuvant therapy is being assessed in combination with LHRH analogues (leuprolide and dutasteride) (NCT01547299) or with of abiraterone acetate and prednisone (NCT01946165, NCT01949337). In bone mCRPC, the combination of enzalutamide and abiraterone is going to be assessed in a phase II study (NCT01650194) as well as the combination of enzalutamide and docetaxel in advanced prostate cancer in a phase I study (NCT01565928).

In other hand, enzalutamide is being tested in combination phase I trials for metastatic castration-resistant prostate cancer patients with everolimus (NCT02125084) and crizotinib (NCT02207504). In phase II trials combining with tivozanib (NCT01885949), sipuleucel T (NCT01981122), Radium 223 (NCT02199197 and NCT02225704) or even PSA-TRICOM vaccine in combination with enzalutamide (NCT01875230). Interestingly, there is a phase II trial comparing Radium 223 alone against Radium 223 with abiraterone acetate or Radium 223 with enzalutamide in metastatic castration-resistant prostate cancer patients (NCT02034552). In some phase III trials other combinations are being tested, such as in the PEACE III trial, where

enzalutamide alone is compared with enzalutamide with Radium 223 (NTC02194842) and the arm J in the STAMPEDE trial where they test the combination of antiandrogens deprivation therapy plus abiraterone acetate plus enzalutamide and prednisolone (NTC00268476).

Enzalutamide is also being studied in other tumours, such as in patients with advanced, androgen receptor-positive, triple negative breast cancer (NCT01889238) and in a phase I study of patients with incurable breast cancer (NCT01597193). A summary of these studies is shown in Table 3.

Table 3. Summary of registered clinical trials of enzalutamide in ClinicalTrials.gov.

ClinicalTrials.gov identifier	Study	Treatment arms	Comments
NCT0121299	Phase III	A: enzalutamide B: placebo	Pre-chemotherapy
NCT01288911	Phase II	A: enzalutamide B: bicalutamide	After LHRH analogue or bilateral surgical orchiectomy
NCT01547299	Phase II	A: enzalutamide B: enzalutamide–leuprolide–dutasteride	Neoadjuvant
NCT01946165	Phase II	A: abiraterone–LHRH analogue B: enzalutamide–abiraterone–LHRH analogue	Neoadjuvant
NCT01949337	Phase III	A: enzalutamide B: enzalutamide–abiraterone	Post-chemotherapy
NCT01650194	Phase II	Enzalutamide–abiraterone	Pre-chemotherapy
NCT01565928	Phase I	Enzalutamide–docetaxel	mCRPC
NTC02125084	Phase I	Enzalutamide–everolimus	mCRPC
NTC02207504	Phase I	Enzalutamide–crizotinib	mCRPC
NTC01885949	Phase II	Enzalutamide–tivozanib	mCRPC
NTC01981122	Phase II	Enzalutamide–sipuleucel T	mCRPC
NTC02034552	Phase II	A: Radium 223 B: Radium 223–enzalutamide C: Radium 223–abiraterone	mCRPC
NTC01875230	Phase II	A: Enzalutamide B: Enzalutamide–PSA-TRICOM	mCRPC
NTC02194842	Phase III	A: Enzalutamide B: Enzalutamide–Radium 223	mCRPC
NTC00268476	Phase III	Antiandrogen deprivation therapy– Enzalutamide–abiraterone	Arm J, STAMPEDE trial
NCT02138383	Phase I	Enzalutamide–nab-paclitaxel–gemcitabine	Pancreatic cancer
NCT01889238	Phase II	Enzalutamide	Triple negative breast cancer, androgen receptor-positive
NCT01597193	Phase I	Enzalutamide	Incurable breast cancer

Concluding remarks

The AR signalling pathway is a crucial element in the natural history of mCRPC. Four drugs have been approved for this indication and are currently available for the treatment of patients with mCRPC progressing after docetaxel therapy: enzalutamide, abiraterone, cabazitaxel and RAD-223. The anti-tumour activity of the first three drugs is explained, at least in part, by the mechanism of action on the androgenic signalling pathway at the AR or the androgen precursors level. Enzalutamide has a much higher binding affinity to the AR than the other anti-androgenic drugs, and is without agonist properties. In contrast to abiraterone, enzalutamide acts through ligand-dependent and independent resistance mechanisms. Enzalutamide also lacks the detrimental effects of mineralocorticoid excess, so contrary to what occurs with abiraterone, concomitant administration of systemic corticosteroids is not needed. Health-related quality of life is an important goal in the treatment of an incurable disease such as mCRPC, so that the best treatment is probably that which allowing control of the disease together with a better and more effective control of symptoms with fewer adverse effects. In this respect, although measurements of quality of life cannot be extrapolated across different studies, results reported support that treatment of mCRPC has clinical benefits for the patient. In relation to drug-related adverse events, abiraterone and enzalutamide appear to be better tolerated, with the difference that in the case of enzalutamide, concurrent administration of corticosteroids is not necessary, so it does not have the risk of corticosteroids-related complications. Finally, it should be pointed out that because of its mechanism of action, good tolerance and results of the PREVAIL study [30], several studies are being conducted aimed at positioning enzalutamide in other phases of the clinical evolution of mCRPC, as well as defining its role in combination with other active drugs for the treatment of this neoplasm.

Conflict of interest

All authors confirm that there is not any conflict of interest.

Acknowledgement

The authors thank Marta Pulido, MD, for editing the manuscript and editorial assistance.

References

- [1] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502–12.
- [2] Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513–20.
- [3] De Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;376:1147–54.
- [4] De Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995–2005.
- [5] Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2012;13(10):983–92.
- [6] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367:1187–97.
- [7] Tsao CK, Galsky MD, Small AC, et al. Targeting the androgen receptor signalling axis in castration-resistant prostate cancer (CRPC). *BJU Int* 2012;110:1580–8.
- [8] Jordan MA, Wilson L. Microtubules as a target for anticancer drugs. *Nat Rev Cancer* 2004;4:253–65.
- [9] Moos PJ, Fitzpatrick FA. Taxanes propagate apoptosis via two cell populations with distinctive cytological and molecular traits. *Cell Growth Differ* 1998;9:687–97.

- [10] Li Y, Li X, Hussain M, Sarkar FH. Regulation of microtubule, apoptosis, and cell cycle-related genes by taxotere in prostate cancer cells analyzed by microarray. *Neoplasia* 2004;6:158–67.
- [11] Komlodi-Pasztor E, Sackett D, Wilkerson J, Fojo T. Mitosis is not a key target of microtubule agents in patient tumors. *Nat Rev Clin Oncol* 2011;8:244–50.
- [12] Darshan MS, Loftus MS, Thadani-Mulero M, et al. Taxane-induced blockade to nuclear accumulation of the androgen receptor predicts clinical responses in metastatic prostate cancer. *Cancer Res* 2011;71:6019–29.
- [13] Zhu ML, Horbinski CM, Garzotto M, et al. Tubulin-targeting chemotherapy impairs androgen receptor activity in prostate cancer. *Cancer Res* 2010;70:7992–8002.
- [14] Gan L, Chen S, Wang Y, et al. Inhibition of the androgen receptor as a novel mechanism of taxol chemotherapy in prostate cancer. *Cancer Res* 2009;69:8386–94.
- [15] Mohler JL, Titus MA, Wilson EM. Potential prostate cancer drug target: bioactivation of androstenediol by conversion to dihydrotestosterone. *Clin Cancer Res* 2011;17:5844–9.
- [16] Yamaoka M, Hara T, Kusaka M. Overcoming persistent dependency on androgen signaling after progression to castration-resistant prostate cancer. *Clin Cancer Res* 2010;16:4319–24.
- [17] Montgomery RB, Mostaghel EA, Vessella R, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res* 2008;68:4447–54.
- [18] Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science* 2009;324:787–90.
- [19] Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *New Engl J Med* 2014;371:1028–38.
- [20] Zhu ML, Kyprianou N. Role of androgens and the androgen receptor in epithelial-mesenchymal transition and invasion of prostate cancer cells. *FASEB J* 2010;24:769–77.
- [21] Sun Y, Wang BE, Leong KG, et al. Androgen deprivation causes epithelial-mesenchymal transition in the prostate: implications for androgen-deprivation therapy. *Cancer Res* 2012;72:527–36.
- [22] Mezynski J, Pezaro C, Bianchini D, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? *Ann Oncol* 2012;23:2943–7.
- [23] Febbo PG, Richie JP, George DJ, et al. Neoadjuvant docetaxel before radical prostatectomy in patients with high-risk localized prostate cancer. *Clin Cancer Res* 2005;11:5233–40.
- [24] Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013;14:149–58.
- [25] Loriot Y, Bianchini D, Illeana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Ann Oncol* 2013;24:1807–12.
- [26] Noonan KL, North S, Bitting RL, et al. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Ann Oncol* 2013;24:1802–7.
- [27] Guerrero J, Alfaro IE, Gómez F, et al. Enzalutamide, an androgen receptor signaling inhibitor, induces tumor regression in a mouse model of castration-resistant prostate cancer. *Prostate* 2013;73:1291–305.
- [28] Scher HI, Beer TM, Higano CS, et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1–2 study. *Lancet* 2010;375:1437–46.
- [29] Scher HI, Fizazi K, Saad F, et al. Impact of on-study corticosteroid use on efficacy and safety in the phase III AFFIRM study of enzalutamide (ENZA), an androgen receptor inhibitor. *J Clin Oncol* 2013;31(Suppl. 6):6.
- [30] Beer TM, Armstrong AJ, Rathkopf Y, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371:424–33.
- [31] Sternberg DC, De Bono JS, Chi KN, et al. Outcomes in elderly patients with metastatic castration-resistant prostate cancer (mCRPC) treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. *J Clin Oncol* 2013;31(Suppl. 6) [abstract 16].
- [32] Loriot Y, Fizazi K, De Bono JS, et al. Outcomes in patients with liver or lung metastatic castration-resistant prostate cancer (mCRPC) treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. *J Clin Oncol* 2013;31(Suppl.) [abstract 5065].
- [33] Fleming MT, Scher HI, Fizazi K, et al. Long-term responders to enzalutamide (ENZA) during the phase III AFFIRM trial: baseline characteristics and efficacy outcomes. *J Clin Oncol* 2013;31(Suppl. 6) [abstract 20].
- [34] Schrader AJ, Boegemann M, Ohlmann CH, et al. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. *Eur Urol* 2014;65:30–6.

- [35] Bournakis E, Gyftaki R, Kafantari E, et al. Enzalutamide (ENZA) in heavily pretreated patients with bone metastatic castration resistant prostate cancer (mCRPC) resistant to androgen biosynthesis inhibitor (ABI) treatment – the Hellenic experience of the Name Patient Access Program (NPAP). The European Cancer Congress, Amsterdam, The Netherlands, 2013, abstract 2906.
- [36] Bianchini D, Lorente D, Rodriguez-Vida A, et al. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. *Eur J Cancer* 2014;50:78–84.
- [37] Thomson D, et al. British Association of Urological Surgeons (BAUS), Newcastle, November 14–16, 2013.
- [38] Treiman DM. GABAergic mechanisms in epilepsy. *Epilepsy* 2001;42(Suppl. 3):8–12.
- [39] Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. *Lancet Oncol* 2012;13:1210–7.
- [40] Esper P, Mo F, Chodak G, et al. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology* 1997;50:920–8.
- [41] Miller K, Scher HI, Fizazi K, et al. Effect of enzalutamide on health-related quality of life (HRQoL) in men with metastatic castration-resistant cancer (mCRPC) following docetaxel-based therapy: results from the AFFIRM study. *J Clin Oncol* 2013;31(Suppl. 6) [abstract 17].
- [42] Fizazi K, Scher HI, Saad F, et al. Impact of Enzalutamide, an androgen receptor signaling inhibitor, on time to first skeletal related event (SRE) and pain in the phase 3 AFFIRM Study. *Ann Oncol* 2012;23(Suppl. 9) [abstract 8960].
- [43] Harland S, Staffurth J, Molina A, et al. Effect of abiraterone acetate treatment on the quality of life of patients with metastatic castration-resistant prostate cancer after failure of docetaxel chemotherapy. *Eur J Cancer* 2013;49:3648–57.
- [44] Baskin-Bey ES, Shore ND, Barber K, et al. TERRAIN: A randomized, double-blind, phase II study comparing MDV3100 with bicalutamide (Bic) in men with metastatic castrate-resistant prostate cancer (CRPC). *J Clin Oncol* 2012;30(Suppl.) [abstract TPTPS4698].