Horizon Scanning in Oncology

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1 Drug description

Generic/Brand name/ATC code:

Enzalutamide/Xtandi®/L02BB03

Developer/Company:

Medivation, Inc. and Astellas Pharma US, Inc.

Description:

Enzalutamide (or MDV3100) targets multiple steps in the androgen-receptor-signaling pathway, the major driver of prostate-cancer growth [1, 2]. Through a mechanism that is reported to be different from other approved androgen-receptor (AR) antagonists, enzalutamide inhibits the activity of prostate cancer cell ARs, which may result in a reduction of prostate cancer cell proliferation and correspondingly, in a reduction of the serum prostate specific antigen (PSA) level. AR over-expression in prostate cancer represents a key mechanism associated with prostate cancer hormone resistance [3, 4].

enzalutamide inhibits the activity of prostate cancer cell androgen-receptor antagonists

Capsules containing 40 mg are available. The recommended dose and schedule for enzalutamide is 160 mg orally once daily until disease progression or unacceptable toxicity [5].

160 mg daily orally administered

2 Indication

Enzalutamide (Xtandi®) is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have previously received docetaxel.

3 Current regulatory status

On April 25, 2013, EMA's Committee for Medicinal Products for Human Use adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Xtandi®, 40 mg, intended for the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy [6].

EMA recommended granting of market authorization in 2013, FDA licensed enzalutamide in 2012

In the US, the U. S. Food and Drug Administration approved enzalutamide for the treatment of patients with metastatic CRPC who have previously received docetaxel on August 31, 2012 [7].

4 Burden of disease

prostate cancer most common cancer affecting men in Austria

In 2010 about 4,500 men were newly diagnosed with prostate cancer in Austria and 1,125 died. Prostate cancer is therefore the most common type of cancer in Austrian men. Due to widespread prostate-specific antigen (PSA) testing, prostate cancer is mostly diagnosed at an early, asymptomatic stage of disease, resulting in 60% of patients which are diagnosed before the tumour has spread [8]. From 2005-2009, the median age at diagnosis for cancer of the prostate was 67 years [9].

risk factors are age, ethnicity, family history, diet, genetic factors

Risk factors for developing prostate cancer include age, ethnicity, family history, diet and genetic factors such as mutations in BRCA1 and BRCA2 genes. Prognostic Factors are age, extent of tumour, histologic grade of tumour and the PSA level [10].

to establish prognosis TNM staging and the Gleason score are used

Staging is done by using the TNM system which provides information for choosing the initial therapy. Other factors which impact on the choice of initial therapy are life expectancy, comorbidities, therapeutic side-effects and patients' preferences. Besides the TNM system, the Gleason score is used in addition to establish prognosis. This score is a histopathologic grading system which distinguishes well and poorly differentiated prostate tissue [11].

prognosis strongly depends on the stage at diagnosis

Prognosis strongly depends on the stage at diagnosis. If the tumour is confined to the prostate gland, a median survival of more than 5 years can be expected. For locally advanced forms of prostate cancer, cure is rarely possible, but median survival is still about 5 years. Patients with metastasised tumours have a median survival of 1-3 years [2, 12].

5 Current treatment

initial treatment for metastatic prostate cancer is androgen deprivation therapy

Androgen deprivation therapy (ADT) is generally the initial treatment for men with metastatic prostate cancer. Despite initial response rates of 80 to 90%, nearly all men eventually develop progressive disease following ADT. Disease progression can either be defined as a rise in serum levels of PSA, as progression of pre-existing disease and/or as the development of new metastases [10].

further treatment options are: secondary hormone therapy, immunotherapy, docetaxel

If PSA level rises despite castrate levels of testosterone (serum testosterone <20 ng/dL) the cancer is called "castrate-resistant", "hormone-refractory" or "androgen-independent". Therapeutic options for CRPC:

- Multiple and sequential secondary hormone therapies including withdrawal of ADT, antiandrogen therapy, cytochrome P450 inhibitors, oestrogens and corticosteroids [10].
- Immunotherapy with sipuleucel-T indicated for minimally symptomatic/asymptomatic and chemotherapy-naive patients [4, 12, 13].
- Docetaxel injection concentrate in combination with prednisone [2, 14].

options after first-line docetaxel therapy ...

After disease progression on first-line docetaxel, other therapy options besides enzalutamide are:

- *Abiraterone acetate:* a CYP17 inhibitor usually administered with prednisone [15-17]
- *Cabazitaxel:* a 'second generation' taxane in addition to prednisone [13, 18]
- *Radium-223 chloride:* a calcium-mimetic radiopharmaceutical with high bone affinity [14, 19, 20].

6 Evidence

literature search in 4 databases: 139 hits included: 1 phase III, 1 phase II

A literature search was conducted on the 4th of April 2013 in 4 databases (Medline, Embase, CRD, Cochrane Central). Search terms were "prostate cancer", "enzalutamide", "MDV 3100"and "xtandi". Overall, 139 references were identified. Eligible for inclusion were phase III trials (full text, abstracts) and phase II studies published as full text but also other study designs such as results from compassionate-use programmes or meta-analyses. After applying these inclusion criteria, one phase III trial [21] and one phase II trial [22] were included in this report.

6.1 Efficacy and safety – Phase III studies

Table 1: Summary of efficacy

Study title Increased survival with enzalutamide in prostate cancer after chemotherapy [21]			
Study identifier	NCT00974311, AFFIRM trail		
Design	double-blind, placebo-controlled trial, phase III, randomization in a 2:1 ratio, international, multi-centre (156 sites in 15 countries)		
	Duration	Enrolment: September 2009 – November 2010 Median follow-up: 14.4 months Cut-off date for analysis: 25. September 2011	
Hypothesis	Superiority 90% to detect a hazard ratio of 0.76 for death in the enzalutamide group, compared with the placebo group, with a two sided type I error rate of 0.05.		
Funding	Medivation and Astellas Pharma Global Development		
Treatment groups	Intervention (n=800)	enzalutamide (160 mg orally once daily as four 40-mg capsules), until unacceptable toxicity, disease progression as defined in the protocol, death, or withdrawal.	
	Control (n=399)	matched placebo capsules, until unacceptable toxicity, disease progression as defined in the protocol, death, or withdrawal.	
Endpoints and definitions	Overall survival (primary outcome)	OS	time from randomization to death from any cause
	PSA response	PSA-RESP	reduction in the PSA level from baseline by 50% or more or 90% or more, as confirmed on an additional PSA evaluation performed 3 or more weeks later

Endpoints and definitions	Soft-tissue response	-	defined by the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1
	Radiographic progression free-survival	R-PFS	time from randomization to the earliest objective evidence of radiographic progression or death due to any cause
	Time to first skeletal-related event	-	time from randomization to the occurrence of the first skeletal-related event. A skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain
	Time to PSA progression	TTPSA	defined as an increase by a factor of 1.25 over the baseline level (for patients in whom the PSA level had not decreased) or over the nadir level (for patients in whom the PSA level had decreased) and an increase in the absolute PSA level by at least 2 ng per milliliter, which was confirmed by a repeat measurement
	Quality of life, FACT-P	QOL, FACT-P	defined as a 10-point improvement in their global FACT-P score, as compared with baseline, on two consecutive measurements obtained at least three weeks apart. FACT-P is a multidimensional, self-reported, quality of life instrument used with prostate cancer patients, consisting of 27 core items to assess patient function in four domains: physical, social/family, emotional, and functional wellbeing; and is supplemented by 12 specific items to assess for prostate-related symptoms.
Results and analysis			
Analysis description	ITT A single interim analysis was planned after 520 deaths (80% of the 650 total events). In the primary analysis, a log-rank test to evaluate overall survival, with stratification according to the ECOG performance-status score was used. Other endpoints were tested by means of the stratified log-rank test in a protected hierarchical manner, each at the two-sided significance level of 0.05		
Analysis population	Inclusion	✿ histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features; ongoing androgen deprivation therapy with a gonadotropin releasing hormone (GnRH) analogue or orchiectomy (i.e., surgical or medical castration); serum testosterone level <1.7 nmol/L (50 ng/dL); progressive disease by PSA or imaging after docetaxel-based chemo-therapy in the setting of medical or surgical castration; disease progression defined as one or more of the following three criteria: 1. PSA progression by a minimum of three rising PSA levels with an interval of ≥1 week between each determination. PSA value ≥2 µg/L (2 ng/ml) 2. Soft tissue disease progression defined by RECIST 3. Bone disease progression defined by two or more new lesions on bone scan ✿ No more than two prior chemotherapy regimens with at least one regimen containing docetaxel ✿ ECOG performance status 0–2
	Exclusion	✿ metastases in the brain or active epidural disease ✿ treatment with androgen receptor antagonists (bicalutamide, flutamide, nilutamide), 5-α reductase inhibitors (finasteride, dutasteride), estrogens, or chemotherapy within four weeks of enrolment ✿ treatment with therapeutic immunizations for prostate cancer (e.g., PROVENGE®) ✿ history of prostate cancer progression on ketoconazole ✿ clinically significant cardiovascular disease

Analysis population	Characteristics	*age* – median (range) (%): I 69 (41–92) vs C 69 (49–89) *≥75 years (number of patients (%)):* I 199 (24.9) vs C 104 (26.1) *years since diagnosis:* I 5.9 vs C 6.0 *ECOG* – 0 or 1/2 (%): I 91.3/8.8 vs C 92.0/80 *prior chemotherapy regimens* 1/2/≥3 (%): I 72.4/24.5/3.1 vs C 74.2/23.8/2.0 *baseline PSA (median (range)):* I 107.7 (0.2–11794.1) vs C 128.3 (0.0–19000.0) *PSA progression at baseline (%):* yes/no : I 88.8/11.3 vs C 89.5/10.5		
Descriptive statistics and estimated variability ***P – value <0.001**	Treatment group		*Control*	*Intervention*
	number of subjects, overall		N= 399	N= 800
	median OS, months 95%CI		13.6 11.3–15.8	18.4 17.3–NR
	confirmed PSA decline: ≥1 postbaseline PSA assessment no. (%) *PSA response, no. of patients/total no. (%):* decline ≥50% from baseline * decline ≥90% from baseline *		330 (83) 5/330 (2) 3/330 (1)	731 (91) 395/731 (54) 181/731 (25)
	soft-tissue objective response: patient with measurable disease no. (%) CR + PR, no. /total no. (%) *		208 (52) 8/208 (4)	446 (56) 129/446 (29)
	QOL response, FACT-P: patients with ≥1 postbaseline assessment no. (%) QOL response no/total no. (%) *		257 (64) 47/257 (18)	651 (81) 281/651 (43)
	median time to PSA progression, months 95%CI		3.0 2.9–3.7	8.3 5.8–8.3
	median R-PFS, months 95%CI		2.9 2.8–3.4	8.3 8.2–9.4
	median time to first skeletal-related event, months 95%CI		13.3 9.9–NR	16.7 14.6–19.1
Effect estimate per comparison	*Comparison groups*			*Intervention vs Control*
	OS		HR	0.63
			95% CI	0.53–0.75
			P value	<0.001
	PSA progression		HR	0.25
			95% CI	0.20–0.30
			P value	<0.001
	R-PFS		HR	0.40
			95% CI	0.35–0.47
			P value	<0.001
	time to first skeletal-related event		HR	0.69
			95% CI	0.57–0.84
			P value	<0.001

Abbreviations: C = control, CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, FACT-P = Functional Assessment of Cancer Therapy-Prostate, HR = hazard ratio, I =intervention, no = number, OS = overall survival, PFS = progression free survival, PR = partial response, PSA-RESP = PSA response, R-PFS = radiographic progression free survival, TSP = time to symptom progression, TTPSA = time to PSA progression, NR = not reached

Table 2: Adverse Events

Outcome, n (%)	I (n=800)		C (n= 399)	
Grade (according to CTC version 3.0)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
≥1 adverse event	785 (98)	362 (45)	390(98)	212 (53)
Any serious adverse event	268 (34)	227 (28)	154 (39)	134 (34)
Discontinuation owing to adverse event	61 (8)	37 (5)	39 (10)	28 (7)
Adverse event leading to death	23 (3)	23 (3)	14 (4)	14 (4)
Fatigue	269 (34)	50 (6)	116 (29)	29 (7)
Diarrhoea	171 (21)	9 (1)	70 (18)	1 (<1)
Hot Flash	162 (20)	0	41 (10)	0
Musculoskeletal pain	109 (14)	8 (1)	40 (10)	1 (<1)
Headache	93 (12)	6(<1)	22 (6)	0
Any cardiac disorder	49 (6)	7 (1)	30 (8)	8 (2)
Myocardinal infarction	2 (<1)	2(<1)	2 (<1)	2 (<1)
Abnormality on liver-function testing	8 (1)	3 (<1)	6 (2)	3 (<1)
Seizure	5 (<1)	5 (<1)	0	0

N = number of patients

AFFIRM trial enrolled 1,199 men treated with enzalutamide or placebo

primary endpoint was overall survival

The AFFIRM trial, a phase III study included 1,199 men with metastatic CRPC after previous docetaxel chemotherapy. 72.4% of the patients treated with enzalutamide and 74.2% of the placebo group had one prior chemotherapy regimen, about 24% in both groups had received two cytotoxic chemotherapy regimens and 25 patients (3.1%) of the intervention group and 8 patients (2.0%) getting placebo had been treated with ≥3 prior chemotherapeutic regimens. ECOG performance status was 0 or 1 in 91.3% in the intervention group and 92.0% in the control group. 199 patients (24.9%) in the intervention group and 104 patients (26.1%) getting placebo were ≥75 years old. Patients were randomly assigned to either the intervention group receiving enzalutamide at a dose of 160 mg per day (800 patients) orally or to the placebo group (399 patients). The primary endpoint was overall survival (OS). The study was stopped after a planned interim analysis at the time of 520 deaths. Placebo groups' patients were offered treatment with enzalutamide.

overall survival improved in the enzalutamide group

For all patients receiving enzalutamide the median overall survival was 18.4 months (95% CI, 17.3 to not yet reached) and 13.6 months (95% CI, 11.3 to 15.8) among all patients receiving placebo. Patients aged ≥65 years showed a median overall survival of 18.4 (intervention group) and 13.9 (control group). 308 of 800 patients (39%) died in the enzalutamide group and 212 of 399 patients (53%) died in the placebo group. The interim analysis indicated, that the use of enzalutamide resulted in a 37% relative reduction in the risk of death compared with placebo (hazard ratio HR for death, 0.63, 95% CI, 0.53 to 0.75, P<0.001).

improved secondary outcomes in the intervention group

Also other outcomes such as PSA-level response rate (54% vs. 2%, P<0.001) and soft-tissue response rate (29% vs. 4%, P<0.001) showed improved results for patients treated with enzalutamide. Of note, separate results for complete and partial responses of the soft-tissue response were not stated. However, 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)

were also statistically improved in the intervention group. Quality of life assessed by the FACT-P scale was improved with enzalutamide (43% vs. 18%, P<0.001).

fatigue, diarrhoea, hot flashes were most frequent adverse events

Adverse events (AEs) of any grade were very common in both groups (98%), with fatigue, diarrhoea and hot flashes being the most frequent ones in the enzalutamide group. AEs of ≥grade 3 were with 45.3% in the enzalutamide group less frequent than in the placebo group (53.1%). The median time to the first adverse event was 12.6 months in the enzalutamide group compared to 4.2 months in the placebo group. Cardiac disorders were noted in 6% of patients receiving enzalutamide and in 8% of patients receiving placebo (with cardiac disorders of ≥grade 3 in 1% and 2%). Seizures were reported in 5 of 800 patients (0.6%) receiving enzalutamide, several of whom had predisposing conditions or concomitant treatments. Discontinuation due to AEs of any grade was recorded in the enzalutamide group in 61 patients (8%) and due to AEs ≥grade 3 in 37 patients (5%). In the placebo group 39 patients (10%) stopped participation because of any grade AE and 28 patients (7%) because of AEs grade ≥3. AEs leading to death occurred in 23 patients (3%) of the enzalutamide group and in 14 patients (4%) of the control group.

discontinuation because of adverse events

6.2 Efficacy and safety – further studies

one phase 1-2 study on safety and tolerability

A phase 1–2 study [22] investigated the safety and tolerability of enzalutamide in patients with metastatic CRPC both previously treated with chemotherapy and chemotherapy-naive. 46% had not received any prior chemotherapy, whereas 54% had been treated with a chemotherapeutic agent. Furthermore the maximum tolerated dose should be defined. 140 patients were given an oral daily dose of either 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) enzalutamide daily. Antitumour effects were shown at all doses: PSA decreased of 50% occured in 78 (56%) patients, partial responses in soft tissue were shown in 13 (22%) of 59 patients. Of these, 4 patients (12%) had received previous chemotherapy and 9 (36%) were chemotherapy-naive. Stabilised bone disease was observed in 61 (56%) of 109 patients. The median time to progression was 47 weeks (95% CI 34 – not reached) for disease progression. The maximum tolerated dose for the treatment (>28 days) was 240 mg. The most common adverse event (grade 3-4) was fatigue, which generally developed after the 30-day safety assessment. 16 patients (11%) reported dose-dependent fatigue. Anorexia and nausea were also related to treatment. At doses of 240 mg and above an increasing proportion of patients needed dose reductions because of AEs but none of the 58 patients given doses of 30 mg, 60 mg and 150 mg per day.

dose reduction because of adverse events

7 Estimated costs

no cost estimates for Austria

No cost estimates are available for Austria. The costs for one month's treatment with Xtandi® in the US are estimated at $7,450 that is an average of $59,600/patient (assuming a median of eight cycles is administered) [23].

8 Ongoing research

At http://clinicaltrials.gov/ one phase III study for the investigated indication was found:

one ongoing phase III trial

- *NCT01606982:* multicenter, single-arm, open label study aiming to provide expanded access to enzalutamide and monitor its safety in patients with progressive CRPC previously treated with docetaxel-based chemotherapy. An estimated study completion date is not available.

Another ongoing phase III study investigates use of enzalutamide at an earlier phase (chemotherapy naive patients):

one trial with enzalutamide in chemotherapy-naive patients

- *NCT01212991:* (PREVAIL): multinational, randomized, double-blind, placebo-controlled efficacy and safety study of enzalutamide in chemotherapy-naive patients with progressive metastatic prostate cancer who have failed ADT. The purpose of this study is to determine the benefit of enzalutamide versus placebo as assessed by overall survival and progression-free survival in patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy but not yet received chemotherapy. Estimated study completion date: September 2014.

several current studies in different disease stages and indications

Several other phase II and III studies are currently conducted in different stages of prostate cancer as not yet hormone treated, localized prostate cancer and CRPC (NCT01193244) or in combination with other drug interventions like abiraterone acetate, cabozantinib, galeterone (NCT00676650, NCT01688492). Enzalutamide is also being assessed for incurable breast cancer (NCT01597193).

9 Commentary

approved by FDA in 2012

Enzalutamide is currently under evaluation by the Committee for Medicinal Products for Human Use and was approved by the FDA in August 2012 for the treatment of patients with metastatic CRPC who were previously treated with docetaxel.

enzalutamide compared with placebo in men with progressive CRPC after prior chemotherapy

A phase III randomized study, the AFFIRM trial, compared enzalutamide with placebo in men with progressive CRPC after docetaxel chemotherapy. 24% had received two prior cytotoxic chemotherapy regimens. For patients treated with enzalutamide overall survival was extended by 4.8 months (18.4 vs. 13.6 months, HR, 0.63, P <0.001). All secondary endpoints including proportion of patients with PSA decline, soft-tissue response, quality-of-life response (FACT-P scale), time to PSA progression, radiographic progression free survival and the time to the first radiographic skeletal event favoured patients treated with enzalutamide.

most common adverse event: fatigue, diarrhoea and hot flashes

AEs of any grade were very common in both groups (98%), with fatigue, diarrhoea and hot flashes being the most frequent ones in patients treated with enzalutamide. Higher grade AEs (i.e. ≥3) were less frequent in the enzalutamide group than in the placebo group, as were any serious AE of grade ≥3. Consequently, fewer patients discontinued therapy with enzalutamide than with placebo. Seizures were reported in 5 (0.6%) of the patients treated with

enzalutamide, but even though the use of enzalutamide is not contraindicated in patients with history of seizures, the AFFIRM and the PREVAIL trial had excluded patients known at risk for seizure. The FDA has therefore required an open-label safety study in high-risk seizure patents to elicit the risk of seizures (study results will be available in 2019) [24-26].

therapy options increase

Until recently, therapeutic options for patients with CRPC progressing on docetaxel therapy were limited. Now, enzalutamide represents the third pharmaceutical agent to significantly increase survival in men with CRPC following docetaxel. However, gains in OS were established for enzalutamide in comparison to placebo which cannot be considered a relevant comparator anymore. Also the authors' of the phase III trial acknowledged that fact but highlighted that at study initiation no treatment option for these patients existed. Since other drugs such as cabazitaxel and abiraterone acetate are licensed for CRPC patients who have received docetaxel previously, studies comparing these agents directly are of interest. Even though the HRs are similar for all these 3 agents, absolute gains in OS differ (enzalutamide 4.8 months, abiraterione acetate 3.9 months, cabazitaxel 2.4 months)[16, 18, 21] but since cross-study comparisons are dangerous these results have to be interpreted with caution. However, until direct comparisons between these different agents have become available, other criteria have to be applied to select the most appropriate therapy. For example, enzalutamide is the first agent for which data on quality of life were available at market authorisation.

placebo not appropriate comparator but other agents

modes of administration influence preferred therapy

Further, different modes of administration may determine patients' preferences since cabazitaxel is administered intravenously every 3 weeks, whereas enzalutamide and abiraterone acetate are taken orally, a route of administration patients may prefer [16, 18]. In addition, co-morbidities, concomitant therapies and especially the toxicity profiles of these drugs have to be taken into account when choosing the most appropriate regimen for previously treated patients with metastatic CRPC.

enzalutamide in earlier therapy settings and in combination with other agents

Currently, enzalutamide is only approved in the US for those who have already received docetaxel, but since the PREVAIL trial (NCT01212991) is investigating this drug for earlier lines of therapy it is likely that future indications will comprise docetaxel-naive patients too. Additionally, several trials are under way investigating enzalutamide in combination with other agents, for example enzalutamide in combination with docetaxel (NCT01565928) or abiraterone (NCT01650194). With $7,450/month, enzalutamide will cost on average $59,600/patient in the US (assuming a median of eight cycles is administered). Cost estimates for Austria are not yet available, but it can be assumed that the costs will be comparable to those of other drugs licensed for this indication, e.g. abiraterone acetate costs about 3,450 € (as reimbursed by health insurance) per month [27, 28]. These costs will rise when enzalutamide will be given in combination with other agents used for prostate cancer but also if enzalutamide moves into the pre-chemotherapy setting, as a greater number of cycles may be administered [25, 29].

question how to best combine and apply treatment options

Recent therapeutic advances for managing advanced prostate cancer offer new treatment options including enzalutamide for patients with CRPC. Multiple challenging questions as how to best combine, optimally sequence and select agents for treatment (like abiraterone acetate, cabazitaxel, enzalutamide) are therefore emerging and should be addressed in further clinical trials [30, 31].

References

1. Hoffman-Censits, J. and W.K. Kelly, *Enzalutamide: a novel antiandrogen for patients with castrate-resistant prostate cancer.* Clinical Cancer Research, 2013. **19**(6): p. 1335-9.
2. Lee, D.J., et al., *Novel therapeutics for the management of castration-resistant prostate cancer (CRPC).* BJU International, 2012. **109**(7): p. 968-85.
3. U.S. National Institutes of Health. *NCI thesaurus: Enzalutamide (Code C71744)*. 2013 [cited 11.04.2013]; Available from: http://ncit.nci.nih.gov/ncitbrowser/pages/concept_details.jsf?dictionary=NCI%20Thesaurus&version=13.02d&code=C71744&type=properties.
4. El-Amm, J. and J.B. Aragon-Ching, *The changing landscape in the treatment of metastatic castration-resistant prostate cancer.* Therapeutic Advances in Medical Oncology, 2013. **5**(1): p. 25-40.
5. U.S. Food and Drug Administration. *Prescribing Information – Enzalutamide*. 2012 [cited 11.04.2013]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203415lbl.pdf.
6. European Medicines Agency. *Applications for new human medicines under evaluation*. 2013 [cited 11.04.2013]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/01/WC500137577.pdf.
7. U.S. Food and Drug Administration. *Information on Drugs – Enzalutamide*. 2013 [cited 11.04.2013]; Available from: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm317997.htm.
8. Statistik Austria. *Krebserkrankungen – Prostata*. 2013 [cited 11.04.2013]; Available from: http://www.statistik.at/web_de/statistiken/gesundheit/krebserkrankungen/prostata/index.html.
9. National Cancer Institute. *Incidence and mortality of prostate cancer*. 2013 [cited 25.04.2013]; Available from: http://seer.cancer.gov/statfacts/html/prost.html#incidence-mortality.
10. UpToDate. Online. *Prostate cancer*. 2013 [cited 11.04.2013]; Available from: http://www.uptodate.com/contents/search?search=prostate+cancer&x=0&y=0.
11. National Cancer Institute. *Treatment Option Overview for Prostate Cancer*. 2013 [cited 11.04.2013]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/prostate/HealthProfessional/page3.
12. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines for Prostate Cancer*. 2013 [cited 11.04.2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
13. Fizazi, K., et al., *Novel and bone-targeted agents for CRPC.* Annals of Oncology, 2012. **23 Suppl 10**: p. x264-7.
14. European Association of Urology. *Guidelines on Prostate Cancer*. 2013 [cited 25.04.2013]; Available from: http://www.uroweb.org/gls/pdf/09_Prostate_Cancer_LR.pdf.
15. Ferraldeschi, R., et al., *Abiraterone and novel antiandrogens: overcoming castration resistance in prostate cancer.* Annual Review of Medicine, 2013. **64**: p. 1-13.
16. de Bono, J.S., et al., *Abiraterone and increased survival in metastatic prostate cancer.* New England Journal of Medicine, 2011. **364**(21): p. 1995-2005.
17. Leibowitz-Amit, R. and A.M. Joshua, *Targeting the androgen receptor in the management of castration-resistant prostate cancer: rationale, progress, and future directions.* Current Oncology, 2012. **19**(Suppl 3): p. S22-31.
18. De Bono JS, O.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**: p. 1147-1154.
19. Antonarakis, E.S. and M.A. Eisenberger, *Expanding treatment options for metastatic prostate cancer.* New England Journal of Medicine, 2011. **364**(21): p. 2055-8.

20. Mukherji, D., et al., *New treatment developments applied to elderly patients with advanced prostate cancer.* Cancer Treatment Reviews, 2013.

21. Scher, H.I., et al., *Increased survival with enzalutamide in prostate cancer after chemotherapy.* New England Journal of Medicine, 2012. **367**(13): p. 1187-1197.

22. Scher, H.I., et al., *Antitumour activity of MDV3100 in castration-resistant prostate cancer: A phase 1-2 study.* The Lancet, 2010. **375**(9724): p. 1437-1446.

23. *Enzalutamide (Xtandi) for prostate cancer.* Medical Letter on Drugs and Therapeutics, 2013. **55**(1411): p. 20-21.

24. Menon, M.P. and C.S. Higano, *Enzalutamide, a second generation androgen receptor antagonist: development and clinical applications in prostate cancer.* Current Oncology Reports, 2013. **15**(2): p. 69-75.

25. Pal, S.K., C.A. Stein, and O. Sartor, *Enzalutamide for the treatment of prostate cancer.* Expert Opinion on Pharmacotherapy, 2013. **14**(5): p. 679-85.

26. U.S. Food and Drug Administration. *Medical Reviews*. 2012 [cited 25.04.2013]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203415Orig1s000MedR.pdf.

27. Apotheker-Verlag. *Warenverzeichnis – Artikelstamm – Zytiga*. 2013 [cited 29.04.2013]; Available from: http://warenverzeichnis.apoverlag.at/artikelstamm/index/dg.

28. European Medicines Agency. *Zytiga -Abiraterone acetate*. 2012 [cited 02.05.2013]; Available from: http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/002321/WC500112858.pdf.

29. Mulders, P., et al., *MDV3100, an androgen receptor signaling inhibitor, improves overall survival in patients with prostate cancer post docetaxel: Results from the Phase 3 AFFIRM study.* Urology, 2012. **80**(3): p. S30.

30. Ha, Y.S., et al., *Enzalutamide for the treatment of castration-resistant prostate cancer.* Drugs of Today, 2013. **49**(1): p. 7-13.

31. Aragon-Ching, J.B., *Enzalutamide (formerly MDV3100) as a new therapeutic option for men with metastatic castration-resistant prostate cancer.* Asian Journal of Andrology, 2012. **14**(6): p. 805-6.