

**PROPOSAL
FOR THE INCLUSION OF ENZALUTAMIDE
IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR
THE TREATMENT OF METASTATIC CASTRATION RESISTANT
PROSTATE CANCER**

List of Contributors

Knowledge Ecology International

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December 2016

1. Name of the focal point in WHO submitting or supporting the application

N/A

2. Name of the organization(s) consulted and/or supporting the application

Knowledge Ecology International (KEI)

3. International Nonproprietary Name (INN, generic name) of the medicine

Enzalutamide

4. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Enzalutamide (trade name Xtandi) is sold in 40 mg capsules, and is prescribed for daily use for as long as the drug continues to be effective and tolerated. The typical dose of enzalutamide for the treatment of prostate cancer is 4 x 40 mg per day.

5. International availability - sources, if possible manufacturers and trade names

The patents on Enzalutamide include a “paid-up license” for the United States government to “practice or have practiced for or on behalf” the inventions “throughout the world.” Recently, Biolyse Pharma, a Canadian drug manufacturer, asked the U.S. government for the right to use this license to supply the drug to patients in developing countries, where price is a barrier to access. The NIH was asked to respond, and rejected this request. However, this decision can be revised at any time. The NIH indicated that its decision was partly a consequence of a lack of general policy on such requests, something that may be remedied in the future.

Biolyse has also indicated that it will be asking the Canadian government to grant a compulsory license under a Canadian compulsory licensing program for export to countries that lack sufficient capacity to manufacture.

In India, the patent on enzalutamide was rejected on November 8, 2016, in a challenge brought by 1) Fresenius Kabi Oncology Limited 2) BDR Pharmaceutical International Pvt. Ltd. 3) Umesh Shah 4) Sheela Pawar and 5) Indian Pharmaceuticals Alliance (IPA), against the Regent of the University of California.

Even without a current robust commercial market for generic enzalutamide, there are several companies selling the APIs, and even in small quantities prices are as low as \$.15 per 40mg tablet. With scaled up production, API prices are expected to fall.

Nine companies have US FDA drug master files (DMF) for the supply of enzalutamide APIs.

Holder	DMF Number	Status	Subject	Submission Date	Type	Country
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WATSON PHARMA PRIVATE LTD	29872	Active	ENZALUTAMIDE	2016-05-24	II	IRELAND
CADILA HEALTHCARE LTD	30304	Active	ENZALUTAMIDE	2016-03-29	II	INDIA
CATALENT PHARMA SOLUTIONS LLC	25814	Active	MDV3100, 40MG, CAPSULES (SOFTGELS)	2012-02-22	II	UNITED STATES
DR REDDYS LABORATORIES LTD	29117	Active	ENZALUTAMIDE	2015-03-31	II	INDIA
MSN LABORATORIES PRIVATE LTD	30279	Active	ENZALUTAMIDE [ROUTE CODE "EI"]	2016-02-29	II	INDIA
MYLAN LABORATORIES LTD	30010	Active	ENZALUTAMIDE	2015-11-28	II	UNITED STATES
SAI LIFE SCIENCES LTD	29062	Active	4-((2-CYANOPROPAN-2-YL)AMINO)-2-FLUORO-N-METHYLBENZAMIDE (ENZALUTAMIDE INTERMEDIATE)	2015-03-23	II	INDIA
SCINOPHARM TAIWAN LTD	30644	Active	ENZALUTAMIDE	2016-07-09	II	TAIWAN
SHILPA MEDICARE LTD	30260	Active	ENZALUTAMIDE	2016-03-17	II	INDIA

See: <http://www.pharmacompass.com/us-drug-master-files-dmfs/enzalutamide>

6. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Individual medicine.

7. Information supporting the public health relevance

Prostate cancer has not been link to specific oncogenes and occurs through a combination of several genetic, environmental and lifestyle factors. Generally, the early stages of prostate cancer are slow growing and many go undiagnosed until a clinical autopsy. However, it is the second most common cancer in men. In 2012, approximately 1.1million men were diagnosed with prostate cancer. ¹

8. Enzalutamide

¹ http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

Enzalutamide is a second generation competitive androgen receptor inhibitor. It antagonises the AR signaling by preventing the ligand from binding to the AR, and downstream events such as nuclear translocation and DNA binding.² By acting directly on this pathway, enzalutamide interferes with a crucial element that contribute to cancer progression. Enzalutamide has a half-life of 5.8 days and is metabolized by CYP2C8 and CYP3A4 and the drug steady state is reached in 28 days.³

When patients are diagnosed with prostate cancer, if they are treated early and tumors are localized, the prognosis is often favorable. However, some patients will relapse, which in nearly all cases, leads to castration resistant prostate cancer (CRPC). At the CRPC stage, the disease is no longer responsive to androgen deprivation therapy (ADT), thus limiting the available treatment options with a greater disease burden. Access to second generation therapies such as enzalutamide becomes critical to extending the life of the patient, and allowing patients to live an improved quality of life.

There are currently six treatments being used to treat CRPC. Enzalutamide has several advantages over the other treatments. Four of the other treatments are invasive and require I.V. administration, leukapheresis, or the use of radiopharmaceuticals. Enzalutamide and abiraterone acetate (trade name Zytiga) are the only daily oral tablets. However enzalutamide's pill burden is lighter since it does not need to be taken in combination with prednisone. As such, enzalutamide is well tolerated and has more favorable toxicity profile. This will be further discussed in section 10.

Quality of life is also more frequently improved and median time to deterioration is significantly longer with enzalutamide compared to placebo, as reported by patients in functional assessment questionnaires administered during clinical trials.⁴

Since 2014, the FDA has expanded the use of enzalutamide to first line treatment for metastatic castration-resistant prostate cancer (mCRPC) based on the phase III PREVAIL clinical trial. Currently enzalutamide (FDA approved, 2012), abiraterone acetate (FDA approved, 2011), and docetaxel (trade name Taxotere, FDA approved, 2004) are the top three prescribed drugs in first line metastatic CRPC treatment.⁵ However, using docetaxel before enzalutamide has been shown to decrease the effectiveness of enzalutamide by a median overall survival of 15.8 months.⁶ Abiraterone acetate and enzalutamide are both oral therapeutics that target the androgen signaling axis, and although prospective head-to-head comparison clinical trials are still ongoing, retrospective analysis data have indicated that

² Mostaghel EA, Montgomery B, Nelson PS. Castration-resistant prostate cancer: targeting androgen metabolic pathways in recurrent disease. *Urol Oncol*. 2009 May-Jun;27(3):251-7.

³ Ramadan WH, Kabbara WK, Al Basiouni Al Masri HS. Enzalutamide for patients with metastatic castration-resistant prostate cancer. *Onco Targets Ther*. 2015 Apr 17;8:871-6.

⁴ Rodriguez-Vida A *et al*. Enzalutamide for the treatment of metastatic castration-resistant prostate cancer. *Drug Des Devel Ther*. 2015 Jun 29;9

⁵ Flaig TW *et al*. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. *Cancer Med*. 2015 Dec 29.

⁶ Crawford ED *et al*. Treating Patients with Metastatic Castration Resistant Prostate Cancer: A Comprehensive Review of Available Therapies. *J Urol*. 2015 Dec;194(6):1537-47.

there is a clear clinical cross-resistance between the two drugs.⁷ In fact, in a study conducted by Schrader *et al.*, it was reported that 48.6% of patients who previously took abiraterone acetate and docetaxel were completely resistant to enzalutamide.⁸ Based on the susceptibilities of individual patients, oncologists may want to prescribe enzalutamide over abiraterone acetate for its toxicity profile or to patients who cannot tolerate low-dose steroids.⁶

With recent and ongoing clinical trials reporting better prostate cancer control when enzalutamide is used in chemotherapy naive CRPC cases or in combination with other agents, it is expected that this drug will soon be prescribed to wider subset of patients.^{9,10,11} In fact experts say that in the next 3 years all CRPC will progress to enzalutamide or abiraterone acetate.¹²

9. Treatment details

Enzalutamide is indicated as first-line therapy for the treatment of patients with metastatic castration-resistant prostate cancer who have not received chemotherapy or who have previously received docetaxel.

Enzalutamide is available as 40 mg capsules. The daily dose is four capsules (160 mg) orally once daily with or without food. If grade 3 or higher side effects occur or if the patient develops toxicity, enzalutamide should be stopped for 1 week or until symptoms subside to grade 2 or less. Notably, enzalutamide strongly interacts with CYP2C8 inhibitors, therefore if coadministration cannot be avoided, the dose of enzalutamide should be reduced to 80 mg once daily.

10. Summary of comparative effectiveness in a variety of clinical settings:

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

We searched systematic reviews, technology assessment reports, and meta-analyses of controlled clinical trials involving enzalutamide in at least one arm were searched on the Database of Abstracts of Reviews of Effectiveness . Additional searches for relevant reviews

⁷ Zhang T. *et al.* Enzalutamide versus abiraterone acetate for the treatment of men with metastatic castration-resistant prostate cancer. *Expert Opin Pharmacother.* 2015 Mar;16(4):473-85.

⁸ Schrader AJ *et al.* Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. *Eur Urol.* 2014 Jan;65(1):30-6.

⁹ Scher HI *et al.* Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med.* 2012 Sep.

¹⁰ Lortot Y *et al.* Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Oncol.* 2015 May.

¹¹ STRIDE results presented at 2015 American Society of Clinical Oncology annual meeting, Clinicaltrials.gov:NCT01981122.

¹² Zhang T. *et al.* Enzalutamide versus abiraterone acetate for the treatment of men with metastatic castration-resistant prostate cancer. *Expert Opin Pharmacother.* 2015 Mar;16(4):473-85.

were undertaken in Clinical Evidence (CE), PubMed, and the Cochrane Database of Systematic Reviews. Unfortunately, there were no meta-analysis reporting exclusively on enzalutamide containing trials. However, meta-analyses were found comparing enzalutamide, abiraterone (although not head-to-head) and other therapies in various treatment exposure settings. We summarize below key RTC for enzalutamide, and report a meta-analysis to compare enzalutamide with another second generation inhibitor.

10.2 Summary of available data

The AFFIRM clinical trial (NCT00974311) was a phase III randomized, double-blind, placebo-controlled, multicenter trial to study the efficacy and safety of enzalutamide in patients with metastatic castration resistant prostate cancer (mCRPC) who had previously taken docetaxel.¹³ 1,199 adult males, ranging from 41 to 92 years, were randomized in a 2:1 ratio, where 800 participants received a dose of 160mg of enzalutamide once a day, 399 participants received a placebo, and all continued on androgen deprivation therapy. The primary endpoint measured was overall survival (OS) and two secondary outcomes were progression free survival and PSA-level response (“reduction in the PSA level from baseline by 50% or more or 90% or more”).¹² OS was found to be 18.4 months for enzalutamide and 13.6 months for the control arm [HR 0.63; 95% CI 0.53–0.75; p< 0.001]. PFS was 8.3 for enzalutamide versus 2.9 for the placebo [HR 0.40; 95% 0.35–0.47; p< 0.001]. 54% of patients in the treatment arm experienced 50% or greater decrease in PSA levels compared to only 2% in the control arm (p<0.001). Overall there were few adverse events (AE), but grade ≥3 events relating to fatigue (6% vs 7%), diarrhea (1% vs >1%), musculoskeletal pain (1% vs >1%), headache (1% vs. 0%) and seizures (0.6% vs 0%) occurred slightly more often in the enzalutamide arm. However, AE causing death occurred in 3% in the enzalutamide arm and 4% in the placebo arm. The trial was stopped at the interim analysis having demonstrated an improved OS. The result from the AFFIRM formed the bases for the initial FDA approval.

PREVAIL investigated enzalutamide in first line setting in mCRPC who had not yet received chemotherapy. This pivotal phase III, placebo controlled clinical trial, enrolled 1717 patients that were randomized 1:1. As with AFFIRM, PREVAIL was halted after interim results were collected due the benefits displayed by enzalutamide. Less deaths were reported in the treatment arm at 28% vs 35% for placebo [HR: 0.71, 95% CI: [0.60–0.84]; p<0.001]. Based in the results from this trials, the FDA approved enzalutamide for used in first-line therapy for mCRPC

Table 10-1: Summary of relevant randomized clinical trials studying enzalutamide (from Luo and Graff, 2016)

¹³ Scher HI et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012 Sep 27;367(13):1187-97.

Trial	Arms	Study design	n	Primary outcome	PRO instruments used
AFFIRM ¹⁵	Enzalutamide vs placebo (mCRPC post-chemo)	Phase III	1,199	OS; mOS 18.4 months vs 13.6 months (HR: 0.63, p<0.001)	FACT-P, BPI-SF
PREVAIL ¹⁶	Enzalutamide vs placebo (mCRPC pre-chemo)	Phase III	1,717	OS, radiographic PFS; deaths 28% vs 35% (HR: 0.71, p<0.001)	FACT-P, EQ-5D, BPI-SF
STRIVE ¹⁷	Enzalutamide vs bicalutamide (CRPC)	Phase II	396	PFS; in mCRPC 16.5 vs 5.5 months (HR: 0.24, p<0.001)	FACT-P
TERRAIN ¹⁸	Enzalutamide vs bicalutamide (mCRPC)	Phase III	375	PFS; 15.7 vs 5.8 months (HR: 0.44, p<0.0001)	FACT-P, BPI-SF

Abbreviations: PRO, patient-related outcome; CRPC, castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; FACT-P, Functional Assessment of Cancer Therapy-Prostate; OS, overall survival; HR, hazard ratio; PFS, progression-free survival; BPI-SF, Brief Pain Inventory – Short Form; mOS, median overall survival.

10.3 Enzalutamide compared with Abiraterone

Roviello *et al* performed a meta-analysis by pooling data from eight studies looking at novel androgen receptor pathway targeted agents.¹⁴ Four trials contained enzalutamide in one arm, two trials investigated abiraterone and two other trials investigated orteronel. Abiraterone is a steroidal androgen synthesis inhibitor and acts on CYP17A1. Abiraterone must be taken in combination with prednisone and together they are also indicated as treatment for mCRPC. Orteronel is a still experimental drug being developed by Takeda Pharmaceuticals and Millennium Pharmaceuticals. Orteronel is androgen synthesis inhibitor similar to abiraterone. Table 10-2 summarizes the clinical trials used in this analysis.

Table 10-2: Characteristic of clinical trials included in the meta-analysis (from: Roviello *et al*)

¹⁴ Roviello G, Sigala S, Sandhu S, Bonetta A, Cappelletti MR, Zanotti L, Bottini A, Sternberg CN, Fox SB, Generali D. Role of the novel generation of androgen receptor pathway targeted agents in the management of castration-resistant prostate cancer: A literature based meta-analysis of randomized trials. *Eur J Cancer*. 2016 Jul;61:111-21.

Trials	Treatment arms	Cases	End-points	Setting	Jadad Score
AFFIRM [4]	Enzalutamide versus placebo	800 399	Primary: overall survival Secondary: time to prostatic antigen specific (PSA) progression, proportion of patients with a decrease in PSA of 50%, radiographic progression-free survival, and time to the first skeletal-related event	Post-chemotherapy	5
COU-AA-301 [3]	Abiraterone + prednisone versus placebo + prednisone	797 398	Primary: overall survival Secondary: time to PSA progression, radiographic progression-free survival, and time to the first skeletal-related event, PSA response rate ($\geq 50\%$ decline in PSA level from baseline)	Post-chemotherapy	5
COU-AA-302 [5]	Abiraterone + prednisone versus placebo + prednisone	546 542	Primary: radiographic progression-free survival and overall survival Secondary: times to opiate use for cancer-related pain, time to initiation of cytotoxic chemotherapy, time to a decline in ECOG performance status, and time to PSA progression, PSA response rate ($\geq 50\%$ decline in PSA level from baseline), rate of objective response according to RECIST criteria, and health-related quality of life, as measured by means of patients' reports of pain and functional status.	Chemotherapy-naïve	5
ELM-PC 4 [8]	Orteronel + prednisone versus placebo + prednisone	781 789	Primary: radiographic progression-free survival and overall survival Secondary: safety assessment, time to initiation of cytotoxic chemotherapy, frequency of skeletal related events, time to PSA progression, duration of PSA response, PSA response rate ($\geq 50\%$ and 90% decline in PSA level from baseline), rate of objective response according to RECIST criteria	Chemotherapy-naïve	5
ELM-PC 5 [7]	Orteronel + prednisone versus placebo + prednisone	734 365	Primary: overall survival Secondary: time to PSA progression, radiographic progression-free survival, PSA response rate ($\geq 50\%$ decline in PSA level from baseline) and pain response at 12 weeks, safety	Post-chemotherapy	5
PREVAIL [6]	Enzalutamide versus placebo	872 875	Primary: radiographic progression-free survival and overall survival Secondary: time until the initiation of cytotoxic chemotherapy, the time until the first skeletal-related event, the best overall soft-tissue response, the time until PSA progression, and a decline in the PSA level of 50% or more from baseline. Prespecified exploratory end-points included quality of life, as measured with the use of the Functional Assessment of Cancer Therapy—Prostate (FACT-P) scale, and a decline in the PSA level of 90% or more from baseline.	Chemotherapy-naïve	5
TERRAIN [17]	Enzalutamide versus bicalutamide	183 189	Primary: progression-free survival Secondary: safety, investigator-review-based progression-free survival, time to PSA progression, PSA response by week 13, and best PSA response	Chemotherapy-naïve	4
STRIVE [18]	Enzalutamide versus bicalutamide	198 198	Primary: progression-free survival. Secondary: time to PSA progression, PSA response $\geq 50\%$, radiographic progression-free survival, best overall soft tissue response, time to a 10-point or greater decline of the global score of the FACT-P questionnaire, and PSA response of $\geq 90\%$	Chemotherapy-naïve	4

ECOG, Eastern Cooperative Oncology Group.

Of the clinical trials that study enzalutamide, only AFFIRM and PREVAIL reported OS. Since the heterogeneity between the clinical trial was slightly above average ($I^2 = 60\%$), a random effects model was employed to calculate the hazard ratio (HR). The OS HR were similarly significant for enzalutamide and abiraterone (figure 10-1). Orteronel reported OS HR, however, were not significant.

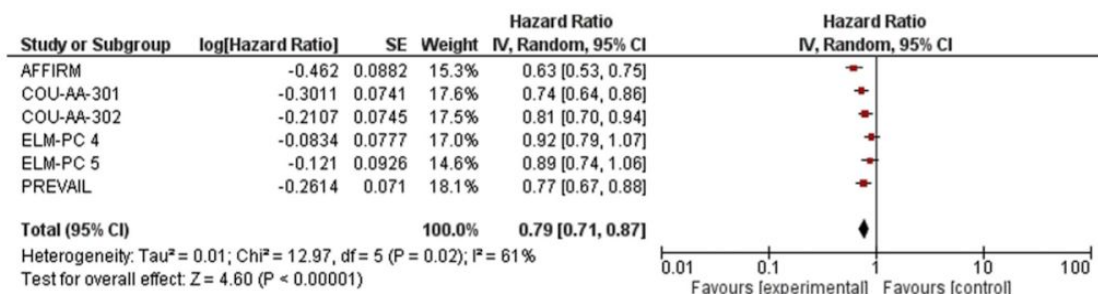


Figure 10-1: Forest plot for the hazard ratio of the overall survival (from: Roviello *et al.*)

As for the PFS, the HR ratios indicated that enzalutamide was favored over a abiraterone (figure X). Again a random effects model was used since there was high heterogeneity among the trials (I² = 96%). Furthermore, the HR for adverse events of grade 3 or higher were not significant for all clinical trials but AFFIRM, although AFFIRM only slightly presented less AE risk than the control arm.

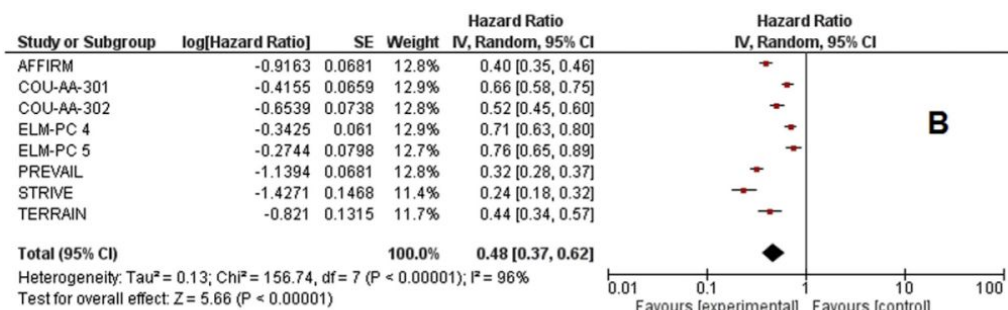


Figure 10-2: Forest plot for the hazard ratio of the progression free survival (from: Roviello *et al.*)

11. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group:

When sourced from Astellas under the brand name Xtandi, enzalutamide is expensive.

There are many available studies of the cost effectiveness of enzalutamide compared to alternatives including ones that are also expensive. (See the Annex on cost effectiveness studies). None of them seem particularly useful when considering if enzalutamide would be cost effective in resource setting, particularly if the drug is available at a much lower price feasible from generic suppliers.

The WHO needs to consider the cost effectiveness of the drug when available from competitive generic suppliers.

One generic supplier in Canada, Biolyse Pharma, has offered to sell generic enzalutamide to the Medicare program for \$3 for a 40mg tablet, or \$12 for a daily dose of four tablets. The Biolyse quote was an offer to a program that was paying \$70 per tablet, and it does not

reflect the lower prices that are likely when competition exists, and/or when generic manufacturers sell in lower income markets.

As discussed in section 5, there are several API suppliers for enzalutamide. With competition, prices for the APIs should fall. One source provides a reference price of \$17,700 per kilo, which is equivalent to API for a daily dose of 40mg x 4 = 160 mgs of \$2.83. One reported sale was at \$3,745 per kilo, which would be \$.15 per 40mg table, or \$.60 per day or \$213 per year for the API cost.

We assume that with competition between generic suppliers and efficient procurement policies prices can fall to less than \$1 per day for a 4x40mg dose.

12. Summary of regulatory status of the medicine

Enzalutamide is approved worldwide and in various jurisdictions such as:

EU (EMA)

Enzalutamide is licensed in the EU for the treatment of:

Metastatic castration resistant prostate cancer when:

- “treatment with docetaxel (a cancer medicine) has not worked or no longer works;
- hormone therapy has not worked, and the patient has either no symptoms or mild symptoms and does not require chemotherapy (another type of cancer treatment).”

US (FDA)

Enzalutamide is licensed in the USA for the treatment of:

“treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.”

Australia (TGA)

“Xtandi is indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.”

Japan (PMDA)

“Castration-resistant prostate cancer”

Annex on cost effectiveness studies

UK

National Institute for Health and Care Excellence

Final appraisal determination – enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen

Issue date: April 2014

Summary of Appraisal Committee's key conclusions

Key conclusion

Enzalutamide is recommended within its marketing authorisation as an option for treating hormone-relapsed metastatic prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy, only if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme. The Committee agreed that enzalutamide should be compared with abiraterone for patients who had received 1 course of docetaxel-containing cytotoxic chemotherapy and with best supportive care for patients who had received 2 or more cytotoxic chemotherapy regimens.

For patients who had received 1 course of cytotoxic chemotherapy, the Committee noted that the analysis reflecting its preferred assumptions, but not the actual patient access scheme discount for abiraterone, gave an incremental cost-effectiveness ratio (ICER) of £22,600 per quality-adjusted life year (QALY) gained for enzalutamide compared with abiraterone. The Committee accepted that this ICER was associated with uncertainty but, on balance, it was satisfied that it would remain below £30,000 per QALY gained. The Committee noted that taking into account the correct patient access scheme for abiraterone would not change its conclusion.

For patients who had received 2 or more courses of chemotherapy, the Committee noted that the ICERs for enzalutamide compared with best supportive care were between £45,500 and £48,000 per QALY gained. The Committee agreed that enzalutamide would be considered an end-of-life treatment as defined by NICE for this subgroup and that the magnitude of the additional weight that would need to be assigned to the QALY benefits would justify enzalutamide being recommended as a cost-effective use of NHS resources.

The Committee did not see sufficient evidence to make any recommendations on the clinical- and cost-effectiveness of sequential use of enzalutamide and abiraterone.

Ireland

Cost Effectiveness of enzalutamide (Xtandi®) for the treatment of adult men with asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. June 2015

Results

The ICER (enzalutamide vs. best supportive care) is 106,271/QALY (incremental cost = 84,634; incremental QALY = 0.796). The ICER (enzalutamide vs. abiraterone) is 74,387/QALY (incremental cost = 25,368; incremental QALY = 0.341). These analyses assume a list price for abiraterone; this may not be realistic.

5. Conclusion

Astellas Pharma Co Ltd submitted a dossier to examine the cost effectiveness of enzalutamide (Xtandi®) for the treatment of adult men with asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. Following NCPE assessment of the company submission, enzalutamide is not considered cost effective for this indication and therefore is not recommended for reimbursement at the submitted price.

Canada

Cost-Utility Analysis of Enzalutamide for Patients with Previously Treated Metastatic Castration-Resistant Prostate Cancer (MCRPC). C. Vicente, V. Babashov, F. Husein, F. Saad, S. Naidoo, S. Holmstrom DOI: <http://dx.doi.org/10.1016/j.jval.2014.03.521>

Objectives: mCRPC is a terminal disease, with a median survival of approximately 1 to 2 years. The AFFIRM study demonstrated that enzalutamide is highly efficacious, prolonging overall survival and progression-free survival compared to placebo in patients with mCRPC previously treated with docetaxel-based chemotherapy. The purpose of this analysis is to assess from the Canadian perspective the costeffectiveness of enzalutamide 160mg once-daily compared with abiraterone acetate (AA) (+ prednisone) and intravenous (IV) cabazitaxel in mCRPC patients previously treated with docetaxel-based chemotherapy. Methods: A Markov model was developed to capture time spent by patients in various health states, including progression, progression free survival (PFS) and death. Results were reported as incremental costs per additional quality adjusted life-years (QALY) gained over a 10-year period. Transition probabilities were derived from patient-level data from AFFIRM and an indirect treatment comparison from available published literature. The base case analysis focused on direct medical costs from the perspective of the Canadian Ministry of Health (MoH), with the second analysis focusing on the societal perspective. Cost data for

2013, jobtained from a variety of sources were reported as Canadian Dollars. A 5% discount rate was applied to both costs and patient outcomes. Multiple sensitivity analyses were undertaken to test the robustness of the model Results: From the MoH perspective, enzalutamide had an incremental costutility ratio (ICUR) of \$42,325 and \$43,105 per additional QALY gained compared to AA and cabazitaxel, respectively. Results were similar from the societal perspective. Results were robust over a wide range of one-way and probabilistic sensitivity analyses. In greater than 85% of iterations the incremental cost-effectiveness ratio ICER was below a willingness-to-pay threshold of \$100,000 per QALY for the comparison versus either AA or cabazataxel. Conclusions: Enzalutamide is a cost-effective treatment compared to AA and cabazitaxel in mCRPC patients previously treated with docetaxel-based chemotherapy.

2016. Dominic Pilon, Marykay Queener, Patrick Lefebvre & Lorie A. Ellis (2016) Cost per median overall survival month associated with abiraterone acetate and enzalutamide for treatment of patients with metastatic castration-resistant prostate cancer, *Journal of Medical Economics*, 19:8, 777-784, DOI: 10.3111/13696998.2016.1173042

<http://dx.doi.org/10.3111/13696998.2016.1173042>

Objective: To calculate costs per median overall survival (OS) month in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone acetate plus prednisone (AApP) or enzalutamide. Methods: Median treatment duration and median OS data from published Phase 3 clinical trials and prescribing information were used to calculate costs per median OS month based on wholesale acquisition costs (WACs) for patients with mCRPC treated with AA+P or enzalutamide. Sensitivity analyses were performed to understand how variations in treatment duration and treatment-related monitoring recommendations influenced cost per median OS month. Cost-effectiveness estimates of other Phase 3 trial outcomes were also explored: cost per month of chemotherapy avoided and per median radiographic progression-free survival (rPFS) month. Results: The results demonstrated that AA\$P has a lower cost per median OS month than enzalutamide (\$3231 vs \$4512; 28% reduction), based on the following assumptions: median treatment duration of 14 months for AA+P and 18 months for enzalutamide, median OS of 34.7 months for AA+P and 35.3 months for enzalutamide, and WAC per 30-day supply of \$8007.17 for AA+P vs \$8847.98 for enzalutamide. Sensitivity analyses showed that accounting for recommended treatment-related monitoring costs or assuming identical treatment durations for AA+P and enzalutamide (18 months) resulted in costs per median OS month 8–27% lower for AA+P than for enzalutamide. Costs per month of chemotherapy avoided were \$4448 for AA+P and \$5688 for enzalutamide, while costs per month to achieve median rPFS were \$6794 for AA+P and \$7963 for enzalutamide. Conclusions: This cost-effectiveness analysis demonstrated that costs per median OS month, along with costs of other Phase 3 trial outcomes, were lower for AA+P than for enzalutamide. The findings were robust to sensitivity analyses. These results have important implications for population health decision-makers evaluating the relative value of therapies for mCRPC patients.

US

One 2014 study by Leslie Wilson et al. for the U.S. context, which features the highest prices in the world for Astellas branded Xtandi, calculated the cost effectiveness of three metastatic castration-resistant prostate cancer (mCRPC) treatments -- Zytiga (abiraterone), Xtandi (enzalutamide), and Jevtana (cabazitaxel) -- and found that the price of Xtandi is the single limiting factor rendering Xtandi less cost-effective than Zytiga. This study was detailed in the Journal of Oncology Pharmacy Practice:

L. Wilson et al. New therapeutic options in metastatic castration-resistant prostate cancer: [Can cost-effectiveness analysis help in treatment decisions?](#) Journal of Oncology Pharmacy Practice 2014, Vol. 20(6) 417–425

According to the authors' incremental cost-effective calculations based upon 2012 prices, Xtandi would be the preferred treatment, if prices were decreased:

Results: Abiraterone was the most cost-effective of the treatments (\$123.4 K/quality-adjusted life year) compared to placebo, enzalutamide was \$437.6 K/quality-adjusted life year compared to abiraterone, and cabazitaxel was \$351.9 K/quality-adjusted life year compared to enzalutamide. Enzalutamide and cabazitaxel were not cost-effective compared to placebo at \$154.3 K/quality-adjusted life year and \$163.2 K/quality-adjusted life year, respectively. Acceptability curves showed abiraterone was cost-effective 29.3% of the time with a willingness to pay threshold of \$100 K. The model was sensitive to changes in cost of the drugs, life expectancy, and survival rate. Sensitivity analysis shows that enzalutamide can become the most cost-effective option if the price of the medication decreased by 26% and other drug costs remained the same. [emphasis added]

<https://smdm.confex.com/smdm/2015mo/webprogram/Paper9446.html>

37th Annual Meeting of the Society for Medical Decision Making
PS1-4 COST EFFECTIVENESS OF THERAPIES FOR CASTRATION RESISTANT
METASTATIC PROSTATE CANCER
Sunday, October 18, 2015
Grand Ballroom EH (Hyatt Regency St. Louis at the Arch)
Poster Board # PS1-4

Niranjan Kathe, M.S., Corey Hayes, Pharm D MPH, Anand Shewale, M.S. and Bradley Martin, Pharm D PhD, University of Arkansas for Medical Sciences, Little Rock, AR

Result: In the base case analysis, cabazitaxel therapy was the most expensive (\$139978), followed by enzalutamide (\$133,834), abiraterone while (\$120,260), mitoxantrone (\$93,255), prednisolone (\$82,930). Quality adjusted life expectancy was highest with cabazitaxel (0.76 QALY), followed by abiraterone (0.70 QALY), mitoxantrone (0.58 QALY), enzalutamide (0.56

QALY) and prednisolone (0.43 QALY). Mitoxantrone was found to be the most cost effective treatment (\$51,524.53/QALYs) compared to prednisolone. When compared to mitoxantrone abiraterone and cabazitaxel have high incremental cost effectiveness ratios (\$220,803/QALY and \$353,203/QALY respectively) while enzalutamide was dominated. At a willingness to pay of \$100,000/QALY, the cost effectiveness acceptability curves showed that mitoxantrone and abiraterone were cost effective 23.4% and 24.6% times respectively. One-way sensitivity analysis showed that abiraterone had an ICER below \$100,000/QALY when the price of abiraterone reduced by 30.1%.

Conclusion: Treatment of mCRPC with recently developed therapies can extend the survival, however, the gains in survival are accompanied by significant costs with abiraterone, cabazitaxel and enzalutamide. At 2015 prices, mitoxantrone which has a lower side effect profile appears would be cost effective at conventional willingness to pay thresholds.