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

List of Contributors

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List of Tables and Figures

1. Summary statement of the proposal for inclusion, change or deletion.

Enzalutamide (sold by Astellas trade name Xtandi, sold by Glenmark trade name Glenza) is indicated to treat metastatic castration-resistant prostate cancer (CRPC) and is a second generation competitive androgen receptor inhibitor. While there are other treatments used to treat CRPC, enzalutamide is far less invasive as it is administered via daily oral tablets, and has a low pill burden compared to the one other oral tablet CRPC treatment (abiraterone acetate).

The first registration was by Astellas, for Xtandi. The patent protection for Xtandi varies from country to country. At least one generic supplier, Glenmark, has entered the market.

With recent 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 an even wider subset of patients. The listing of enzalutamide is being sought for the core Essential medicines List.

Abiraterone acetate (sold by Johnson and Johnson under the trade name Zytiga), is an antiandrogen medication which is used in the treatment of prostate cancer. It is specifically indicated for use in conjunction with castration and prednisone for the treatment of metastatic castration-resistant prostate cancer (mCRPC) and in the treatment of metastatic high-risk castration-sensitive prostate cancer (mCSPC).

The US patent 8,822,438, which covered Zytiga, was invalidated in October 2018.[1] There several generic suppliers of abiraterone acetate.

Both drugs offer significant medical benefits for target populations, although for some patients, one will better tolerated with few adverse effects than the other.

2. Relevant WHO technical department and focal point (if applicable).

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

Knowledge Ecology International (KEI)

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN: Enzalutamide
ATC Code: L02BB04

[1] BTG Int'l Ltd. v. Amneal Pharm. LLC, No. 15-CV-5909 (KM)(JBC) (D.N.J. Oct. 31, 2018)

INN: Abiraterone acetate
ATC Code: L02BX03

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Enzalutamide (originator 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.

Enzalutamide is available from Astellas at very high prices. Glenmark has introduced a generic version in India under the trade name Glenza.

Abiraterone acetate (originator trade name Zytiga) is sold in 500 mg and 250 mg tablets. The dose as described on the label is 1000 mg orally once per day with 5mg of prednisone orally twice daily. This dosage is for both its indications, metastatic castration-resistant prostate cancer and metastatic castration-sensitive prostate cancer. Note that patients receiving abiraterone acetate should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

Abiraterone acetate is available from Johnson and Johnson at high prices, and also available from a large number of generic suppliers at lower prices.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

The request for inclusion is for two individual medicines, the prostate cancer drugs enzalutamide and abiraterone acetate.

7. Treatment details (requirements for diagnosis, treatment and monitoring). The application should specify the proposed therapeutic dosage regimen and duration of treatment.

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 and is also indicated for the treatment of non-metastatic castration-resistant prostate cancer.

Enzalutamide is sold in 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 subsides 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.

Enzalutamide is prescribed for daily use for as long as the drug continues to be effective and tolerated.

Abiraterone acetate is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer as well as metastatic castration-sensitive prostate cancer. Abiraterone acetate is a CYP17 inhibitor that is sold in 500 mg and 250 mg coated tablets and 250 mg uncoated tablets. For both indications, patients take 1000 mg of abiraterone acetate once daily along with 5 mg of prednisone twice daily.

Patients taking abiraterone acetate should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. When taking abiraterone acetate, avoid concomitant strong CYP3A4 inducers. If a strong CYP3A4 inducer must be co-administered, it is advised to increase the dosing frequency of abiraterone acetate. Additionally, when taking abiraterone acetate, avoid co-administration with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, the label advises to exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate.

Abiraterone acetate is prescribed for daily use for as long as the drug continues to be effective and tolerated.

8. Information supporting the public health relevance.

Prostate cancer has not been linked 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 and the fourth most common cancer overall.[2] In 2018, approximately 1.3 million men were diagnosed with prostate cancer. [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.

[2] Bray, F. , Ferlay, J. , Soerjomataram, I. , Siegel, R. L., Torre, L. A. and Jemal, A. (2018), Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 68: 394-424. doi:10.3322/caac.21492
[3] Ibid.

9. Review of benefits: summary of evidence of comparative effectiveness.

ENZALUTAMIDE

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.[4] 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.[5]

There are currently six treatments being used to treat CRPC. Enzalutamide and abiraterone acetate have 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 are the only daily oral tablets.

Enzalutamide has certain advantages over abiraterone acetate, including a lighter pill burden, a smaller daily dose of 160 milligrams (4 x 40mg) as opposed to 1000 milligrams (4 x 250mg), which may lead to lower per unit manufacturing costs for enzalutamide once there are additional generic manufacturers and greater economies of scale and competition. Enzalutamide also does not need to be taken in combination with prednisone.

For some patients, enzalutamide is better tolerated and has more favorable toxicity profile than abiraterone acetate.

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.[6]

In 2018 the FDA expanded the use of enzalutamide to first line treatment for both non-metastatic and metastatic castration-resistant prostate cancer (CRPC) based on a randomized, multicenter clinical trial (PROSPER, NCT020032924), that randomized 1,401 patients 2:1 to take either enzalutamide 160 mg orally once daily or placebo orally once daily.[7] Currently enzalutamide (FDA approved, 2012), abiraterone acetate (FDA approved, 2011), and docetaxel (trade name Taxotere, FDA approved, 2004) are the top three

[4] 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.
[5] 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.
[6] Rodriguez-Vida A *et al.* Enzalutamide for the treatment of metastatic castration-resistant prostate cancer.Drug Des Devel Ther. 2015 Jun 29;9
[7] Hussain, M., Fizazi,K., Saad, F., Rathenborg, P., Shore, N., Demirhan, E. et al. PROSPER: A phase 3, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with nonmetastatic castration-resistant prostate cancer (M0 CRPC). Journal of Clinical Oncology 36, no. 6_suppl (February 2018) 3-3.

prescribed drugs in first line metastatic CRPC treatment.[8] However, using docetaxel before enzalutamide has been shown to decrease the effectiveness of enzalutamide by a median overall survival of 15.8 months.[9] 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 there is a clear clinical cross-resistance between the two drugs.[10] 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.[11] 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.[12,13,14] In fact experts say that in the next 3 years all CRPC patients will progress to enzalutamide or abiraterone acetate.[15] In July 2018, the US FDA approved an expanded indication for enzalutamide to include the treatment of non-metastatic castration-resistant prostate cancer, making it the first and only FDA-approved oral treatment for both non-metastatic and metastatic CRPC.[16]

There are also current studies underway to test the effectiveness of enzalutamide to treat metastatic and non-metastatic hormone-sensitive prostate cancer.[17] According to

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[8] 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.
[9] 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.
[10] 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.
[11] Schrader AJ *et al*. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. Eur Urol. 2014 Jan;65(1):30-6.
[12] Scher HI *et al.* Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012 Sep.
[13] Loriot 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.
[14] Daniel Peter Petrylak, Charles G. Drake, Christopher Michael Pieczonka, John M. Corman, Jorge A. Garcia, Curtis Dunshee, Tim Van Mouwerik, Robert C. Tyler, Nancy N. Chang, and David Quinn. Overall survival and immune responses with sipuleucel-T and enzalutamide: STRIDE study. Journal of Clinical Oncology 2018 36:6_suppl, 246-246
[15] 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.
[16] Astellas. “U.S. FDA Approves XTANDI® (enzalutamide) for the Treatment of Men with Non-Metastatic Castration-Resistant Prostate Cancer (CRPC).” News Release. 13 July 2018. https://newsroom.astellas.us/2018-07-13-U-S-FDA-Approves-XTANDI-R-enzalutamide-for-the-Treatment-of-Men-with-Non-Metastatic-Castration-Resistant-Prostate-Cancer-CRPC
[17] Pfizer, Inc. US Securities and Exchange Commission, Form 10-Q. Filed 8 November 2018. Retrieved January 15, 2019 from: https://www.sec.gov/Archives/edgar/data/78003/000007800318000091/pfe-09302018x10q.htm

Clinicaltrials.gov, there are three current trials to study its treatment of metastatic hormone-sensitive prostate cancer, two trials (NCT02677896, NCT03246347) are supported by Astellas and Medivation (a subsidiary of Pfizer), and the third (NCT02058706) is supported by the US NIH National Cancer Institute and the Barbara Ann Karmanos Cancer Institute.

Identification of clinical evidence

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 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 acetate (although not head-to-head) and other therapies in various treatment exposure settings. We summarize below key randomized controlled trials (RTC) for enzalutamide.

Summary of available data

The phase III PROSPER trial supported the 2018 expanded indication for enzalutamide to non-metastatic CRPC. The trial demonstrated that the use of enzalutamide plus androgen deprivation therapy (ADT), "significantly reduced the risk of developing metastasis or death compared to ADT alone in men with non-metastatic CRPC."[18]

The results of the PROSPER trial were published in the New England Journal of Medicine and showed that among men with non-metastatic CRPC with a rapidly rising PSA level, treatment with enzalutamide led to a clinically meaningful and significant lower risk of death (71%) than placebo. Per the NEJM article:

> "A total of 1401 patients (median PSA doubling time, 3.7 months) underwent randomization. As of June 28, 2017, a total of 219 of 933 patients (23%) in the enzalutamide group had metastasis or had died, as compared with 228 of 468 (49%) in the placebo group. The median metastasis-free survival was 36.6 months in the enzalutamide group versus 14.7 months in the placebo group (hazard ratio for metastasis or death, 0.29; 95% confidence interval, 0.24 to 0.35; P<0.001). The time to the first use of a subsequent antineoplastic therapy was longer with enzalutamide treatment than with placebo (39.6 vs. 17.7 months; hazard ratio, 0.21; P<0.001; such therapy was used in 15% vs. 48% of patients) as was the time to PSA progression (37.2 vs. 3.9 months; hazard ratio, 0.07; P<0.001; progression occurred in 22% vs. 69% of patients). At the first interim analysis of overall survival, 103 patients (11%)

[18] Astellas. "U.S. FDA Approves XTANDI® (enzalutamide) for the Treatment of Men with Non-Metastatic Castration-Resistant Prostate Cancer (CRPC)." News Release. 13 July 2018. Retrieved January 15, 2019 from: https://newsroom.astellas.us/2018-07-13-U-S-FDA-Approves-XTANDI-R-enzalutamide-for-the-Treatment-of-Men-with-Non-Metastatic-Castration-Resistant-Prostate-Cancer-CRPC

receiving enzalutamide and 62 (13%) receiving placebo had died. Adverse events of grade 3 or higher occurred in 31% of the patients receiving enzalutamide, as compared with 23% of those receiving placebo."[19]

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.[20] 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 end point 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% vs7%), 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 1: Summary of relevant randomized clinical trials studying enzalutamide

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.

[19] Hussain, Maha; Fizazi, Karim; Saad, Fred; et al. "Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer." New England Journal of Medicine. 28 June 2018. 378:2465-2474. doi: 10.1056/NEJMoa1800536

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

Source: Luo and Graff, 2016

Roviello et al. performed a meta-analysis by pooling data from eight studies looking at novel androgen receptor pathway targeted agents.[21] Four trials contained enzalutamide in one arm, two trials investigated abiraterone acetate and two other trials investigated orteronel. Abiraterone acetate is a steroidal androgen synthesis inhibitor and acts on CYP17A1. Abiraterone acetate 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 acetate. Table 2 (below) summarizes the clinical trials used in this analysis.

[21] 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.

Table 2: Characteristic of clinical trials included in the meta-analysis

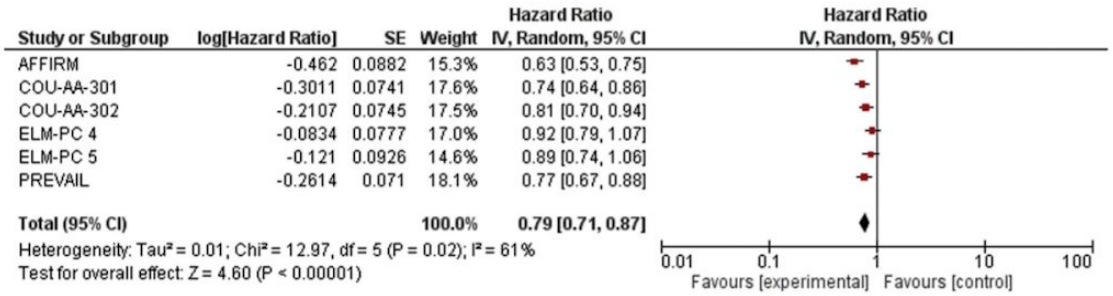
Trials	Treatment arms	Cases	End-points	Setting	Jadad Score
AFFIRM [4]	Enzalutamide versus placebo	800 399	**Primary:** overall survival **Secondary:** time to prostatic antigen specific (PSA) progression, proportion of patients with a decrease in PSA of 50%, radiographic progression-free survival, and 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 (≥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 (≥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 (≥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 (≥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 ≥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 ≥90%	Chemotherapy-naïve	4

ECOG, Eastern Cooperative Oncology Group.

Source: Roviello et al.

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.

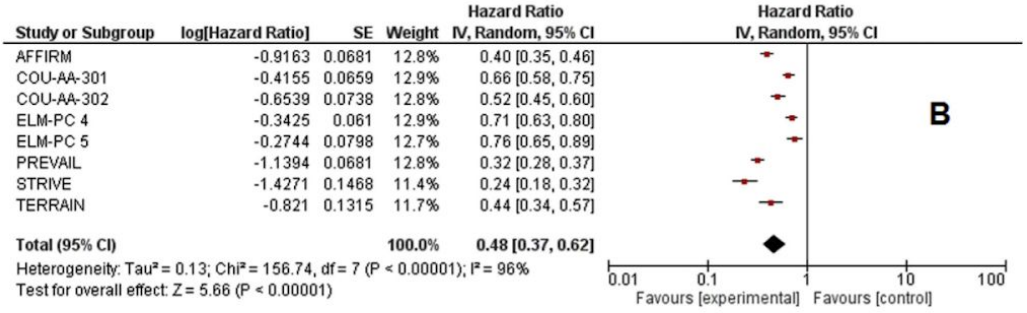
Figure 1: Forest plot for the hazard ratio of the overall survival



Source: Roviello et al.

As for the PFS, the HR ratios indicated that enzalutamide was favored over abiraterone acetate (Figure 2). Again a random effects model was used since there was high heterogeneity among the trials (I^2 = 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 2: Forest plot for the hazard ratio of the progression free survival



Source: Roviello et al.

ABIRATERONE ACETATE

Abiraterone acetate is a type of hormone therapy. This medication is classified as an “adrenal inhibitor". Abiraterone acetate selectively inhibits cytochrome P450 17 (CYP17) α-hydroxylase and cytochrome17,20 (C17,20)-lyase, which are enzymes critical for androgen synthesis.[22] In patients with metastatic CRPC, the mean terminal half-life of abiraterone acetate in plasma (mean ± SD) is 12 ± 5 hours.[23]

Each Zytiga tablet, the brand name of abiraterone acetate sold by Janssen, contains either 250 mg or 500 mg of abiraterone acetate. Abiraterone acetate is designated chemically as

[22] Harshman, L. C., & Taplin, M. E. (2013). Abiraterone acetate: targeting persistent androgen dependence in castration-resistant prostate cancer. Advances in therapy, 30(8), 727-47.
[23] FDA. Highlights of Prescribing Information for Zytiga. Issued April 2011. Retrieved January 15, 2019 from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202379lbl.pdf

(3β)-17-(3-pyridinyl) androsta5,16-dien-3-yl acetate. Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is C26H33NO2 and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water.

The FDA initially approved abiraterone acetate with prednisone in 2011 for patients with metastatic castration-resistant prostate cancer (CRPC) who had received prior chemotherapy, and expanded the indication in 2012 for patients with metastatic CRPC. On February 7, 2018, the FDA approved abiraterone acetate tablets in combination with prednisone for metastatic high-risk castration-sensitive prostate cancer (CSPC). The new indication approved in February 2018 was based on LATITUDE (NCT01715285), a placebo controlled international clinical trial that randomized 1,199 patients with metastatic high-risk CSPC.[24] Patients received either abiraterone acetate, 1,000 mg orally once daily with prednisone 5 mg once daily (n=597), or placebos orally once daily (n=602). Patients in both arms received a gonadotropin releasing hormone or had a bilateral orchiectomy. The major efficacy end point was overall survival (OS). Median OS was not estimable and 34.7 months in the abiraterone acetate and placebos arms, respectively (HR 0.621; 95% CI: 0.509, 0.756; p<0.0001). The median time-to-initiation of chemotherapy was not reached for patients on abiraterone acetate with prednisone and 38.9 months for those receiving placebos (HR 0.44; 95% CI: 0.35, 0.56; p<0.0001).

Summary of available data

The COU-AA-301 clinical trial (NCT00638690), funded by Cougar Biotechnology, was a phase III, randomized, double-blind, placebo-controlled study of abiraterone acetate (CB7630) plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy. According to the description of the clinical trial published in the NEJM, the study randomly assigned, in a 2:1 ratio, 1195 patients who had previously received docetaxel to receive 5 mg of prednisone twice daily with either 1000 mg of abiraterone acetate (797 patients) or placebo (398 patients). The primary end point was overall survival. The secondary end points included time to prostate-specific antigen (PSA) progression (elevation in the PSA level according to prespecified criteria), progression-free survival according to radiologic findings based on pre-specified criteria, and the PSA response rate.[25] According to the NEJM article, the results of the study were:

> "After a median follow-up of 12.8 months, overall survival was longer in the abiraterone acetate–prednisone group than in the placebo–prednisone group (14.8 months vs. 10.9 months; hazard ratio, 0.65; 95% confidence interval, 0.54 to 0.77;

[24] Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med 2017; 377:352-360

[25] Johann S. de Bono, M.B., Ch.B., Ph.D., Christopher J. Logothetis, M.D., Arturo Molina, M.D., Karim Fizazi, M.D., Ph.D., Scott North, M.D., Luis Chu, M.D., Kim N. Chi, M.D., Robert J. Jones, M.D., Oscar B. Goodman, Jr., M.D., Ph.D., Fred Saad, M.D., John N. Staffurth, M.D., Paul Mainwaring, M.D., M.B., B.S., et al., Abiraterone and Increased Survival in Metastatic Prostate Cancer. N Engl J Med 2011; 364:1995-2005

P<0.001). Data were unblinded at the interim analysis, since these results exceeded the preplanned criteria for study termination. All secondary end points, including time to PSA progression (10.2 vs. 6.6 months; P<0.001), progression-free survival (5.6 months vs. 3.6 months; P<0.001), and PSA response rate (29% vs. 6%, P<0.001), favored the treatment group. Mineralocorticoid-related adverse events, including fluid retention, hypertension, and hypokalemia, were more frequently reported in the abiraterone acetate–prednisone group than in the placebo–prednisone group."

The COU-AA-302 clinical trial NCT00887198, funded by Janssen Research & Development, was a placebo-controlled, double-blind, randomised phase III study, in which 1088 asymptomatic or mildly symptomatic patients with chemotherapy-naive prostate cancer stratified by Eastern Cooperative Oncology performance status (0 vs 1) were randomly assigned with a permuted block allocation scheme via a web response system in a 1:1 ratio to receive either abiraterone acetate (1000 mg once daily) plus prednisone (5 mg twice daily; abiraterone acetate group) or placebo plus prednisone (placebo group). Coprimary end points were radiographic progression-free survival and overall survival analysed in the intention-to-treat population. The Lancet Oncology article for this study summarizes the finding as follows[26]:

> “At a median follow-up of 49·2 months (IQR 47·0–51·8), 741 (96%) of the prespecified 773 death events for the final analysis had been observed: 354 (65%) of 546 patients in the abiraterone acetate group and 387 (71%) of 542 in the placebo group. 238 (44%) patients initially receiving prednisone alone subsequently received abiraterone acetate plus prednisone as crossover per protocol (93 patients) or as subsequent therapy (145 patients). Overall, 365 (67%) patients in the abiraterone acetate group and 435 (80%) in the placebo group received subsequent treatment with one or more approved agents. Median overall survival was significantly longer in the abiraterone acetate group than in the placebo group (34·7 months [95% CI 32·7–36·8] vs 30·3 months [28·7–33·3]; hazard ratio 0·81 [95% CI 0·70–0·93]; p=0·0033). The most common grade 3–4 adverse events of special interest were cardiac disorders (41 [8%] of 542 patients in the abiraterone acetate group vs 20 [4%] of 540 patients in the placebo group), increased alanine aminotransferase (32 [6%] vs four [<1%]), and hypertension (25 [5%] vs 17 [3%]).”

Based on this study, treatment with abiraterone acetate prolonged overall survival compared with prednisone alone by a margin that was both clinically and statistically significant. In 2012 this study was the basis for expanding the indication for abiraterone acetate to metastatic castration-resistant prostate cancer, in combination with prednisone. Prior to this abiraterone acetate had only been approved with prednisone for use in men with mCRPC after chemotherapy.

The LATITUDE clinical trial (NCT01715285), funded by Janssen Research and Development, was a double-blind, placebo-controlled, phase III trial, that randomly assigned

[26] Ryan, Charles J et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. The Lancet Oncology , Volume 16 , Issue 2 , 152 - 160

1199 patients to receive either androgen-deprivation therapy plus abiraterone acetate (1000 mg daily, given once daily as four 250-mg tablets) plus prednisone (5 mg daily) (the abiraterone group) or androgen-deprivation therapy plus dual placebos (the placebo group). The two primary end points were overall survival and radiographic progression-free survival.

According to the NEJM article,[27] the results of the study were as follows:

> "After a median follow-up of 30.4 months at a planned interim analysis (after 406 patients had died), the median overall survival was significantly longer in the abiraterone group than in the placebo group (not reached vs. 34.7 months) (hazard ratio for death, 0.62; 95% confidence interval [CI], 0.51 to 0.76; P<0.001). The median length of radiographic progression-free survival was 33.0 months in the abiraterone group and 14.8 months in the placebo group (hazard ratio for disease progression or death, 0.47; 95% CI, 0.39 to 0.55; P<0.001). Significantly better outcomes in all secondary end points were observed in the abiraterone group, including the time until pain progression, next subsequent therapy for prostate cancer, initiation of chemotherapy, and prostate-specific antigen progression (P<0.001 for all comparisons), along with next symptomatic skeletal events (P=0.009). These findings led to the unanimous recommendation by the independent data and safety monitoring committee that the trial be unblinded and crossover be allowed for patients in the placebo group to receive abiraterone. Rates of grade 3 hypertension and hypokalemia were higher in the abiraterone group."

Based on these results, this study concluded that the addition of abiraterone acetate and prednisone to androgen-deprivation therapy significantly increased overall survival and radiographic progression-free survival in men with newly diagnosed, metastatic, castration-sensitive prostate cancer.

The LATITUDE (NCT01715285) clinical trial was the basis for expanding, in February 2018, the indication of abiraterone acetate in combination with prednisone for metastatic high-risk castration-sensitive prostate cancer (CSPC).

Comparisons of abiraterone acetate and enzalutamide

Recent studies have compared the clinical efficacy; medication adherence, treatment patterns, and dose reductions; and the duration of treatment in patients taking abiraterone acetate and enzalutamide. This section summarizes three of those studies.

One study,[28] funded by the Seoul National University Hospital Research Fund and with no conflict of interests declared, performed a network meta-analysis of randomized controlled

[27] Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med 2017; 377:352-360

[28] Kang, M., Jeong, C. W., Kwak, C., Ku, J. H., & Kim, H. H. (2017). Comparing the clinical efficacy of abiraterone acetate, enzalutamide, and orteronel in patients with metastatic castration-resistant prostate cancer by performing a network meta-analysis of eight randomized controlled trials. Oncotarget, 8(35), 59690-59697. doi:10.18632/oncotarget.17741

trials (RCTs). This study included eight RCTs for men with mCRPC treated with one of the AR targeting agents: abiraterone acetate, enzalutamide, or orteronel. The primary end point was overall survival (OS), while the secondary end points were progression-free survival (PFS), prostate-specific antigen (PSA) responsiveness, time to PSA progression, time to first skeletal-related events (SRE), and adverse events (AEs). Pairwise meta-analysis and network meta-analysis were conducted to obtain direct and indirect evidence, respectively.

This study found that:

> "[...] enzalutamide was the most efficacious drug (HR = 0.71), followed by abiraterone (HR = 0.78). Orteronel did not show a significant effect on OS (HR = 0.90). Enzalutamide was also the most efficacious drug for secondary endpoints, particularly PFS (HR = 0.56) and time to PSA progression (HR = 0.20). Additionally, AE risks did not differ between enzalutamide and control arms, suggesting that enzalutamide is safe for clinical use in mCRPC patients. Based on these pieces of evidence together, enzalutamide can be the most efficacious and safe agents for patients with mCRPC and abiraterone can be the second most efficacious drug. Conversely, orteronel had both the least efficacy and was associated with higher AEs. This is the key finding of our study."

Another study,[29] funded by Janssen Scientific Affairs, conducted retrospective analyses using the Truven Health MarketScan research databases among patients with metastatic CRPC who initiated treatment with abiraterone acetate or enzalutamide between October 1, 2012, and December 31, 2014 (index date). The patients were followed for up to 12 months, and their baseline characteristics were assessed during the 6 months before the index date. Medication adherence was measured at 3, 6, 9, and 12 months postindex using medication possession ratios (MPRs), and dose reduction was measured using refill gaps and relative dose intensity over the entire observation period. Kaplan-Meier survival analyses and Cox proportional hazards models were used to assess the association between the initial treatment and the risk for dose reduction. The summary of the results are as follows:

> "The study included 2591 and 807 patients who initiated treatment with abiraterone acetate and enzalutamide, respectively. At 6, 9, and 12 months postindex, the patients who initiated abiraterone acetate had higher MPRs than the patients who initiated enzalutamide. In addition, the patients who initiated abiraterone acetate had lower Kaplan-Meier rates of dose reduction across 4 measurements for dose reduction. All hazard ratios for treatment (abiraterone acetate vs enzalutamide) were significantly lower than 1 (range, 0.57-0.80), indicating a lower risk for dose reduction associated with abiraterone acetate."

This study concluded that patients who initiated abiraterone acetate therapy had higher medication adherence and lower risk for dose reduction than those who initiated

[29] Behl, A. S., Ellis, L. A., Pilon, D., Xiao, Y., & Lefebvre, P. (2017). Medication Adherence, Treatment Patterns, and Dose Reduction in Patients with Metastatic Castration-Resistant Prostate Cancer Receiving Abiraterone Acetate or Enzalutamide. American health & drug benefits, 10(6), 296-303.

enzalutamide therapy. Improved medication adherence may be associated with longer duration of treatment, which in turn may lead to better survival.

Another study,[30] funded by Janssen Scientific Affairs, used the Truven Health MarketScan Research Databases from March 2012 to December 2014 to identify males with prostate cancer initiated on abiraterone acetate (AA) or enzalutamide (ENZ) (index therapy). Baseline characteristics were assessed during the 6 months pre-index. Inverse probability of treatment weights (IPTWs) were used to reduce baseline confounding. Treatment duration spanned from the index date to the earliest of treatment discontinuation (defined as a > 60-day gap in treatment), 24 months post-index, health plan disenrollment, or end of data. Weighted Kaplan-Meier and Cox proportional hazard models were used to compare the combined duration of mCRPC treatments (AA, ENZ, chemotherapy, sipuleucel-T, and radium 223) and any prostate cancer treatments (mCRPC, hormonal, and corticosteroid treatments) between patients initiated on either AA or ENZ. The results of this study were summarized as follows:

> "A total of 2,591 patients initiated on AA and 807 patients initiated on ENZ were selected for the study. Patients' characteristics were generally well balanced after IPTW. At 3 months, patients initiated on AA were associated with fewer discontinuations of mCRPC treatments (hazard ratio [HR] = 0.73, P = 0.004) or of any prostate cancer treatments (HR = 0.61, P = 0.002), compared with patients initiated on ENZ. This result was maintained at 6, 9, 12, 18, and 24 months for mCRPC treatments (HR = 0.75, P < 0.001) and for any prostate cancer treatments (HR = 0.69, P < 0.001). Median duration of mCRPC treatments was 4.1 months longer for patients initiated on AA compared with those initiated on ENZ (18.3 vs. 14.2 months, P < 0.001) and similarly, the median duration of any prostate cancer treatment was longer for patients initiated on AA compared with those initiated on ENZ (not reached vs. 22.2 months, P < 0.001)."

According to the study, these results can be interpreted as suggesting that patients initiated on abiraterone acetate, compared with those initiated on enzalutamide, had a longer combined duration of mCRPC or prostate cancer treatments.

10. Review of harms and toxicity: summary of evidence of safety.

ENZALUTAMIDE

Enzalutamide is approved for the treatment of three indications, (1) mCRPC in patients who have previously taken docetaxel, (2) mCRPC in patients who have not previously undergone chemotherapy, and most recently, (3) patients with non-metastatic CRPC. Discussions of the safety, toxicity, and adverse events (AE) follow below.

[30] Dominic Pilon, Ajay S. Behl, Lorie A. Ellis, Bruno Emond, Patrick Lefebvre, and Nancy A. Dawson. Duration of Treatment in Prostate Cancer Patients Treated with Abiraterone Acetate or Enzalutamide. Journal of Managed Care & Specialty Pharmacy 2017 23:2, 225-235

Indication 1: Metastatic castration-resistant prostate cancers in patients who have previously taken docetaxel

As previously discussed, in the AFFIRM trial of patients with mCRPC who had previously taken docetaxel, there were overall few adverse events (AE), but grade ≥3 events relating to fatigue (6% vs7%), 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.

In the key phase III trial (CRPC2) discussed on the medical review for the indication for which enzalutamide received its first approved indication from the US FDA, more patients from the placebo arm withdrew from the study due to adverse events than the enzalutamide arm.[31]

Table 3 (below) from the Medical Review of the US FDA initial approval of enzalutamide compares the safety and efficacy of enzalutamide with two other products that treat mCRPC.

Table 3: Key Efficacy and Safety Information about Three Products Used for Treatment of mCRPC After Docetaxel Therapy (Reviewer Benefit-Risk Evaluation Table)

[31] FDA. Medical Review in support of US Food and Drug Administration approval of Xtandi (enzalutamide). Application No.: 203415. Approved August 2012. Retrieved January 15, 2019 from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203415Orig1s000MedR.pdf

	Cabazitaxel	Abiraterone	Enzalutamide (MDV3100)
Approval Year	2010	2011	
Drug Class	Cytotoxic	Hormonal	Hormonal
Trial Demonstrating Clinical Benefit	EFC6193	COU-AA-301	CRPC2
Study Disease Setting	mCRPC s/p Docetaxel	mCRPC s/p Docetaxel	mCRPC s/p Docetaxel
Study Control*	Mitoxantrone	Placebo	Placebo
Study Size (# to treatment arm)	755 (378)	1195 (797)	1199 (800)
Survival Difference** HR (95% CI)	0.70 (0.59-0.83)	0.65 (0.543, 0.768)	0.63 (0.53, 0.75)
Improvement in Median OS (mos)	2.4	3.9	4.8
Key Toxicity Profile***			
Infusion Reaction/ Boxed Warnings	Yes	N/A	N/A
Severe Toxicity (Grade 3/4)			
Neutropenia (%)	82%	NS	1%
Febrile Neutropenia (%)	7%	NS	NS
Infection or UTI (%)	2%	2%	1%
Fluid Retention/Edema (%)	<1%	2%	1%
Hepatic ALT/AST (%)	1%	2%	0.3%
Seizure (%)	NS	NS	1%
Adverse Reaction of Interest (Grade 3/4)			
Hypokalemia (%)	NS	5%	NS
Hypertension (%)	NS	1%	2%
Adrenocortical Insufficiency	NS	<1%	NS

* Use of glucocorticoids varied among the trials
** Compared to Study Control in each trial. Inherent bias prevents from inter-trial comparisons.
*** Based on information from the active treatment arm only.
N/A denotes "not applicable"
NS denotes "not specified", meaning not found in relevant product's label or the review.

Indication 2: Metastatic castration-resistant prostate cancer in patients who have not previously undergone chemotherapy

In the PREVAIL trial of mCRPC treatment-naive patients discussed in the previous section, 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].

Indication 3: Non-metastatic castration-resistant prostate cancer

As observed in the PROSPER trial for the 2018 expanded indication of the use of enzalutamide for the treatment of non-metastatic CRPC:

> "At the first interim analysis of overall survival, 103 patients (11%) receiving enzalutamide and 62 (13%) receiving placebo had died. Adverse events of grade 3

> or higher occurred in 31% of the patients receiving enzalutamide, as compared with 23% of those receiving placebo."[32]

As noted in a comparison of clinical trials of enzalutamide, abiraterone acetate, and orteronel by Kang et al.:

> "...AE risks did not differ between enzalutamide and control arms, suggesting that enzalutamide is safe for clinical use in mCRPC patients. Based on these pieces of evidence together, enzalutamide can be the most efficacious and safe agents for patients with mCRPC and abiraterone can be the second most efficacious drug."[33]

ABIRATERONE ACETATE

In the key phase III trial (COU-AA-301) submitted in support of the US FDA approval of abiraterone acetate, more treatment discontinuation and more deaths occurred in the placebo arm of the study versus the abiraterone acetate arm. Also, more patients discontinued treatment due to adverse events in the placebo arm that in the abiraterone acetate arm.[34]

Table 4 (below) from the Medical Review of the US FDA approval of abiraterone acetate compares the safety and efficacy of abiraterone acetate with two other products that treat mCRPC.

[32] Hussain, Maha; Fizazi, Karim; Saad, Fred; et al. "Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer." New England Journal of Medicine. 28 June 2018. 378:2465-2474. doi: 10.1056/NEJMoa1800536

[33] Kang, M., Jeong, C. W., Kwak, C., Ku, J. H., & Kim, H. H. (2017). Comparing the clinical efficacy of abiraterone acetate, enzalutamide, and orteronel in patients with metastatic castration-resistant prostate cancer by performing a network meta-analysis of eight randomized controlled trials. Oncotarget, 8(35), 59690-59697. doi:10.18632/oncotarget.17741

[34] FDA. Medical Review in support of US Food and Drug Administration approval of Zytiga (abiraterone acetate). Application No.: 202379. Approved April 2011. Retrieved January 15, 2019 from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202379Orig1s000MedR.pdf

Table 4: Key Efficacy and Safety Information from Trials in Support of Three Drug Products for the Treatment of Patients with mCRPC (Reviewer Benefit-Risk Evaluation Table)

	Docetaxel	Cabazitaxel	Abiraterone
Approval Year	2004	2010	2011
Drug Class	Cytotoxic	Cytotoxic	Hormonal
Trial Supporting Approval	TAX327	EFC6193	COU-AA-301
Study Disease Setting	mCRPC**	mCRPC s/p Docetaxel	mCRPC s/p Docetaxel
Study Control*	Mitoxantrone	Mitoxantrone	Placebo
Study Size (# to treatment arm)	1006 (335)	755 (378)	1195 (797)
Survival Difference***			
HR (95% CI)	0.76 (0.619, 0.936)	0.70 (0.59-0.83)	0.65 (0.543, 0.768)
Improvement in Median OS (mos)	2.4	2.4	3.9
Key Toxicity Profile	Yes	Yes	N/A
Infusion Reaction	Yes	Yes	No
Boxed Warnings			
Severe Toxicity (Grade 3/4)	32%	82%	NS
Neutropenia (%)	3%	7%	NS
Febrile Neutropenia (%)	6%	2%	2%
Infection or UTI (%)	1%	<1%	2%
Fluid Retention/Edema (%)	NS	1%	2%
Hepatic ALT/AST (%)	4%	<1%	NS
Neutopathy (%)			
Adverse Reaction of Interest (Grade 3/4)			
Hypokalemia (%)	NS	NS	5%
Hypertension (%)	NS	NS	1%
Adrenocortical Insufficiency	NS	NS	<1%

* All treatment was in combination with prednisone 5 mg BID
** About 50% patients with pain.
*** Compared to Study Control in each trial
N/A denotes not applicable.
NS denotes "not specified", meaning not found in relevant product's label or the review.
All the trials showed a statistically significant improvement in OS as compared to control.
Only the products relevant to this NDA are shown in the Table.

In another phase III trial (COU-AA-302) of abiraterone acetate, researchers found that:

> "The most common grade 3–4 adverse events of special interest were cardiac disorders (41 [8%] of 542 patients in the abiraterone acetate group vs 20 [4%] of 540 patients in the placebo group), increased alanine aminotransferase (32 [6%] vs four [<1%]), and hypertension (25 [5%] vs 17 [3%]).

…
In this randomised phase 3 trial with a median follow-up of more than 4 years, treatment with abiraterone acetate prolonged overall survival compared with prednisone alone by a margin that was both clinically and statistically significant. These results further support the favourable safety profile of abiraterone acetate in patients with chemotherapy-naive metastatic castration-resistant prostate cancer."[35]

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

When sourced from the originators (Xtandi for enzalutamide and Zytiga for abiraterone acetate), both drugs are expensive. Many of the cost-benefit studies have been done using the prices from originators. Both drugs are now also available from generic suppliers, and as competition among generic suppliers expands, prices should decline considerably.

At the high originator prices, there are many studies of the cost-effectiveness of enzalutamide compared to alternatives, including ones that are also expensive (see section on cost-effectiveness studies below). The studies cited may be of limited use when considering if enzalutamide would be cost-effective in resource setting, when and where the drug is available at lower prices from generic suppliers.

The WHO needs to consider the cost-effectiveness both for cases where the drugs are expensive, from the originator, and when the drugs are less expensive from generic suppliers, including looking at reasonable scenarios for generic prices falling over time.

Costs of manufacturing enzalutamide and abiraterone acetate

In 2016, Canada-based Biolyse Pharma offered to sell generic enzalutamide to the US Medicare program for $3 for a 40mg tablet, or $12 for a daily dose of four tablets. But generic prices could fall much further, given API costs.

In previous years, before generic entry, some publicly quoted prices for the active pharmaceutical ingredient enzalutamide were in the range of $6,000 to $13,000 per kilo. At the $6,000 per kilo figure, the cost of the API for one 40 milligram capsule of enzalutamide would be $0.24 (API cost of $.006 per mg). API prices would fall over time, as generic producers enter the market.

Prices of generic abiraterone acetate vary. One company offers a CIPLA version of abiraterone acetate 120-tablet package of 250mg tablets for 17,000 INR, or $238.40 in USD

[35] Ryan, Charles J et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. The Lancet Oncology, Volume 16, Issue 2, 152 - 160

at current[36] exchange rates. This is $2 per tablet. The price for a unit of the API is $7,947 per kilo and $0.007947 per milligram.

The prices for the APIs for both products will fall over time, dramatically. Andrew M Hill, Melissa J Barber, Dzintars Gotham and others have recently published a series of papers reporting the costs of active pharmaceutical ingredients for various drugs, including several drugs for cancer.[37] In the 2018 BMJ paper on the WHO EML drugs, the authors reported API prices for 21 antineoplastic and immunosuppressive drugs in the WHO EML. Three products were reported to have API prices higher than $6,000 per kilo: methotrexate ($77,181/kg), anastrozole ($48,669/kg), and etoposide ($8,463/kg). The two products with the highest API prices were sold with only 2.5/mg or 1/mg or API per tablet. The remaining 18 products had API prices from $34/kg to to $2,284/kg. These included such products as tamoxifen ($271/kg), capecitabine ($393/kg), prednisolone ($962/kg) and imatinib ($2,284/kg).

Cost-effectiveness Studies

United Kingdom

The National Institute for Health and Care Excellence (NICE published an evaluation of the cost benefit analysis is 2014.

Enzalutamide

Enzalutamide for metastatic hormone‑relapsed prostate cancer previously treated with a docetaxel‑containing regimen. Technology appraisal guidance [TA316] Published date: 23 July 2014

This guidance was reevaluated in 2016 and 2017. The 2017 evaluation stated: “We found nothing new that affects the recommendations in this guidance.”[38]

According to the “Technology appraisal guidance [TA316]”, published July 23, 2014:

> Enzalutamide is recommended as an option for treating hormone‑relapsed metastatic prostate cancer in adults, only if:
>
> 1. their disease has progressed during or after docetaxel-containing chemotherapy and

[36] As of January 19, 2019.
[37] For example, Hill A, Redd C, Gotham D, et al Estimated generic prices of cancer medicines deemed cost-ineffective in England: a cost estimation analysis BMJ Open 2017;7:e011965. doi: 10.1136/bmjopen-2016-011965; Hill AM, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. BMJ Glob Health. 2018;3(1):e000571. Published 2018 Jan 29. doi:10.1136/bmjgh-2017-000571
[38] Enzalutamide for metastatic hormone‑relapsed prostate cancer previously treated with a docetaxel‑containing regimen. Technology appraisal guidance [TA316] Published July 2014. https://www.nice.org.uk/guidance/ta316

2. they have not had treatment with abiraterone and 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 chemotherapy, and with best supportive care for patients who had received 2 or more courses of chemotherapy.

For patients who had received 1 course of chemotherapy, the Committee noted that the analysis reflecting its preferred assumptions, but not the actual patient access scheme discount for abiraterone, gave an ICER of £22,600 per 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 ICER estimated by the manufacturer for enzalutamide compared with best supportive care was £45,500 per QALY gained and that the ERG's ICER was £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. Because the Committee had not seen evidence for patients who had received abiraterone as 1 of the 2 or more courses of chemotherapy, it agreed that the evidence it had considered could not be generalised to patients who had received abiraterone.[39]

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

Abiraterone acetate

The NICE evaluation of abiraterone acetate was:

Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. Technology appraisal guidance [TA387] Published date: 27 April 2016 Last updated: 27 July 2016

The recommendation was:

Abiraterone in combination with prednisone or prednisolone is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer:

[39] Ibid.

1. in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated
2. only when the company provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England.[40]

Ireland

Enzalutamide

A June 2015 evaluation of enzalutamide by the NCPE, found that enzalutamide was not cost effective.

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.

The NCPE evaluation stated:

> "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."[41]

The December 2015 guidance has approved reimbursement following confidential price negotiations.[42]

Abiraterone acetate

As in the case of enzalutamide, the NCPE first rejected abiraterone acetate, and then approved coverage following confidential price negotiations.[43]

In 2012, the NCPE evaluation stated: "Reimbursement not recommended at the submitted price."

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[40] Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. Technology appraisal guidance [TA387] Published April 2016. Last updated July 2016. Retrieved January 15, 2019 from: https://www.nice.org.uk/guidance/ta387

[41] 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. Retrieved January 15, 2019 from: http://www.ncpe.ie/wp-content/uploads/2014/12/Final-enzalutamide-LM-Web-Summary-June-2015.pdf

[42] National Centre for Pharmacoeconomics. NCPE Ireland. Enzalutamide (Xtandi®) on or after chemotherapy. Retrieved January 15, 2019 from: http://www.ncpe.ie/drugs/enzalutamide-xtandi/

[43] National Centre for Pharmacoeconomics. NCPE Ireland. Abiraterone Acetate (Zytiga®) for mCRPC. Retrieved January 15, 2019 from: http://www.ncpe.ie/drugs/abiratone-acetate-zytiga/

In May 2014, the update NCPE evaluation stated: “The HSE has approved reimbursement following confidential price negotiations.”

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 cost-effectiveness of enzalutamide 160 mg 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, obtained 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 cost-utility 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.[44]

United States of America

One 2014 study by Leslie Wilson et al. for the US 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 acetate), Xtandi (enzalutamide), and Jevtana (cabazitaxel) -- and found that the price of enzalutamide

[44] 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

was the single limiting factor rendering enzalutamide less cost-effective than abiraterone acetate. 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-effectiveness calculations based upon 2012 prices, enzalutamide 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][45]

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. COST EFFECTIVENESS OF THERAPIES FOR CASTRATION RESISTANT METASTATIC PROSTATE CANCER, 37th Annual Meeting of the Society for Medical Decision Making, PS1-4 , Sunday, October 18, 2015, Poster Board # PS1-4[46]

The study by Niranjan et al. concluded:

> 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

[45] 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

[46] https://smdm.confex.com/smdm/2015mo/webprogram/Paper9446.html

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.[47]

Vicente, C et al. Cost-Utility Analysis Of Enzalutamide For Patients With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer (Mcrpc) After Failure Of Androgen Deprivation Therapy (Adt). Value in Health, Volume 18, Issue 7, A474. (November 2015).

The study by Vicente et al. stated:

NMA results suggested no difference between enzalutamide and ABI+P for overall survival, but indicated that enzalutamide is superior to ABI+P for rPFS (hazard ratio 0.35; credible interval 0.27, 046). The improvement in rPFS translated into a longer mean duration of stable disease with enzalutamide (36.7 months) than with ABI+P (16.4 months), and greater total QALYs (enzalutamide 2.65; ABI+P 2.23). From the Canadian MoH perspective, enzalutamide had an incremental cost-effectiveness ratio (ICER) of $92,690 per additional QALY gained versus ABI+P. The ICER was robust over a wide range of sensitivity analyses. In the probabilistic sensitivity analysis, the mean ICER was $110,036 per QALY gained versus ABI+P, with >60% of iterations falling below a willingness-to-pay threshold of $100,000 per QALY gained.

Conclusions
Enzalutamide is considered a cost-effective treatment option compared to ABI+P in patients with chemotherapy-naïve mCRPC after failure of ADT.[48]

Three of the authors in this study were affiliated with Astellas at the time of publication.

Avxentyev, NA et al., Pharmacoeconomic Analysis of Enzalutamide and Abiraterone for Treatment of Chemotherapy-Naïve Patients with Metastatic Castration-Resistant Prostate Cancer, Value in Health, Volume 20, Issue 9, A436. (October-November 2017)

[47] Niranjan Kathe, M.S., Corey Hayes, Pharm D MPH, Anand Shewale, M.S. and Bradley Martin. Presented at the 37th Annual Meeting of the Society for Medical Decision Making. October 18 - 21, 2015.
[48] Vicente, C et al. Cost-Utility Analysis Of Enzalutamide For Patients With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer (Mcrpc) After Failure Of Androgen Deprivation Therapy (Adt). Value in Health, Volume 18, Issue 7, A474. (November 2015).

The study by Avxentyev et al. concluded:

> Enzalutamide was found to be a cost-saving option compared to abiraterone. Monthly medication costs for enzalutamide were $3760 per patient, 11.7% less than for abiraterone. The 8-year discounted total medical costs for enzalutamide and abiraterone were $114,307 and $121,272 per patient, respectively, indicating that the 8-year health budget could be cut by $696,500 per 100 mCRPC patients through treatment with enzalutamide. Enzalutamide was also found to be cost-effective compared to abiraterone when both were compared against chemotherapy alone.
>
> Conclusions
> Enzalutamide is a cost-saving and cost-effective option compared to abiraterone and should be recommended for inclusion into the VEDL in Russia.[49]

Avxentyev, N.A. et al., Pharmacoeconomic Evaluation Of Enzalutamide For The Treatment Of Post-chemotherapy Patients With Metastatic Castration-resistant Prostate Cancer In Russia, Value in Health, Volume 21, S29. 2018.

This study by Avxentyev et al. on patients in Russia found:

> Use of enzalutamide, abiraterone and cabazitaxel resulted in 1.04, 0.94 and 0.96 quality-adjusted life years respectively. Monthly medication costs for enzalutamide were US$2973 per patient, 15% less for abiraterone and 49% less than for cabazitaxel. Five-year total medical costs were US$53,959, US$53,975 and US$71,836 per patient for enzalutamide, abiraterone and cabazitaxel, respectively. The smaller difference in total medical costs resulted from longer progression-free survival on enzalutamide compared to abiraterone or cabazitaxel. If included in GDRP, enzalutamide results in the lowest budget impact. . . .[50]

This study was funded by Astellas Pharma Inc and Pfizer Inc, as disclosed by the authors in one of their presentations of this study.[51]

Devlin, N et al. Health-Related Quality Of Life (Hrqol) Benefits Of Enzalutamide In Patients With Metastatic Castration-Resistant Prostate Cancer (Mcrpc): An In-Depth Analysis Of Eq-5d Data From The Prevail Trial, Value in Health, Volume 18, Issue 7, A475. (November 2017).

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[49] Avxentyev, NA et al., Pharmacoeconomic Analysis of Enzalutamide and Abiraterone for Treatment of Chemotherapy-Naïve Patients with Metastatic Castration-Resistant Prostate Cancer, Value in Health, Volume 20, Issue 9, A436. (October-November 2017)
[50] Avxentyev, N.A. et al., Pharmacoeconomic Evaluation Of Enzalutamide For The Treatment Of Post-chemotherapy Patients With Metastatic Castration-resistant Prostate Cancer In Russia, Value in Health, Volume 21, S29. 2018.
[51] Avxentyev, N.A. et al., Pharmacoeconomic Evaluation Of Enzalutamide For The Treatment Of Post-chemotherapy Patients With Metastatic Castration-resistant Prostate Cancer In Russia. Scientific Presentations Database. Retrieved January 15, 2019 from: https://tools.ispor.org/ScientificPresentationsDatabase/Presentation/88583

The study by Devlin et al. stated:

> HRQOL deterioration (indicated by decreases in EQ-5D Index and VAS scores) was more gradual with enzalutamide versus placebo; reductions were significantly ($p<0.05$) smaller with enzalutamide in EQ-5D Index up to Week 37 and in EQ-VAS up to Week 61 (except Week 49). Benefits of enzalutamide were primarily in the Pain/Discomfort dimension, with significant between-group differences ($p<0.05$) through to Week 37. PCHC analysis showed a higher percentage of enzalutamide patients reporting improvements on EQ-5D dimensions up to Week 49 and a higher proportion of placebo patients reporting worsening up to week 25. Time to event analysis showed superiority of enzalutamide on time to shift from full health (state 11111) and time to first worsening on the Pain/Discomfort and Anxiety/Depression dimensions. At Week 61, of patients originally randomised to enzalutamide, 20.1% reported being in full health (state 11111), 28.2% reported no pain or discomfort, and 43.1% reported no anxiety/depression compared with 5.1%, 6.5%, and 10.2%, respectively, of placebo patients.
>
> Conclusions
> In PREVAIL, as well as improving overall survival versus placebo, enzalutamide showed HRQOL benefits captured through EQ-5D Index and VAS scores, including benefits in the Pain and Discomfort dimension of EQ-5D, and reporting being in full health, having no pain/discomfort, or no anxiety/depression.[52]

Two of the authors in this study were affiliated with Astellas at the time of publication.

Aguirre, A et al., Cost Per Median Overall Survival Associated with Abiraterone Acetate and Enzalutamide For Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer in Colombia, Value in Health, Volume 20, Issue 9, A876 - A877. (October-November 2017)

The study by Aguirre et al. concluded:

> The results demonstrated that AA+P has a lower cost per monthly median OS than enzalutamide ($846.00 vs. 1,573.00; 46% reduction), based on the following assumptions: exchange rate USD 1 = COP 2967, 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 EFP per 30-day supply of $2,096.57 for AA+P versus $3,084.11 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 31% to 44% lower for AA+P than for enzalutamide. Costs per month of chemotherapy avoided were $1,165.00 for AA+P and $1,983.00

[52] Devlin, N et al. Health-Related Quality Of Life (Hrqol) Benefits Of Enzalutamide In Patients With Metastatic Castration-Resistant Prostate Cancer (Mcrpc): An In-Depth Analysis Of Eq-5d Data From The Prevail Trial, Value in Health, Volume 18, Issue 7, A475. (November 2017).

for enzalutamide, while costs per month to achieve median rPFS were $1,779.00 for AA+P and $2,776.00 for enzalutamide.

Conclusions
Costs per monthly median OS, 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.
[53]

The two authors in this study were affiliated with Janssen at the time of publication.

Gay J, Schultz N, Braun, Cost-Effectiveness Evaluation of Enzalutamide and Abiraterone for the Treatment of Metastatic Castration-Resistant Prostate Cancer Patients Progressing after Docetaxel in the Mexican Public Healthcare System. Value in Health, 21. S29-30. (2018)

The study by Gay, Schultz, and Braun (note that Schultz and Braun are employees of Astellas) stated:

Objectives: Enzalutamide (ENZA) and abiraterone acetate plus prednisone (ABI) are approved oral treatments for patients with metastatic castration-resistant prostate cancer (mCRPC) after progression on docetaxel in the Mexican public healthcare (PHC) system. Financial schemes have been proposed to facilitate access to these new treatment options. This analysis evaluated the cost-effectiveness of ENZA and ABI for patients with mCRPC progressing after docetaxel treatment in the Mexican PHC system.

Methods: A three health-state Markov model was developed in which “free of progression”, “progression”, and “death” were defined as health states. Safety and efficacy inputs of ENZA and ABI were obtained from a published meta-analysis and the clinical trials AFFIRM (for ENZA) and COU-AA-301 (for ABI). Cost per month in each health state considered direct medical costs from local sources of the Mexican Social Security Institute (IMSS), and included the cost of treatment and adverse event management. A risk-sharing agreement was modeled, eliminating the cost of ENZA for patients with treatment failure before 12 months of treatment. A 3-year time horizon was utilized and a deterministic sensitivity analysis was performed to identify the most relevant variables.

Results: For the base-case scenario, the results showed a 0.21-year increase in overall survival in favor of ENZA and an incremental cost of MX$3435. This represents an incremental cost-effectiveness ratio (MX$/life-year gained) of MX$16,197, which is considered cost-effective at the willingness-to-pay threshold of

[53] Aguirre, A et al., Cost Per Median Overall Survival Associated with Abiraterone Acetate and Enzalutamide For Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer in Colombia, Value in Health, Volume 20, Issue 9, A876 - A877. (October-November 2017)

MX$167,583. The sensitivity analysis showed that the cost of drugs and length of the risk-sharing agreement were the most relevant variables.

Conclusions: From the IMSS perspective in Mexico, ENZA is a cost-effective alternative treatment for patients with mCRPC after progression on docetaxel. The introduction of financial schemes to purchase innovative technologies seems a highly promising method of improving access to modern and more effective drugs for cancer patients in the Mexican PHC system.[54]

JG Gay, NM Schultz, S Braun, Cost-Effectiveness Evaluation of Enzalutamide and Abiraterone for the Treatment of Metastatic Castration-Resistant Prostate Cancer Patients Progressing after Docetaxel in the Mexican Public Healthcare System, Value in Health, Vol. 21, S29–S30, May 2018.

Two of the three authors in this study were affiliated with Astellas at the time of publication.

Rachael McCool, Kelly Fleetwood, Julie Glanville, Mick Arber, Howard Goodall, Shevani Naidoo, Systematic Review and Network Meta-Analysis of Treatments for Chemotherapy-Naive Patients with Asymptomatic/Mildly Symptomatic Metastatic Castration-Resistant Prostate Cancer, Value in Health, Vol. 21, Issue 10, p1259–1268, May 3, 2018

Conclusions
For rPFS, the NMA suggests that enzalutamide is superior to abiraterone/prednisone and sipuleucel-T. There is no evidence of a statistically significant difference in OS between enzalutamide and abiraterone/prednisone, sipuleucel-T, or radium-223. Given the limitations in network construction and underlying assumptions made to complete these analyses, results should be interpreted with caution.

One of the authors in this study was affiliated with Astellas at the time of publication.

J De La Cruz-Vargas, N Chavez-Villanueva, E Guerrero, A Aguirre, G Ojeda-Botteri, Cost Treatment Comparison of Abiraterone Acetate Plus Prednisone in the Pre-Chemotherapy Setting Followed by Enzalutamide in the Post-Chemotherapy Setting Versus the Opposite Treatment Sequence in Metastatic Castration-Resistant Prostate Cancer Patients With Non-Visceral Metastases in Peru, Value in Health, Vol. 21, S24, May 2018

Three of the authors in this study were affiliated with Janssen at the time of publication.

N.A. Avxentyev, E.V. Derkach, A.S. Makarov, PCN91 - PHARMACOECONOMIC EVALUATION OF ENZALUTAMIDE FOR THE TREATMENT OF POST-CHEMOTHERAPY

[54] Gay J, Schultz N, Braun, Cost-Effectiveness Evaluation of Enzalutamide and Abiraterone for the Treatment of Metastatic Castration-Resistant Prostate Cancer Patients Progressing after Docetaxel in the Mexican Public Healthcare System. Value in Health, 21. S29-30. (2018)

PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER IN RUSSIA, Value in Health, Vol. 21, S29, October 2018

This study was funded by Astellas Pharma Inc and Pfizer Inc.

H Metin, K McQuarrie, P Thilakarathne, J Diels, T Ito, T Li, G Sulur, KN Chi, and others, Benefit Of Abiraterone Acetate Plus Prednisone (AA+P) Added To Androgen Deprivation Therapy (ADT) In Patients With High-Risk, Newly Diagnosed Metastatic Hormone-Sensitive Prostate Cancer (MHSPC): Post Hoc Analysis Of EQ-5D-5L From The Latitude Study, Value in Health, Vol. 21, S38, May 2018

Seven of the authors in this study were affiliated with Janssen at the time of publication.

J Lam, C Yang, C Kaiser, W Wong, Real-World Treatment Patterns And Care Pathways In Metastatic Castration Resistant Prostate Cancer, Value in Health, Vol. 21, S41, May 2018

Three of the authors in this study were affiliated with Genentech at the time of publication.

J. Hu, A. Aprikian, M. Vanhuyse, A. Dragomir, PCN248 - USE OF CANCER DRUGS IN THE END-OF-LIFE IN MEN DYING OF CASTRATION-RESISTANT PROSTATE CANCER: POPULATION-BASED STUDY, Value in Health, Vol. 21, S56, October 2018

J Scott, R Concepcion, D Garofalo, S Verma-Kurvari, B Xu, J Montgomery, Real-World Data Analysis Of Metastatic Castration-Resistant Prostate Cancer (MCRPC) Treatment Decisions With The Introduction Of Newer Treatment Options, Value in Health, Vol. 21, S43, May 2018

PA Alfonso Quiñones, M Carrasquilla-Sotomayor, NJ Alvis-Zakzuk, ME Romero Prada, N Alvis-Guzmán, LM Huerfano, Efficacy and Safety Analysis of Radium-223 in Patients with Prostate Cancer Castration-Resistant and Bone Metastasis, Value in Health, Vol. 21, S16–S17, May 2018

B Wu, S Li, O Tunceli, C Pericone, Z Ding, A Behl, K Mangla, N Dawson, Cost of Care for Patients with Metastatic Castration-Resistant Prostate Cancer in US Commercially Insured and Medicare Supplement Plans, Value in Health, Vol. 21, S28, May 2018

Six of the authors in this study were affiliated with Janssen at the time of publication.

Z. Zhou, X. Hu, PCN153 - COST-EFFECTIVENESS ANALYSIS OF APALUTAMIDE FOR TREATMENT IN NON- METASTASIS CASTRATION-RESISTANT PROSTATE CANCER, Value in Health, Vol. 21, S40–S41, October 2018

12. Summary of regulatory status and market availability of the medicine.

Enzalutamide is approved worldwide and in various jurisdictions such as:

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.”

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).”

In October 2018, enzalutamide was approved in the EU for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer.

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”

Canada (Health Canada)
Enzalutamide is approved in Canada for, “the treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC),” and is also, “indicated in the setting of medical or surgical castration for the treatment of metastatic castration-resistant prostate cancer (CRPC) in patients who:

- are chemotherapy-naïve with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy.
- have received docetaxel therapy.“

Abiraterone acetate is approved worldwide and in various jurisdictions such as:

US (FDA)
Abiraterone acetate is licensed in the USA for the following indication:

- “in combination with prednisone for metastatic high-risk castration-sensitive prostate cancer (CSPC).”

EU (EMA)
Abiraterone acetate is licensed in the EU for the following indication::
“with prednisone or prednisolone for:

- the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) [ ]
- the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated [ ]
- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen."

Australia (TGA)
Abiraterone acetate is licensed in Australia for the following indication:
"in combination with prednisone or prednisolone for the treatment of:

- newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT), or
- patients with metastatic advanced prostate cancer (castration resistant prostate cancer, mCRPC) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) or
- patients with mCRPC who have received prior chemotherapy containing a taxane."

Japan (PMDA)
Abiraterone acetate is licensed in Japan for:

- "castration-resistant prostate cancer."

Canada (Health Canada)
Abiraterone acetate is approved in Canada for the following indication:
"in combination with prednisone for the treatment of metastatic prostate cancer (castration-resistant prostate cancer, mCRPC) in patients who:

- are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy
- have received prior chemotherapy containing docetaxel after failure of androgen deprivation therapy."

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."

In 2016, Biolyse Pharma, a Canadian drug manufacturer, asked the US 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.

As noted above, the US patent 8,822,438 covering Zytiga (abiraterone acetate) has been invalidated.

The sole generic version of enzalutamide is sold by Glenmark, selling a version under the trade name of Glenza. The number of India-based firms selling enzalutamide will increase if the patent status in India, which is currently litigated by the University of California, is resolved.

There are many generic versions of abiraterone acetate available.

Currently, seven firms have received US FDA approval to sell abiraterone acetate and one firm has received a tentative approval.

Table 7: US FDA approvals for abiraterone acetate

1. ABIRATERONE ACETATE (ABIRATERONE ACETATE) | ANDA #208327 | TABLET;ORAL | Prescription | AMNEAL PHARMS
2. ABIRATERONE ACETATE (ABIRATERONE ACETATE) | ANDA #208339 | TABLET;ORAL | Prescription | HIKMA PHARMS
3. ABIRATERONE ACETATE (ABIRATERONE ACETATE) | ANDA #208380 | TABLET;ORAL | None (Tentative Approval) | WOCKHARDT BIO AG
4. ABIRATERONE ACETATE (ABIRATERONE ACETATE) | ANDA #208432 | TABLET;ORAL | Prescription | TEVA PHARMS USA
5. ABIRATERONE ACETATE (ABIRATERONE ACETATE) | ANDA #208446 | TABLET;ORAL | Prescription | MYLAN PHARMS INC
6. ABIRATERONE ACETATE (ABIRATERONE ACETATE) | ANDA #208453 | TABLET;ORAL | Prescription | APOTEX INC
7. YONSA (ABIRATERONE ACETATE) | NDA #210308 | TABLET;ORAL | Prescription | SUN PHARMA GLOBAL
8. ZYTIGA (ABIRATERONE ACETATE) | NDA #202379 | TABLET;ORAL | Prescription | JANSSEN BIOTECH

Several other firms, such as CIPLA, are selling abiraterone acetate in India.

As of the third quarter of 2018, nine companies have US FDA drug master files (DMF) for the supply of enzalutamide APIs.

Table 8: US FDA drug master files (DMF) for the supply of enzalutamide APIs

DMF#	STATUS	TYPE	SUBMIT DATE	HOLDER	SUBJECT

29062	A	II	3/23/2015	SAI LIFE SCIENCES LTD	4-((2-CYANOPROPAN-2-YL)AMINO)-2-FLUORO-N-METHYLBENZAMIDE (ENZALUTAMIDE INTERMEDIATE)
29117	A	II	3/31/2015	DR REDDYS LABORATORIES LTD	ENZALUTAMIDE
29872	A	II	5/24/2016	TEVA PHARMACEUTICAL INDUSTRIES LTD	ENZALUTAMIDE
30010	A	II	11/28/2015	MYLAN LABORATORIES LTD	ENZALUTAMIDE
30260	A	II	3/17/2016	SHILPA MEDICARE LTD	ENZALUTAMIDE
30279	A	II	2/29/2016	MSN LABORATORIES PRIVATE LTD	ENZALUTAMIDE [ROUTE CODE "EI"]
30304	A	II	3/29/2016	CADILA HEALTHCARE LTD	ENZALUTAMIDE
30644	A	II	7/9/2016	SCINOPHARM TAIWAN LTD	ENZALUTAMIDE
31196	A	II	12/30/2016	LAURUS LABS LTD	ENZALUTAMIDE

As of the third quarter of 2018, 25 companies have US FDA drug master files (DMF) for the supply of abiraterone acetate APIs.

Table 9: US FDA drug master files (DMF) for the supply of abiraterone acetate APIs

DMF#	STATUS	TYPE	SUBMIT DATE	HOLDER	SUBJECT
26725	A	II	11/28/2012	STERLING SPA	ABIRATERONE ACETATE
26779	A	II	12/24/2012	CHONGQING PHARMACEUTICAL RESEARCH INSTITUTE CO LTD	ABIRATERONE ACETATE (NON-STERILE BULK DRUG SUBSTANCE)
26894	A	II	7/30/2014	CHEMWERTH INC	ABIRATERONE ACETATE
27376	A	II	8/1/2013	OLON SPA	ABIRATERONE ACETATE
27737	I	II	11/15/2013	ICEUTICA INC	SOLUMATRIXT ABIRATERONE ACETATE DRUG PRODUCT INTERMEDIATE
27829	A	II	12/24/2013	MSN LABORATORIES PRIVATE LTD	ABIRATERONE ACETATE USP [ROUTE CODE - "AY"]
27853	A	II	12/24/2013	HUBEI BIOCAUSE HEILEN PHARMACEUTICAL CO LTD	ABIRATERONE ACETATE
27989	A	II	2/12/2014	STERLING CHEMICAL MALTA LTD	ABIRATERONE ACETATE
28038	A	II	3/27/2014	DR REDDYS LABORATORIES LTD	ABIRATERONE ACETATE
28292	A	II	6/24/2014	ALP PHARM BEIJING CO LTD	ABIRATERONE ACETATE
28383	A	II	6/13/2014	HETERO LABS LTD	ABIRATERONE ACETATE
28412	A	II	7/7/2014	ZACH SYSTEM SA	ABIRATERONE ACETATE

28701	A	II	10/8/2014	INDUSTRIALE CHIMICA SRL	ABIRATERONE ACETATE USP
28764	A	II	10/30/2014	TEVA PHARMACEUTICAL INDUSTRIES LTD	ABIRATERONE ACETATE
28789	A	II	10/30/2014	OPTIMUS DRUGS PRIVATE LTD	17-IODO-ANDROSTA-5,16-DIENE-3BETA-OL (ABIRATERONE INTERMEDIATE)
28806	A	II	11/5/2014	OPTIMUS DRUGS PRIVATE LTD	3-DIETHYLBORANYL-PYRIDINE (ABIRATERONE INTERMEDIATE)
28905	A	II	12/23/2014	RAKS PHARMA PVT LTD	ABIRATERONE ACETATE USP
28959	A	II	2/11/2015	SUN PHARMACEUTICAL INDUSTRIES LTD	ABIRATERONE ACETATE
29125	A	II	3/31/2015	CIPLA LTD	ABIRATERONE ACETATE
30587	A	II	6/1/2016	SCINOPHARM TAIWAN LTD	ABIRATERONE ACETATE USP
31309	A	II	3/3/2017	AURISCO PHARMACEUTICAL CO LTD	ABIRATERONE ACETATE
31392	A	II	4/25/2017	ICEUTICA INC	SOLUMATRIX™ ABIRATERONE ACETATE DRUG PRODUCT INTERMEDIATE
31582	A	II	4/12/2017	TIANJIN WEIJIE PHARMACEUTICAL CO LTD	ABIRATERONE ACETATE
32637	A	II	2/24/2018	QILU ANTIBIOTICS LINYI PHARMACEUTICAL CO LTD	ABIRATERONE ACETATE (NON-STERILE)
32658	A	II	3/26/2018	MSN LABORATORIES PRIVATE LTD	ABIRATERONE

KEI anticipates that API costs will decline to $300/kg to $900/kg over time for both products, in line with prices for tamoxifen ($271/kg), capecitabine ($393/kg) and prednisolone ($962/kg).

A decline of that magnitude would result in API costs of $0.012 to $0.036 per 40mg capsule, or $0.048 to $0.144 per day, for enzalutamide, and $0.075 to $0.225 per 250mg tablet or $0.30 to $0.90 per day for abiraterone acetate (without prednisone).

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

The application should address whether the proposed medicine is included in at least one of the following Pharmacopeia:

- *The British Pharmacopoeia*
- *The International Pharmacopoeia*
- *The United States Pharmacopoeia*
- *The European Pharmacopoeia*

14. Comprehensive reference list and in-text citations.

The application should be clearly referenced with in-text citations using the Vancouver style. Where possible, a copy of the electronic reference library files should be provided in EndNote™.