pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Enzalutamide (Xtandi) for Metastatic Castration-Resistant Prostate Cancer

July 23, 2013

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the safety and efficacy of enzalutamide (Xtandi) on patient outcomes compared to standard therapies or placebo in patients with metastatic castration-resistant prostate cancer (mCRPC) who have received docetaxel therapy.

Enzalutamide is an oral hormone therapy that prevents the binding of androgen to the androgen receptor (AR) and the binding of the AR-complex to DNA in prostate cancer cells. Enzalutamide has a Health Canada indication for the treatment of patients with metastatic castration-resistant prostate cancer in the setting of medical or surgical castration who have received docetaxel therapy.

The recommended dose is 160mg (four 40mg capsules) orally and once daily with or without food.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The AFFIRM study was an international, multicenter, double-blind, placebo-controlled, phase III RCT that evaluated the efficacy and safety of enzalutamide (160 mg once-daily) compared to placebo.[1] The study recruited patients with mCRPC who have been previously treated with docetaxel-based chemotherapy. A total of 1199 patients were randomly assigned 2:1 to receive treatment with enzalutamide (n=800) or placebo (n=399). Baseline characteristics were generally well balanced across treatment groups, with the majority of patients having an ECOG performance status of 0 (37-39%) or 1 (53-54%), and less than 10% of patients having an ECOG performance status of 2.

Patients with a history of seizure or any condition that may predispose to seizure were excluded from the study.

Efficacy

The primary efficacy endpoint was overall survival (OS). As of the interim analysis (September 25, 2011), there were 520 deaths, 308 deaths (39%) in the enzalutamide group and 212 deaths (53%) in the placebo group. The median OS was 18.4 vs.13.6 months in the enzalutamide vs. placebo group, respectively (hazard ratio (HR) = 0.63, 95% confidence interval (CI) 0.53 to 0.75, p<0.001). Subgroup analyses showed consistent OS benefit of enzalutamide in various subpopulations.

Secondary efficacy outcomes included radiographic progression-free survival (rPFS), time to PSA progression, PSA response rate defined as >50% reduction in PSA , time to first skeletal-related event (SRE), and quality of life (QoL). The median rPFS was 8.3 vs. 2.9 months in the enzalutamide vs. placebo group, respectively (HR=0.40, 95% CI 0.35-0.47, p<0.001). The median time to PSA progression was 8.3 months vs. 3.0 months in the enzalutamide vs. placebo group, respectively (HR=0.25, 95% CI 0.20-0.30, p<0.001). The proportion of patients that achieved a ≥50% reduction in PSA levels from baseline was 54% in the enzalutamide group and 2% in the placebo group

(p<0.001). While the proportion of patients that achieved a ≥90% reduction in PSA levels from baseline was 25% in the enzalutamide group and 1% in the placebo group (p<0.001).

Harms

There were more AEs leading to discontinuation in the placebo group (9.8%) compared to the enzalutamide group (7.6%). Serious adverse events (SAEs) that occurred more commonly in the enzalutamide group compared to the placebo group included spinal cord compression, hematuria, bone pain, pathological fracture, metastatic pain, general physical health deterioration, and pneumonia. Twenty-three fatal AEs (3%) occurred in the enzalutamide group and 14 fatal AEs (4%) occurred in the placebo group. Seizures occurred in 7(seven) or 0.9% of patients on enzalutamide. No patients on the placebo arm experienced seizures.

1.2.2 Additional Evidence

pCODR received input on enzalutamide from the following patient advocacy group, Prostate Cancer Canada and Canadian Cancer Survivor Network. Provincial Advisory group input was obtained from seven of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

In addition, two supplemental questions were identified during the development of the review protocol as relevant to the pCODR review of enzalutamide and are discussed as supporting information.

- The validity and limitations of skeletal-related events as an endpoint in prostate cancer studies was examined.No studies were identified that formally evaluated the validity and reliability SREs as an endpoint in advanced prostate cancer trials.
- A critical appraisal of an indirect comparison of enzalutamide with abiraterone, cabazitaxel, or mitoxantrone was conducted.
- Limitations surrounding the indirect comparison were a cause for concern regarding the robustness of any provided results and, therefore, any conclusions drawn from this indirect comparison should be interpreted with caution.

1.2.3 Interpretation and Guidance

Burden of Illness and Need
Prostate cancer is the most common cancer in Canadian men with 26,500 new cases and the third leading cause of cancer related death with 4,000 deaths reported in 2012.

The current standard of care for first-line treatment of mCRPC is docetaxel-based chemotherapy, given with prednisone. In the event that patients progress post-docetaxel therapy there are a number of new agents which demonstrated survival benefits in the post docetaxel setting including cabazitaxel and abiraterone. Retreatment with docetaxel chemotherapy is also an option in some patients, though the survival benefit of this has not yet been demonstrated. Patients progressing on docetaxel based chemotherapy have limited treatment options and a short life expectancy, underscoring the need for novel therapeutic strategies that are both effective and well tolerated.

Effectiveness

The AFFIRM study demonstrated significant efficacy of enzalutamide over placebo, in improving OS of mCRPC patients previously treated with docetaxel-based chemotherapy. Statistically significant benefits of enzalutamide over placebo were also seen in the secondary endpoints including rPFS, PSA response rate, and time to PSA progression. Patients receiving enzalutamide also had an improved QoL.

The comparative efficacy of enzalutamide and abiraterone was indirectly assessed. This indirect comparison showed no statistically significant differences between the two treatments. The indirect comparisons had limitations and should thus be interpreted with caution. Unlike abiraterone, patients receiving enzalutamide do not require the co-administration of steroids.

It is acknowledged that at this time the optimal sequencing of therapies in the post-docetaxel setting remains unknown. Nonetheless, enzalutamide is an oral, well tolerated, effective treatment option, in the post-docetaxel setting for patients with mCRPC.

Safety

Overall enzalutamide was well tolerated. The AE more commonly seen with enzalutamide were fatigue, diarrhea, hot flush, musculoskeletal pain and headache, however there were more AE leading to discontinuation in the placebo group than in the enzalutamide group. Seizures occurred in (5 pts) 0.9% of patients on enzalutamide while no patients on the placebo arm experienced seizures. In the clinical trial, patients experiencing a seizure were permanently discontinued from therapy and patients with a history of seizure, taking medications known to decrease the seizure threshold, or with other risk factors for seizures were excluded from the clinical trial. Therefore the safety of enzalutamide in patients with predisposing factors for seizures is unknown.

1.3 Conclusions

The Genitourinary Clinical Guidance Panel concluded that there is a net overall clinical benefit to enzalutamide in the treatment of patients with mCRPC previously treated with docetaxel-based chemotherapy. Enzalutamide has demonstrated a clear clinically and statistically significant benefit in terms of overall survival as well as a number of key secondary endpoints, compared to placebo in a single large randomized controlled Phase III study, AFFIRM.

In making this conclusion, the Clinical Guidance Panel also considered that:

- Enzalutamide is a well-tolerated oral drug that does not require the co-administration of a steroid. A few patients on enzalutamide experienced seizures, but the overall implications of this are not well understood at this time.
- At this time there is no data on how best to sequence available treatments in the post-docetaxel setting. However, maximizing the availability of effective, well tolerated, oral treatment options is important in improving patient outcomes in this disease.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding enzalutamide (Xtandi) for metastatic castration-resistant prostate cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website,www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding enzalutamide (Xtandi) for metastatic castration-resistant prostate cancer conducted by the Genitourinary Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on enzalutamide (Xtandi) and a summary of submitted Provincial Advisory Group Input enzalutamide (Xtandi) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Prostate cancer is the second most commonly diagnosed cancer in Canadian men and accounts for 10% of all cancer deaths in Canada.[4]

As prostate cancer growth depends on androgens, the current standard of care for prostate cancer is androgen deprivation therapy via medical or surgical castration.[5] However, progression occurs in many patients within 12 to 24 months of initial androgen deprivation as evidenced by increasing prostate-specific antigen (PSA) levels, radiologic progression, or progression of disease-related symptoms.[6] Once prostate cancer progresses in the face of castrate levels of androgens (<50 ng/dL), it is known as metastatic castration-resistant prostate cancer (mCRPC).[2] It is estimated that 10-20% of prostate cancer cases will evolve to mCRPC within approximately five years of follow-up.[7]

The current standard of care for first-line treatment of mCRPC is docetaxel-based chemotherapy, given with prednisone.[2] Docetaxel was the first systemic treatment shown to have a survival advantage in patients with mCRPC.[6] Patients are often concomitantly administered bisphosphonate therapies such as zoledronic acid or denosumab to treat bone fragility that results from bone metastases, a common occurrence in patients with mCRPC.[2]

In the event that patients progress post-docetaxel therapy, other options are available. Cabazitaxel is a chemotherapy administered intravenously and used in combination with prednisone.[2] Abiraterone is an oral hormone therapy, administered with prednisone, that inhibits the androgen biosynthesis pathway through the CYP17A enzyme.[2] Retreatment with docetaxel chemotherapy is also an option in some patients, although the survival benefit of this has not yet been demonstrated. Both cabazitaxel and abiraterone were approved by Health Canada in 2011 and are indicated for patients with mCRPC who have previous been treated with docetaxel-based chemotherapy.[3]

Enzalutamide is an oral hormone therapy that prevents the binding of androgen to the androgen receptor (AR) and the binding of the AR-complex to DNA in prostate cancer cells. Enzalutamide has a Health Canada approval for use in the treatment of patients with metastatic castration-resistant prostate cancer in the setting of medical or surgical castration who have received docetaxel therapy.[8] In August 2012, the Food and Drug Administration (FDA) granted approval for the use of enzalutamide for the treatment of patients with mCRPC who have previously received docetaxel.[9] In April 2013, the European Medicines Agency (EMA) recommended the granting of a market authorization for enzalutamide.[10] The recommended dose of enzalutamide is 160 mg once daily.[9]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of enzalutamide (Xtandi) on patient outcomes compared to standard therapies or placebo in patients with metastatic castration-resistant prostate cancer (mCRPC) who have received docetaxel therapy.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to Section 2.2 for the clinical interpretation of this evidence and Section 7 for more details of the systematic review.

The AFFIRM study was an international, multicenter, double-blind, placebo-controlled, phase III RCT.[1] AFFIRM evaluated the efficacy and safety of enzalutamide 160 mg once-daily compared to placebo in patients with mCRPC who have been previously treated with docetaxel-based chemotherapy. A total of 1199 patients were randomly assigned to receive treatment with enzalutamide (n=800) or placebo (n=399). Baseline characteristics were generally well balanced across treatment groups, with the majority of patients having an ECOG performance status of 0 (37-39%) or 1 (53-54%), and less than 10% of patients having an ECOG performance status of 2. Patients with a history of seizure or any condition that may predispose to seizure were excluded from the study. The primary efficacy endpoint was overall survival (OS), while secondary efficacy outcomes included radiographic progression-free survival (rPFS), time to PSA progression, PSA response, time to first skeletal-related event (SRE), and quality of life (QoL). Safety outcomes included death, serious adverse events (SAEs), adverse events leading to discontinuation, and any AEs. All 1199 patients received at least one dose of study drug, and all patients were evaluated for efficacy and safety outcomes.

As of the interim analysis (September 25, 2011), there were 520 deaths: 308 deaths (39%) in the enzalutamide group and 212 deaths (53%) in the placebo group. The median OS was 18.4 months in the enzalutamide group and 13.6 months in the placebo group (hazard ratio (HR) = 0.63, 95% confidence interval (CI) 0.53 to 0.75, p<0.001). Subgroup analyses showed consistent OS benefit of enzalutamide in various subpopulations.

The median rPFS was 8.3 months in the enzalutamide group and 2.9 months in the placebo group (HR=0.40, 95% CI 0.35-0.47, p<0.001). The median time to PSA progression was 8.3 months in the enzalutamide group and 3.0 months in the placebo group (HR=0.25, 95% CI 0.20-0.30, p<0.001). The proportion of patients

that achieved a ≥50% reduction in PSA levels from baseline was 54% in the enzalutamide group and 2% in the placebo group (p<0.001). The proportion of patients that achieved a ≥90% reduction in PSA levels from baseline was 25% in the enzalutamide group and 1% in the placebo group (p<0.001).

A QoL response was defined as a 10-point improvement in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) global score compared to baseline. The proportion of patients achieving a QoL response was 43% in the enzalutamide group and 18% in the placebo group (p<0.001).

Adverse events (AEs) that occurred more commonly in the enzalutamide group compared to the placebo group included fatigue, diarrhea, hot flash, musculoskeletal pain, and headache. Serious adverse events (SAEs) that occurred more commonly in the enzalutamide group compared to the placebo group included spinal cord compression, hematuria, bone pain, pathological fracture, metastatic pain, general physical health deterioration, and pneumonia. There were more AEs leading to discontinuation in the placebo group (9.8%) compared to the enzalutamide group (7.6%). Twenty-three fatal AEs (3%) occurred in the enzalutamide group and 14 fatal AEs (4%) occurred in the placebo group.

The FDA analysis identified 7 seizures in the enzalutamide group while no patients in the placebo group did.[11] There was no difference in the overall incidence of SREs while on study treatment between the enzalutamide and placebo groups.[11] However, the incidence of fractures was higher in the enzalutamide group compared to the placebo group (6.8% vs. 4.0%).

Potential limitations in the AFFIRM study include the involvement of the sponsor's staff in the planning, conduct, and analyses of the study. In addition, there was a lack of patients with poorer ECOG performance status and high risk for seizure, limiting the generalizability of the study findings to these populations.

Table 1. Key efficacy and safety outcomes from the AFFIRM study

	Enzalutamide (N=800)	Placebo (N=399)
Overall Survival		
Median (months)	18.4	13.6
Hazard Ratio (95% CI)	0.63 (0.53, 0.75)	
P-value	<0.001	
Radiographic Progression-Free Survival		
Median (months)	8.3	2.9
Hazard Ratio (95% CI)	0.40 (0.35, 0.47)	
P-value	<0.001	
Time to Skeletal-Related Events		
Median (months)	16.7	13.3
Hazard Ratio (95% CI)	0.69 (0.57, 0.84)	
P-value	<0.001	
Time to PSA Progression		
Median (months)	8.3	3.0
Hazard Ratio (95% CI)	0.25 (0.20, 0.30)	
P-value	<0.001	
PSA Response		
≥50% decrease, n/N (%)	395/731 (54)	5/330 (2)
≥90% decrease, n/N (%)	181/731 (25)	3/330 (1)
P-value	<0.001	

	Enzalutamide (N=800)	Placebo (N=399)
FACT-P Quality of Life Response*		
n/N (%)	281/651 (43)	47/257 (18)
P-value	<0.001	
Safety, n (%)		
All deaths	308 (39)	212 (53)
Disease progression	274 (34)	192 (48)
Fatal AEs	23 (3)	14 (4)
SAEs	268 (34)	154 (39)
AEs leading to discontinuation	61 (8)	39 (10)
Any AEs	785 (98)	390 (98)
Seizures	5 (<1)	0
AE=adverse event; **CI=**confidence interval; **FACT-P=**Functional Assessment of Cancer Therapy-Prostate; **HR=**hazard ratio; **PSA=**prostate-specific antigen; **SAE=**serious adverse event		

Source: Scher 2012,[1] FDA Medical Review[11]
Cut-off date: September 25, 2011
*FACT-P Quality of Life response was defined as a 10-point improvement in global FACT-P score from baseline on two consecutive measurements obtained at least three weeks apart

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

Validity and Limitations of Skeletal-Related Events as an Endpoint in Prostate Cancer Studies

The definition of SREs as an endpoint is somewhat variable across studies among patients with advanced prostate cancer, including those with mCRPC. Hence, there is some question as to whether or not prevention of SREs represents a clinically meaningful outcome and whether it is a reasonable surrogate for OS.

The incidence of SREs post bone metastases is high and the prevention of SREs has been labeled by the US FDA as both a patient- and a physician-relevant endpoint.[12,13] Nonetheless, no studies were identified that formally evaluated the validity and reliability SREs as an endpoint in advanced prostate cancer trials.

Although some studies[14-17] have shown a relationship between SREs and OS, indicating the potential for using SREs as a surrogate endpoint for OS, others did not.[18] These studies were limited, at least in part, by small sample sizes and observational designs. Likewise, only two studies provided information on SREs as a potential surrogate endpoint for pain and HRQOL. As with the studies on SREs and OS, there was a correlation between SREs and HRQOL and pain, but important limitations prevent one from drawing concrete conclusions from these data. Therefore, well-designed studies are needed to replicate these results in order to conclude reduction of SREs as a valid surrogate endpoint for OS, HRQOL and pain in patients with mCRPC.

See section 7.1 for more information.

Critical Appraisal of an Indirect Comparison of Enzalutamide with Abiraterone, Cabazitaxel, or Mitoxantrone

The comparative efficacy of enzalutamide and abiraterone acetate treatment for OS in men with mCRPC was indirectly assessed using Bucher's method. No statistically significant differences were found between these treatments. In addition, differences between enzalutamide and cabazitaxel or mitoxantrone could not be assessed as the results of this portion of the indirect comparison were not provided. Limitations surrounding the indirect comparison were also a cause for concern regarding the robustness of any provided results and, therefore, any conclusions drawn from this indirect comparison should be interpreted with caution.

See section 7.2 for more information.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) input, respectively.

Patient Advocacy Group Input

The following patient advocacy groups provided input on enzalutamide for the treatment of metastatic castration-resistant prostate cancer: Prostate Cancer Canada and Canadian Cancer Survivor Network. From a patient perspective, access to additional therapies that will stop progression of their disease with minimal side effects and are convenient to use are important aspects when consideration is given to treatment. Patients seek a therapy that will help improve their quality of life and enable them to partake in normal daily activities while extending their life. In addition, controlling pain, fatigue, urinary incontinence and erectile dysfunction are important priorities to advanced prostate cancer patients, as is the reduction of bone metastasis and PSA levels. The hope of patients is that all of these can be achieved at the same time. Patients with prostate cancer are willing to tolerate side effects of treatment and seek choice in selecting a therapy to manage their disease.

PAG Input

Input on the enzalutamide (Xtandi) review was obtained from six of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, treatment with enzalutamide will not require concomitant use of prednisone, as is part of the treatment with the current standard of care and other comparators. PAG noted this to be especially useful in patients with diabetes. PAG also noted the availability of a treatment that is oral and requires once daily dosing will allow for ease of use and accessibility to patients.PAG noted several barriers to implementation. If implemented, enzalutamide will be one of several treatment options in the second line setting for mCRPC. This may potentially result in the sequencing of therapies despite the lack of evidence to support the practice. PAG also noted indication creep as a potential barrier to implementation if enzalutamide is used in earlier lines of therapy prior to the availability of clinical data to support such use.

2.2 Interpretation and Guidance

Prostate cancer is the most common cancer in Canadian men with 26,500 new cases and the third leading cause of cancer related death with 4,000 deaths reported in 2012. Patients progressing on

docetaxel based chemotherapy have limited treatment options, and a short life expectancy, underscoring the need for novel therapeutic strategies that are both effective and well tolerated.

The international, multicenter, double-blind, placebo controlled, randomized Phase III AFFIRM study has demonstrated significant efficacy of enzalutamide over placebo, in improving OS mCRPC patients previously treated with docetaxel-based chemotherapy.

The primary efficacy endpoint was overall survival (OS). At the pre-specified interim analysis after 520 events, a statistically significant improvement in OS [HR 0.63 (95% CI: 0.53, 0.75), $p < 0.0001$, log rank test] was observed. The median OS was 18.4 and 13.6 months in the enzalutamide and placebo arms, respectively

Statistically significant benefits of enzalutamide over placebo were also seen in the secondary endpoints including rPFS (8.3 mo vs. 2.9 mo), PSA response rate defined as a $\geq$ 50% reduction in PSA (54% vs. 2%), and time to PSA progression (8.3 mos vs. 3.0 mos). Patients receiving enzalutamide also had an improved QoL. The proportion achieving a QoL response was 43% compared to 18% in the placebo group ($p<0.001$).

Overall enzalutamide was well tolerated. The AE more commonly seen with enzalutamide were fatigue, diarrhea, hot flush, musculoskeletal pain and headache, however there were more AE leading to discontinuation in the placebo group than in the enzalutamide group.

The one AE seen with enzalutamide that deserves mention is seizures. Seizures occurred in (5 pts) 0.9% of patients on enzalutamide. No patients on the placebo arm experienced seizures. In the clinical trial, patients experiencing a seizure were permanently discontinued from therapy; all seizures resolved. Patients with a history of seizure, taking medications known to decrease the seizure threshold, or with other risk factors for seizures were excluded from the clinical trial. The safety of enzalutamide therefore in patients with predisposing factors for seizures is unknown.

Overall the AFFIRM RCT has effectively demonstrated the efficacy and safety of enzalutamide in mCRPC patients progressing on docetaxel-based chemotherapy.

In the post-docetaxel setting, another drug available is abiraterone. The comparative efficacy of enzalutamide and abiraterone was indirectly assessed. This indirect comparison showed no statistically significant differences between the two treatments. The indirect comparisons had limitations and should thus be interpreted with caution. Unlike abiraterone, patients receiving enzalutamide do not require the co-administration of steroids.

It is acknowledged that at this time the optimal sequencing of therapies in the post-docetaxel setting remains unknown. Nonetheless, enzalutamide is an oral, well tolerated, effective treatment option, in the post-docetaxel setting for patients with mCRPC.

2.3 Conclusions

The Genitourinary Clinical Guidance Panel concluded that there is a net overall clinical benefit to enzalutamide in the treatment of patients with mCRPC previously treated with docetaxel-based chemotherapy. Enzalutamide has demonstrated a clear clinically and statistically significant benefit in terms of overall survival as well as a number of key secondary endpoints, compared to placebo in a single large randomized controlled Phase III study, AFFIRM.

In making this conclusion, the Clinical Guidance Panel also considered that:

- Enzalutamide is a well-tolerated oral drug that does not require the co-administration of a steroid. A few patients on enzalutamide experienced seizures, but the overall implications of this are not well understood at this time.
- At this time there is no data on how best to sequence available treatments in the post-docetaxel setting. However, maximizing the availability of effective, well tolerated, oral treatment options is important in improving patient outcomes in this disease.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Genitourinary Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Prostate cancer is the most common cancer among Canadian men (excluding non-melanoma skin cancers), and the third leading cause of cancer related death. According to the Canadian Cancer Society, in 2012, there were 26,500 new cases and 4,000 deaths due to prostate cancer.[4] Overall the incidence of prostate cancer is gradually increasing due to an ageing population, and although controversial, widespread use of PSA screening.

3.2 Accepted Clinical Practice

Patients diagnosed with localized prostate cancer are usually offered radical prostatectomy, radical radiotherapy or active surveillance. Despite these approaches, some patients will progress and develop recurrent or metastatic disease. Standard first-line therapy for recurrent or metastatic disease remains androgen deprivation therapy. This is initially very effective but progression to castrate resistant prostate cancer (CRPC) defined as progressive disease despite castrate testosterone levels is inevitable.

Treatment for CRPC failing Docetaxel

In the post-docetaxel setting, the main comparators to enzalutamide would be abiraterone, cabazitaxel and mitoxantrone. Both abiraterone and cabazitaxel have demonstrated a survival benefit, as described below. While mitoxantrone does not have a survival benefit, it does have some palliative benefit.

Cabazitaxel

Cabazitaxel is a novel, semi-synthetic taxane that appears to overcome docetaxel resistance and may also penetrate the blood brain barrier. In the TROPIC Phase III study, 755 mCRPC patients failing docetaxel were randomized to either cabazitaxel (25 mg/m2) or mitoxantrone (12mg/m2). Cabazitaxel significantly improved median OS compared to mitoxantrone (15.1 mo vs. 12.7 mo, respectively; HR 0.72; 95% CI 0.61-0.84; p<0.0001). Secondary endpoints such as PFS (2.8 mo vs. 1.4 mo), response rate (RR) (14.4% vs. 4.4%; p=0.005), median time to progression (TTP) by tumor assessment (8.8 mo vs. 5.4 mo; p<0.001) also favoured cabazitaxel. Febrile neutropenia, neutropenia, leukopenia and diarrhea were more common with cabazitaxel.[19] Based on the TROPIC study, Cabazitaxel was approved by both the FDA and Health Canada for use in the post-docetaxel setting for mCRPC.

Abiraterone Acetate

Another drug, recently approved in the post-docetaxel setting is abiraterone acetate. Abiraterone acetate is an oral irreversible inhibitor of CYP-17, the enzyme involved in two critical steps in testosterone biosynthesis: conversion of pregnenolone to 17-OH pregnenolone and conversion of 17OH pregnenolone to dihydropepiandrostenedione (DHEA). Since inhibition of androgen synthesis causes a secondary rise in ACTH and mineralocorticoid excess, abiraterone acetate is co-administered with prednisone. In a randomized double blind placebo controlled Phase III trial, COU 301, 1195 mCRPC patients were randomized to

abiraterone acetate 1000 mg daily plus 5 mg of prednisone twice daily or prednisone alone. At an interim analysis, abiraterone acetate /prednisone showed a median OS of 14.8 months compared to 10.9 months with placebo/prednisone (HR 0.65, 95% CI 0.54-0.77) leading to early trial closure after review by the independent data monitoring committee (IDMC). An updated survival analysis, conducted after 775 events, demonstrated a median OS of 15.8 months for abiraterone acetate compared to 11.2 mos for placebo (HR = 0.740; 95 percent CI: 0.638, 0.859). The key secondary endpoints including PSA response, time to PSA progression and radiographic progression free survival (PFS) were also significantly improved with abiraterone acetate. Toxicities such as hypertension, edema, hypokalemia and atrial fibrillation, joint discomfort, and elevations in liver function tests were more common with abiraterone acetate, but grade 3 and higher toxicities were infrequent.[20] Based on these results from COU 301, abiraterone acetate was approved by both the FDA and Health Canada in the post-docetaxel setting.

Summary

The management of mCRPC has changed significantly over the last 2 years with the approval of a number of new agents which demonstrated survival benefits in the post docetaxel setting. In particular, novel hormonal agents such as abiraterone acetate, which is a well-tolerated oral agent, has renewed interest in targeting androgen receptor mediated pathways in mCRPC. Therapies targeting either androgen synthesis or the androgen receptor continue to be evaluated. Many are now currently being evaluated in mCRPC patients who have not received prior docetaxel chemotherapy. The main clinical question now facing physicians is how best to sequence the new agents to maximize benefit for patients with mCRPC.

3.3 Evidence-Based Considerations for a Funding Population

The currently available evidence supports the use of enzalutamide for patients with the following criteria:

Metastatic castration-resistant prostate cancer who have previously received docetaxel

3.4 Other Patient Populations in Whom the Drug May Be Used

Enzalutamide has not been approved for any other indication than for patients with metastatic CRPC who have previously received docetaxel.

There is however a large randomized, double-blind, placebo-controlled, multi-national Phase 3 trial known as PREVAIL, evaluating enzalutamide in 1717 CRPC patients who have not received prior docetaxel which completed accrual in May 2012. Results of this trial are anticipated in 2013. (NCT01212991)

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy groups provided input on enzalutamide for the treatment of metastatic castration-resistant prostate cancer and their input is summarized below:

- Prostate Cancer Canada
- Canadian Cancer Survivor Network

Prostate Cancer Canada conducted an anonymous online survey to gather information about patient and caregiver experiences with prostate cancer. Of the 45 respondents to the survey, one (1) person was a caregiver, 40 people had prostate cancer and 4 did not respond. Of those with prostate cancer, 38 respondents identified the stage of their disease: 14 were in the metastatic/advanced stage, 13 had localized prostate cancer, 10 were in remission, and 3 did not know or hadn't been told. Survey respondent were from across Canada: 22 from Ontario, 5 from Alberta, 2 from British Columbia, 5 from Saskatchewan, 3 from Manitoba, 5 from Nova Scotia and 1 from Newfoundland and Labrador.

The Canadian Cancer Survivor Network (CCSN) conducted an on-line survey to gather information about patient and caregiver experiences with prostate cancer. The survey was publicized on the CCSN website, in two e-letters and to the CCSN Prostate Cancer Advisory Council. The survey was also circulated to approximately 100 prostate cancer support groups. A total of 30 advanced prostate cancer patients and caregivers completed the survey.

From a patient perspective, access to additional therapies that will stop progression of their disease with minimal side effects and are convenient to use are important aspects when consideration is given to treatment. Patients seek a therapy that will help improve their quality of life and enable them to partake in normal daily activities while extending their life. In addition, controlling pain, fatigue, urinary incontinence and erectile dysfunction are important priorities to advanced prostate cancer patients, as is the reduction of bone metastasis and PSA levels. The hope of patients is that all of these can be achieved at the same time. Patients with prostate cancer are willing to tolerate side effects of treatment and seek choice in selecting a therapy to manage their disease.

Please see below for a summary of specific input received from the patient advocacy groups. Certain responses to open-ended questions reflected the sentiment of a majority of the respondents is included verbatim to provide a deeper understanding of the patient and caregiver perspective. Cited responses are not corrected for spelling or grammar.

4.1 Condition and Current Therapy Information

4.1.1 Experiences patients have with Prostate Cancer

To represent the range of prostate cancer experiences, Prostate Cancer Canada separated responses into two groups: those with advanced prostate cancer (14) and those with localized prostate cancer (13). Those who were dealing with metastatic/advanced prostate cancer experienced a greater physical and emotional

range of problems than did those whose cancer was localized. However, one commonality between both groups was the negative effects of incontinence and erectile dysfunction on their physical and mental well-being.

Among the people who self-identified as having metastatic/advanced prostate cancer, metastasis to the bone was a source of great discomfort and concern due to the increase of skeletal events, and associated pain. Two (2) respondents noted that the pain was focused in the lower back, ribs and spine, but many others were less specific about the location of the pain.

Another major source of difficulty arose from the side effects of hormone therapy. One (1) respondent noted that "*All of the usual associated with radiation and hormone treatment. Neuropathy in lower legs, hot flushes, loss of libido, fatigue, memory loss, changed eyesight, urgency and frequency of urination, mood change, cognitive impairment, insomnia, etc.*" Two (2) other respondents indicated that they experienced loss of muscle mass, fatigue, weight gain and depression because of the prostate cancer.

Other aspects of the disease were related to sexual function and urinary tract complications. One (1) respondent noted that incontinence impacted their day to day life, and another said that they experienced "*numbness of right foot due to pressure of swollen prostate against sciatic nerve slight pain across the lower back and hips*."

The impact of advanced prostate cancer is not limited to its physical limitations. Respondents noted that: "*tiredness, nausea, pain, emotional feelings, stress of the unknown*" also impacted their day to day lives.

Of the above identified issues, responses varied as to which were the priority. Three (3) people answered that pain was the most important issue, two (2) said that all were of concern, two (2) said urinary incontinence, and for three or four (3 or 4), the spread of the cancer and the rising PSA were of the greatest concern. One (1) person answered that in lieu of physical symptoms, depression was the most important issue to control.

The impact of these symptoms on men's lives varied, however it generally fell into two categories: 1) the demand of time and the extra arrangements needed to accommodate side effects of cancer and/or treatment, and 2) the impact on the mental health of those affected.

In the first category, one (1) person explicitly states that the effect of the cancer is that it is "*Limiting to the number of hours that are available after trying to manage the adverse effects*." The incontinence means that men are sometimes required to wear pads, and arrange their days around access to facilities while the presence of pain requires men to limit their physical activity, or plan their day around the extent of the pain. The fatigue necessitates naps affecting daily plans and also affects cognitive function.

Often it is a combination of these symptoms that impact one's life: "*Fatigue, cognitive impairment, urgency and frequency of urination, mood changes, lack of restful sleep. The treatments have been the main adverse effects that ruin most of my days*." Such limitations negatively impacted life. This is not only because plans had to be broken, but also because spontaneity was no longer an option. Some of the

responses indicated this: "*Stress, depression, difficult to plan ahead for social activities*." It *"has limited my travel to other countries, something that I was planning to do*." The impact on spontaneity was eloquently reflected in the following response: "*because of the unknown, it effects all of your decisions—i.e., vacation plans, ability to commit to things like volunteering for events*."

In the second category of mental health it was identified that there is an increase of anxiety and depression. Life changes considerably when a person is diagnosed with prostate cancer and it is difficult to take charge of one's health. As one (1) respondent stated there is the *"challenge of difficult decisions ahead, knowing of availability of treatments in US and EU that are not yet available in Canada, even in research trials.*" Responses included: "*Disappointment after eight years. Resignation*." And "*without antidepressants, I have been sad, angry, worried and frightened about PCa*".

Responses relating to the experiences patients have with advanced prostate cancer were similar for both the Prostate Cancer Canada survey and the Canadian Cancer Survivor Network (CCSN) survey.

The CCSN survey asked respondents "what are the symptoms or problems you experienced with advanced prostate cancer that affect your day-to-day living and quality of life?" The thirty (30) responses from advanced prostate cancer patients and caregivers are summarized in the table below. Respondents were able to select more than one response from a list of symptoms.

Symptoms of Advanced Prostate Cancer Affecting Day-to-Day Living and Quality of Life	**Percentage (%) of CCSN Respondents Experiencing Symptom**	**Symptoms of Advanced Prostate Cancer Affecting Day-to-Day Living and Quality of Life**	**Percentage (%) of CCSN Respondents Experiencing Symptom**
Sexual dysfunction	86%	Urinary incontinence	36%
Fatigue	71%	Fractures or fear of fracture	32%
Living with uncertainty	68%	Anxiety, panic attacks or depression	29%
Not sleeping at night or restlessness	43%	Weight loss, lack of appetite	21%
Pain	43%	Feeling isolated or lonely	14%

Patients reported being both physically and psychologically impacted by living with advanced prostate cancer. Just under half reported suffering from pain and being sleep deprived, nearly three-quarters have fatigue, and over 85% are dealing with sexual dysfunction, all of which affect their quality-of-life and the ability to enjoy life. Added to this are the fear of getting worse, depression and anxiety and for 68% of respondents, living with uncertainty about what will happen next.

One patient wrote, "*I doubt about what will come next, and how that will affect my daily life. I am still working full time as a sales manager, and I am having doubts as to how effective I can be as an active leader."*

The respondents to the CCSN survey were then asked "which of these symptoms are the most important to control. Please pick your top 5". Responses to this question are summarized in the table below.

Symptoms of Advanced Prostate Cancer Affecting Day-to-Day Living and Quality of Life Most Important to Control	**Percentage (%)**	**Symptoms of Advanced Prostate Cancer Affecting Day-to-Day Living and Quality of Life Most Important to Control**	**Percentage (%)**
Fatigue	61%	Sexual dysfunction	28%
Pain	50%	Fractures or fear of fracture	25%
Living with uncertainty	46%	Weight loss, loss of appetite	21%
Urinary incontinence	39%	Feeling isolated or lonely	18%
Not sleeping at night or restlessness	32%	Anxiety, panic attacks or depression	18%

In an open ended question that invited respondents to add anything else they wanted to share about their experience with prostate cancer, 17 responses dealt with one of two issues that preoccupied those with cancer: intimacy (6) and mortality (7).

The sentiments that were expressed about the loss of intimacy in relationships pointed to feelings of loss and despair. Some of the responses that reflect this include:

> "*Intimacy is likely the greatest impact. Injecting the penis with a needle is not the most romantic way to begin. Especially when I have a good libido*."
>
> "*Love life is gone!*"; "*unable to maintain erections*"; "It affects my outlook on the future. My sexual relationship."

The experience of prostate cancer brought on reflections on mortality that ranged from hopeful: "*mortality wake up… gave chance to be involved with awesome support network*" to anxiety and/or despair: "*I am worried*"; "*Life changing, death*"; "One *full year of depression prior to surgery*"; "*Emotional roller coaster simply due to allowing sad thoughts to enter the mind*."

Also of note were the people who indicated their frustration and anxiety with making an informed decision, the "*vastly conflicting information*" was as stressful as the experience of cancer itself and excessively long wait times.

4.1.2 Patients' Experiences with Current Therapy for Prostate Cancer

Current therapies used to treat prostate cancer include surgery, radiation and hormone therapy. Depending on the choice of therapy, different side effects are more prevalent than others. There is a need for treatments that reduce disease progression while also addressing incontinence and erectile dysfunction.

Treatments for prostate cancer have side effects that can be difficult to distinguish in severity from the symptoms of the cancer itself.

The following table summarizes the treatments that respondents to the CCSN survey were using to treat their prostate cancer.

Treatments Used for Prostate Cancer	Percentage (%) of Treatments Used By CCSN respondents
Abiraterone acetate	40%
Docetaxel	32%
Cabaziltaxel	0%
Mitoxantrone	0%
Other hormone therapy	88%
Radiation therapy	40%
Clinical trial	20%

Given that 88% indicated they were using another hormone therapy, information on which other hormone therapies were utilized was reported as follows:

- *Taxitere and Zytiga a few years ago - now stopped. Zometa for bones.*
- *Zoladex.*
- *MDV 3100*
- *Zoladex, Xgeva plus clinical trial MDV 3100*
- *Hormone therapy: Eligard and MDV 3100*
- *Hormone therapy: Zometa and clinical trial drug 3100*
- *Hormone therapy: Zoladex + MDV 3100*
- *Chemo, Radiation, Zoladex, Elmiron, Tautoloc – pantobrazole, Tredonisone, Celebrex + Test MDV 3100*
- *Radiation three years ago. MDB3100. Needle every three months.*
- *XGeva for bone maintenance. I was on a clinical trial but was bumped off due to disease progression. I am hoping to get on another trial soon (Alpharadin 223, or a viral treatment trial. Note: I have not yet had chemo (Taxotere) but my Oncologist has been pushing me to start it. Problem is the treatment is seven months (i.e.10 treatments, once every 3 weeks=30 weeks). Treatment supposedly helps manage pain (I have none). Benefit to me is questionable (maybe get a 2 month life extension, for 7 months of feeling rotten! I am currently feeling well, pain free.*
- *Vitamin C injection and taking E-Tea herbal supplement and cut nettle tea.*
- *Lupron Depot, cortisone, vit D, calcium, Xgeva (Zometa previous to Xgeva (denosumab).*

- *Xtandi (Expanded Access Program), Zoladex, Avodart, Celebrex, Prednisone.*
- *I have been through Bicalutamide, Cabazitaxel treatments, Radiation, and Zytiga. I am now on two chemo drugs - Epirubicin and Cisplatin given with Dexamethason, Ondansetron, Epirubicin, Lasix, Amend and normal saline; Prednisone and ratio-tamsulosin daily. Also on Xgeva (once a month) and Elegard (every 4 months). Pain medications have only been needed as a result of side-effects from Cabazitaxed and the current chemo drugs*.

Many of the symptoms associated with prostate cancer, such as, erectile dysfunction, urinary incontinence, fatigue, cognitive changes – often are side effects of treatment. The following are some responses from the Prostate Cancer Canada survey that reflect this:

> *"radiation, cystosis ,weight gain, breast development, fatigue, impact on the emotions as due to the hormone treatments."*
>
> *"I had incontinence after my surgery"*
>
> *"Some short term memory loss which started with Lupron*."
>
> *"The treatment are have been the main adverse effects that ruin most of my days"*

Common side effects of current therapies experienced by respondents to the CCSN survey include:

Common Side Effects To Treatments for Prostate Cancer	**Percentage (%) Experienced by CCSN respondents**
Diarrhea	38%
Nausea and vomiting	38%
Anemia	19%
Risk of infection	13%

Fifty (50%) of respondents to the CCSN survey reported other side effects of treatment for prostate cancer.

> *"I've taken many other therapies over the years with varying degrees of success before they lost the effectiveness and oncologist would start me on something new to me, not necessarily new as in one case we decided to try a older hormone and it worked for a while."*
>
> *"Side effects of some medications are quite disruptive. For example I feel lousy for three days every month after getting my monthly hormone injection of Firmagon. That's 10% of every month I am not well as a result of receiving this treatment. Injection site becomes swollen, very inflamed and extremely sore."*

"Sex organ regression causes constant discomfort. Testosterone suppression causes loss of muscle mass as well as loss of body hair."

"A bit of nausea and vomiting. Radiation left me with a swollen leg."

"When on chemo, lost hair, lost energy, and experienced dizziness when on feet."

"No appetite when on chemo, and lost sense of taste, but now it has come back because of prednisone."

"I have done pretty well to this point with fatigue and some joint pain."

"Constipation, pain, weakness, loss of appetite, lack of feeling of 'well-being'. The constipation and pain are somewhat manageable. Weakness, loss of appetite and general feeling of not being well is very difficult to deal with."

Twenty- five (25) respondents to the CCSN survey answered a question on the survey that asked what therapies they found to be most effective at controlling common aspects of their advanced prostate cancer. Twelve (12) reported that 'Other Hormone Therapy' was the most effective; nine (9) radiation therapy; five (5) abiraterone acetate; and three (3) docetaxel.

Seventy- seven (77%) of respondents to the CCSN survey did not experience any issues accessing treatment, while twenty-three (23%) did. Respondents were able to select more than one response from a pre-specified list of reasons for difficult in access to current therapies. Reasons given for access issues included limited availability in patient's community (8%); financial hardship due to cost (15%); travel costs associated with getting treatment (12%); and supplies or issues with administration (4%). Some patients indicated more than one issue when attempting to access treatment:

"Abiraterone acetate (Zytiga) is currently paid by my private insurance company. My oncologist has submitted a request for OHIP funding under the Early Access Drug Program and am awaiting response. I have been told OHIP would pay for Zytiga if I had already had chemo (Taxotere), which I have not."

"Third chemo treatments due Feb.27....so too early to access effectiveness on cancer, and side-effects are tolerable to-date. The Amend is a cost of $100 for 3 pills, so along with travel (100 miles) and $14.00 parking, food, treatment days are expensive when you live strictly on government pension."

Fifty-eight (58%) of CCSN survey respondents report that there are needs in their current therapies that are not being met. These include:

"No significant improvement with meds so far. Stiffness."

"Would like to prolong treatment until attenuation of symptoms. Did so for Zytiga, but not for MDV 3100."

"I was on the Prevail (Phase 3 XTandi/placebo) trial for 15 months before I was bumped off the trial due to disease progression. I then started Zytiga. I would like to try Xtandi (for certain, as opposed to blind trial…maybe placebo). Also I'd like to try Xtandi in combination with Zytiga, as a combined drug therapy."

4.1.3 Impact of Prostate Cancer and Current Therapy on Caregivers

Patient advocacy group input indicates prostate cancer impacts caregivers' lives substantially. Caregivers are required to take on a number of additional roles, including helping patients in managing adverse effects of treatment, making up for lost income, assuming more household responsibilities, and providing emotional support.

The CCSN survey included several questions for caregivers relating to how their day-to-day lives are affected and responses included:

> *"Managing side effects is a huge responsibility. Helplessness when there are days of severe pain or discomfort. Finances - of course. Staying positive."*
>
> *"Don't do as much. Don't plan too far ahead. Don't travel."*
>
> *"He was diagnosed 2-1/2 years ago....brought my business to a halt. Planning - not sure what that is anymore. Daily routines and lifestyle have been totally changed."*
>
> *"making sure that everything that can be done is being done. Meal planning, nourishing snacks, outings, staying on top of medication/vitamins schedule, reinforcing the good times ahead...planning the future (both for the good times and for the 'end'). Being open to all conversation and just like when raising kids, making sure that patient knows 'you' will always be there, no matter what!"*

In the Prostate Cancer Canada survey one (1) person self-identified as being a caregiver, but did not provide a response to the impact of prostate cancer on the caregiver's daily routine or lifestyle.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Enzalutamide

Sixty-seven percent (67%) of respondents to the CCSN survey expressed that they would like to be better able to control symptoms of prostate cancer, while fifty percent (50%) said they would like to reduce side effects from current medications and treatments, with another thirty-three (33%) wanting the medication to be easier to use.

Regarding side effects patients would be willing to tolerate with a new drug, respondents gave the following responses: mild to moderate; "*I'm already managing mood shifts, hot flashes, complete loss of libido, loss of taste; sexual dysfunction"*; "*almost anything considered 'tolerable' would be just that if it meant prolonging life with reasonable well-being*". Patients struggling with disease progression and uncertainly about the future are willing to tolerate fairly significant side effects.

For patients with no experience with enzalutamide, it was difficult for Prostate Cancer Canada to ascertain expectations, as they had no frame of reference for what the enzalutamide can or cannot do, and its attendant side effects. Controlling pain, fatigue, urinary incontinence and erectile dysfunction are all important priorities to prostate cancer patients, as is the reduction of bone metastasis and PSA levels. The hope of patients is that all of these can be achieved simultaneously and that they can have an increased length in life.

Only two (2) patients self-identified as having had an experience with enzalutamide in the Prostate Cancer Canada survey. It was therefore difficult to draw broad conclusions as there was no information derived from the responses relating to how long either of the two (2) respondents was on enzalutamide. Both were on treatments prior to the enzalutamide, and both found that it was more difficult for their caregivers to administer enzalutamide than previous medications, and that enzalutamide's side effects were worse. Both patients found enzalutamide to be more effective at treating their symptoms than their previous treatments.

The effect that enzalutamide had on the two (2) patients' prostate cancer was that it lowered both patients' PSA levels. However it was unable to treat the symptom of incontinence of one (1) respondent. When asked a yes or no question about whether enzalutamide helped with their symptoms, only one (1) patient responded "yes".

Positive responses regarding treatment were received when respondents to the Prostate Cancer Canada survey were asked whether the use of enzalutamide had made any difference to the patients' long term health and well-being. The two (2) responses for this question were: "*It has given me hope that the improvements will continue" and "Feeling much better, than having to go thru that chemo again !!!!"*. Similar sentiments were echoed when questioned about whether quality of life had changed: *" Hope based on marker progress." and " better quality of life !!!"*. In terms of practical benefits, the respondents were divided on whether enzalutamide had saved them time, but both agreed that it had saved them money.

Respondents to the Prostate Cancer Canada survey were also divided when asked about side effects of enzalutamide. One (1) responded that the side effects of enzalutamide were "*much easier to deal with than previous treatments or drugs*" and one (1) responded that the side effects were "*much harder to deal with than previous treatments or drugs*". Side effects noted by one (1) respondent included intense fatigue and an upset stomach. Both of these side effects were tolerable with "modifications" and "supporting measures".

The two (2) respondents differed in their opinion on the impact enzalutamide had on their lives. One (1) respondent was unsure of enzalutamide's impact, and the other (1) respondent was positive about its effect on quality of life, stating "*yes it is the pits having cancr but that is life the people at the cancer clinic in Edmonton have been great the MDV 3100 trial has been great for me thanks a lot been on two years no progession of the bone mets.*"

Eight (8) respondents to the CCSN survey had direct experience with enzalutamide as part of a clinical trial. Of these, 63% reported experiencing positive effects, while 88%

reported negative effects. The table below summarizes the positive effects of treatment experienced by survey respondents.

Positive Effects of Enzalutamide	Experienced by CCSN Survey Respondents with Direct Experience with Enzalutamide
Easier to use	86%
Better able to control symptoms	60%
Halted disease progression	60%
Reduction in side effects from current medications or treatments	25%

When asked whether patients were able to control side effects better than on their previous therapy, respondents to the CCSN survey indicated they had better control of diarrhea and lower PSA. Two (2) of the three (3) respondents found that side effects were reduced on enzalutamide ("*less nausea"*; "*fatigue is less than during chemo"*). One (1) respondent reported he had the "*worst side effects of any previous treatment*."

Regarding ease of use, the majority of respondents to the CCSN survey (4 of 5 who responded to the question) reported that enzalutamide was easier to use than previous treatments due to its oral administration and less rigid treatment schedule compared to other treatment options *("Oral admin is easier."; "Found oral administration easier."; "Less rigid schedule. Zytega used to be taken at very controlled times – one hour before meals."; "Oral administration at any time").* One (1) respondent wrote that enzalutamide is the hardest to use but did not provide an explanation.

Common adverse effects reported by the patients with direct experience with enzalutamide were fatigue (100%), diarrhea (43%) and hot flashes (29%). *"Nausea, stiff joints"; "loss of appetite"; "headache, dizziness and muscle pain"* were also identified as adverse effects experienced by respondents to the CCSN survey.

The following side effects were stated as being either acceptable or not acceptable by respondents to the CCSN survey with direct experience with enzalutamide.

Side Effect of Enzalutamide	Acceptable by CCSN Respondents	Not Acceptable by CCSN Respondents
Fatigue	50%	50%
Diarrhea	67%	33%
Hot flashes	89%	11%

Side Effect of Enzalutamide	Acceptable by CCSN Respondents	Not Acceptable by CCSN Respondents
Other Side Effects: nausea, stiff joints, loss of appetite, headaches, dizziness, muscle pain	100%	0%

Although there were significant adverse effects reported by those who took enzalutamide, a majority of survey respondents (60%) to the CCSN survey reported that enzalutamide halted disease progression and the same percentage (60%) were better able to control symptoms. It was evident there is a willingness among most advanced prostate cancer patients to tolerate most side effects.

4.3 Additional Information

No additional information was provided.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for enzalutamide (Xtandi) for metastatic castration resistant prostate cancer (mCRPC). The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the enzalutamide (Xtandi) review was obtained from six of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, treatment with enzalutamide will not require concomitant use of prednisone, as is part of the treatment with the current standard of care and other comparators. PAG noted this to be especially useful in patients with diabetes. PAG also noted the availability of a treatment that is oral and requires once daily dosing will allow for ease of use and accessibility to patients.

PAG noted several barriers to implementation. If implemented, enzalutamide will be one of several treatment options in the second line setting for mCRPC. This may potentially result in the sequencing of therapies despite the lack of evidence to support the practice. PAG also noted indication creep as a potential barrier to implementation if enzalutamide is used in earlier lines of therapy prior to the availability of clinical data to support such use.

Lastly, PAG noted concerns with regards to accessibility of enzalutamide in some jurisdiction as oral medications are not covered in the same way as intravenous cancer medications. For these jurisdictions, patients would first require an application to their pharmacare program, and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

The current standard treatment in the majority of patients with metastatic castration resistant prostate cancer (mCRPC) who have progression on or after first line docetaxel is oral abiraterone acetate. A minority of patients receive cabazitaxel (IV) as a second line option instead of abiraterone. PAG noted that enzalutamide may potentially be an alternative to abiraterone however the pivotal trial presented in the submission compares enzalutamide to placebo. PAG indicated that a head-to-head trial with the standard of care would have been preferable. PAG did however note that the economic analysis presents a comparison to relevant treatment comparators. PAG was unclear around the use of mitoxantrone and whether it is a relevant comparator in this setting.

As an enabler to implementation PAG noted that treatment with enzalutamide will not require concomitant use of prednisone, as is part of the treatment with abiraterone acetate and cabazitaxel. PAG noted this to be especially advantageous in patients with diabetes. PAG noted that the current standard of care also requires concomitant use of luteinizing hormone releasing hormone (LHRH). PAG was however unable to determine whether enzalutamide treatment would also require LHRH therapy but indicated it to be an enabler to implementation if LHRH is not required. PAG would like clarity on the possibility of concomitant LHRH use.

5.2 Factors Related to Patient Population

PAG noted that the pivotal trial evaluates the use of enzalutamide in patients that have failed first line therapy with docetaxel. PAG noted that despite the unavailability of clinical data, the patient population in the product labelling is broadened to include those that are intolerant to docetaxel (similar to the current standard of care). This was noted to be a barrier to implementation.

If implemented, PAG noted that enzalutamide will be one of several treatment options in the second line setting for mCRPC. This may potentially result in the sequencing of therapies rather than directing the choice of therapy to one regimen that is most suited to an individual patient and was noted to be a barrier to implementation.

PAG anticipates the availability of data on a trial (PREVAIL Study, anticipated Fall 2013 or Winter 2014) which is expected to inform the use of enzalutamide in the first line setting in place of docetaxel. PAG expects that if results indicate superiority of enzalutamide over the current standard of care, oncologists will likely prefer to use enzalutamide as it does not require concomitant therapy with steroids. PAG did however note indication creep as a potential barrier to implementation if enzalutamide is used in earlier lines of therapy prior to the availability of clinical data to support such use.

5.3 Factors Related to Accessibility

PAG identified that as enzalutamide is an oral drug it will generally be more easily accessed by patients. In some jurisdictions however, oral medications are not covered in the same way as intravenous cancer medications, which may limit accessibility. For these jurisdictions, patients would first require an application to their pharmacare program, and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of- pocket expenditure.

5.4 Factors Related to Dosing

PAG noted that the dosing of enzalutamide requires 4 pills once daily similar to the dosing regimen of the current comparator. Although pill burden may be a potential issue, it will be similar to what patients are currently receiving with the exception of the concomitant prednisone required with the current standard of care.

PAG indicated potential implementation issues around the use of enzalutamide. This concern stemmed from potential drug-drug interaction with concomitant use of CYP2C8 inhibitors or modulators. In this event, PAG noted dose reduction or increase may be required. PAG requested clarity as to the impact of this concern on the use of enzalutamide.

5.5 Factors Related to Implementation Costs

As an enabler to implementation, PAG identified that the use of enzalutamide will minimize drug wastage as only one capsule strength is available. PAG would however like

further clarity on the potential cost neutrality of enzalutamide compared to the current standard of care.

As a potential barrier to implementation, PAG noted that enzalutamide is associated with a small risk of seizures and as a result careful patient selection and monitoring will require resources.

5.6 Other Factors

No other issues were identified.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of enzalutamide (Xtandi) on patient outcomes compared to standard therapies or placebo in patients with metastatic castration-resistant prostate cancer (mCRPC) who have received docetaxel therapy. See Table 1 in Section 6.2.1 for outcomes of interest and comparators.

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Validity and limitations of skeletal-related events as an endpoint in prostate cancer studies.
- Critical Appraisal of an indirect comparison of enzalutamide with abiraterone, cabazitaxel, or mitoxantrone.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished double-blind RCTs	Patients with metastatic castration-resistant prostate cancer who have received docetaxel therapy	Enzalutamide 160 mg QD orally	Abiraterone + prednisone Cabazitaxel + prednisone Chemotherapy (e.g. Docetaxel, Mitoxantrone) + prednisone Anti-androgen therapy (e.g. Bicalutamide) Best supportive care/Placebo	OS PFS QoL ORR CBR TTP SAE AE (Seizures) WDAE PSA response Pain Skeletal-related events Bone metastases

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
AE=adverse events; **CBR=**clinical benefit rate; **ORR=**objective response rate; **OS=**overall survival; **PFS=**progression-free survival; **PSA=**prostate-specific antigen; **QD=**once daily; **QoL=**health related quality of life; **RCT=**randomized controlled trial; **SAE=**serious adverse event; **TTP=**time to progression; **WDAE=**withdrawal due to adverse events				

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was enzalutamide (Xtandi).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but was not limited by publication year. The search is considered up to date as of June 3, 2013.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

Two members of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

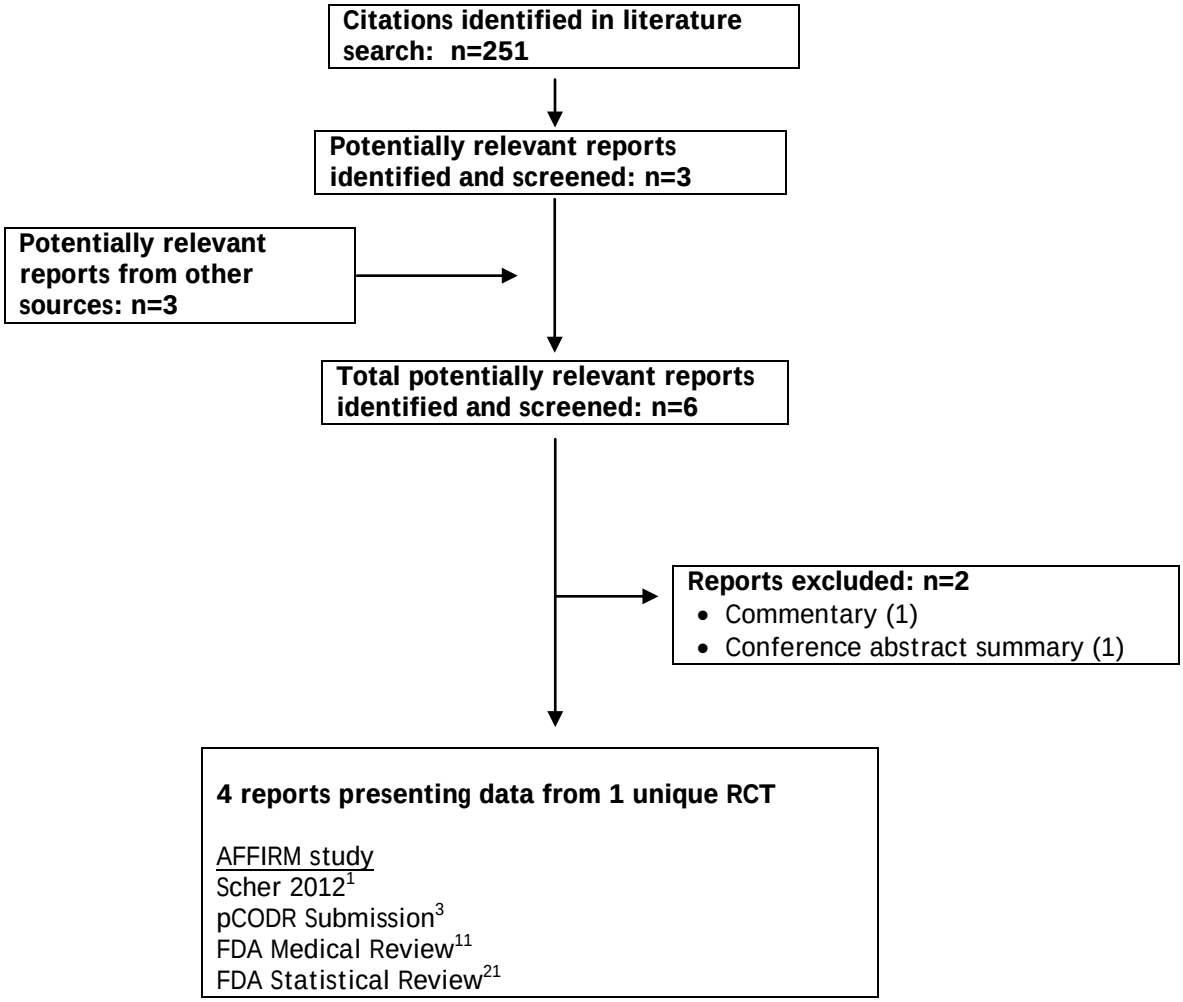
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 6 potentially relevant reports identified, 4 reports were included in the pCODR systematic review[1,3,11,21] and 2 reports were excluded. Reports were excluded because they were a commentary[22] and conference abstract[23] of the main study.

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of the AFFIRM Trial[1]

Trial Design	Key Inclusion and Exclusion Criteria	Intervention and Comparator	Outcomes
International, DB, placebo-controlled, phase 3 RCT 156 centers in 15 countries (including Canada) Randomization period: Sept 2009-Nov 2010 Method of randomization: centrally using an interactive voice recognition system Randomization was performed at a 2:1 (enzalutamide:placebo) ratio and stratified by: • ECOG performance status (0 or 1 vs. 2) • BPI-SF pain score (0-3 no pain vs. 4-10 moderate to severe pain) Data cut-off for primary analysis: September 25, 2011 Funded by: Medivation and Astellas Pharma Global Development	**Inclusion criteria** Patients with mCRPC (serum testosterone level <50 ng/dL at screening) who have been previously treated with docetaxel-based chemotherapy ECOG performance status 0 to 2 Estimated life expectancy ≥6 months **Exclusion criteria** Brain metastases or active untreated epidural disease History of other malignancy within previous 5 years More than two prior chemotherapy regimens Treatment with therapeutic immunizations for prostate cancer History of seizure or any condition that may predispose to seizure (e.g. prior stroke, brain arteriovenous malformation, head trauama with loss of consciousness requiring hospitalization)	Enzalutamide 160 mg, orally QD Placebo, orally QD	**Primary** • Overall survival **Secondary** • Radiographic progression-free survival • Time to first skeletal-related event • Time to PSA progression • PSA response • QoL • Safety
BPI-SF=Brief Pain Inventory-Short Form; **DB=**double-blind; **ECOG=**Eastern Cooperative Oncology Group; **mCRPC=**metastatic castration-resistant prostate cancer; **PSA=**prostate-specific antigen; **QD=**once daily; **QoL=**quality of life; **RCT=**randomized controlled trial			

a) Trials

One phase III, double-blind, placebo-controlled RCT was included in this review (see Table 2). AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) was designed to evaluate the efficacy and safety of oral enzalutamide in men with metastatic castration-resistant prostate cancer that had previously received docetaxel-based chemotherapy. This study was conducted at 156 centers across 15 countries including Canada, and was sponsored by the manufacturer.

Patients were randomized at a 2:1 ratio to orally receive treatment with either enzalutamide (160 mg daily) or placebo. Randomization was stratified by baseline ECOG performance score and baseline BPI-SF pain score. Patients were enrolled from September 2009 through November 2010 and randomized to a study treatment centrally using an interactive voice recognition system. Blinding was obtained using placebo capsules that appear identical in appearance to the enzalutamide capsules.

The AFFIRM study was powered to evaluate treatment efficacy using OS. A planned enrollment of 1170 patients was required to have a power of 90% to detect a hazard ratio of 0.76 (α=0.05), assuming a median survival of 15.7 months in the enzalutamide group and 12.0 months in the placebo group. The final analysis was to be performed when 650 deaths occurred, with an interim analysis performed when 520 deaths (80% of total events) occurred.

b) Populations

The intention-to-treat (ITT) population (n=1199) in the AFFIRM trial was defined as all randomly assigned patients, regardless of whether they received study medication. Of the 1199 randomized patients, 800 patients were assigned to receive enzalutamide and 399 patients were assigned to receive placebo. All randomized patients received at least one dose of their allocated intervention. There were 82 (10.3%) Canadian patients in the enzalutamide group and 25 (6.3%) Canadian patients in the placebo group.[11] Safety analyses were assessed for all randomized patients who received any study drug. A summary of the study population and patient disposition in the AFFIRM trial is presented in Figure 1.

Overall, baseline characteristics were balanced across both enzalutamide and placebo groups in terms of demographics, disease severity, and prior treatments received (Table 3). The median age was 69 years for both the enzalutamide group (range 41-92) and placebo group (range 49-89). The two stratification factors used for randomization, ECOG performance status and BPI-SF pain score, were balanced between the treatment arms. For disease progression type, 41% of patients had PSA-only progression at enrollment and 59% of patients had radiographic evidence of progression. All patients had received prior docetaxel-based chemotherapy and 24% of the patients had received two chemotherapy regimens. Disease metastases sites were similar between groups, with 92% of patients having bone metastases. In both groups, 43% of patients were taking bisphosphonates at baseline. Baseline median serum PSA levels were higher in the placebo group (128 ng/mL) than in the enzalutamide group (108 ng/mL).

Table 3. Baseline patient demographics and clinical characteristics in AFFIRM

	Enzalutamide (N=800)	Placebo (N=399)
Age, years		
Median (range)	69 (41, 92)	69 (49, 89)
Race, N (%)		
Caucasian	745 (93)	366 (92)
Black	27 (3)	20 (5)
Asian	5 (1)	8 (2)
Other	23 (3)	5 (1)
ECOG performance status, N (%)		
0	298 (37)	156 (39)
1	432 (54)	211 (53)
2	70 (9)	32 (8)
Mean BPI-SF pain score		
≥4	225 (28)	115 (29)
<4 but >0	429 (54)	199 (50)
=0	146 (18)	85 (21)
Disease progression type, N (%)		
PSA-only progression	326 (41)	164 (41)
Radiographic progression	470 (59)	234 (59)
Disease metastasis site, N (%)		
Bone	735 (92)	364 (92)
Lymph node	442 (56)	219 (55)
Visceral liver	92 (12)	34 (9)
Visceral lung	122 (15)	59 (15)
Total Gleason score at diagnosis, N (%)		
≤7	360 (50)	175 (48)
>7	366 (50)	193 (52)
Serum PSA level (ng/mL)		
Median (range)	108 (0.2, 11794)	128 (0, 19000)
Number of prior chemotherapy regimens, N (%)		
1	579 (72)	296 (74)
2	196 (25)	95 (24)
≥3 (protocol deviation)	25 (3)	8 (2)
Prior docetaxel usage		
Median total dose, mg (range)	600 (25, 2520)	600 (75, 2175)
Median number of cycles	8.5	8.0
Months from first docetaxel treatment to study initiation, median (range)	13.6 (2.5, 95.9)	13.1 (1.8, 97.8)
Months from last docetaxel treatment to study initiation, median (range)	6.1 (1, 80.8)	5.8 (0.9, 94.3)
Bisphosphonate use, N (%)		
Any bisphosphonate	345 (43.1)	173 (43.4)
Zoledronic acid	303 (37.9)	149 (37.3)

BPI-SF=Brief Pain Inventory-Short Form; **ECOG=**Eastern Cooperative Oncology Group; **PSA=**prostate-specific antigen

Source: Scher 2012,[1] FDA Medical Review[11]

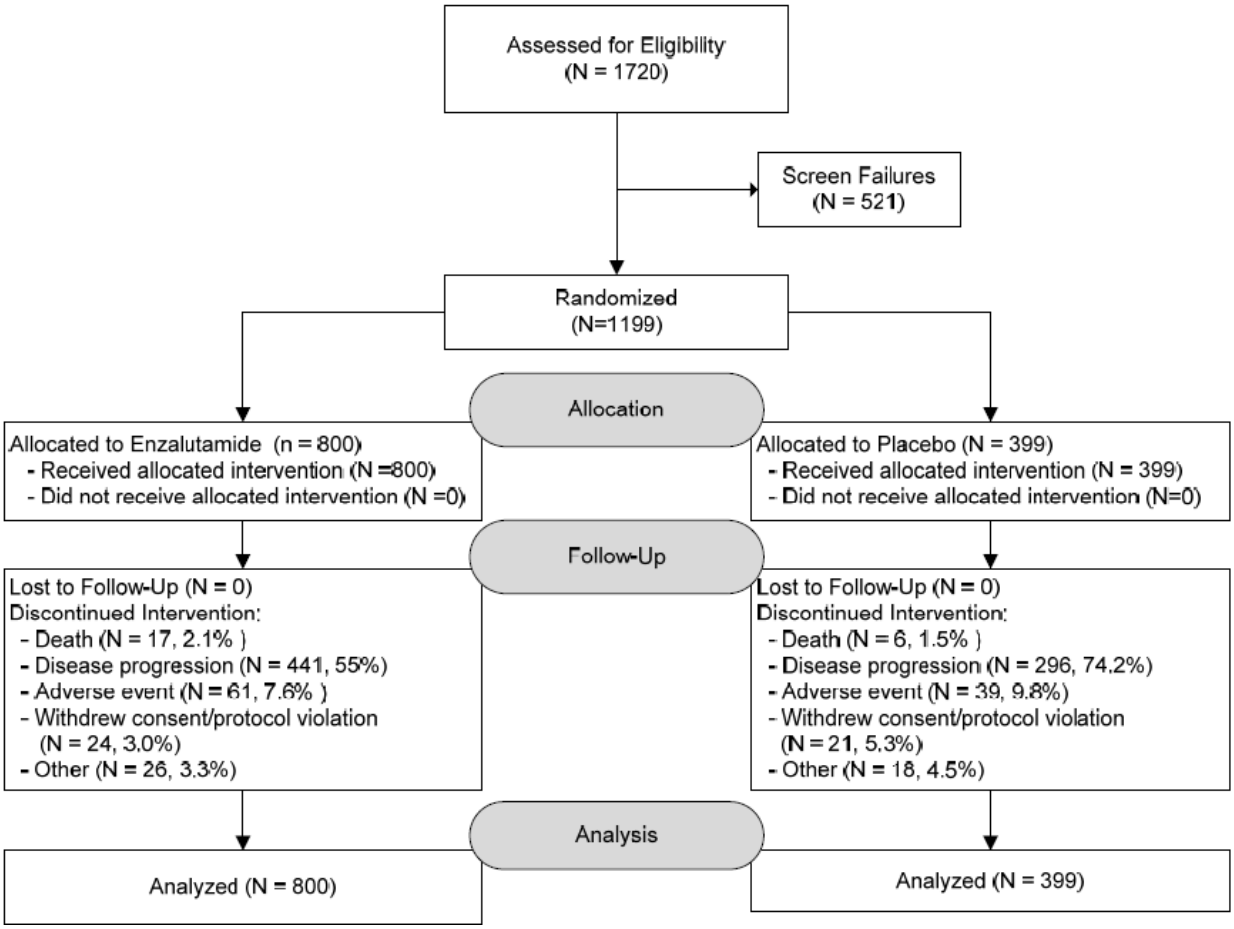


Figure 1. Patient disposition in the AFFIRM study
Source: Scher 2012[1]

c) Interventions

Patients received enzalutamide 160 mg orally once daily as four 40 mg capsules or matched placebo capsules, taken close to the same time every day with or without food. If a dose was missed, double-dosing was not to occur on the next day. Patients experiencing a Grade 3 or greater toxicity that was not ameliorated with adequate medical intervention had their study treatment interrupted until the toxicity decreased to Grade 2 or lower (grades based upon the CTCAE, version 4.0). Once the toxicity decreased, patients could be restarted on study medication at a reduced dose with written approval from the sponsor. During the study, patients were permitted to use prednisone or other glucocorticoids at a dose of less than 10 mg per day. Systemic glucocorticoids were used in 48% of patients in the enzalutamide group and 46% of patients in the placebo group (source: FDA Medical Review).[11] Treatment was continued until confirmed disease progression (radiographic, clinical, or skeletal-related event), intolerable adverse events, withdrawal of patient consent, or death. Crossovers were not permitted upon disease progression. However, patients were permitted to use other systemic antineoplastic treatments after discontinuation of study drug and these are listed in Table 4.

Table 4. Antineoplastic therapy administered after study drug discontinuation

Antineoplastic treatment, N (%)	Enzalutamide (N=800)	Placebo (N=399)
Total	336 (42)	245 (61)
Abiraterone acetate	167 (21)	97 (24)
Cabazitaxel	78 (10)	55 (14)
Docetaxel	68 (9)	57 (14)
Mitoxantrone	21 (3)	44 (11)

Source: Scher 2012[1]

At the time of the interim analysis, 231 (29%) patients were receiving study drug in the enzalutamide group compared with 19 (5%) patients in the placebo group. The median time on treatment was 8.3 months in the enzalutamide group and 3.0 months in the placebo group, while the median duration of follow-up was 14.4 months. Compliance rates for each treatment arm were not reported in the published articles.

d) Patient Disposition

All randomly assigned patients in the AFFIRM study (ITT population) received study medication. Of the 1199 randomized patients, 800 patients were assigned to receive enzalutamide and 399 patients were assigned to receive placebo.

As of the data cut-off date on September 25, 2011, 231 (29%) patients randomized to enzalutamide remained on treatment, while 19 (5%) patients randomized to placebo remained on treatment. The primary reason for discontinuation from study drug was disease progression in both arms (55% enzalutamide vs. 74.2% placebo). Other reasons for discontinuation from study drug included death (2.1% enzalutamide vs. 1.5% placebo), adverse events (7.6% enzalutamide vs. 9.8% placebo), withdrawal of consent (3.0% enzalutamide vs. 5.3% placebo), or other (3.3% enzalutamide vs. 4.5% placebo). No patients were lost to follow-up.

e) Limitations/Sources of Bias

AFFIRM was a phase III, double-blind, randomized controlled trial. The method of randomization and blinding were reported in the published articles and were acceptable. Baseline patient characteristics were well balanced between treatment groups. An independent data monitoring committee was formed before study initiation to monitor safety during the study and to evaluate efficacy and safety findings from pre-specified analyses, including the interim overall survival analysis. All clinical laboratory tests were performed by a central laboratory. The interim analysis showed a statistically significant improvement in overall survival in the enzalutamide group compared to the placebo group, thus the trial was halted and unblinded at this point, suggesting that the study was overpowered.

Potential limitations in the AFFIRM study include:

- The study design, conduct, analyses, and publication were overseen by a steering committee consisting of experts in prostate cancer and members of the sponsor's staff and not an independent committee.
- The trial population was composed largely of patients with an ECOG status of 0 or 1, with few patients having an ECOG status of 2 and no patients enrolled with an ECOG status >2. This limits the generalizability of results to patients with a poorer performance status.
- Patients at high risk for seizure were excluded from the study, limiting information about the use of enzalutamide in this subpopulation.

- While proportion of patients achieving a FACT-P response was reported, FACT-P QoL baseline and post-baseline scores were not reported.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The primary efficacy endpoint in the AFFIRM study was overall survival (OS), which was defined as the time from randomization to death from any cause. OS data was analyzed in the ITT population, which included all randomized patients. This endpoint was powered at 90% to detect a hazard ratio of 0.76 (α=0.05) with 650 events, but a pre-specified interim analysis performed after 520 deaths (80% of total events) found an improvement in survival and the study was subsequently halted and unblinded. At this point, eligible patients in the placebo group were offered treatment with enzalutamide. Secondary outcomes included radiographic progression-free survival (rPFS), time to PSA progression, PSA response, time to first skeletal-related event (SRE), quality of life (QoL), and safety. QoL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire.

Safety analyses were assessed for all randomized patients who received any study drug and occurred monthly for the first 6 months, followed by every 3 months until study drug discontinuation, and 30 days after the last dose of study drug or prior to the initiation of subsequent antineoplastic therapy. Adverse events were classified by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) and monitored by an independent data monitoring committee.

A summary of efficacy and safety outcomes from the AFFIRM study are presented in Table 5 and Table 6.

Table 5. Summary of efficacy outcomes from the AFFIRM study

	Enzalutamide (N=800)	Placebo (N=399)
Overall Survival		
Median (months)	18.4	13.6
Hazard Ratio (95% CI)	0.63 (0.53, 0.75)	
P-value	<0.001	
Radiographic Progression-Free Survival		
Median (months)	8.3	2.9
Hazard Ratio (95% CI)	0.40 (0.35, 0.47)	
P-value	<0.001	
Time to Skeletal-Related Events		
Median (months)	16.7	13.3
Hazard Ratio (95% CI)	0.69 (0.57, 0.84)	
P-value	<0.001	
Time to PSA Progression		
Median (months)	8.3	3.0
Hazard Ratio (95% CI)	0.25 (0.20, 0.30)	
P-value	<0.001	
PSA Response		
≥50% decrease, n/N (%)	395/731 (54)	5/330 (2)
≥90% decrease, n/N (%)	181/731 (25)	3/330 (1)
P-value	<0.001	
FACT-P Quality of Life Response*		
n/N (%)	281/651 (43)	47/257 (18)
P-value	<0.001	
CI=confidence interval; **FACT-P=**Functional Assessment of Cancer Therapy-Prostate; **HR=**hazard ratio; **PSA=**prostate-specific antigen		

Source: Scher 2012[1]
Cut-off date: September 25, 2011
*FACT-P Quality of Life response was defined as a 10-point improvement in global FACT-P score from baseline on two consecutive measurements obtained at least three weeks apart

Table 6. Summary of safety outcomes from the AFFIRM study*

n (%)	Enzalutamide (N=800)	Placebo (N=399)
All deaths	308 (39)	212 (53)
Disease progression	274 (34)	192 (48)
Fatal AEs	23 (3)	14 (4)
SAEs	268 (34)	154 (39)
AEs leading to discontinuation	61 (8)	39 (10)
Any AEs	785 (98)	390 (98)
Seizures	7 (<1)	0
AE=adverse event; **SAE=**serious adverse event		

Source: Scher 2012,[1] FDA Medical Review[11]
*Cut-off date: September 25, 2011

Efficacy Outcomes

a) Overall Survival (OS)

The primary end point in the AFFIRM study was OS, which was defined as the time from randomization to death from any cause. Kaplan-Meier estimates of survival

probabilities were used to obtain median survival times and their 95% confidence intervals. Kaplan-Meier survival curves were used to compare survival in the treatment arms and to assess the appropriateness of the proportional hazard model. A log-rank test was used to evaluate overall survival, with stratification according to ECOG performance-status score and baseline mean pain score.

At the pre-specified interim analysis of 520 deaths, 308 deaths (39%) occurred in the enzalutamide group and 212 deaths (53%) occurred in the placebo group. The median OS was 18.4 months in the enzalutamide group and 13.6 months in the placebo group (hazard ratio (HR) = 0.63, 95% confidence interval (CI) 0.53 to 0.75, p<0.001). Enzalutamide demonstrated a statistically significant improvement in median overall survival versus placebo (Figure 2). An updated OS analysis performed after 576 deaths had occurred support the interim analysis, showing a median OS of 17.8 months in the enzalutamide group and 13.3 months in the placebo group (stratified HR=0.63, 95% CI 0.52-0.73, p<0.0001) (source: FDA Statistical Reviews).[21]

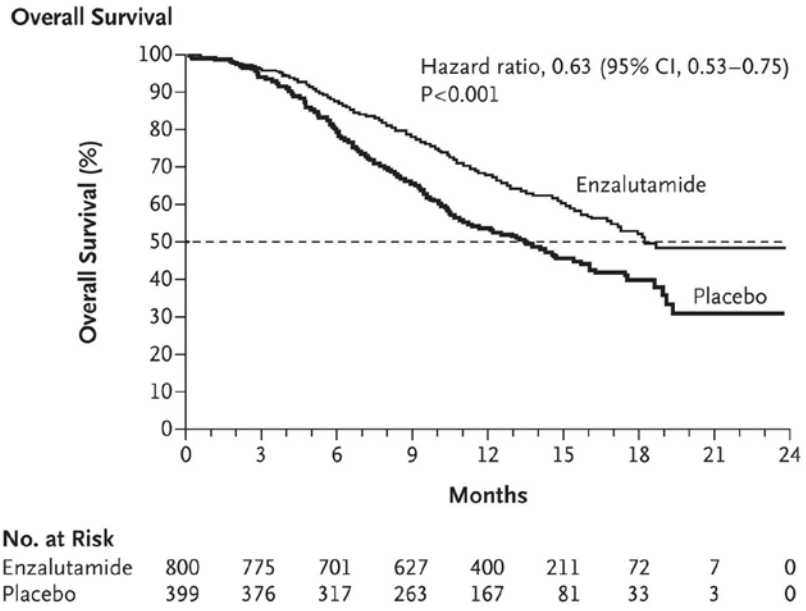


Figure 2. Kaplan-Meier estimates of overall survival in the AFFIRM study after 520 deaths
Source: Scher 2012[1]

Subgroup analyses showed consistent OS benefit of enzalutamide in various subpopulations (Figure 3).

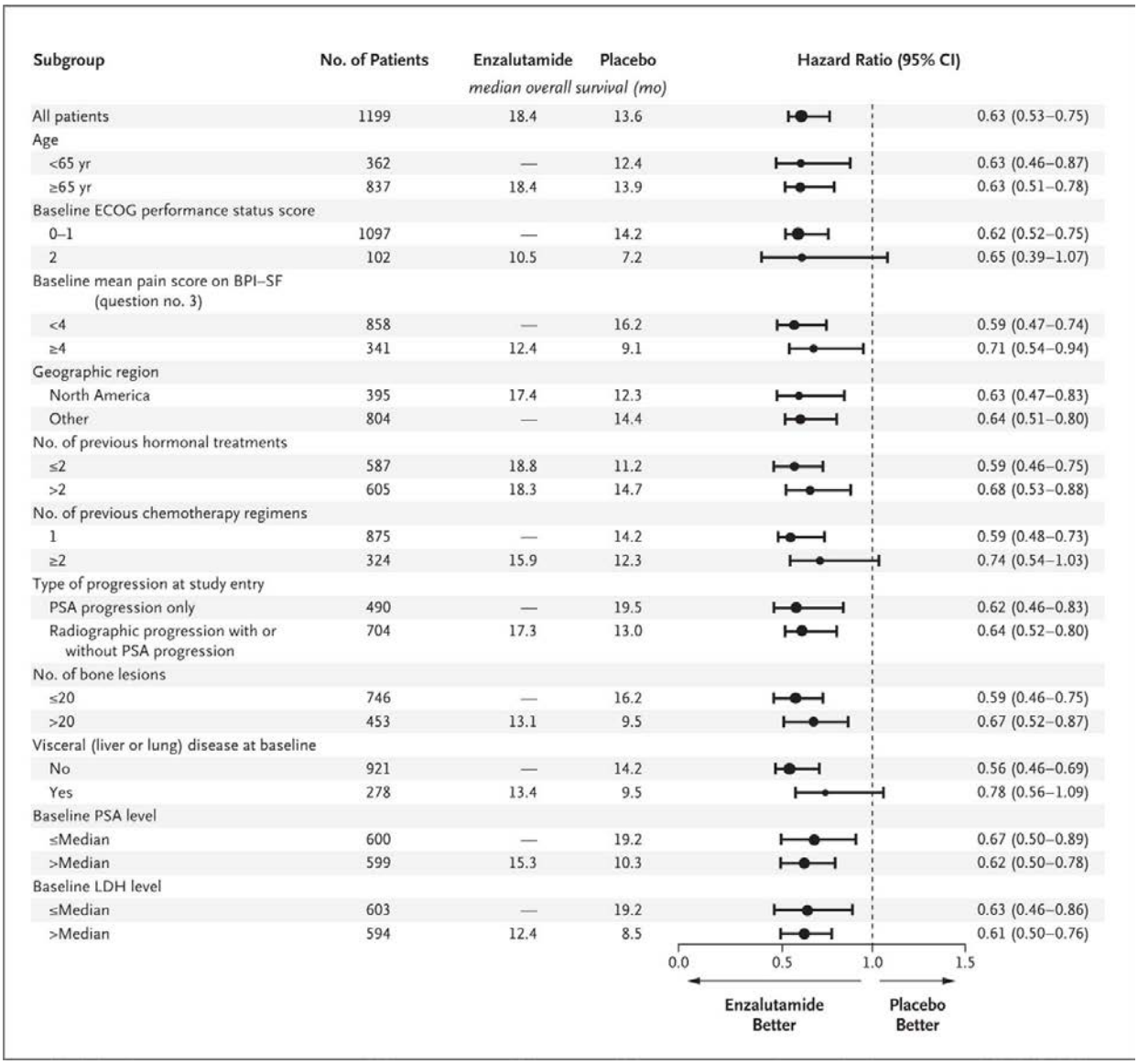


Figure 3. Subgroup analysis of hazard ratios for death
Source: Scher 2012[1]

b) Radiographic Progression-Free Survival (rPFS)

Radiographic progression-free survival was defined as the time from randomization to the earliest objective evidence of radiographic progression or death due to any cause. Radiographic disease progression was defined by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) for soft tissue the disease or as the appearance of two or more new bone lesions on bone scan as per Prostate Cancer Working Group (PCWG2) guidelines. Kaplan-Meier median rPFS times and their 95% confidence intervals as well as rPFS curves were used. A log-rank test stratified by baseline ECOG performance-status score and mean pain score was used to compare treatment groups.

The median rPFS was 8.3 months in the enzalutamide group and 2.9 months in the placebo group (HR=0.40, 95% CI 0.35-0.47, p<0.001). Kaplan-Meier curves of rPFS are shown in Figure 4.

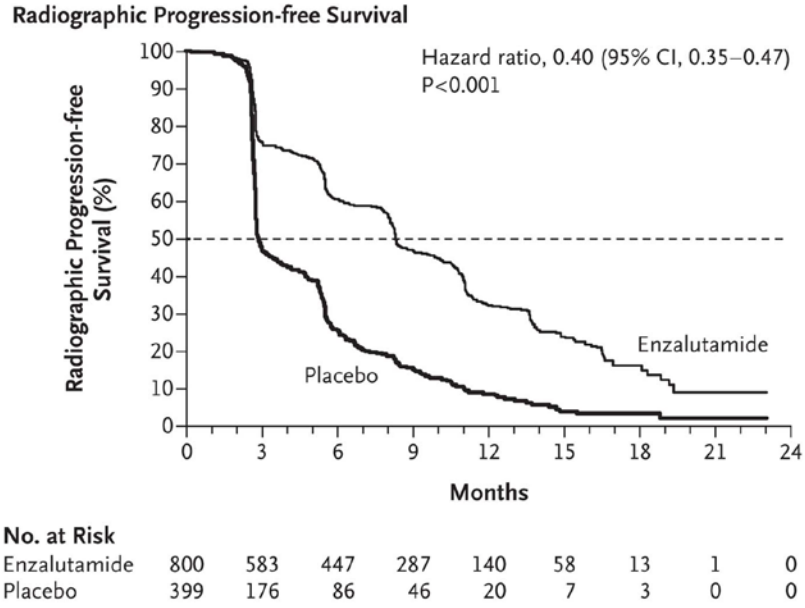


Figure 4. Kaplan-Meier estimates of rPFS in the AFFIRM study (source: Scher 2012[1])

c) Time to PSA Progression and PSA Response

Time to PSA progression was defined as the time from randomization to the first documented date of PSA progression, as assessed using PCWG2 criteria. The PSA progression date was defined as the date that a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir (for patients with PSA declines at week 13) or baseline (for patients with no PSA declines at week 13) was documented, which was confirmed by a second consecutive value obtained 3 or more weeks later. Kaplan-Meier median times to PSA progression and their 95% confidence intervals as well as Kaplan-Meier curves were used. A log-rank test stratified by baseline ECOG performance-status score and mean pain score was used to compare treatment groups.

The median time to PSA progression was 8.3 months in the enzalutamide group and 3.0 months in the placebo group (HR=0.25, 95% CI 0.20-0.30, p<0.001). Kaplan-Meier curves of time to PSA progression are shown in Figure 5.

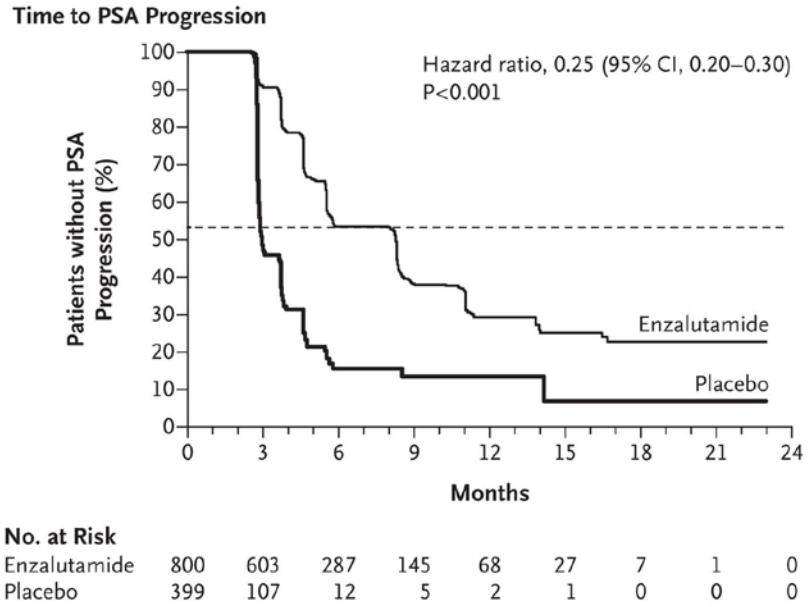


Figure 5. Kaplan-Meier estimates of time to PSA progression in the AFFIRM study
Source: Scher 2012[1]

PSA response was defined as a ≥50% or ≥90% reduction in PSA levels from baseline as confirmed on an additional PSA evaluation performed 3 or more weeks later. Fifty-four percent of patients in the enzalutamide group had confirmed PSA declines of ≥50% compared to 2% of patients in the placebo group. Twenty-five percent patients in the enzalutamide group had confirmed PSA declines of ≥90% compared to 1% of patients in the placebo group.

d) Time to First Skeletal-Related Event

The time to first skeletal-related event was defined as the time from randomization to the occurrence of the first skeletal-related event (SRE). A SRE was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. Kaplan-Meier median times to first SRE and their 95% confidence intervals were used. Kaplan-Meier curves were also used, but were not included in the publications. A log-rank test stratified by baseline ECOG performance-status score and mean pain score was used to compare treatment groups.

The median time to first SRE was 16.7 months in the enzalutamide group and 13.3 months in the placebo group (HR=0.69, 95% CI 0.57-0.84, p<0.001). Kaplan-Meier curves.

e) Quality of Life

Quality of life was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. The FACT-P is a multidimensional, self-reported instrument consisting of 27 core items to assess patient function in four domains (physical, social/family, emotional, functional well-being) and 12 specific items to assess for prostate-related symptoms. Each item is rated on a scale from 0 to 4, and

then combined to produce subscale scores for each domain in addition to a global score. Higher scores indicate better QoL. A clinically meaningful change was estimated to be 6 to 10 for FACT-P total score.[24]

The baseline mean FACT-P scores and the scores of the various domains are shown in Table 7. Baseline scores were balanced between the enzalutamide and placebo groups.

Table 7. Baseline FACT-P scores in the AFFIRM study

Scale (maximum score)	Enzalutamide (N=800)	Placebo (N=399)
FACT-P total score (156)	[redacted]	[redacted]
Physical (28)	[redacted]	[redacted]
Social/Family (28)	[redacted]	[redacted]
Emotional (24)	[redacted]	[redacted]
Functional (28)	[redacted]	[redacted]
Prostate Cancer Subscale (48)	[redacted]	[redacted]

Source: pCODR Submission[3]

Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.

In the AFFIRM study, a QoL response was defined as a 10-point improvement in the global score on the FACT-P questionnaire, as compared with baseline, on two consecutive measurements obtained at least 3 weeks apart. A two-sided stratified Cochran-Mantel-Haenszel mean score test (α=0.05) was used to compare the proportion of subjects achieving a QoL response in both treatment groups. The proportion of patients achieving a QoL response was statistically significantly greater in the enzalutamide group compared to the placebo group (43% vs. 18%, p<0.001).

Harms Outcomes

The safety analysis population consisted of 1199 patients (ITT population) and safety assessments were performed continuously throughout the study until 30 days after the last dose of study drug or prior to the initiation of subsequent antineoplastic therapy. Adverse events were classified using the NCI-CTCAE and monitored by an independent data monitoring committee.

As of the interim analysis, the median time on treatment was 8.3 months in the enzalutamide group and 3.0 months in the placebo group.

Overall, the rates of adverse events were similar in the enzalutamide and placebo groups.

a) Death

In the safety population, 308 patients (39%) in the enzalutamide group and 212 patients (53%) in the placebo group died. The primary cause of all deaths was disease progression. Deaths due to adverse events occurred in 23 patients (3%) in the enzalutamide group and 14 patients (4%) in the placebo group. It was not reported how many of these fatal adverse events were considered to be drug-related.

b) Serious Adverse Events

Serious adverse events (SAEs) were more commonly reported in the placebo group (n=154, 39%) than the enzalutamide group (n=238, 34%). The number of SAEs that were considered related to the study drug by the investigator was not reported in the published article. SAEs reported in ≥1% of patients and reported more frequently in the enzalutamide group than the placebo group using a cut-off date of January 31, 2012 are listed in Table 8 (source: FDA Medical Reviews).[11] Overall, SAEs were more common in the placebo group compared to the enzalutamide group, with the largest increase of SAEs occurring in spinal cord compression and pathological fracture.

Table 8. SAEs in the AFFIRM study

n (%)	Enzalutamide (N=800)	Placebo (N=399)
Total SAEs	279 (34.9)	149 (37.3)
Spinal cord compression	50 (6.3)	15 (3.8)
Hematuria	14 (1.8)	5 (1.3)
Bone pain	13 (1.6)	4 (1.0)
Pathological fracture	13 (1.6)	2 (0.5)
Metastatic pain	13 (1.6)	3 (0.8)
General physical health deterioration	12 (1.5)	4 (1.0)
Pneumonia	12 (1.5)	5 (1.3)

Source: FDA Medical Review[11]
Cut-off date: January 31, 2012

c) Adverse Events Leading to Discontinuation

Overall, treatment discontinuation due to AEs was more common in the placebo group (n=39, 10%) than the enzalutamide group (n=61, 8%). More patients discontinued treatment due to seizure in the enzalutamide group than the placebo group.

Table 9. AEs leading to discontinuation

n (%)	Enzalutamide (N=800)	Placebo (N=399)
Total	61 (7.6)	39 (9.8)
Seizure*	6 (0.8)	0
Fatigue	5 (0.6)	2 (0.5)
Thrombocytopenia	2 (0.2)	0
Colonic obstruction	2 (0.2)	0
Diarrhea	2 (0.2)	0
Rash	2 (0.2)	0

Source: FDA Medical Review[11]
Cut-off date: September 25, 2011
*One seizure occurred after patient had discontinued therapy

d) Adverse Events of Interest

Seizures

Seizure was identified as a potential toxicity associated with enzalutamide from an earlier phase I-II study.[25] Due to these results, patients with a history of seizure or any

condition that may predispose to seizure were excluded from the AFFIRM study. As of the cut-off date of September 25, 2011, Scher et al reported that a total of 5 patients in the enzalutamide group experienced a seizure.[1] No patients in the placebo group experienced a seizure. Upon a retrospective review of the data, 2 additional seizures were identified in the enzalutamide group. The FDA analysis identified 7 seizures in the enzalutamide group.[11]

Skeletal-Related Events (SREs)

An analysis conducted by the FDA found that there was no difference in the overall incidence of SREs while on study treatment between the enzalutamide and placebo groups (Table 10).[11] There was an increase in spinal cord compression in patients treated with enzalutamide compared with placebo (8.3% vs. 7.3%). The incidence of fracture was higher in the enzalutamide group compared to the placebo group (6.8% vs. 4.0%).

Table 10. A summary of SREs in the AFFIRM study

n (%)	Enzalutamide (N=800)	Placebo (N=399)
SREs while on study treatment	167 (21)	82 (21)
Total SREs	[redacted]	[redacted]
Radiation to bone	[redacted]	[redacted]
Surgery to bone	[redacted]	[redacted]
Spinal cord compression	66 (8.3)	29 (7.3)
All fracture	[redacted]	[redacted]
Pathologic fracture	[redacted]	[redacted]
Nonpathologic fracture	28 (3.5)	3 (0.8)

Source: FDA Medical Review,[11] pCODR Submission[3]
Cut-off date: September 25, 2011
Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.

Pain

The Brief Pain Inventory-Short Form (BPI-SF) is a questionnaire consisting of four numeric rating scale items asking patients to rate their pain severity (0-no pain; 10-pain as bad as you could imagine) and seven items concerning the degree to which the pain interferes with day-to-day activities (0-does not interfere; 10-interferes completely).[26] A lower score indicates lower pain severity and pain interference.

In the AFFIRM trial, the BPI-SF was used to assess patients at baseline and at week 13 (Table 11). There was a mean reduction in pain severity of 0.65 in the enzalutamide group compared to the placebo group. There was a mean reduction in pain interference of 0.79 in the enzalutamide group compared to the placebo group.

Table 11. Change from baseline to week 13 in BPI-SF scores.

n (%)	Enzalutamide (N=800)	Placebo (N=399)
Number of patients evaluated	[redacted]	[redacted]
Pain severity		
Adjusted mean change from baseline (SE)	[redacted]	[redacted]
Difference (SE)	[redacted]	
P-value	[redacted]	
Pain interference		
Adjusted mean change from baseline (SE)	[redacted]	[redacted]
Difference (SE)	[redacted]	
P-value	[redacted]	

SE=standard error
Source: pCODR Submission[3]
Cut-off date: September 25, 2011
Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed

e) Any Adverse Events

In both treatment groups, 98% of patients experience at least one AE throughout the study at the interim analysis (cut-off date September 25, 2011) and after a safety update (cut-off date January 31, 2012). There was a higher incidence of all grades of fatigue, diarrhea, hot flashes, musculoskeletal pain and headache in the enzalutamide group than in the placebo group (Table 12, bolded).

Table 12. AEs that occurred in ≥5% in any treatment group in the AFFIRM study

n (%)	Enzalutamide (N=800)	Placebo (N=399)
Any AE	785 (98.1)	390 (97.7)
Blood and Lymphatic System Disorders	134 (16.8)	84 (21.1)
Anemia	115 (14.4)	76 (19.0)
Gastrointestinal Disorders	539 (67.4)	279 (69.9)
Nausea	265 (33.1)	167 (41.9)
Constipation	188 (23.5)	110 (27.6)
Diarrhea	**171 (21.4)**	**70 (17.5)**
Vomiting	130 (16.3)	88 (22.1)
Abdominal Pain	41 (5.1)	23 (5.8)
General Disorders and Administration Site Conditions	506 (63.3)	231 (57.9)
Fatigue	**269 (33.6)**	**116 (29.1)**
Peripheral Edema	122 (15.3)	53 (13.3)
Asthenia	140 (17.5)	67 (16.8)
Pyrexia	54 (6.8)	28 (7.0)
Infections and Infestations	285 (35.6)	117 (29.3)
Urinary Tract Infection	63 (7.9)	28 (7.0)
Investigations	148 (18.5)	77 (19.3)
Weight Decreased	94 (11.8)	41 (10.3)

n (%)	Enzalutamide (N=800)	Placebo (N=399)
Metabolism and Nutrition Disorders	280 (35.0)	155 (38.8)
Decreased Appetite	225 (28.1)	121 (30.3)
Musculoskeletal and Connective Tissue Disorders	516 (64.5)	259 (64.9)
Back Pain	197 (24.6)	96 (24.1)
Arthralgia	152 (19.0)	69 (17.3)
Pain in Extremity	119 (14.9)	65 (16.3)
Musculoskeletal Pain	**116 (14.5)**	**46 (11.5)**
Bone Pain	101 (12.6)	61 (15.3)
Muscular Weakness	74 (9.3)	27 (6.8)
Muscular Chest Pain	62 (7.8)	34 (8.5)
Myalgia	50 (6.3)	26 (6.5)
Nervous System Disorders	389 (48.6)	149 (37.3)
Headache	**93 (11.6)**	**22 (5.5)**
Dizziness	55 (6.9)	22 (5.5)
Parasthesia	52 (6.5)	18 (4.5)
Spinal Cord Compression	51 (6.4)	18 (4.5)
Psychiatric Disorders	199 (24.9)	77 (19.3)
Insomnia	70 (8.8)	24 (6.0)
Anxiety	51 (6.4)	16 (4.0)
Depression	44 (5.5)	18 (4.5)
Renal and Urinary Disorders	185 (23.1)	97 (24.3)
Hematuria	52 (6.5)	18 (4.5)
Respiratory, Thoracic, and Mediastinal Disorders	210 (26.3)	102 (25.6)
Dyspnea	79 (9.9)	39 (9.8)
Cough	47 (5.9)	25 (6.3)
Vascular Disorders	249 (31.1)	78 (19.5)
Hot Flush	**162 (20.3)**	**41 (10.3)**
Hypertension	49 (6.1)	11 (2.8)

Source: pCODR Submission[3]
Cut-off date: September 25, 2011

6.4 Ongoing Trials

No additional on-going and/or unreported trials were identified that would have been included had they been completed.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of enzalutamide for metastatic castration-resistant prostate cancer:

- Validity and limitations of skeletal-related events as an endpoint in prostate cancer studies
- Critical appraisal of an indirect comparison of enzalutamide with abiraterone, cabazitaxel, or mitoxantrone

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Validity and limitations of using skeletal-related events as an endpoint in prostate cancer studies

7.1.1 Objective

To assess the validity and limitations of skeletal-related events (SREs), also known as skeletal complications, as an endpoint in advanced prostate cancer, with particular interest in mCRPC.

7.1.2 Findings

The definition of SREs in clinical trials typically includes bone pain, spinal cord compression, and pathological fracture.[13-15,17,18,27,28] The definition has also included impaired mobility[18] (including limb paralysis),[28] symptomatic hypercalcemia,[13,18] radiation to bone,[13,15,16] surgery to bone,[15] and change in anti-neoplastic therapy due to bone pain.[27] Given this variability in definition and that SREs are a composite endpoint, the question arises: is reduction in SREs a clinically meaningful endpoint in advanced prostate cancer clinical trials? And in particular, do SREs correlate with patient important outcomes such as health-related quality of life and survival?

With bone being one of the most common sites for metastases in prostate cancer with 70%-80% of patients presenting with or developing bone metastases[16] (85%-100% in the case of hormone refractory prostate cancer),[28] SREs remain an frequent outcome that may cause deterioration in quality of life.[16,18,28] The development of SREs is more likely in men with metastatic prostate cancer as they generally have relatively long survival times and the synergistic effect of bone metastases and the use of androgen-deprivation therapy subsequently increases the likelihood of experiencing SREs.[18,28]

The US Food and Drug Administration (FDA) regulatory approval criteria for neoplastic drugs in patients with mCRPC remains consistent, focusing on the clinical benefit of improvement in how patients function and feel and their length of survival post diagnosis. In all recent mCRPC trial approvals, the FDA standard has concentrated on treatments that improve OS and reduce incidence of SREs as the primary endpoints.[12,13]

Nonetheless, we did not identify any studies that formally evaluated the validity and reliability SREs as an endpoint in advanced prostate cancer trials.

SREs as a Surrogate Endpoint for OS

Several studies have evaluated the relationship between SRE incidence and OS, including a post hoc analysis of a phase III trial,[14] a population based cohort study,[15] a population based analysis of a medical database,[16] and two non-randomized studies.[17,18] With the exception of Berruti et al,[18] the identified studies observed a correlation between experiencing one or more SREs and a poor prognosis for survival.[14-17] In the post hoc analysis of a clinical trial including men with metastatic prostate cancer, DePuy et al[14] observed statistically significant survival differences between patients who experienced one or more SREs compared with those who did not experience any, with the latter having better survival times. In addition, patients experiencing more than one SRE had a significantly worse survival prognosis than those experiencing only one SRE.[14] Norgaard et al[15] found that bone metastasis itself confers a poor survival prognosis which is further worsened with the incidence of a subsequent SRE. These results were irrespective of the initial pathological stage of the disease at diagnosis.

In contrast, Berruti et al[18] indicated that the incidence of SREs had no correlation on OS. When evaluating SRE incidence in men with prostate cancer and those with hormone refractory disease, the authors determined patients with SREs had an OS similar to that of those without such complications (median 14.4 versus 12.7 months, respectively).

Limitations of these studies included small sample sizes,[14,17,18] post hoc analysis of clinical trial data,[14] some variability in SRE definition and observational study data that may be subject to bias from unaccounted for confounding and/or effect modification, selection bias, and missing clinically relevant information.[15-18]

Although there appears to be the suggestion of a correlation between SREs and OS, the evidence comes from lower quality evidence; hence, whether a true association between SREs and OS exists remains to be determined.

SREs as a Surrogate Endpoint for Health-Related Quality of Life and Pain

Few studies have examined how well SREs correlate with pain and health-related quality of life (HRQOL), and if SREs may be an appropriate surrogate endpoint for these.

In the post hoc analysis of the clinical trial by DePuy et al,[14] patients who experienced at least one SRE had significant increases in pain in the 360-day post-landmark period compared to those who did not experience any SREs. Decreased HRQOL was also observed in patients who had experienced SREs.

Upon analyzing data from a clinical trial in men with advanced prostate cancer and a history of bone metastases, Weinfurt et al[27] observed statistically significant declines in physical well-being after SREs, as well as significant declines in functional ability after radiation therapy for bone lesions. Emotional well-being was also significantly negatively affected after experiencing SREs and after bone irradiation. SREs often indicate disease progression and may subsequently cause anxiety or depression in the patient, thus potentially accounting for the decrease in HRQOL scores.[27] The only pain measure that significantly changed was a decrease in pain intensity after radiation therapy, but not with other SREs.[27]

Limitations regarding these studies included post hoc analysis of RCT data, small sample sizes, and, for Weinfurt et al., scheduled outcome assessments occurred 90 days apart potentially leading to a misrepresentation of the severity or intensity of pain associated with SREs.[27]

While these studies highlight some association between SREs, pain, and HRQOL additional well-designed studies replicating these data are required in order to better assess the use of SREs as a surrogate endpoint for pain and HRQOL in advanced prostate cancer.

7.1.3 Summary

The definition of SREs as an endpoint is somewhat variable across studies among patients with advanced prostate cancer, including those with mCRPC. Hence, there is some question as to whether or not prevention of SREs represents a clinically meaningful outcome and whether it is a reasonable surrogate for OS.

The incidence of SREs post bone metastases is high and the prevention of SREs has been labeled by the US FDA as both a patient- and a physician-relevant endpoint.[12,13] Nonetheless, we did not identify any studies that formally evaluated the validity and reliability SREs as an endpoint in advanced prostate cancer trials.

Although some studies[14-17] have shown a relationship between SREs and OS, indicating the potential for using SREs as a surrogate endpoint for OS, others did not.[18] These studies were limited, at least in part, by small sample sizes and observational designs. Likewise, only two studies provided information on SREs as a potential surrogate endpoint for pain and HRQOL. As with the studies on SREs and OS, there was a correlation between SREs and HRQOL and pain, but important limitations prevent one from drawing concrete conclusions from these data. Therefore, well-designed studies are needed to replicate these results in order to conclude reduction of SREs as a valid surrogate endpoint for OS, HRQOL and pain in patients with mCRPC.

7.2 Critical Appraisal of an Indirect Comparison of Enzalutamide with Abiraterone, Cabazitaxel, or Mitoxantrone

7.2.1 Objective

To summarize and critically appraise the methods and findings of the manufacturer-submitted indirect comparison of enzalutamide versus abiraterone, cabazitaxel, or mitoxantrone for the treatment of men with mCRPC.

7.2.2 Findings

The manufacturer provided an indirect comparison to estimate the efficacy of enzalutamide versus abiraterone acetate, cabazitaxel, or mitoxantrone arms in the model for their cost-utility analysis. No network diagram was provided.

The indirect comparison submitted by the manufacturer was based on the treatment versus placebo in the AFFIRM,[1] COU-AA-3018,[20] and TROPIC7[19] trials. These Phase III RCTs assessed second line treatments in men with mCRPC after docetaxel chemotherapy. AFFIRM[1] compared enzalutamide with placebo, COU-AA-3018,[20] compared abiraterone acetate + prednisone with placebo + prednisone, and TROPIC7[19] compared cabazitaxel + prednisone/prednisolone with mitoxantrone + prednisone/prednisolone. Study characteristics are listed in Table 13.

Table 13. Summary of studies used for indirect comparison.

Trial, Publications	Study design	Patient population	Intervention and Comparator	Outcomes
AFFIRM Scher et al 2012[1]	Multinational, multicenter, Phase III, DB RCT	1199 men with mCRPC after docetaxel chemotherapy	Enzalutamide 160 mg orally QD (n=800) Placebo, orally QD (n=399)	Primary: OS Secondary: Radiographic PFS, PSA, HRQOL, PSA TTP, time to SRE
COU-AA-3018 de Bono et al 2011[20] Fizazi et al 2012[29]	Multinational, multicenter, Phase III, DB RCT	1195 men with mCRPC after docetaxel chemotherapy	Abiraterone acetate 1g orally QD + 5 mg prednisone orally BID (n=797) Placebo, orally QD + 5 mg prednisone orally BID (n=398)	Primary: OS Secondary: PSA TTR, PSA TTP, radiographic PFS
TROPIC7 de Bono et al 2010[19]	Multinational, multicenter, Phase III, DB RCT	920 men with mCRPC after docetaxel chemotherapy	Cabazitaxel 25 mg/m^2 intravenously over 1 hr every 3 wks + 10 mg prednisone[a] QD (n=378) Mitoxantrone 12 mg/m^2 intravenously over 15-30 min every 3 wks + 10 mg prednisone[a] QD (n=377)	Primary: OS Secondary: PFS, PSA TTR, PSA TTP, OTR, pain response, pain progression, tumor TTP

BID = twice daily**; DB =** double blind; **HRQoL =** health-related quality of life; **mCRPC** = metastatic castrate-resistant prostate cancer; **min** = minutes; **OS =** overall survival; **OTR** = objective tumor response**; PFS =** progression free survival; **QD =** once daily; **RCT =** randomized controlled trial; **TTR =** time to response; **TTP =** time to progression; **wks** = weeks

[a] Prednisone was given (or similar doses of prednisolone where prednisone was unavailable)

The Bucher method was used to perform the indirect comparison, which is an adjusted indirect comparison approach using aggregate data. The effect measure comparing two treatments within an RCT is used rather than the individual results for each treatment group in order to partially maintain the strength of randomization. One assumption of this model is that the relative efficacy of a treatment is similar in all trials included in the indirect comparison.[30]

Hazard ratios for OS from the individual studies are presented in Table 14. A partial results summary of the indirect comparison between enzalutamide and abiraterone acetate for OS is presented in Table 15. This result indicated a 20% increased risk of death with abiraterone acetate treatment when compared with enzalutamide treatment (using the updated hazard ratio data from 20.2 months for abiraterone[29]); however, the results were not statistically significant. Results for PFS were not provided for enzalutamide compared with abiraterone acetate or cabazitaxel, and results for OS were not provided for enzalutamide compared with cabazitaxel.

Table 14. Individual Trial Summary of Hazard Ratios for OS

OS				
Trial	**Treatment**	**Hazard Ratio**	**95% CI**	**P-value**
AFFIRM Scher et al 2012[1]	Enzalutamide vs placebo	0.63	0.53, 0.75	<0.001
COU-AA-3018	abiraterone	0.65[a]	0.54, 0.77	<0.001

OS				
Trial	**Treatment**	**Hazard Ratio**	**95% CI**	**P-value**
de Bono et al 2011[20]	acetate vs placebo			
COU-AA-3018 Fizazi et al 2012[29]	abiraterone acetate vs placebo	0.74[b]	0.64, 0.86	<0.001
TROPIC7 de Bono et al 2010[19]	cabazitaxel vs mitoxantrone	0.70	0.59, 0.83	<0.001
CI = confidence interval; **OS** = overall survival				

[a] Follow-up time of 12.8 months
[b] Follow-up time of 20.2 months

Table 15. Summary of indirect comparison results for OS

OS		
Treatment	**Hazard Ratio**	**95% CI**
Abiraterone acetate vs enzalutamide	1.20	0.958, 1.497
CI = confidence interval; **OS** = overall survival		

Limitations

The manufacturer did not provide any information surrounding the information sources, search strategy, study selection process, data extraction, or the validity of the individual studies included in the indirect comparison.

The Bucher's method was mathematically sound; however, the manufacturer did not provide a narrative description or justification of the method used, how potential bias or inconsistency would be handled, or a clear and precise narrative on the analysis framework.

Brief descriptions of the patient and trial characteristics were provided; however, the lack of in depth reporting made it difficult to determine whether the baseline patient characteristics and trial characteristics were similar between trials. (Patient and trial characteristics were relatively homogeneous when upon examination of the original articles.) Additionally, there was no framework of the actual indirect comparison provided making the treatment comparisons hard to conceptualize.

The only results that were provided included the hazard ratios and their corresponding 95 percent confidence intervals for OS between enzalutamide and abiraterone acetate. Assessment of the indirect comparison for the other agents was impossible as no other results were provided in the submission.

The quality of the manufacturer-submitted indirect comparison was assessed according to the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[31] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 16.

Table 16. Appraisal of the indirect comparison analyses using ISPOR criteria[31]

ISPOR Checklist Item		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting an indirect comparison analysis and the study objectives were stated.
2.	Does the methods section include the following? • Eligibility criteria	• The eligibility for the RCTs was stated and included treatments versus placebo in men with metastatic castrate-resistant prostate cancer.

ISPOR Checklist Item		Details and Comments
	• Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• No information was provided on the information sources, search strategy, study selection process, the data extraction, or the validity of the individual studies.
3.	Are the outcome measures described?	• Outcome assessed in the indirect comparison analysis (included overall survival, OS and progression free survival, PFS) were stated.
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• The Bucher method was used for the indirect comparisons between enzalutamide and abiraterone acetate or cabazitaxel for statistically indirect comparisons. • No in depth narrative description of the methodology was reported; however, an example of the hazard ratio and their 95% CI calculations for overall survival was provided. • Description and justification of using the Bucher method was not provided.
5.	Are sensitivity analyses presented?	• Not applicable.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• The selection process of included studies was not reported. • No table summarizing patient characteristics of the studies used for the indirect comparisons was provided; only a brief description highlighting their similarities. • Brief trial characteristics were provided in narrative form but no table with raw data was provided. • No figure showing the network of studies was provided.
7.	Does the study describe an assessment of model fit? Are competing models being compared?	• Not applicable.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were not clearly reported or complete.

7.2.3 Summary

The comparative efficacy of enzalutamide and abiraterone acetate treatment for OS in men with mCRPC was indirectly assessed using Bucher's method. No statistically significant differences were found between these treatments. In addition, differences between enzalutamide and cabazitaxel or mitoxantrone could not be assessed as the results of this portion of the indirect comparison were not provided. Limitations surrounding the indirect comparison were also a cause for concern regarding the robustness of any provided results and, therefore, any conclusions drawn from this indirect comparison should be interpreted with caution.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Genitourinary Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on enzalutamide for metastatic castration-resistant prostate cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Genitourinary Clinical Guidance Panel is comprised of three medical oncologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **Embase** 1974 to 2013 May 31 (oemezd)**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present (pmez)

#	Searches	Results
1	(enzalutamide or xtandi* or MDV3100 or MDV-3100).ti,ot,ab,sh,rn,hw,nm.	581
2	(915087-33-1 or 93T0T9GKNU).rn,nm.	368
3	or/1-2	725
4	3 use pmez	173
5	*enzalutamide/	42
6	(enzalutamide or xtandi* or MDV3100 or MDV-3100).ti,ab.	384
7	or/5-6	388
8	7 use oemezd	229
9	4 or 8	402
10	limit 9 to english language	362
11	exp animals/	35528275
12	exp animal experimentation/ or exp animal experiment/	1700582
13	exp models animal/	1094567
14	nonhuman/	4065738
15	exp vertebrate/ or exp vertebrates/	34606674
16	animal.po.	0
17	or/11-16	36712983
18	exp humans/	27415480
19	exp human experimentation/ or exp human experiment/	324418
20	human.po.	0
21	or/18-20	27417557
22	17 not 21	9297013

23	10 not 22	350
24	remove duplicates from 23	236

2. Literature search via PubMed

Search	Add to builder	Query	Items found	Time
#3	Add	Search **(#1 AND #2)**	15	10:25:30
#2	Add	Search **publisher[sb]**	426348	10:25:17
#1	Add	Search **(Enzalutamide OR xtandi* OR MDV3100 OR MDV-3100 OR 915087-33-1[rn] OR 93T0T9GKNU[rn])**	178	10:24:56

3. Cochrane Central Register of Controlled Trials (Central)

Issue 5 of 12, May 2013

"There is 1 result from 697938 records for your search on "enzalutamide or xtandi or MDV3100 or MDV 3100 in title abstract keywords in Trials"

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: enzalutamide or Xtandi or MDV3100 or MDV 3100

Select international agencies including:

Food and Drug Administration (FDA):
www.fda.gov

European Medicines Agency (EMA):
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp

Search terms: enzalutamide or Xtandi

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

Search terms: enzalutamide or xtandi or MDV3100 or MDV 3100 / last 5 years

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