pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Enzalutamide (Xtandi) for First-Line Metastatic Castration-Resistant Prostate Cancer

June 22, 2015

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TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

1.1 Background

Prostate cancer is the most common cancer diagnosed in Canadian men (excluding non-melanoma skin cancers), and is the third leading cause of cancer related death, with 4000 deaths expected in 2014.[1] Standard treatment for prostate cancer is androgen deprivation therapy via surgical or medical castration;[2] however, most patients will develop metastatic castration resistant prostate cancer (mCRPC) which is incurable, with death occurring within 2 to 4 years after the onset of castration-resistance.[3,4] Patients with asymptomatic or minimally symptomatic mCRPC may receive treatment with other hormonal therapies, docetaxel-based chemotherapy, or, more recently, abiraterone acetate plus prednisone.

Enzalutamide is an androgen receptor antagonist that prevents the binding of androgen to the androgen receptor and the binding of the androgen receptor complex to DNA in prostate cancer cells.

The objective of this review was to evaluate the effect of enzalutamide on patient outcomes compared with standard therapies or placebo in patients with mCRPC who have not received prior chemotherapy.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The systematic review identified and included one international, multicentre, double-blind, placebo-controlled randomized phase 3 trial, the PREVAIL study.[5] A total of 1,717 patients with mCRPC who had not received prior chemotherapy were randomized to receive either enzalutamide (n=872) or placebo (n=845). Baseline patient characteristics were generally well balanced across treatment groups, with the majority of patients having an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (67% to 69%). Patients with ECOG performance status of 2 or higher were not eligible for inclusion. Patients with brain metastases were excluded as were patients with a history of seizure or any condition that may predispose to seizure. The trial used overall survival (OS) and radiographic progression-free survival (rPFS) as co-primary endpoints. Secondary endpoints included time to prostate specific antigen (PSA) progression, PSA response, time to first skeletal-related event (SRE), time to initiation of cytotoxic chemotherapy, health-related quality of life (HRQoL), and safety. All 1,717 randomized patients were evaluated for efficacy and 1,715 patients who received at least one dose of the study drug were evaluated for safety.

Efficacy

At the pre-planned interim analysis (September 16, 2013), there were 241 deaths in the enzalutamide group and 299 deaths in the placebo group. A statistically significant difference in OS was demonstrated in favour of enzalutamide (median 32.4 months) compared with placebo (median 30.2 months; hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.60 to 0.84; p<0.001). After a median of 12 months of follow-up, a statistically significant difference in rPFS was also demonstrated in favour of enzalutamide (median not reached) compared with placebo (median 3.9 months; HR 0.19, 95% CI 0.15 to 0.23; p<0.001). In addition, statistically significant differences in favour of enzalutamide compared with placebo, were demonstrated for time to PSA progression (median 11.2 months versus [vs.] 2.8 months, respectively; HR 0.17, 95% CI 0.15 to 0.20; p<0.001) and

time to initiation of cytotoxic chemotherapy (median 28.0 months vs. 10.8 months; HR 0.35, 95% CI 0.30 to 0.40; p<0.001).

HRQoL was assessed using the time to a 10-point decrease in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) global score compared to baseline. The time to decline in FACT-P was statistically significantly longer in the enzalutamide group (median 11.3 months) compared with the placebo group (median 5.6 months; HR 0.63, 95% CI 0.54 to 0.72; p<0.001).

Pain was assessed using the Brief Pain Inventory-Short Form (BPI-SF). At 6 months, fewer enzalutamide-treated patients (32% of 698 patients) reported severe pain (≥ 30% increase in BPI-SF score from baseline) compared with those treated with placebo (37% of 358 patients; however the difference was not statistically significant (p=0.092). A lower percentage of patients in the enzalutamide group (23% of 675 patients) reported pain interference (≥ 50% increase in the baseline standard deviation of the BPI-SF score) compared with the placebo group (29% of 344 patients; p=0.019).

Harms

The proportion of patients who experienced an adverse event was similar between the enzalutamide group (97%) and the placebo group (93%). Adverse events more commonly reported in the enzalutamide group than in the placebo group included fatigue, back pain, constipation, and arthralgia. More patients who received enzalutamide reported Grade 3 or higher adverse events (43%) than those who received placebo (37%). The proportion of patients who withdrew due to adverse events was 6% in both groups.

1.2.2 Additional Evidence

pCODR received input on enzalutamide (Xtandi) for the treatment of mCRPC in men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy who have not received prior chemotherapy from two patient advocacy groups, the Canadian Cancer Survivor Network (CCSN) and Prostate Cancer Canada. Provincial Advisory group input was obtained from nine of the nine provinces participating in pCODR.

In addition, one supplemental question was identified during development of the review protocol as relevant to the pCODR review of enzalutamide and is discussed as supporting information:

- Critical appraisal of an indirect treatment comparison (ITC) of enzalutamide with abiraterone provided by the Submitter.
    - The comparative efficacy of enzalutamide and abiraterone acetate treatment for OS in mCRPC patients who were chemotherapy-naïve was assessed in an indirect comparison analysis. However, only findings from individual studies were presented (PREVAIL study and COU-AA-302 study). Results from the pooled analysis were not available in this ITC. Limitations surrounding the indirect comparison were a cause for concern regarding the robustness of any provided results, such as the substantial heterogeneities existing in the included studies of this analysis, the use of mixed population instead of chemo-naïve mCRPC patients only, the limited clinical relevance of comparisons between enzalutamide and the other treatments, and the lack of common comparator between study drugs. Therefore, any conclusions drawn from this indirect comparison regarding the comparative clinical effectiveness between enzalutamide and abiraterone should be interpreted with caution.

1.2.3 Interpretation and Guidance

Prostate cancer is the most commonly diagnosed cancer in men in Canada with 23,600 new cases and was the third leading cause of cancer death in 2014. Historically, patients with asymptomatic or minimally symptomatic mCRPC were often observed closely without intervention as there were no studies that demonstrated improvement in OS with either secondary hormonal therapy or chemotherapy. Recently, the COU-AA-302 study demonstrated an improvement in OS and rPFS in favour of abiraterone and prednisone compared with prednisone alone in patients with asymptomatic or minimally symptomatic mCRPC.

The PREVAIL study demonstrated statistically and clinically significant improvements in OS, rPFS, time to PSA progression, time to initiation of cytotoxic chemotherapy, and time to deterioration in HRQoL in patients receiving enzalutamide compared with placebo.

The rates of adverse events in the PREVAIL study were similar in the enzalutamide and placebo groups. The most common Grade 3 or higher adverse event in the enzalutamide group was hypertension (7%). The proportion of patients who withdrew due to adverse events was 6% in both the enzalutamide group and the placebo group. One patient in each treatment group experienced a seizure, although patients with a pre-existing seizure history were excluded.

The mCRPC population is relatively large and the current standard of care in seven provinces is abiraterone with prednisone, based on the significant improvement in OS demonstrated in the COU-AA-302 study comparing treatment with abiraterone plus prednisone to treatment with prednisone alone. The Clinical Guidance Panel noted that there is substantial heterogeneity between the PREVAIL study and the COU-AA-302 study that would make an indirect comparison between the two inappropriate, including the differences in patient populations in the studies and the lack of a common comparator.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to enzalutamide compared to placebo in the treatment of chemotherapy-naive mCRPC patients with an ECOG performance status of 0 or 1 who are either asymptomatic or minimally symptomatic. This conclusion is based on one high-quality randomized, double-blind, placebo-controlled trial that demonstrated a clinically and statistically significant benefit in overall survival. Several clinically relevant secondary endpoints including radiographic progression-free survival, time to initiation of cytotoxic chemotherapy, PSA response and health related quality of life also statistically significantly favoured the enzalutamide group compared with the placebo group. The adverse event rate was not significantly higher in the enzalutamide arm. Furthermore, the seizure rate was rare and not higher in those who received enzalutamide compared to placebo.

Patients receiving enzalutamide require ongoing monitoring for toxicity and follow-up of both biochemical and radiologic progression.

The Clinical Guidance Panel acknowledges that the current standard in many jurisdictions is abiraterone and prednisone which has also been found to be superior to placebo plus prednisone in a similar patient population. The magnitude of benefit with enzalutamide over placebo appears to be similar to that observed with abiraterone and prednisone over prednisone. However, a significant knowledge gap currently exists as to which therapy (enzalutamide or abiraterone) is superior in terms of efficacy due to the lack of a direct

comparison of enzalutamide and abiraterone/prednisone. Furthermore, the optimal sequencing of enzalutamide, abiraterone, and docetaxel in mCRPC remains undefined.

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 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 on 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 one of the most commonly diagnosed cancers in Canadian men.[6] In 2013, it was estimated that 3,900 prostate cancer-related deaths occurred, and it accounts for about one-quarter (24%) of all new cancer cases in men based on 2014 estimates.[4,7]

As prostate cancer growth depends on androgens, the current standard of care for prostate cancer is androgen deprivation therapy via medical or surgical castration.[8] 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.[9] Virtually all men who receive androgen deprivation therapy eventually develop metastatic castration-resistant prostate cancer (mCRPC), which is incurable and death usually occurs 2 to 4 years after the onset of castration-resistance.[3,4]

The current standard of care for first-line treatment of mCRPC is docetaxel-based chemotherapy, given with prednisone.[10] Docetaxel was the first systemic treatment shown to have a survival advantage in patients with mCRPC.[9] It is increasingly recognized that the androgen receptor (AR) remains overexpressed despite apparently castrate levels of testosterone. The understanding of the role of androgens in stimulating the growth of prostate cancer has led to the development and approval of new agents, especially the AR-targeted therapies (abiraterone acetate and enzalutamide) in the past few years.[3,8] Survival benefits and quality of life benefit of abiraterone, sipuleucel-T, cabazitaxel, radium-223 and enzalutamide have been demonstrated in large clinical trials of mCRPC patients, in the pre- or post-chemotherapy setting.[11] In 2013, the pCODR Expert Review Committee recommended funding abiraterone acetate for patients with asymptomatic or mildly symptomatic mCRPC who have not received prior chemotherapy and who have ECOG performance status 0 or 1, based on the net clinical benefit of abiraterone plus prednisone compared with prednisone alone.[12]

Enzalutamide is a second generation AR antagonist that prevents the binding of androgen to the AR and the binding of the AR-complex to DNA in prostate cancer cells. In May 2013, enzalutamide received Health Canada approval for use in the treatment of patients with mCRPC in the setting of medical or surgical castration who have received docetaxel chemotherapy.[13] A previous pCODR report has evaluated the efficacy and safety of enzalutamide in patients who had received prior chemotherapy.[14] The first-line use of enzalutamide in mCRPC patients without prior chemotherapy was approved by Health Canada in 2014.[15] The recommended dose of enzalutamide is 160 mg once daily.[15] Study treatment continued until disease progression (evidence of radiographic progression-free survival, a skeletal related event, or clinical progression) and the initiation of either a cytotoxic chemotherapy or an investigational agent, or until unacceptable toxicity or withdrawal.

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 not received prior chemotherapy.

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 6 for more details of the systematic review.

The PREVAIL study was an international, multicenter, double-blind, placebo-controlled, phase 3 RCT.[5] PREVAIL evaluated the efficacy and safety of enzalutamide 160 mg once daily compared to placebo in patients with mCRPC who have not received chemotherapy. A total of 1,717 patients were randomly assigned to receive treatment with enzalutamide (n=872) or placebo (n=845). Baseline characteristics were generally well balanced across treatment groups, with the majority of patients having an ECOG performance status of 0 (67-69%); patients having an ECOG performance status of ≥2 were not eligible. Patients with a history of seizure or any condition that may predispose to seizure were excluded from the study. Patients with brain metastasis were also excluded. The baseline serum PSA level was higher in the enzalutamide group (54 µg/L) than in the placebo group (44 µg/L); however, this difference is unlikely to have significant impact on the treatment effect from the study drug. The co-primary efficacy endpoints were overall survival (OS) and radiographic progression-free survival (rPFS), while secondary efficacy outcomes included time to PSA progression, PSA response, time to first skeletal-related event (SRE), time to initiation of cytotoxic chemotherapy, and health-related quality of life (HRQoL). Safety outcomes included adverse events, serious adverse events (SAEs), and adverse events leading to discontinuation. In total, 1,715 patients received at least one dose of study drug. All 1,717 patients were evaluated for efficacy outcomes, and 1,715 patients were evaluated for safety outcomes.

As of the interim analysis (September 16, 2013), there were 540 deaths: 241 (28%) in the enzalutamide group and 299 (35%) in the placebo group. The median OS was 32.4 months in the enzalutamide group and 30.2 months in the placebo group

(hazard ratio [HR] = 0.71, 95% confidence interval [CI] 0.60 to 0.84, p < 0.001). The analysis of rPFS was performed at 12 months follow-up, on May 6, 2012. The median rPFS was not reached on this date of data cut-off in the enzalutamide group, and it was 3.9 months in the placebo group (HR=0.19, 95% CI 0.15-0.23, p<0.001).

The median time to PSA progression was 11.2 months in the enzalutamide group and 2.8 months in the placebo group (HR=0.17, 95% CI 0.15-0.20, p<0.001). The proportion of patients that achieved a ≥ 50% reduction in PSA levels from baseline was 78% in the enzalutamide group and 3% in the placebo group (p<0.001). The time to initiation of chemotherapy was 28.0 months in the enzalutamide group and 10.8 months in the placebo group (HR=0.35, 95% CI 0.30-0.40, p< 0.001).

HRQoL was assessed using time to ≥ 10-point decrease in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) global score compared to baseline. The time to decline in FACT-P was 11.3 months in the enzalutamide group and 5.6 months in the placebo group, p<0.001.

Pain outcomes measured at month 6 indicated that fewer enzalutamide-treated patients reported severe pain compared with those in the placebo group: 32% vs. 37%; however, the between-group difference was not statistically significant (p = 0.092). A lower percentage of patients in the enzalutamide group reported pain interference: 23% vs. 29%, p = 0.019.

The risk of adverse events was similar between enzalutamide and placebo, 97% vs. 93%, respectively. Adverse events that occurred more commonly in the enzalutamide group compared to the placebo group included fatigue, back pain, constipation and arthralgia. More patients treated with enzalutamide reported adverse events of Grade 3 or higher than those treated with placebo: 43% vs. 37%, respectively. The most common event of Grade 3 or higher in the enzalutamide group was hypertension at 7%, compared to 2% in the placebo group. The proportion of patients withdrew due to adverse events was 6% in both groups.

One patient from each group experienced seizure.

Summary of the efficacy outcomes and harms outcome is presented in Table 1.

Potential limitations in the PREVAIL study include the involvement of the sponsor's staff in the planning, conduct, data analyses and manuscript writing of the study. The inconsistent antineoplastic therapies received in the two treatment groups after disease progression may have affected the treatment effect of the study drug on overall survival. 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 PREVAIL study

	Enzalutamide (N=872)	Placebo (N=845)
Overall Survival (data cut-off: September 16, 2013)		
Median (months)	32.4 (31.5 - upper limit NR)	30.2 (28 - upper limit NR)
Hazard Ratio (95% CI)	0.71 (0.60 - 0.84)	
P-value	< 0.001	
Radiographic Progression-Free Survival (data cut-off: May 6, 2012)		
Median (months)	NR (13.8 - upper limit NR)	3.9 (3.7 - 5.4)
Hazard Ratio (95% CI)	0.19 (0.15-0.23)	

	Enzalutamide (N=872)	Placebo (N=845)
P-value	< 0.001	
Time to Skeletal-Related Events		
Median (months)	31.1	31.3
Hazard Ratio (95% CI)	0.72 (0.61-0.84)	
P-value	< 0.001	
Time to PSA Progression		
Median (months)	11.2	2.8
Hazard Ratio (95% CI)	0.17 (0.15-0.20)	
P-value	< 0.001	
Decline of PSA ≥ 50%		
n/N (%)	666/854 (78)	27/777 (3)
P-value	<0.001	
Time to Initiation of Chemotherapy		
Median (months)	28.0	10.8
Hazard Ratio (95% CI)	0.35 (0.30-0.40)	
p-value*	< 0.001	
Health-Related Quality of Life (time to decline in FACT-P, ≥ 10-point decrease from baseline)		
Median (months)	11.3	5.6
Hazard Ratio (95% CI)	0.63 (0.54-0.72)	
p-value*	< 0.001	
Safety, n (%)*		
All deaths	241 (28)	299 (35)
Any AEs	844 (97)	787 (93)
Any events of grade ≥ 3	374 (43)	313 (37)
AEs leading to discontinuation	49 (6)	51 (6)
Seizures	1 (<1)	1 (<1)
AE=adverse event; CI=confidence interval; NR=not reached; PSA=prostate-specific antigen;		

*Safety analysis was performed in 871 patients in the enzalutamide group and 844 patients in the placebo group

Source: Beer 2014[5,17-19]

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

The COU-AA-302 study of abiraterone plus prednisone compared with placebo plus prednisone in patients with asymptomatic or mildly symptomatic chemotherapy-naïve mCRPC.[20] provided contextual information that was relevant to this review. Details of that study can be found in Section 7 of this report. In addition, the COU-AA-302 study formed the basis of a pCODR review of abiraterone acetate

(Zytiga) for mCRPC for which a final recommendation by the pCODR Expert Review Committee (pERC) was issued on October 22, 2013.[21]

2.1.5 Summary of Supplemental Questions

Question 1: Critical Appraisal of an Indirect Comparison of Enzalutamide with Abiraterone

The comparative efficacy of enzalutamide and abiraterone acetate treatment for OS in mCRPC patients who were chemotherapy-naïve was assessed in an indirect comparison analysis. However, only findings from individual studies were presented. Results from the pooled analysis were not available in this ITC. Limitations surrounding the indirect comparison were a cause for concern regarding the robustness of any provided results, such as the substantial heterogeneities existing in the included studies of this analysis, the use of mixed population instead of chemo-naïve mCRPC patients only, the limited clinical relevance of comparisons between enzalutamide and the other treatments, and the lack of common comparator between study drugs. Therefore, any conclusions drawn from this indirect comparison regarding the comparative clinical effectiveness between enzalutamide and abiraterone should be interpreted with caution.

See section 7.1 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

From a patient perspective, survey respondents are looking for a cure for their cancer and want to live longer. While a large number of respondents agreed or strongly agreed that their current therapy/therapies are able to manage their prostate cancer symptoms, they reported that there are needs in their current therapies that are not being met, such as significant adverse effects. Access to enzalutamide would be beneficial to patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy and have not received prior chemotherapy. According to the survey, half of the respondents reported that enzalutamide halted disease progression and improved quality of life compared to the therapies they have used in the past. Enzalutamide was also found easier to use. Respondents to the CCSN survey indicated that most side effects of enzalutamide were not acceptable, including fatigue, diarrhea and hot flashes; however those who struggling with disease progression and uncertainty about the future were willing to tolerate significant side effects. Similarly, respondents to the PCC survey indicated that they were willing to tolerate many of the side effects from enzalutamide if it was able to stop disease progression, prolong survival, and improve overall daily functioning.

PAG Input

Input on the enzalutamide review was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, the key enablers include familiarity with enzalutamide and it is an oral therapy. Key barriers to implementation are the high cost of enzalutamide and the potentially large budget impact associated with the large patient

population and concerns with inappropriate use since a number of these patients are seen by urologists outside the cancer programs. PAG also noted the lack of direct comparative data with abiraterone plus prednisone and the unknown sequencing of the therapy with existing treatments.

Other

The Health Canada product monograph for enzalutamide (Xtandi) provided by the manufacturer (Astellas Pharma Canada, Inc.) provides the following warnings: [15]

- *Xtandi is associated with an increased risk of seizure. Data from in vitro studies show that enzalutamide and its active metabolite cross the blood brain barrier, bind to, and inhibit the activity of the GABA-gated chloride channel.*
- *The dose of Xtandi may be a predictor of seizure in humans, with a greater risk of seizure at daily doses higher than 160 mg.*
- *Patients with a history of seizure or conditions that may pre-dispose them to seizure were generally excluded from clinical trials; therefore limited safety data are available in these patients.*

Enzalutamide and abiraterone acetate are both indicated for chemo-naïve mCRPC. There are no head-to-head clinical trials available to directly compare the clinical effectiveness between these two drugs. In addition, proper sequencing of treatment in this patient population has been recognized as an important consideration. However, evidence from randomized trials for sequential therapy is not available. There are ongoing clinical trials that may provide future evidence with respect to the sequential therapy and combination therapy of enzalutamide and abiraterone in the target population.

2.2 Interpretation and Guidance

Prostate cancer is the most commonly diagnosed cancer in men in Canada with 23 600 new cases and was the third leading cause of cancer death in 2014. Historically, patients with mCRPC but with no or minimal symptoms were often observed closely without intervention as there were no studies that have demonstrated improvement in overall survival with either secondary hormonal interventions or chemotherapy. In 2013, the COU-AA-302 study demonstrated an improvement in overall survival and radiographic progression in favour of abiraterone and prednisone versus prednisone alone in this group of patients with asymptomatic or minimally symptomatic disease. Despite crossover, a recently published follow-up study demonstrated a statistically significant improvement in overall survival for those who received abiraterone (median 34.7 months versus 30.3 months; HR 0.81; p=0.0033) after a median follow-up of 49.2 months.[22]

The current systematic review identified only one unique randomized controlled trial of enzalutamide in patients with metastatic CRPC who have not received chemotherapy. The PREVAIL study incorporated co-primary endpoints of overall survival and radiographic progression-free survival. Secondary efficacy outcomes included time to PSA progression, PSA response, time to first skeletal-related event (SRE), time to initiation of cytotoxic chemotherapy, health-related quality of life (HRQoL) and safety.

As of September, 2013, the median overall survival in the enzalutamide arm was 32.4 months versus 30.2 months in the placebo arm (HR=0.71, p<0.001). An update survival analysis supported the interim analysis with the median OS not yet being reached for the enzalutamide arm. The median rPFS was not yet reached at the date of the data cut-off in the enzalutamide group whereas it was 3.9 months in the placebo group (HR 0.19, p<0.001). In addition, the median time to PSA progression, the proportion of patients with ≥50% reduction in PSA levels from baseline, proportion of patients with pain interference, deterioration of quality of life, the time to initiation of chemotherapy were all in favour of the enzalutamide arm. In terms of safety, the rate of adverse events was similar in the enzalutamide and the placebo groups. The most common grade 3 or higher in the enzalutamide arm was hypertension with 7% of patients experiencing the specific adverse event. The proportion of patient withdrawal due to adverse events was not higher in the enzalutamide arm (6%) than placebo. Only one patient in each group experienced a seizure although patients with a pre-existing seizure history were excluded.

The mCRPC population is relatively large and the current standard of care in seven provinces is abiraterone with prednisone. Long-term follow-up of the COU-AA-302 study demonstrated a significant improvement in overall survival in favour of abiraterone plus prednisone compared with placebo and prednisone (HR 0.81, 95% CI 0.70 to 0.93; p=0.0033).[22] Since no trials have directly compared enzalutamide with the current available treatment of abiraterone with prednisone in this patient population, an indirect treatment comparison was conducted and submitted by the manufacturer. Enzalutamide was compared to a number of available treatments including docetaxel, mitoxantrone, radium-223, and sipuleucel-T. The comparison of enzalutamide to mitoxantrone, docetaxel and radium are of limited clinical relevance given the differences in patient population in the studies and current use of these agents. The weaknesses of the methodology used in the analysis are described in section 7.1.2.

Although the reported patient experience with enzalutamide is limited, the patient advocacy group input have suggested that the lack of prednisone related side effects made enzalutamide more attractive than abiraterone and prednisone.

The current evidence only allows an indirect comparison of enzalutamide to the current standard as there is no direct comparative study. The only ongoing studies include a randomized phase II study of currently examining the sequencing of enzalutamide with abiraterone with prednisone and a second, larger phase III study evaluating the combination of enzalutamide with abiraterone and prednisone.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to enzalutamide compared to placebo in the treatment of chemotherapy-naive mCRPC patients with an ECOG performance status of 0 or 1 who are either asymptomatic or minimally symptomatic. This conclusion is based on one high-quality randomized, double-blind, placebo-controlled trial that demonstrated a clinically and statistically significant benefit in overall survival. Several clinically relevant secondary endpoints including radiographic progression-free survival, time to initiation of cytotoxic chemotherapy, PSA response and health related quality of life also statistically significantly favoured the enzalutamide group compared with the placebo group. The adverse event rate was not significantly higher in the enzalutamide arm. Furthermore, the seizure rate was rare and not higher in those who received enzalutamide compared to placebo.

Patients receiving enzalutamide require ongoing monitoring for toxicity and follow-up of both biochemical and radiologic progression.

The Clinical Guidance Panel acknowledges that the current standard in many jurisdictions is abiraterone and prednisone which has also been found to be superior to placebo plus prednisone in a similar patient population. The magnitude of benefit with enzalutamide over placebo appears to be similar to that observed with abiraterone and prednisone over prednisone. However, a significant knowledge gap currently exists as to which therapy (enzalutamide or abiraterone) is superior in terms of efficacy due to the lack of a direct comparison of enzalutamide and abiraterone/prednisone. Furthermore, the optimal sequencing of enzalutamide, abiraterone, and docetaxel in mCRPC remains undefined.

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 diagnosed in Canadian men (excluding non-melanoma skin cancers), and is the third leading cause of cancer related death with 4000 deaths expected in 2014.[1]

3.2 Accepted Clinical Practice

Treatment for Localized Prostate Cancer

Treatment options for localized prostate cancer include prostatectomy, radiation therapy (intensity modulated radiation therapy or brachytherapy) or active surveillance for patients with lower risk disease. There is no definitive evidence that one treatment modality is superior in efficacy. However, despite local ablative treatment, some patients develop recurrent disease as evidenced by a biochemical recurrence (elevation in PSA) with or without metastases. Aside from salvage local therapies, standard first-line therapy for recurrence remains androgen deprivation therapy. The majority of patients initially respond to androgen deprivation therapy but almost all eventually progress to castration resistant prostate cancer (CRPC).

Treatment for Asymptomatic or Minimally Symptomatic CRPC

CRPC is defined as disease progression in the setting of castrate testosterone levels. Biochemical progression as manifested by a rising PSA alone is often the initial sign of disease progression before developing metastatic disease to bone or visceral organs. For patients with biochemical-only progression and no evidence of metastasis, observation is often recommended. Although no secondary hormonal therapy has been found to extend survival for patients with CRPC, initial therapy with the addition of an anti-androgen such as bicalutamide or an androgen synthesis inhibitor such as ketoconazole can be used.[23] If patients are treated with combined androgen blockade, anti-androgen withdrawal as well as low dose prednisone are considered options. In general, early chemotherapy with docetaxel is not recommended for those without metastatic disease outside the context of a clinical trial.[24] There has been no widely accepted standard of care for patients with non-metastatic CRPC as no phase 3 study has demonstrated improved survival. Importantly, patients with non-metastatic CRPC were not included in the COU-AA-302 study and their treatment remains an unmet need.

For those with mCRPC who are asymptomatic or minimally symptomatic, secondary hormonal maneuvers as described above are often used although, no clear survival benefit has been demonstrated. Chemotherapy with docetaxel has previously been recommended for those with a good performance status. A large randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of oral abiraterone acetate in this CRPC population who had not received chemotherapy. Although overall survival (OS) and radiographic progression-free survival (rPFS) were co-primary endpoints, initially, only rPFS was statistically in favour of abiraterone versus prednisone (HR=0.53, 0.45-0.62, p<0.0001). Long-term follow-up (median 49.2 months; 741 deaths occurred [96%] out of 773 required death events for final analysis) of the COU-AA-302 study demonstrated a statistically significant improvement in overall survival in favour of abiraterone plus prednisone compared with placebo plus prednisone (34.7 months vs. 30.3 months,

respectively; HR 0.81, 95% CI 0.70 to 0.93; p=0.0033).[22] Other endpoints, including time to PSA progression, PSA response, objective tumour response and patient reported outcomes, were improved and in favour of abiraterone. In terms of safety, abiraterone was well tolerated with the most common adverse events being fatigue, back pain, arthralgias, nausea and constipation which were all also observed in the placebo arm. Based on the results of the COU-AA-302 study, abiraterone acetate was approved by Health Canada in 2013 and recommended for funding by pCODR.

Treatment for Symptomatic CRPC

When secondary hormonal therapies fail, suitable patients are treated with docetaxel chemotherapy. In two large randomized phase 3 studies,[25,26] docetaxel significantly improved overall survival by over 2 months, was associated with a PSA response rate of approximately 50% and also improved quality of life. Docetaxel was approved by Health Canada in 2004 for the treatment of mCRPC. Although effective, docetaxel is a palliative treatment and eventually all patients develop progressive disease. Radium-223 is an alpha-emitting radiopharmaceutical which has been approved by Health Canada in 2013 for treatment of symptomatic bone metastasis in patients with CRPC with no visceral metastasis based on a modest survival advantage over placebo (14.9 vs 11.3 months, HR 0.70, 0.58-0.83, P<0.001).[27]

For patients who have progressed on docetaxel, recent data supports the use of both chemotherapy, such as cabazitaxel, or alternatively, hormonal therapies such as enzalutamide and abiraterone. Cabazitaxel, a novel semi-synthetic taxane was shown to increase overall survival as well as response rates and time progression when compared to mitoxantrone.[28] Both enzalutamide,[16] an androgen receptor antagonist, and abiraterone acetate,[2] an androgen synthesis inhibitor, were compared to placebo and prednisone respectively in the phase 3 setting and were found to be associated with improved overall survival. Importantly the enzalutamide trial did not include patients treated with abiraterone prior to docetaxel so the optimal sequencing of these new therapies remains undefined. Furthermore, the repeat use of abiraterone in the post chemotherapy setting in patients previously exposed to abiraterone in the minimally symptomatic setting is undefined.

Summary

The management of mCRPC has changed significantly over the last five years with the approval of a number of new agents which have demonstrated survival benefits in both the pre and post chemotherapy setting. In particular, the efficacy of novel hormonal agents such as enzalutamide and abiraterone with prednisone in the post-docetaxel setting has renewed interest in targeting the androgen receptor pathway in CRPC. More recently this approach has been extended to the prechemotherapy setting, with abiraterone and prednisone having been demonstrated to be effective in the treatment of asymptomatic or minimally symptomatic mCRPC in terms of improvement in time to radiographic progression and overall survival, thus leading to its use as a standard of care. As abiraterone is given with prednisone, there is concern that the prevalence of conditions with a contraindication for steroids such as concurrent cardiac conditions or diabetes in this patient population may limit the use of abiraterone. Furthermore, clinicians have expressed concern regarding the hepatotoxicity associated with abiraterone. Although the use of abiraterone has represented an effective therapeutic choice for patients with minimally symptomatic or asymptomatic mCRPC, not all patients respond underscoring the need for other equally well tolerated oral hormonal treatment options in this setting. Like abiraterone, these agents used in this setting may also delay the need for cytotoxic chemotherapy.

3.3 Evidence-Based Considerations for a Funding Population

Nearly all patients who begin androgen ablative therapy develop castration resistant prostate cancer. The majority of patients experience a rise in PSA as the first sign of castration resistance and patients can remain without evidence of metastatic disease even at this stage of the disease. The PREVAIL study included only patients with metastatic castration resistant prostate cancer with either minimal or no symptoms as defined by a low score on the Brief Pain Inventory and an ECOG performance status of 0 or 1.

3.4 Other Patient Populations in Whom the Drug May Be Used

Enzalutamide has been shown to be effective in the POST-chemotherapy setting for mCRPC. It has also recently been shown in the PREVAIL study to be effective in the PRE-chemotherapy setting. Insufficient evidence exists for the use of either enzalutamide or abiraterone in non-metastatic CRPC. Although trials are ongoing, there is no evidence for the use of enzalutamide in the hormone sensitive setting. The combination of abiraterone and enzalutamide is currently being investigated and remains experimental. The optimal sequencing of abiraterone and enzalutamide is also being addressed as patients in neither phase III study received the other drug.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following two patient advocacy groups provided input on enzalutamide (Xtandi) for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy who have not received prior chemotherapy, and their input is summarized below:

- Canadian Cancer Survivor Network
- Prostate Cancer Canada

The Canadian Cancer Survivor Network (CCSN) conducted an online survey in September and October 2014, which was publicized on CCSN's website and in a CCSN e-letter. In addition, an email about the survey was also circulated to approximately 125 prostate cancer support groups and to CCSN's Prostate Cancer Advisory Council.

CCSN reported having 12 advanced prostate cancer patients and one (1) caregiver respondents to the survey. It was also reported that six (6) respondents had experience with enzalutamide.

Prostate Cancer Canada (PCC) gathered information through two separate online surveys (one for patients/survivors and one for caregivers), which were open from Sept 16 – Oct 9, 2014. The information from both surveys were de-identified.

PCC reported 34 respondents for the patient/survivor survey, with 32 respondents completing the entire survey. Specifically, 32 respondents were able to identify the stage of their disease: 9 respondents have localized prostate cancer, six (6) respondents have metastatic disease, 15 respondents were in remission and two (2) did not know or had not been told the stage of their disease. Of the total number of patient respondents who completed the survey, 17 respondents were from Ontario, four (4) respondents from Alberta, four (4) from British Columbia, three (3) from Quebec, one (1) from Manitoba, one (1) from New Brunswick, one (1) from Nova Scotia and one (1) from Saskatchewan. There were no respondents from any of the Territories.

Of the 34 patients who responded to the PCC survey, a total of three (3) reported having experience with enzalutamide.

Four (4) caregivers responded to and completed PCC's caregiver survey. When asked what category best describes their relationship with the person they were caring for, all four (4) caregivers identified themselves as the 'spouse/partner' of the prostate cancer patient. All respondents were able to identify the stage of disease of the individual they are caring for: two (2) have localized disease, one (1) has metastatic disease and one (1) is in remission. Of the four (4) caregivers who completed the survey, three (3) were from Ontario and one (1) resides in New Brunswick. None of the caregivers reported having experience with enzalutamide.

From a patient perspective, respondents to both CCSN and PCC's surveys are looking for a cure for their cancer and want to live longer. While a large number of respondents agreed or strongly agreed that their current therapy/therapies are able to manage their prostate cancer symptoms, respondents reported that there are needs in their current therapies that are not being met. Respondents who have experienced with the drug treatment reported significant adverse effects, but generally are willing to tolerate the side effects. According to the respondents in the CCSN survey, half of the respondents reported that enzalutamide halted disease progression and the same percentage also found it easier to use. Respondents from the PCC survey also reported improved quality of life compared to therapies they have used in the past.

Please see below for a summary of specific input received from the patient advocacy groups. Cited responses are not corrected for spelling or grammar.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Metastatic Castration-Resistant Prostate Cancer

According to CCSN, metastatic prostate cancer patients are both physically and psychologically impacted by living with advanced prostate cancer. CCSN reported that 9/10 respondents suffer from fatigue, and the same number is also experiencing sexual dysfunction. Moreover, about two out of three respondents are sleep deprived, and more than half are living with uncertainty, and half are suffering from pain. In addition, one third are experiencing urinary incontinence, feeling isolated or lonely or suffering from depression.

CCSN survey respondents reported the following when asked what symptoms or challenges they experienced with advanced prostate cancer that affected their day-to-day living and quality of life:

- Sexual dysfunction: 92%
- Fatigue: 92%
- Not sleeping at night - restless: 67%
- Living with uncertainty: 58%
- Pain: 50%
- Urinary incontinence/blood in the urine: 33%
- Depression: 33%
- Feeling isolated or lonely: 33%
- Fractures or fear of fracture: 25%
- Anxiety, panic attacks: 17%
- Weight loss, lack of appetite: 17%
- Constipation: 17%

In addition to the above symptoms, respondents to the CCSN survey also added "*Having to rely on others*"; "*Not being able to do the everyday actions I love*"; and "*Having hot flashes*." One respondent noted that "*The sexual dysfunction and urinary incontinence bother me the most*."

Respondents to the PCC survey were also asked to rate how much certain symptoms impacted on their overall quality of life.

A majority of respondents (n=5 of 6) with metastatic disease reported that the most common cancer symptoms that have a large or somewhat large impact on their quality of life are fatigue and frequent urination at night. All respondents also described the impact of metastatic cancer on their sex life, with one respondent indicating "*With stage 4 prostate cancer there is no sex life!*"

In addition, the responses provided below represent the complete range of prostate cancer experiences; this includes those with advanced disease, localized disease as well as those in remission or who do not know the stage of their illness.

Erectile Dysfunction: The majority of respondents (n=20) discussed the negative impact of erectile dysfunction or their reduced sexual desire and satisfaction on their physical well-being. One respondent noted that the inability to perform sexual activity greatly impacted his quality of life. "*While it is not a cancer symptom this item is a result of my cancer treatment and that is not being able to perform sexual activity!*" Many respondents reported relying on medication to allow them to achieve an erection. "*I used medication to get an erection for a while but it resolved after 4 years and I can get a spontaneous erection*." One respondent who expressed concerns about the effect of future treatments on his new relationship. "*I am in a new relationship and I am very worried about the effects from the surgery and or radiation*". While sexual function was a common theme, there were some respondents who reported being in a relationship with an understanding partner and tried not to allow problems with erectile dysfunction become of great concern. "*Sexual function has also deteriorated, but this has not been an issue with either myself or my spouse; we maintain a warm and amicable relationship*."

Incontinence: 18 respondents indicated frequent urination, especially at night, was a large or somewhat large impact on their quality of life and 11 respondents rated the intense/urgent need to urinate as having a large or somewhat large impact on their quality of life. Incontinence negatively impacted patients and appeared to inhibit daily activities. "*The leaking limited my ability to walk long distances or in the afternoon or evening*."

Mental Well-Being: Mental well-being was another concern for some respondents. One respondent indicated that prostate cancer in general changed his whole life and that the side effects of treatment negatively impacted the "mental sharpness" he once had. Another respondent acknowledged that because of his diagnosis and the resulting stress of treatments, great efforts had to be made on his part on a daily basis to "*make sure I don't get depressed*." One patient indicated that they experience anxiety as a result of knowing they have prostate cancer. "*Sometimes, I wish I didn't know I had cancer because it is always on the back of my mind and I get rushes of anxiety a few times a day when I consciously think about the situation. I know it is important that I know about the cancer so that I can have it treated quickly when it needs to be treated*." In addition to the anxiety felt about knowing their diagnosis, anxiety and fear of the cancer returning was another theme that came up among respondents, with one individual summing up how many patients feel: "*I live in constant fear of recurrence*."

Sleep/Fatigue: Respondents discussed the effect of prostate cancer and its treatment on changes to their sleep patterns. This could be due to the therapy than being a symptom of cancer itself. One respondent noted that they required taking additional medication to be able to sleep. "*Hormone treatment also triggered a lighter sleeping pattern and difficulty getting to sleep that means gravol each evening for proper sleep*." The impact of fatigue on quality of life was wide ranging. 10 respondents reported no impact of fatigue on quality of life, while 13 respondents noted that fatigue had a large or somewhat large impact on their quality of life. The fatigue experienced by a number of respondents did appear to have an impact on daily living. Respondents who were once active reported being "*not very active*" compared to the past as they had a lack of energy. This was echoed by another individual who indicated that they "*do not lead an active life*" as they did before.

Bone Pain: Another symptom that emerged was the issue of bone pain and broken bones. Some respondents discussed the brittleness of their bones as a result of the progression of their disease. "*My bones have become brittle and I have broken 6 ribs in the last yr and half*." Additionally, someone discussed changes in bone density indicating, "*My bone density has dramatically dropped.*" There were, however, 27 respondents who reported no

impact on bone pain and 32 respondents who indicated that broken bones did not impact on their quality of life.

Side Effects of Hormone Therapy: Some respondents receiving hormone therapy noted changes to their body image as a result of the treatment. One respondent discussed breast enlargement as being an issue that resulted in them having a "*breast reduction 3 years ago*." Another prostate cancer survivor did acknowledge that breast enlargement was one of the side effects they experienced but this was of "little concern" for them.

Dietary Changes: Two respondents mentioned changing their diet after learning of their diagnosis. "*Change in diet to reduced red, and fatty meats; not important but a factor*." Another patient mentioned the changes he has made to his diet, stating, "*I have become very aggressive on my diet – 'no' sugar, juicing of eatables 2x per day, fruit smoothies, red meet 1x per week, etc etc.*"

Effect on Family: Not only did respondents discuss the impact of prostate cancer on their daily living, they also commented on the effect of a prostate cancer diagnosis and subsequent treatments on their family as they are all sharing this experience. "*For my family this has been a roller coaster as I fail each treatment over time*."

Social Well-Being: Respondents also reported impact on social well-being and perceptions and attitudes experienced from those around them. One respondent noted that "*It has cost me numerous jobs after employers discovered I had been diagnosed with cancer. It has impacted income, relationships, feeling 'normal' within society*." This was also repeated by another respondent who mentioned the "social stigma" attached to a diagnosis of prostate cancer and the impact this has on his daily functioning. One respondent indicated that he retired as a result of the known side effects after noticing that his "performance at work was declining". The stress of knowing they have prostate cancer also impacted on daily living. "I think that finding out that I have caner definitely contributed to my stress levels."

Finances: Respondents also reported being concerned about their finances and being able to afford treatments. "*I worry about being able to get the treatments I need at their huge price tags. I am not wealthy*." Another respondent noted, "*Financially I have spent many thousands of dollars (likely in the tens of thousands) on get other opinions from medical people, sourcing and buy quality supplements*." Another respondent mentioned not just the cost of immediate treatment but the cost of therapies to treat the side effects of the treatments, such as erectile dysfunction drugs that are not covered, by provincial or private plans, as being a financial burden.

PCC reported that while many respondents discussed the negative effects of prostate cancer on their well-being, there were two (2) respondents who noted that even with these side effects they still "*enjoy a great quality of life*." There were respondents who reported no major changes to their daily activities. One respondent reported "*8 months after surgery no change to daily routines or physical functioning*." Another respondent mentioned that there were no changes to their daily routine but because of their age, they believed the reduction in their activity level could also be attributed to "*normal age-related deterioration of muscle function*."

According to the CCSN survey, respondents were asked to rate their top symptoms that are the most important to control. Responses were provided as follows:

- Fatigue: 92%
- Pain: 58%
- Not sleeping at night – restless: 42%

- Fractures or fear of fracture: 42%
- Depression: 42%
- Living with uncertainty: 42%
- Urinary incontinence: 33%
- Sexual dysfunction: 33%
- Weight loss, loss of appetite: 16%
- Constipation: 16%
- Feeling isolated or lonely: 8%
- Anxiety, panic attacks: 8%

4.1.2 Patients' Experiences with Current Therapy for Metastatic Castration-Resistant Prostate Cancer

Respondents to the CCSN's survey were asked about the management of advanced prostate cancer, including which therapies and treatments they are currently using to treat their disease; how effective these therapies and treatments have been; which side effects they experienced; whether they have had issues accessing current therapies and treatment.

When asked about which treatments they were using, respondents reported the following:

- Bicalutamide (Casodex): 17%
- Cyproterone Acetate (Androcur): 0%
- Flatamide (Euflex): 0%
- Docetaxel (Taxotere): 8%
- Cabaziltaxel (Jevtana): 8%
- Mitoxantrone: 8%
- Prednisone: 17%
- Abiraterone acetate (Zytiga): 25%
- Radiation therapy: 17%
- Other hormone therapy: 58%
- Clinical trial: 17%

Because the majority of respondents (58%) indicated that they were using another hormone therapy, CCSN included the following additional information. One respondent noted "*I am paying for Xgeva and taking natural ingredients to boost my immune system 50mg Novo-Bicalutamide – 1 tablet once a day Xgeva (Denosumab) – injection monthly Zoladex Depot LA – injection every three months 40 mg APO Fluoxetine – once a day 5mg APO-Ramipril – once a day 40mg Ratio Atorvastatin – once a day 500mg Metformin – once a day*." Other respondents reported using: "ADT"; "Zoladex Injection Xgiva injection"; "SC/IM Injection (Androgen deprivation therapy)"; and "Eligard"

Respondents to the PCC survey were also asked to describe their experience with current therapies they are receiving to treat their prostate cancer. According to PCC, current therapies that are being used include: chemotherapy, radiation, HIFU, holistic medicine, androgen deprivation therapy, surgery, brachytherapy and active surveillance. There were 14 respondents who reported not currently receiving any active treatment to manage their cancer.

The majority of respondents to the PCC survey agreed or strongly agreed that their current therapy/therapies are able to manage their prostate cancer symptoms. They were pleased that their "PSA was lower" and they are able to "*enjoy each day and experiences in a fashion that probably would not have been available without treatments*." One

respondent on abiraterone noted that because their PSA was dropping this "*seems to be a good indication that it is working*".

According to CCSN, all respondents answered the survey question on which therapies were most effective at controlling common aspects of advanced prostate cancer. Three (3) respondents reported that "Other Hormone Therapy" was the most effective. The same number of respondents also reported that bicalutamide was the most effective, while two respondents reported that docetaxel was most effective.

Respondents to the CCSN survey reported that the common side effects of current therapies included:

- Diarrhea: 42%
- Nausea and vomiting: 42%
- Anemia: 47%
- Risk of infection: 28%

Other respondents reported experiencing pain, fatigue, hot flashes, energy loss, breast tenderness and enlargement, weight gain and emotional changes. Half of patients reported that nausea and vomiting were the most difficult side effects to manage, while one out of three found that diarrhea, anemia and risk of infection were the most difficult to manage.

When asked to describe their overall experience with their current therapies, respondents to the PCC survey discussed many of the symptoms, such as fatigue, that have impacted on their quality of life, including "*trouble sleeping*" and "*being a bit more tired*". One respondent also discussed the effect of radiation on incontinence and that hormone therapy negatively impacting their libido. The majority of respondents to the survey indicated that reduced sexual desire (n=23) and erectile dysfunction (n=27) had a large or somewhat large impact on their quality of life as a result of their current therapy.

Some respondents, however, did note that they are tolerating their therapies well, as their symptoms appear to be under control. Additionally, they reported being satisfied with the treatment decisions they made. One respondent noted that "*Mentally, physically and emotionally relieved by the decision to have surgery and radiation*."

According to PCC, general satisfaction seemed to be reported with current therapies, particularly for those individuals who found a therapy they are able to respond well to. This, however, has come with other drawbacks as one respondent reported developing resistance to their current therapy and has noticed that their PSA is doubling every 4 months. Another respondent did note that they were pleased to learn that with their current therapy, their PSA level is undetectable but they are experiencing "*brain fog, weight gain, fatigue, lack of energy, mood swings, nerve pain in legs and hot flashes*". This same respondent noted that one of the worst feelings for them was not knowing how they will feel on a daily basis until they woke up.

CCSN reported that 83% of respondents did not have issues accessing treatment, while 17% of respondents had issues with access. Reasons given for access issues included financial hardship due to cost (17%) or supplies or issues with administration (8%). It was noted that some respondents indicated more than one issue when attempting to access treatment.

Similarly, PCC reported the majority of respondents (n=23) indicated that it was "not at all difficult" to access their current therapy/therapies as they had the costs of treatment covered by "medical plans or manufacturer." Those who did indicate that it was at least somewhat difficult to access their therapies reported difficulties with paying for

medication, notably in particular provinces, as a result of lack of access to funded therapies. Another respondent discussed the costs spent on therapies and doctors saying "*I spent close to $20k last year on other doctors and alternative therapies*."

While some cancer medications are covered under provincial or private drug plans, one individual noted that some medications for treating the side effects of therapies are not covered: "*medicine for erectile dysfunction is not covered in basic medical coverage*". Only one respondent discussed the cost of parking at the cancer centre, in response to access to therapies, but did not indicate whether this was of concern for them. One caregiver also mentioned additional costs, such as parking, in response to access to therapies but noted that she and her husband are able to manage those costs "comfortably".

4.1.3 Impact of Metastatic Castration-Resistant Prostate Cancer and Current Therapy on Caregivers

CCSN included several questions in its survey for caregivers relating to challenges they face and how their day-to-day lives have been affected. One caregiver responded to these questions. Key responses included:

- "Loss of appetite, weight loss, PSA rising."
- "Hard to manage all the symptoms."
- "Very hard to manage, work, home, etc., needs lots of care (medications, bathing, all personal needs as he is unable to walk)."
- "Pain management, personal needs."

Four (4) caregivers responded to and completed the PCC caregiver survey. Caregivers were asked to comment on how their lives have been impacted by prostate cancer including physical functioning, daily routines and emotional impact of the disease on their lives. A number of similar themes to those echoed by patients were reiterated by caregivers. These common themes are summarized below with accompanying quotes.

Prostate cancer and the subsequent side effects of treatment had a profound impact on the sexual relationship experienced by caregivers and their partners. One caregiver noted "*He lost his ability to have a normal erection so both of us suffered a very deep sense of loss. We had a very close and intimate relationship that included an amazing sex life. The responsibility to initiate has fallen to me and before pc I never had to initiate, he was very passionate and always wanting to make love. This change has affected our relationship very much emotionally and mentally. It is very painful*". This was described by caregivers as a frustrating time for both them and their partner. "*He was eager to see if he could get his erectile function back. It was much more difficult than he thought it would be and he became frustrated, then depressed. He started to watch more TV and eat and gained weight*." This particular caregiver found it challenging watching her husband fall into depression and was unsure how to help his situation.

Caregivers were also asked to comment on current therapies that are used by the individuals they are caring for. One caregiver indicated that their partner was to go for surgery within weeks of completing this survey. Two respondents indicated that their partner was not currently receiving any treatment, other than taking medications for side effects such as erectile dysfunction.

The additional strain of traveling to and from appointments was another concern for caregivers. "*I don't even know how to put to words our life this year..I couldn't continue working this year alone we have travelled almost 9000km to medical appointments and*

treatments. The stress alone at time is unbearable. How would anyone feel watching the love of their life die just a bit more each day."

All caregivers commented on being worried about the prostate cancer diagnosis and its effects. "*We never get away from the worry that there is no stopping or cure that is a fix*." Another spouse commented that they are constantly filled with "*worry, anxiety*" as they feel overwhelmed with the amount of information they need to process while also managing a full-time workload and assuming primary caregiver responsibilities for their husband. This person also commented on the impact of this on their children. "I am worries also about his surgery and the side effects and how it will impact him and my kids."

A diagnosis of prostate cancer has a great impact on the emotional state of being a caregiver. "*Emotionally I am a train wreck who tries to put on a happy face..I cant say anything else because I may break if I put it all in words and I cant afford to breakdown*."

Caregivers did discuss the challenges they experienced while managing the side effects of the cancer or the therapy that the person they are caring for experiences. One caregiver discussed the difficulties she has in encouraging her husband without pressuring him.

One caregiver discussed the stress experienced with no extended health care in caring for a patient with metastatic disease. This caregiver also mentioned having challenges with the "*lack of self control*" her husband appears to be losing over his life and not being sure of how his illness would progress. This caregiver does not currently have experience with enzalutamide but suspects this will be the next course of treatment her husband tries to manage his condition. She is also concerned that with "*no extended health care, we are only offered standard of care. There is only one time chance that we have to get Xtandi and if we get it there won't be any other options This is very stressful its self*."

While there are a number of challenges experienced by caregivers, one was pleased to see her routine and the routine of her husband return to normal. "*At first it was hard to fathem my husband having cancer as he has always been so healthy and activity in his hockey. It is getting back to normal lately…*"

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Enzalutamide

According to PCC, three (3) caregivers and 24 patient respondents reported being not at all knowledgeable about enzalutamide.

PCC reported that it was difficult to ascertain the expectations of patients who do not have experience with enzalutamide, as many do not know about the drug. Patient respondents appeared to be divided on what symptoms they believed would be most important for enzalutamide to manage, because of their lack of knowledge. Some felt it was important for enzalutamide to effectively manage bone pain (n=11)/broken bones (n=9), fatigue (n=11) and pain related to urination (n=12) while others believe enzalutamide should manage painful urination (n=9).

CCSN reported that the long-term expectations expressed by respondents about enzalutamide included:

"*Less bone pain, less fatigue, increased appetite*."

"*I hope that I won't get worse. I want something that will stop disease progression*."
"*Delay of terminal illness and death*."

According to CCSN, respondents indicated that they would like the new drug to address the following:

- Stop disease progression: 86%
- Reduce side effects from current medications/treatments: 57%
- Better able to control symptoms: 43%
- Ease of use: 43%

CCSN found that 33% of survey respondents reported that there are needs in their current therapies that are not being met. Some of the comments included:

"*I would like to be able to live a normal life and have fewer side effects*."
"*Would like to stop disease progression*."
"*More energy; libido; better sleep*."
"*Uncertain with the sequencing of viable treatments*."

When asked how much of an improvement would be needed from the new drug to make it better than the current treatment, respondents to the CCSN survey said:

"*Stop disease progression*."
"*Better than the Zytiga option as it will be easier to administer*."
"*The drug would have to remove most of the symptoms, which in my opinion is very unlikely*."

When respondents were asked in the PCC survey as to which side effects they would be willing to tolerate if enzalutamide was able to improve overall daily functioning, the most common side effect respondents reported being willing to tolerate were:

- anemia (n=8)
- breast swelling or tenderness (n=7)
- decreased sexual desire (n=12)
- erectile dysfunction (n=15)
- hot flashes (n=8)
- weight gain and/or muscle loss (n=8)

PCC believes this is likely because respondents are already tolerating these side effects from therapies they are currently or previously have been using. One respondent said, "*I already have so many of them and if there is any benefit tobthe Xtandi I would tolerate them*". Another respondent mentioned that as long as prostate cancer would be stopped from spreading then any side effect would be tolerable.

On the other hand, a few respondents indicated that they would not be willing to "voluntarily" tolerate any of the symptoms. Despite these findings, PCC believes that patients would be willing to tolerate many side effects so long as it allows them to "stay alive", improve "quality of life" or "prolong life".

Respondents to the CCSN survey reported that they would tolerate side effects under the following conditions:

"*I am already having side effects and would like them to be fewer but would tolerate pretty much the same if it would stop disease progression*."
"*I would be willing to accept existing side effects (fatigue, loss of libido, disturbed sleep) provided there was an improvement in survival*."

According to CCSN, respondents struggling with disease progression and uncertainly about the future are willing to tolerate fairly significant side effects.

CCSN reported that six (6) survey respondents have experience with enzalutamide. Most reported being part of a clinical trial. PCC also reported that three (3) patients have experienced with enzalutamide.

Of the six (6) respondents to the CCSN survey, it was reported that all had experienced positive effects, but a majority (83%) also reported negative effects with the treatment.

The CCSN survey found the positive effects reported included:

- 50% of respondents were better able to control symptoms.
- 50% of respondents found enzalutamide easier to use.
- 33% of respondents found that enzalutamide halted disease progression.

When asked whether they were better able to control side effects than on their previous therapy, one-third of respondents indicated that they had lower PSA.
The CCSN survey found the negative effects reported included:

- "Fatigue, weight loss, loss of appetite, nausea, bone pain."
- "Extreme Fatigue; not being able to do daily activities and chores."

Specifically, respondents to the CCSN survey reported the following adverse effects while taking enzalutamide:

- Fatigue: 75%
- Diarrhea: 50%
- Hot flashes: 50%

One respondent noted "*Extreme tiredness Took the 'life out of me.' Not able to do the things I love*."

When asked what symptoms that enzalutamide managed better than other therapies respondents to the PCC survey had tried, bone pain and overall pain were mentioned. One respondent remarked that their mental capacity was much improved after starting enzalutamide. One respondent has tried both abiraterone and enzalutamide and reported that by comparison, they preferred enzalutamide because of fewer side effects experienced. "*Xtandi has not improved my life over Zytiga but I prefer it to Zytiga because of the prednisone side effects*".

According to the respondents to the CCSN survey, most side effects were not acceptable:

- Fatigue: 20% of respondents said that fatigue was acceptable, 80% not acceptable;
- Diarrhea: 0% acceptable, 100% not acceptable;
- Hot flashes: 0% acceptable, 100% not acceptable.

Although there were significant adverse effects reported by those who took enzalutamide, half of survey respondents reported that enzalutamide halted disease progression and the same percentage found it easier to use than previous treatments. CCSN noted that respondents seemed to be less willing than in previous surveys on metastatic prostate cancer drugs to tolerate side effects.

PCC found that respondents experienced a wide range of side effects as a result of being on enzalutamide. Side effects experienced include:

- anemia (n=1)
- breast swelling or tenderness (n=1)
- decreased sexual desire (n=2)
- depression (n=1),
- erectile dysfunction (n=2)
- fatigue (n=2)
- hot flashes (n=1)
- loss of bone density (n=1)
- weight gain and/or muscle loss (1)

PCC noted that it was unclear if these side effects were experienced on previous therapies used prior to enzalutamide or if they resulted from the use of enzalutamide alone.

Respondents to the PCC survey believe it is extremely important for enzalutamide to manage side effects including bone pain, broken bones, painful urination, fatigue, frequent urination as well as overall pain. Two respondents reported still being on enzalutamide; one respondent indicated that enzalutamide worked for the first 15 months and from this it would appear as though he is no longer receiving this therapy. It is unknown if anyone experienced any adverse reactions to enzalutamide.

According to PCC, all three (3) respondents agreed (n=2) or strongly agreed (n=1) that enzalutamide improved their quality of life compared to previous therapies they used, which PCC believes this indicates an overall positive experience to enzalutamide. One respondent noted "*I responded to Xtandi exceptionally well. My PSA dropped by >90%. The effect was durable to a good length of time (~3 ½). My mental capacity was greatly improved.*"

One respondent from the PCC survey also commented on the ease of using enzalutamide, as compared to abiraterone: "*Xtandi had very similar side effects to Zytiga as a user. BUT Xtandi is easier to take and you don't have to take prednisone with it. I am very grateful that Xtandi is available and it is much easier to take as a medicine*."

One respondent noted that after being on enzalutamide for a while, they are now becoming resistant to it and will likely need to try another therapy.

One respondent also expressed concern about coverage of enzalutamide if they failed another therapy such as abiraterone because of restrictions on coverage. "*After this chemo Xtandi or Zytiga and if they fail there isn't the luxery of trying the other one*."

4.3 Additional Information

No additional comments were received.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact implementation of enzalutamide in the first-line treatment of metastatic castration-resistant prostate cancer (mCRPC):

Clinical factors:

- Lack of comparative data with abiraterone/prednisone
- Treatment sequence after progression on enzalutamide and re-treatment

Economic factors:

- Potentially a large group of eligible patients
- High cost of enzalutamide

Health System factors:

- Funding mechanism of oral cancer drugs in some provinces
- Treatment by urologists

Please see below for more details.

5.1 Factors Related to Comparators

The current standard of care for first-line mCRPC in seven of the provinces is abiraterone acetate with prednisone (abiraterone/prednisone). PAG has noted that the pivotal trial for enzalutamide compared it to placebo and would like pERC to address comparison of enzalutamide to abiraterone/prednisone.

5.2 Factors Related to Patient Population

PAG indicated that this group of mCRPC patients is a relatively large population and is requesting clarity regarding whether enzalutamide would be replacing abiraterone/prednisone or would be an alternate to abiraterone/prednisone. PAG would like pERC to address what the unmet need would be in this patient population. However, PAG noted that enzalutamide may be appropriate for patients who have contra-indications to treatment with abiraterone/prednisone since enzalutamide does not require concomitant use of prednisone.

5.3 Factors Related to Dosing

PAG noted that enzalutamide is once daily dosing schedule and does not require concomitant prednisone which would enhance patient compliance.

5.4 Factors Related to Implementation Costs

PAG noted that enzalutamide is already funded in seven of the provinces in the second-line treatment of mCRPC and there is familiarity amongst health care providers with the administration and monitoring.

Given the high cost of enzalutamide and the large patient population with asymptomatic or mildly symptomatic mCRPC, use in this setting could have a significant budget impact and could be an important barrier to implementation. However, enzalutamide could also share the same patient population as abiraterone/prednisone.

PAG is seeking available information on the sequencing of treatment with enzalutamide and abiraterone/prednisone that would help determine funding sequence. It is unclear whether patients who receive enzalutamide in early first-line setting would receive abiraterone/prednisone or docetaxel second-line and whether there is evidence to support re-treatment with enzalutamide after docetaxel.

5.5 Factors Related to Health System

PAG noted that enzalutamide is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they 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 and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

In addition, PAG expressed concerns on appropriate use of enzalutamide since the majority of patients with asymptomatic or mildly symptomatic mCRPC are not seen by oncologists in the cancer system but by urologists.

5.6 Factors Related to Manufacturer

The high cost of enzalutamide would be a barrier to implementation.

PAG also noted that there is a compassionate supply program that provides patients access to enzalutamide, at no cost, for any line of treatment of mCRPC. PAG has expressed concerns that not all of these patients would meet criteria for public funding of enzalutamide, if and when the program closes.

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 not received prior chemotherapy (see Table 2 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.

- Critical appraisal of a manufacturer-submitted indirect comparison of enzalutamide with abiraterone plus prednisone

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 2. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs	Patients with mCRPC who have not received prior chemotherapy	Enzalutamide 160 mg QD orally	Chemotherapy (e.g. docetaxel plus prednisone) Abiraterone + prednisone Other hormonal therapies (e.g. steroids, ketoconazole, estrogen therapies) Best supportive care/placebo	Efficacy • **OS** • rPFS • PSA response rate as per PCWG2 criteria (% of patients with ≥ 50% decrease in PSA levels) • ORR • Time to PSA progression • **Change in pain** • **HRQoL** • Skeletal-related events (time to first events; % of patients with the events) • Time to chemotherapy initiation **Safety** • SAE** • AE

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
				•WDAE
AE=adverse event; CBR=clinical benefit rate; HRQoL=health-related quality of life; mCRPC=metastatic castration-resistant prostate cancer; ORR=objective response rate; OS=overall survival; PCWG2=Prostate Cancer Working Group 2; PSA=prostate-specific antigen; RCT=randomized controlled trial; ; rPFS= radiographic progression-free survival SAE=serious adverse event; WDAE=withdrawal due to adverse event				

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

*** SAE was not defined in the published articles*

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-present) with in-process records & daily updates via Ovid; EMBASE (1974 to 2014 October 1) via Ovid; The Cochrane Central Register of Controlled Trials (2014, Issue 10) 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 concepts were Xtandi and enzalutamide.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. 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 May 6, 2015.

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 - clinicatrials.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 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:

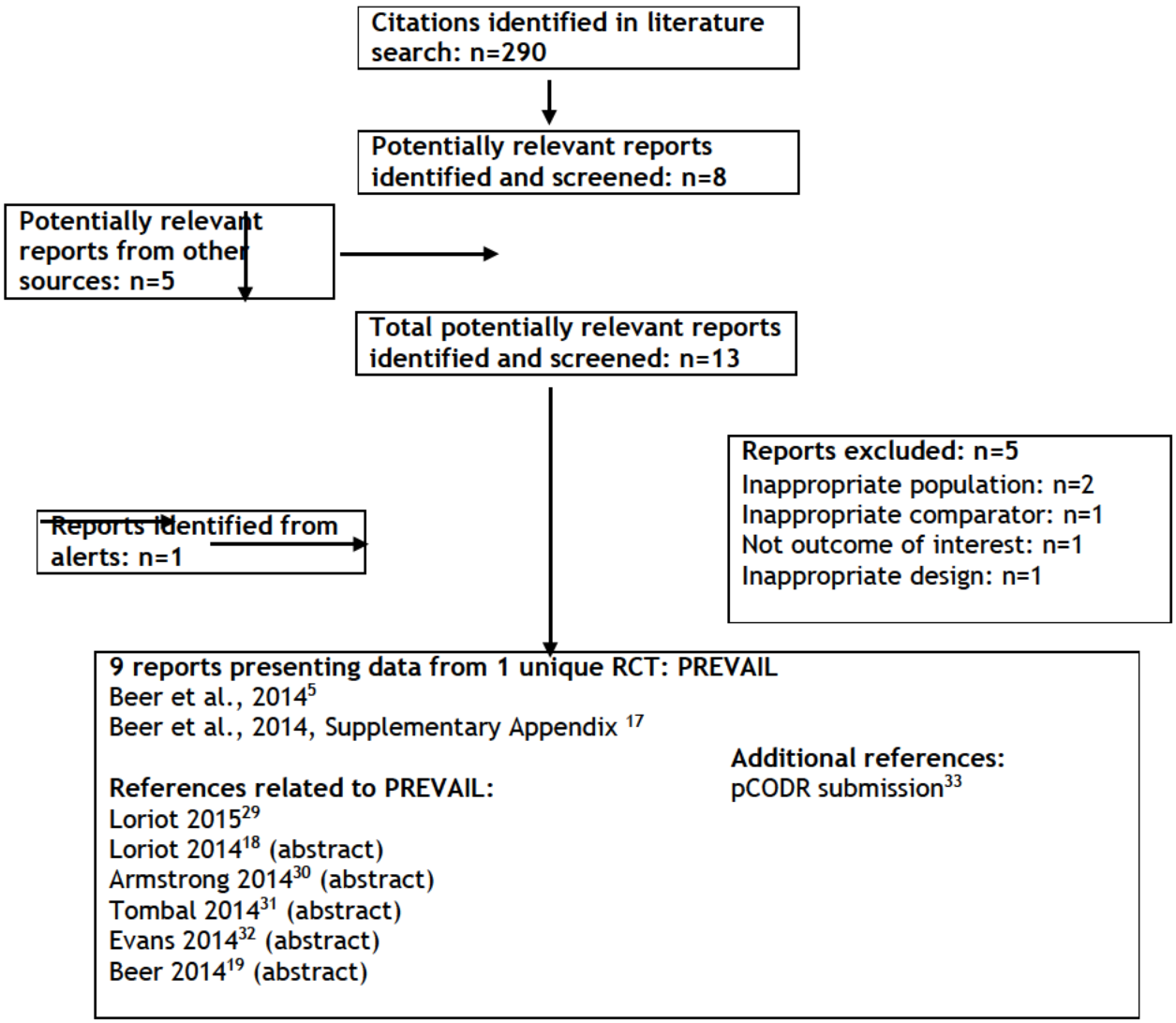
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions 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 290 potentially relevant reports identified, one study was included in the pCODR systematic review[5] and five studies were excluded (see Figure 1 for study selection). Studies were excluded due to inappropriate patient population, inappropriate comparator, not outcome of interest, or inappropriate study design.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

a) Trials

One phase III, double-blind, placebo-controlled RCT (PREVAIL, NCT01212991) was included in this review (see Table 3 for detailed information).[5] It was designed to evaluate the efficacy and safety of oral enzalutamide in men with mCRPC that had not previously received chemotherapy. Patients were randomized to receive either enzalutamide or placebo. The co-primary efficacy endpoints in the PREVAIL study were overall survival (OS) and radiographic progression-free survival (rPFS). Secondary outcomes included PSA response rate, the best overall soft-tissue response (partial response or complete response), time to PSA progression, HRQoL, time to initiation of cytotoxic chemotherapy, time to the first skeletal-related event, and safety. HRQoL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire.

Patients, investigators and outcomes assessors were blinded during the study. In the PREVAIL study, radiologists at a central location, who were unaware of the study-group assignments, determined whether there was progressive disease; an independent data and safety monitoring committee reviewed safety data at regular intervals and reviewed the pre-specified interim analysis conducted by an independent statistical group.

The PREVAIL study was powered to evaluate treatment efficacy using radiographic progression-free survival (rPFS) and overall survival (OS). The planned enrollment was 1680 patients in the intention-to-treat (ITT) population. For the estimation of power, the total type I error rate was 0.05, with an error rate of 0.049 allocated to OS and an error rate of 0.001 allocated to rPFS.[19,32] With 1680 patients in the ITT population, there would be 80% power to detect a target OS hazard ratio (HR) of 0.815 with 765 deaths, or sufficient power (level of power was not specified) to detect a target rPFS HR of 0.57 with at least 410 events. The interim analysis of OS was planned after the occurrence of 516 deaths, or 67% of the 765 deaths specified for the final analysis (540 deaths had occurred when the interim analysis was performed). The final analysis of rPFS was planned after the occurrence of at least 410 events (439 events had occurred when this analysis was performed; the results were reported in the PREVAIL study and included in this pCODR report). Overall survival and rPFS between enzalutamide and placebo were compared using a 2-sided unstratified log-rank test, with a level of significance of 0.05.

The interim analysis showed a statistically significant improvement in OS, thus the study was halted.

Table 3. Summary of Trial characteristics of the PREVAIL Study

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Multinational, DB, placebo-controlled, phase III RCT 207 sites in multiple countries including Canada Randomization period: Sept 2010 to Sept 2012 Randomization was performed at a 1:1 (enzalutamide:placebo) ratio and stratified by study sites. Data cut-off for primary analysis: September 16, 2013 Funded by: Medivation and Astellas Pharma	<u>Inclusion criteria:</u> Patients with mCRPC and PSA progression, radiographic progression or both in bone or soft tissue, despite castration therapy (a serum testosterone level ≤ 1.73 nmol/L); previous antiandrogen therapy was allowed; Asymptomatic or mildly symptomatic prostate cancer; Had not received cytotoxic chemotherapy, ketoconazole, or abiraterone acetate; continued androgen-deprivation; ECOG PS of 0 or 1. <u>Exclusion criteria:</u> Severe concurrent disease, infection, or co-morbidity that would make the patient inappropriate for enrollment; Brain metastasis or active leptomeningeal disease; History of another malignancy within the previous 5 years other than curatively treated non-melanomatous skin cancer; Patients with history of seizure or condition that could confer a predisposition to seizure.	Enzalutamide 160 mg, orally QD Placebo, orally QD	<u>Primary</u> • rPFS • OS <u>Secondary</u> • Time to initiation of chemotherapy • Time to first skeletal-related event • Best overall soft-tissue response • Time to PSA progression • Decline in the PSA level of ≥ 50% • HRQOL • Safety

DB= double-blind; ECOG PS= Eastern Cooperative Oncology Group performance status; HRQOL= health-related quality of life; mCRPC= metastatic castration-resistant prostate cancer; OS= overall survival; PSA= prostate specific antigen; QD= once daily; RCT= randomized controlled trial; rPFS= radiographic progression-free survival

Data sources: Beer 2014[5], Clinicaltrials.gov[34]

b) Populations

A total of 1,717 patients were randomized in the PREVAIL study, with 872 in the enzalutamide group and 845 in the placebo groups.

Overall, baseline characteristics were balanced across both enzalutamide and placebo groups in terms of demographics, disease severity, and prior treatments received, except that the baseline median serum PSA levels were higher in the enzalutamide group (54.1 µg/L, range 0.1 to 3182.0) than in the placebo group (44.2 µg/L, range 0.3 to 3637.0) (Table 4).

Table 4. Baseline Patient Demographics and Disease Characteristics in PREVAIL

	Enzalutamide (n=872)	Placebo (n=845)
Age, years		
Median (range)	72.0 (43-93)	71.0 (42-93)
Race, n (%)		
American Indian or Alaska Native	1 (0.1)	0
Asian	85 (9.7)	82 (9.7)
Black or African American	21 (2.4)	13 (1.5)
Native Hawaiian or other Pacific Islander	1 (0.1)	1 (0.1)
White	669 (76.7)	655 (77.5)
Other, multiple, unknown	95 (10.9)	94 (11.1)
ECOG performance status, n (%)		
0	584 (67.0)	585 (69.2)
1	288 (33.0)	260 (30.8)
2	0	0
Mean BPI-SF pain score - question 3*		
0-1	569 (66.2)	567 (67.5)
2-3	275 (32.0)	262 (31.2)
> 3	15 (1.7)	11 (1.3)
FACT-P total score		
Median (range)	121 (63-156)	122 (60-155)
Serum PSA, µg/L		
Median (range)	54.1 (0.1-3182.0)	44.2 (0.3-3637.0)
Time from initial diagnosis or first treatment of prostate cancer to randomization, months		
Median (range)	62.7 (0.2-326.6)	64.6 (0.1-275.4)
Total Gleason score, n (%)		
≤ 7	414 (49.4)	385 (47.6)
≥ 8	424 (50.6)	423 (52.4)
Disease progression type, n (%)		

	Enzalutamide (n=872)	Placebo (n=845)
PSA-only progression	375 (43.0)	369 (43.7)
Radiographic progression with or without PSA	475 (54.4)	451 (53.4)
No progression per protocol	22 (2.5)	25 (3.0)
Disease metastasis site, n (%)		
Bone	741 (85.0)	690 (81.7)
Lymph node	437 (50.1)	434 (51.4)
Visceral liver or lung	98 (11.2)	106 (12.5)
Other soft tissue	113 (13.0)	105 (12.4)
Number of prior antiandrogen therapy, n (%)		
0	112 (12.8)	115 (13.6)
1	573 (65.7)	561 (66.4)
2	165 (18.9)	151 (17.9)
≥ 3	22 (2.5)	18 (2.1)

BPI-SF=Brief Pain Inventory-Short Form; ECOG=Eastern Cooperative Oncology Group; FACT-P=the Functional Assessment of Cancer Therapy-Prostate; PSA=prostate-specific antigen

*Question 3 in BPI-SF: *Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.* The numbers range from 0 (no pain) to 10 (pain as bad as you can imagine).
Source: Beer 2014[5,17]

c) *Interventions*

Patients received enzalutamide 160 mg orally once daily as four 40 mg capsules or placebo capsules once daily. Continued androgen-deprivation therapy was required during the study. Concurrent use of glucocorticoids was permitted but not required. Treatment was continued until the occurrence of unacceptable side effects or confirmed radiographic progression and the initiation of chemotherapy or an investigational agent. The median time that patients received the study drug was longer in the enzalutamide group than in the placebo group, 16.6 months vs. 4.6 months, respectively. When disease progression occurred, the originally assigned study drug was discontinued. All data collection was stopped except for overall survival.[35] Table 5 presents other systemic antineoplastic treatments received after progression. Overall, patients in the placebo group received more antineoplastic therapies compared with the enzalutamide group. The most commonly prescribed antineoplastic agents were docetaxel and abiraterone acetate in both treatment groups.

Table 5. Post Progression Antineoplastic Therapy Use (ITT Population), data source: Beer[17]

	Enzalutamide (n=872)	Placebo (n=845)
Patients taking at least one postbaseline antineoplastic therapy, n (%)	382 (43.8)	642 (76.0)
Docetaxel	286 (32.8)	479 (56.7)
Abiraterone acetate	179 (20.5)	385 (45.6)
Cabazitaxel	51 (5.8)	110 (13.0)
Sipuleucel-T	12 (1.4)	10 (1.2)
Enzalutamide	9 (1.0)	37 (4.4)

d) Patient Disposition

The ITT population (n=1717) in the PREVAIL trial was defined as randomized patients, regardless of whether they received the study medication. Safety analyses were assessed for all randomized patients who received any study drug. Of the 1717 randomized patients, 872 patients were assigned to receive enzalutamide and 845 patients were assigned to receive placebo. One patient from each treatment group (ITT population) did not receive the allocated study medication.

As of the data cut-off date on September 16, 2013, 368 (42.2%) patients randomized to enzalutamide remained on treatment, while 62 (7.3%) patients randomized to placebo remained on treatment. The primary reason for discontinuation from study drug was disease progression in both arms. Other reasons for discontinuation from the study drug included death, adverse events, withdrawal of consent, or other. The authors indicated that majority of patients discontinued due to rising PSA in the category of "other". One patient in the enzalutamide group was lost to follow-up.

A summary of the study population and patient disposition in the PREVAIL trial is presented in Table 6.

Table 6. Patient Disposition in the PREVAIL Study, data source: Beer[5,17]

	Enzalutamide	Placebo
Randomized	872	845
Not treated (n, %)	1 (0.1)	1 (0.1)
Treated (n, %)	871 (99.9)	844 (99.9)
Discontinued study (n, %)	504 (57.8)	783 (92.7)
Disease progression	355 (40.7)	577 (68.3)
Adverse events	49 (5.6)	51 (6.0)
Protocol violation	1 (0.1)	NR
Lost to follow up	1 (0.1)	0 (0)
Patient withdrawal consent	21 (2.4)	40 (4.7)
Death	17 (1.9)	7 (0.8)
Other	60 (6.9)	108 (12.8)
Death	241 (27.6)	299 (35.4)
Still on treatment (n, %)	368 (42.2)	62 (7.3)
Intention-to-treat population (n, %)	872 (100)	845 (100)
Safety population (n, %)	871 (99.9)	844 (99.9)
NR=not reported		

e) Limitations/Sources of Bias

Baseline patient characteristics were well balanced between treatment groups. In the PREVAIL study, centralized blinded assessment of tumour progression would reduce the potential for bias in the measurement of rPFS.

Limitations in the PREVAIL study:

- The manufacturer was involved in study design, data analyses and manuscript writing;
- The post-progression antineoplastic therapy use was unbalanced between groups. Overall, patients in the placebo group received more antineoplastic therapies compared with the enzalutamide group. When disease progression occurred, the originally assigned treatment was discontinued and all data collection was stopped except for overall survival. Therefore, the difference in post-progression antineoplastic therapy may affect the interpretation of the survival data.
- Only patients with ECOG performance status of 0 or 1 were eligible for the study. This limits the generalizability of results to patients with poorer performance status;
- The majority of patients had mild or no pain at baseline, which would limit the ability to see improvement on the pain outcomes;
- Patients in the two groups dropped out differently. For example, data of pain interference were available in 77% of the patients in the enzalutamide group but only available in 41% of those in the placebo group. Findings should be interpreted with caution.

- Generalizability is also affected by excluding patients with brain metastasis and those with high risk of seizure.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

After review of the interim results, the data and safety monitoring committee recommended stopping the study and offering enzalutamide to eligible patients receiving placebo since this analysis found an improvement in survival in enzalutamide-treated patients.

A summary of efficacy and safety outcomes from the PREVAIL study are presented in Tables 7-9.

Table 7. Summary of efficacy outcomes from the PREVAIL study

	Enzalutamide (n=872)	Placebo (n=845)
Overall Survival (data cut-off: September 16, 2013)		
Median (months) (95% CI)	32.4 (31.5 - upper limit NR)	30.2 (28 - upper limit NR)
Hazard Ratio (95% CI)	0.71 (0.60 - 0.84)	
p-value*	< 0.001	
Radiographic Progression-Free Survival (data cut-off: May 6, 2012)		
Median (months) (95% CI)	NR (13.8 - upper limit NR)	3.9 (3.7 - 5.4)
Hazard Ratio (95% CI)	0.19 (0.15-0.23)	
p-value*	< 0.001	
Decline of PSA ≥ 50%		
n/N (%)	666/854 (78)	27/777 (3)
p-value**	< 0.001	
Objective Soft-Tissue Response Rate		
Overall response rate, n (%)	233 (59)	19 (5)
Complete response	78 (20)	4 (1)
Partial response	155 (39)	15 (4)
p-value	< 0.001	
Time to PSA progression		
Median (months)	11.2	2.8
Hazard Ratio (95% CI)	0.17 (0.15-0.20),	
p-value*	< 0.001	
Health-Related Quality of Life (time to decline in FACT-P, ≥ 10-point decrease from baseline)		
Median (months)	11.3	5.6
Hazard Ratio (95% CI)	0.63 (0.54-0.72)	
p-value*	< 0.001	

	Enzalutamide (n=872)	Placebo (n=845)
Change in Pain		
Pain severity, n/N (%)	225/698 (32)	134/358 (37)
p-value	0.092	
Pain interference, n/N (%)	153/675 (23)	101/344 (29)
p-value	0.019	
Time to Initiation of Chemotherapy		
Median (months)	28.0	10.8
Hazard Ratio (95% CI)	0.35 (0.30-0.40)	
p-value*	< 0.001	
Time to First Skeletal-Related Event		
Median (months)	31.1	31.3
Hazard Ratio (95% CI)	0.72 (0.61-0.84)	
p-value*	< 0.001	
CI=confidence interval; NR=not reached; PSA=prostate-specific antigen		

*an unstratified log-rank test was used to compare treatment groups;
**an unstratified Cochran-Mantel-Haenszel score test was used to compare treatment groups.
Sources: Beer 2014[5,17-19,29], Loriot 2015[29]

Efficacy Outcomes

1. *Overall Survival (OS)*

One of the co-primary end points in the PREVAIL 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 (CI). The hazard ratio (HR) was based on unstratified Cox regression models with treatment as the only covariate.

At the pre-specified interim analysis of 540 deaths, 241 deaths (28%) occurred in the enzalutamide group and 299 deaths (35%) occurred in the placebo group at the date of data cut-off (September 16, 2013). The median OS was 32.4 months in the enzalutamide group and 30.2 months in the placebo group (HR = 0.71, 95% CI 0.60 to 0.84, p<0.001). Compared to placebo, treatment with enzalutamide was associated with statistically significant decrease (29%) in the risk of death. An updated OS analysis performed after 656 deaths had occurred (January 15, 2014)[17] supported the interim analysis: the median duration of OS has not reached in the enzalutamide group and it was 31.0 months in the placebo group (HR=0.73, 95% CI 0.63 to 0.85, p < 0.001).

2. *Radiographic Progression-Free Survival (rPFS)*

rPFS was defined as the time from randomization to the first objective evidence of radiographic disease progression or death due to any cause within 168 days after treatment discontinuation.[34] Radiographic disease progression was defined

by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) for soft tissue or on the basis of criteria adapted from the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) for osseous disease. Kaplan-Meier median rPFS times and their 95% CI as well as rPFS curves were used. The HR was based on unstratified Cox regression models with treatment as the only covariate.

As of May 6, 2012, fewer patients in the enzalutamide group than in the placebo group had radiographic progression or died, 118 of 832 (14%) vs. 321 of 801 (40%), respectively. The median rPFS was not reached in the enzalutamide group, as compared with 3.9 months in the placebo group (HR = 0.19, 95% CI 0.15 to 0.23, $p < 0.001$). Compared to placebo, treatment with enzalutamide was associated with statistically significant decrease (81%) in the risk of disease progression or death.

3. *Decline of PSA ≥ 50%*

PSA response was defined as a ≥ 50% reduction in PSA levels from baseline to the lowest post-baseline PSA result, as determined by the local laboratory.

Seventy-eight percent of patients in the enzalutamide group had confirmed PSA declines of ≥50% compared to 3% of those in the placebo group, $p < 0.001$.

4. *Objective Response Rate (ORR)*

This was defined as partial response or complete response while on study treatment based on investigator assessments of target, non-target, and new lesions using RECIST 1.1. Only patients with measurable soft tissue disease at baseline were included in the analysis. The percentages of patients with measurable soft tissue disease were comparable at baseline (74.3% in the enzalutamide group vs. 76.3% in the placebo group).

Higher objective response rates were reported in the enzalutamide group as compared to the placebo group, 233 (59%) vs. 19 (5%), $p < 0.001$.

5. *Time to PSA progression*

This outcome was defined as time from randomization to date of first confirmed observation of PSA progression for each patient. For patients with PSA declines at week 13, the PSA progression date was defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir was documented, and confirmed 3 or more weeks later. For patients with no PSA decline at week 13, the PSA progression date was defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above baseline was documented, and confirmed 3 or more weeks after. Kaplan-Meier estimates for time to an increased level of PSA and their 95% CIs were reported.

The median time to PSA progression was 11.2 months in the enzalutamide group and 2.8 months in the placebo group (HR=0.17, 95% CI 0.15 to 0.20, $p<0.001$).

6. *Change in Pain*

Pain outcomes were assessed with the BPI-SF at baseline, and month 3 and month 6. BPI has been validated and is used to assess the severity of pain and the impact of pain on daily functions in patients with pain from chronic diseases or conditions such as cancer. The BPI-SF is a shorter version of the BPI and contains four pain severity items and seven pain interference items rated on 0 to 10 scales. Pain severity is assessed in four scenarios: pain at its worst in the last 24 hours, at its least in the last 24 hours, on the average, and right now. Higher scores indicate more pain intensity. For items of pain interference, the impact of pain on seven daily functions including general activity, mood, walking, work, relations with other people, sleep, and enjoyment of life is assessed. Higher scores indicate more impact. BPI pain interference is typically scored as the mean of the seven interference items. The BPI-SF reflects the patient's pain outcomes within 24 hours prior to the assessment.[36]

Pain severity was reported as dichotomous outcome (defined as an increase of ≥ 30% in BPI-SF score from baseline).[18,29] Six month data indicated that fewer enzalutamide-treated patients (225 of 698, 32%) reported severe pain compared with those treated with placebo (134 of 358, 37%); however, the between-group difference was not statistically significant $p = 0.092$. A lower percentage of patients in the enzalutamide group reported pain interference (defined as an

increase of ≥ 50% of baseline standard deviation in BPI-SF score): 153 of 675 (23%) vs. 101 of 344 (29%), respectively, p = 0.019.

7. Health-Related Quality of Life (HRQoL)

The FACT-P is a multidimensional, self-reported HRQoL instrument used with prostate cancer patients. It consists of 27 core items to assess patient function in 4 domains: physical, social/family, emotional and functional well-being. It is supplemented by 12 specific items to assess disease-related symptoms. Each item is rated on a scale from 0 to 4 and then combined to produce subscale score for each domain, as well as a global score. Higher scores represent better quality of life. A clinically meaningful change was estimated to be 6 to 10 for FACT-P total score.[36,37] The time to degradation of the FACT-P global score was defined as time from randomization to first assessment with at least a 10-point decrease from baseline in the total FACT-P score. An unstratified log-rank test was used to compare treatment groups.

In PREVAIL, the median baseline FACT-P score in the treatment groups was comparable, 121 (range 63 – 156) in the enzalutamide group and 122 (range 60 – 155) in the placebo group. The median time to decline in the FACT-P global score was 11.3 months (95% CI 11.1 to 13.9) in the enzalutamide group and 5.6 months (95% CI 5.5 to 5.6) in the placebo group (HR = 0.63, 95% CI 0.54 to 0.72, p < 0.001).[5,18,29]

8. Skeletal-Related Events

The time to first skeletal-related event was defined as the time from randomization to the occurrence of the first skeletal-related event (SRE). An SRE was defined as radiation therapy or surgery to bone for prostate cancer, 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% CIs were used. An unstratified log-rank test was used to compare treatment groups.

At the data cut-off, patients in the enzalutamide group reported fewer first SRE than in the placebo group, 278 patients (32%) vs. 309 patients (37%), respectively (HR = 0.72, 95% CI 0.61 to 0.84, p < 0.001). However, the median time to first SRE was similar in the two groups, 31.1 months in the enzalutamide group and 31.3 months in the placebo group.

9. Time to Chemotherapy Initiation

This outcome was defined as the time from randomization to initiation of a cytotoxic chemotherapy (use of any of the following for prostate cancer: docetaxel, cabazitaxel, mitoxantrone, estramustine, cisplatin, carboplatin, cyclophosphamide, doxorubicin, mitomycin, irinotecan, 5-fluorouracil, gemcitabine, or etoposide). An unstratified log-rank test was used to compare treatment groups.

The median time to cytotoxic chemotherapy initiation was 28.0 months in the enzalutamide group and 10.8 months in the placebo group (HR=0.35, 95% CI 0.30 to 0.40, p < 0.001).

Harms Outcomes

The safety analysis population consisted of 1,715 patients who had received at least one dose of the study drug. 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 reporting period for adverse events was 17.1 months in the enzalutamide group and 5.4 months in the placebo group, indicating a longer exposure of patients to enzalutamide.

Details of adverse events associated with the use of enzalutamide are presented in Tables 8 and 9.

10. Any Adverse Events

Overall, the rates of adverse events were similar in the enzalutamide and placebo groups: 97% vs. 93%, respectively. The most common adverse events observed were fatigue, back pain, constipation, arthralgia, hot flush, hypertension and falls.

11. Serious Adverse Events

A definition of serious adverse events was not provided.

A larger proportion of patients treated with enzalutamide reported adverse events of Grade 3 or higher than those treated with placebo: 43% vs. 37%, respectively. The most common event of Grade 3 or higher in the enzalutamide group was hypertension at 7%, compared to 2% in the placebo group.

12. Withdrawal due to Adverse Events

The proportion of patient withdrawal due to adverse events was similar between the two treatment groups: 49 patients (6%) vs. 51 (6%), respectively.

13. Adverse Events of Special Interest

One patient in each group had a seizure.

Table 8. Summary of Harm Outcomes in the PREVAIL Study

n (%)	Enzalutamide (n=871)	Placebo (n=844)
Any AEs	844 (97)	787 (93)
Any events of grade ≥ 3	374 (43)	313 (37)
Any AE leading to treatment discontinuation	49 (6)	51 (6)
Any AEs leading to death	37 (4)	32 (4)
AE=adverse event		

Sources: Beer 2014[5,17]

Table 9. Most Common Adverse Events (reported in ≥ 10% of patients treated with enzalutamide) from the PREVAIL study, sources: Beer 2014[5,17]

Adverse events	Enzalutamide (n=871)		Placebo (n=844)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Fatigue	310 (36)	16 (2)	218 (26)	16 (2)
Back pain	235 (27)	22 (3)	187 (22)	25 (3)
Constipation	193 (22)	4 (<1)	145 (17)	3 (<1)
Arthralgia	177 (20)	12 (1)	135 (16)	9 (1)
Decreased appetite	158 (18)	2 (<1)	136 (16)	6 (1)
Hot flush	157 (18)	1 (<1)	65 (8)	0
Diarrhea	142 (16)	2 (<1)	119 (14)	3 (<1)
Hypertension	117 (13)	59 (7)	35 (4)	19 (2)
Asthenia	113 (13)	11 (1)	67 (8)	8 (1)
Fall	101 (12)	12 (1)	45 (5)	6 (1)
Weight loss	100 (11)	5 (1)	71 (8)	2 (<1)
Edema peripheral	92 (11)	2 (<1)	69 (8)	3 (<1)
Headache	91 (10)	2 (<1)	59 (7)	3 (<1)

6.4 Ongoing Trials

- Clinical trials evaluating sequencing abiraterone and enzalutamide in mCRPC patients:

  NCT02125357: this is a phase 2 open-label RCT. Eligible participants are randomized to 1) abiraterone 1000 mg PO QD + prednisone 5 mg PO BID or 10 mg PO QD as per standard of care, or until PSA progression then cross-over to another treatment arm; 2) enzalutamide 160 mg PO QD as per standard of care, or until PSA progression then cross-over to another treatment arm. The primary outcome is PSA response rate in mCRPC patients with PSA progression on first-line therapy when crossed over to second-line therapy with the opposite agent. The estimated sample size is 118. The estimated final data collection date for primary outcome measure is December 2015.

- Clinical trials evaluating the treatment effect of combination of enzalutamide plus abiraterone + prednisone:

  NCT01949337: this is a phase 3 open-label study. Eligible participants will be randomized to enzalutamide 160 mg PO QD, or enzalutamide 160 mg PO QD + abiraterone 1000 mg PO QD + prednisone 5 mg PO BID. The primary outcome is overall survival. The estimated sample size is 1224. The final data collection date for primary outcome measure is December 2019.

7 SUPPLEMENTAL QUESTIONS

7.1 Critical Appraisal of an Indirect Comparison of Enzalutamide with Abiraterone

7.1.1 Objective

The manufacturer submitted an indirect treatment comparison (ITC) of enzalutamide versus other treatments in current use including abiraterone acetate, in order to evaluate the relative effectiveness of these therapies in the chemotherapy naïve mCRPC population.[38] An ITC may provide information in the situation where trials have not been designed to directly compare the specific treatments. This section of this report provides a summary and critical appraisal of the methods and findings of this ITC.

7.1.2 Findings

The manufacturer provided an indirect comparison to estimate the relative efficacy of enzalutamide versus abiraterone acetate for their cost-utility analysis.

The indirect comparison was based on the antineoplastic treatment versus placebo or prednisone in nine studies: PREVAIL, COU-AA-302, TAX327, D9901, D9902A, D9902B, CALGB9182, Berry 2002 and ALSYMPCA. The literature search strategies and selection criteria used to identify these studies were not reported in this report.

The following comparisons were included in the ITC:

- PREVAIL: comparing enzalutamide with placebo;
- COU-AA-302: comparing abiraterone + prednisone with prednisone alone;
- TAX327: comparing docetaxel + prednisone with mitoxantrone + prednisone;
- D9901, D9902A and D9902B: comparing sipuleucel-T with placebo;
- CALGB 9182 and Berry 2002: comparing mitoxantrone + corticosteroid with corticosteroid alone;
- ALSYMPCA: comparing radium-223 with placebo.

All included studies were Phase 3 RCTs that enrolled mCRPC patients with or without prior chemotherapy. Definitions of mCRPC were not provided. Information of patient characteristics, such as baseline ECOG performance status and visceral disease, was not available in a number of these studies. For those studies that reported such data, the demographic characteristics of age were similar across the studies, but there were differences in the performance status, prior treatments and baseline use of corticosteroids. Substantial heterogeneity existed among these studies: the level of disease severity varied across the studies; some recruited asymptomatic or mildly symptomatic patients but others recruited symptomatic patients; some studies were published more than 15 years ago, while the enzalutamide/abiraterone/radium-223 studies were recently published. OS was the primary endpoint in all studies but one (the Berry 2002 study).

Data on trial characteristics, patient characteristics and study results were not reported for the Berry 2002 study.

Study characteristics are listed in Table 10.

Table 10. Summary of Studies Used for Indirect Comparison

Trial	Study design	Patient population	Intervention and comparator	Primary outcomes
PREVAIL, 2014	Phase 3 RCT, DB	1717 asymptomatic or mildly symptomatic chemo-naïve mCRPC patients	• Enzalutamide • Placebo	OS, PFS
COU-AA-302, 2013	Phase 3 RCT, DB	1088 asymptomatic or mildly symptomatic chemo-naïve mCRPC patients	• Abiraterone + prednisone • Placebo + prednisone	OS, PFS
TAX327, 2004	Phase 3 RCT, OL	1006 symptomatic chemo-naïve mCRPC patients	• Docetaxel q3w + prednisone • Docetaxel qw + prednisone • Mitoxantrone + prednisone	OS
D9902B (D9901 and D9902A provided supportive data)	Phase 3 RCT, DB	512 mCRPC patients with or without prior chemo	• Sipuleucel-T • Placebo	OS
CALGB 9182, 799	Phase 3 RCT, OL	242 mCRPC patients with ≤ 1 prior endocrine manipulation, prior chemo unknown	• Mitoxantrone + hydrocortisone • Hydrocortisone	OS
Berry, 2002	Phase 3 RCT, unknown blinding	120 asymptomatic mCRPC patients, prior chemo unknown	• Mitoxantrone + prednisone • Prednisone	Time to treatment failure*
ALSYMPCA, 2013	Phase 3 RCT, DB	921 symptomatic mCRPC patients with or without prior chemo	• Radium-223 • Placebo	OS

DB=double blind; HRQoL=health-related quality of life; mCRPC=metastatic castration-resistant prostate cancer; OL=open label; OS=overall survival; PFS=progression-free survival; PSA=prostate-specific antigen; qw=once a week; RCT=randomized controlled trial

* This was an aggregate end point comprised of time to disease progression, time to toxicity or death, or time to initiation of alternate therapy.

In these studies, abiraterone and mitoxantrone were compared with prednisone, whereas enzalutamide was compared with placebo. Because there were no studies that compared prednisone with placebo which would permit the indirect comparison of these two treatments, one assumption was made: although all patients in the placebo arm of the COU-AA-302 study received prednisone, while only 30% of patients in the placebo arm of PREVAIL received prednisone, the two control arms were considered reasonably similar, therefore it was assumed that both patient groups were comparable and can be used as basis for a treatment comparison between enzalutamide and abiraterone. The authors indicated that this assumption may not be justifiable, given that the OS curves and PFS curves from COU-AA-302 and PREVAIL differed in

the survival (PFS in particular: 5.4 months in PREVAIL vs. 8.2 months in COU-AA-302) over time for the control arms. This discrepancy could be due to differences in study population, study setting or study design, as well as the impact of prednisone on PFS. A naïve comparison (study results were compared directly) was also used to compare enzalutamide and abiraterone in an exploratory scenario analysis, when assuming the two studies were similar in study design and setting. Data on efficacy outcomes were inadequately reported. While all studies reported OS, data on PFS and Time to Chemotherapy Initiation were not available in a majority of them. Table 11 presents a summary of the reported efficacy outcomes in PREVAIL and COU-AA-302, when abiraterone was considered the most appropriate comparator for enzalutamide in the study population.

Table 11. Summary of Findings for PREVAIL and COU-AA-302

Trial	OS (months) median	rPFS (months) median	TTC (months) median
PREVAIL, 2014			
ENZ	32.4	19.7	28.0
PL	30.2	5.4	10.8
HR(95% CI)	0.71 (0.60-0.84) p < 0.0001	0.31 (0.27-0.35) p < 0.0001	0.35 (0.30-0.40) p < 0.0001
COU-AA-302, 2013			
ABI+Pred	34.7	16.5	26.5
PL+Pred	30.3	8.2	16.8
HR(95% CI)	0.81 (0.66-0.95) p = 0.0033	0.52 (0.45-0.61) p < 0.0001	0.61 (0.51-0.72) p < 0.0001

ABI=abiraterone; CI=confidence interval; ENZ=enzalutamide; HR=hazard ratio; OS=overall survival; PL=placebo; Pred=prednisone; rPFS=radiographic progression-free survival; TTC=time to chemotherapy

Efficacy data from each individual study were presented in the ITC. There was no depiction on how the evidence from the included studies was used, or whether statistical approaches were employed in this indirect comparison. In addition, the authors did not indicate how the findings from this analysis contributed to the economic evaluation. The conclusion of this analysis was not clearly stated.

Limitations

The manufacturer did not provide any information surrounding the information sources, search strategy, study selection process, data extraction, or the validity or quality of the individual studies included in the indirect comparison. Therefore, it is unclear if a systematic review approach was employed in this ITC. There were substantial heterogeneities in the study designs, patient characteristics, clinical characteristics, and data reporting. In addition, a limited number of studies was included in the network. On the other hand, the target population for the current pCODR submission and this ITC was mCRPC patients who had no prior chemotherapy. However, many included studies in the ITC had a mixed population, and study drugs with different mechanism of action were investigated in different clinical settings, while some of them may not be an appropriate comparator for enzalutamide, such as radium. The clinical relevance of comparisons between enzalutamide and these drugs is uncertain. Quality of the ITC was further compromised by the lack of a common comparator between interventions. In addition, the

methods of data analysis were not explicitly described. The manufacturer did not provide a narrative description or justification of the method used, how potential bias would be handled, or how the heterogeneity was addressed. In terms of external validity, the validity of extrapolating the ITC results to mCRPC patients without prior chemotherapy is questionable. Findings from this ITC should be interpreted with caution. Safety profile of enzalutamide against other treatments was not examined in this analysis.

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.[39] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 12.

TABLE 12: APPRAISAL OF THE INDIRECT COMPARISON ANALYSES USING ISPOR CRITERIA

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 not clearly stated.
2. Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual RCTs were not presented. • Details regarding literature search, study selection and data extraction were not provided. • Quality assessment of included studies was not provided.
3. Are the outcome measures described?	• Outcomes assessed in the indirect comparison analysis (symptom scores and medication scores) were not described.
4. Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• Analyses methods/models were not described; • Statistical and clinical heterogeneity were not examined. • Publication bias was not examined.
5. Are sensitivity analyses presented?	• No.
6. Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A table with trial characteristics of all included studies was provided. Also there was a table of patient baseline characteristics in the included trials. • A figure showing the network of studies was provided. • Tables with raw data by study and treatment were provided for the indirect comparison analysis.
7. Does the study describe an assessment of model fit? Are competing models being compared?	• N/A
8. Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure including point estimates and 95% confidence intervals as a measure of uncertainty.
9. Sensitivity/scenario analyses	• Scenario analysis was reported.

7.1.3 Summary

The comparative efficacy of enzalutamide and abiraterone acetate treatment for OS in mCRPC patients who were chemotherapy-naïve was assessed in an indirect comparison analysis. However, only findings from individual studies were presented, and results from pooled analysis were not available in this ITC. Limitations surrounding the indirect comparison were a cause for concern regarding the robustness of any provided results, such as the substantial heterogeneities existing in the included studies of this analysis, the use of mixed population instead of chemo-naïve mCRPC patients only, the limited clinical relevance of comparisons between enzalutamide and the other treatments, and the lack of common comparator between study drugs. Therefore, any conclusions drawn from this indirect comparison regarding the comparative clinical effectiveness between enzalutamide and abiraterone 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 first-line mCRPC. 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.cadth.ca/pcodr).

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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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.cadth.ca/pcodr). 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

Embase 1974 to 2014 October 01, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

#	Searches	Results
1	(enzalutamide* or xtandi* or MDV3100 or MDV-3100).ti,ot,ab,sh,rn,hw,nm.	1476
2	(915087-33-1 or 93T0T9GKNU).rn,nm.	790
3	or/1-2	1619
4	3 use pmez	406
5	*enzalutamide/	220
6	(enzalutamide* or xtandi* or MDV3100 or MDV-3100).ti,ab.	1019
7	or/5-6	1030
8	7 use oemezd	652
9	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	474597
10	Randomized Controlled Trial/	742442
11	Randomized Controlled Trials as Topic/	155262
12	"Randomized Controlled Trial (topic)"/	58663
13	Controlled Clinical Trial/	477104

14	Controlled Clinical Trials as Topic/	8344
15	"Controlled Clinical Trial (topic)"/	3269
16	Randomization/	145689
17	Random Allocation/	145689
18	Double-Blind Method/	247734
19	Double Blind Procedure/	117985
20	Double-Blind Studies/	208954
21	Single-Blind Method/	38894
22	Single Blind Procedure/	18845
23	Single-Blind Studies/	38894
24	Placebos/	292233
25	Placebo/	258819
26	Control Groups/	66974
27	Control Group/	66974
28	(random* or sham or placebo*).ti,ab,hw.	2318288
29	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	397074
30	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	909
31	(control* adj3 (study or studies or trial*)).ti,ab.	735831

32	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.	63438
33	allocated.ti,ab,hw.	89916
34	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	52568
35	or/9-34	2917084
36	and/4,35	77
37	and/8,35	258
38	or/36-37	335
39	remove duplicates from 38	268
40	Limit 39 to English language	259

2. Literature search via PubMed

Search	Query	Items found
#5	Search **#3 AND #4**	35
#4	Search **publisher [sb]**	462162
#2	Search **Enzalutamide* OR xtandi* OR MDV3100 OR MDV-3100 OR 915087-33-1[rn] OR 93T0T9GKNU[rn]**	414

3. Cochrane Central Register of Controlled Trials (Central)

Issue 10 of 12, October 2014

There are 2 results from 704315 records for your search on 'Xtandi* or enzalutamide or MDV3100 or MDV-3100 in title abstract keywords in Trials'

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: Xtandi* or enzalutamide or MDV3100 or MDV-3100

Select international agencies including:

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

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search terms: Xtandi* or enzalutamide

Conference abstracts:

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

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

Search terms**:** Xtandi or enzalutamide or MDV3100 or MDV-3100 (last 5 years)

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