pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Abiraterone Acetate (Zytiga) for Metastatic Castration-Resistant Prostate Cancer

October 22, 2013

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of the review was to evaluate the efficacy and safety of abiraterone acetate (Zytiga) in combination with prednisone on patient outcomes compared to standard therapies or placebo in patients with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC) who have failed on androgen deprivation therapy and have not received prior chemotherapy.

Abiraterone acetate has a Health Canada indication for use in combination with prednisone for the treatment of patients with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one international, multicenter, double-blind, placebo-controlled, phase III RCT, COU-AA-302 study, that evaluated the efficacy and safety of abiraterone acetate (1000 mg orally once daily) plus prednisone (5mg) compared to placebo plus prednisone (5mg).[2]

COU-AA-302 recruited patients with asymptomatic or mildly symptomatic mCRPC, as defined according to the Brief Pain Inventory–Short Form (BPI-SF) where asymptomatic patients had scores of 0 to 1 or mildly symptomatic patients had scores 2 to 3. Patients must have also failed on androgen deprivation therapy, which generally includes an LHRH agonist or orchiectomy, and have not received prior chemotherapy. A total of 1088 patients were randomly assigned to receive treatment with abiraterone plus prednisone (n=546) or placebo plus prednisone (n=542). Baseline characteristics were generally well balanced across treatment groups, patients had an ECOG performance status of 0 (76%) or 1 (24%), 25% and 26% of subjects had metastatic disease (M1) at initial diagnosis in the abiraterone group and placebo group, respectively.

Patients with prior use of chemotherapy or ketoconazole were excluded from the study.

Efficacy

The co-primary efficacy endpoints were overall survival (OS) and radiographic progression-free survival (rPFS) evaluated by an independent review at the first interim analysis and after that radiographic progression was assessed by an investigator.

At the time of the second interim (20 December 2011), the median OS was not reached in the abiraterone group and was 27.2 months in the placebo group (hazard ratio (HR) = 0.75, 95% confidence interval (CI) 0.61 to 0.93, p=0.0097), neither was the prespecified boundary for significance (p= 0.0005) reached. Based on an Independent Data Monitoring Committee's (IDMC) recommendations that noted the consistent pattern of benefit in one arm of the study compared with the other arm, after the second interim analysis, patients were unblinded and allowed to crossover from the placebo group to abiraterone treatment. Results of the third interim analysis were similar to those of second interim analysis with HR = 0.79 and 95% CI 0.66 to 0.96, p= 0.0151, and the analysis the prespecified boundary for significance (p= 0.0034) was not reached. However, these

results may be confounded because of the crossover. For the co-primary endpoint of rPFS, the median rPFS, at the time of the second interim (20 December 2011), was 16.5 months in the abiraterone group and 8.3 months in the placebo group (HR=0.53, 95% CI 0.45-0.62, p<0.0001).

For the secondary outcomes, significant improvements in time to PSA progression (11.1 vs 5.6 months, HR=0.49, 95% CI 0.42-0.57, p<0.0001), PSA response as defined by a ≥50% decrease in PSA (61.5% vs 23.8%, p<0.0001), objective tumour responses (36% vs. 16%), delay in time to opiate use (not reached vs. 23.7 months) as well as patient reported outcomes favoured those on abiraterone. Specifically, there was a reduced risk of average pain intensity progression (HR=0.82 p=0.049).

Time to functional status decline of 10 points or more in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) global score was used as a proxy to measure the worsening of QOL. The median time to FACT-P degradation was 12.65 and 8.31 months in the abiraterone and placebo group, respectively (HR=0.78, 95% CI 0.66-0.92, p=0.0028). In all FACT-P categories except Social/Family Well Being there seem to be significant decreases in the median time to degradation for subjects in the abiraterone group compared to the placebo group.

Harms

Adverse events (AEs) that occurred more commonly in the abiraterone group compared to the placebo group included Fatigue, arthralgia, and peripheral edema. There were more AEs leading to discontinuation in the abiraterone compared to the placebo group (10.1% vs 9.1%, respectively).

Serious adverse events (SAEs) that occurred more commonly in the abiraterone compared to the placebo group included infections and infestations, nervous system disorders, renal and urinary disorders, gastrointestinal disorders, general disorders and administration site conditions, cardiac disorders, and metabolism and nutrition disorders. Twenty fatal AEs (3.7%) occurred in the abiraterone group and 12 fatal AEs (2.2%) occurred in the placebo group.

1.2.2 Additional Evidence

pCODR received input on abiraterone acetate from two patient advocacy group (Prostate Cancer Canada and Canadian Cancer Survivor Network). Provincial Advisory Group input was obtained from eight of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

No supplemental issues were identified during the development of the review.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

> Prostate cancer is the most commonly diagnosed cancer in men in Canada with 26, 500 new cases and the third leading cause of cancer death in 2012. The majority of patients who are started on androgen ablative therapy will develop progression to castrate resistance and can potentially be candidates for a well tolerated effective

treatment. Currently, patients with mCRPC but with no or minimal symptoms are often observed closely without intervention as there have been no studies that have demonstrated improvement in overall survival with either secondary hormonal interventions or chemotherapy. Low dose prednisone is sometimes recommended for this group of patients with only a minority of patients experiencing benefit.

Effectiveness

The results of the COU-AA-302 study demonstrated an improvement in overall survival and radiographic progression free survival (rPFS) in favour of abiraterone. The difference in rPFS was statistically significant, however, the prespecified boundary for statistical significance was not reached for the overall survival at the second and third interim analysis. Based on the recommendations by the independent data monitoring committee, unblinding and crossover of patients after the second interim analysis from placebo to abiraterone was permitted and may have attenuated any future observed survival benefit. There was a statistically significant improvement in all secondary outcomes as well as patient reported outcomes that favoured abiraterone. Specifically, there was a reduced risk of average pain intensity progression and deterioration of most quality of life domains as measured by FACT-P.

Safety

In general, abiraterone was well tolerated with the most common adverse events being fatigue, back pain, arthralgias, nausea and constipation which were all observed in the placebo arm. Adverse events of special interest related to mineralocorticoid-associated events were also more commonly seen in the abiraterone group. Treatment related adverse events leading to treatment discontinuation was however similar between the abiraterone and placebo arms except for those discontinuations due hepatotoxicity. The demonstrated efficacy of abiraterone in this setting potentially fills a void in which there is significant clinical need.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to the use of abiraterone acetate in the treatment of asymptomatic or minimally symptomatic mCRPC based on one high-quality randomized, placebo-controlled trial that demonstrated a clinically and statistically significant benefit in radiographic progression-free survival for abiraterone acetate compared with prednisone. Several secondary endpoints including quality of life were also demonstrated to be statistically significant and clinically meaningful in favour of the abiraterone group.

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

- The COU-AA-302 study did not meet its prespecified boundary for significance for the co-primary endpoint of overall survival observed at the time of the second and third interim analysis and that the recommendations by the independent data monitoring committee of unblinding and crossover of patients after the second interim analysis from placebo to abiraterone may attenuate any future observed survival benefit. Although the improvement in overall survival was not statistically significant, the results of both the second and third interim analysis favoured the abiraterone arm.
- Abiraterone acetate given with prednisone is a well-tolerated oral regimen which appears to provide a clinically meaningful improvement in survival as well as delaying radiographic

progressions in patients with few or no symptoms from metastatic CRPC who may otherwise receive prednisone only or be observed without intervention.

- Although adverse events leading to treatment discontinuation were similar between the two groups, the adverse event profiles were higher with abiraterone acetate than with prednisone including treatment emergent serious adverse events.
- The role of abiraterone acetate remains undefined in patients with CRPC without metastasis.
- The repeated use of abiraterone in mCRPC patients post-docetaxel who have received abiraterone pre-chemotherapy is also 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 abiraterone acetate (Zytiga) 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 abiraterone acetate 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 abiraterone acetate and a summary of submitted Provincial Advisory Group Input on abiraterone acetate are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Therapies such as first-generation anti-androgen therapy, ketoconazole plus steroid, abiraterone acetate plus prednisone, docetaxel, or immunotherapy with sipuleucel-T are used for patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy.[3] Sipuleucel-T has not yet been approved for use in Canada.
Abiraterone is an inhibitor of CYP17, where abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17, 20-lyase (CYP17) which is expressed in and is required for androgen biosynthesis in testicular, adrenal and prostatic tumor tissues. Abiraterone acetate decreases serum testosterone and other androgens in patients to levels lower than those achieved by the use of gonadotropin releasing hormone agonists alone or by orchiectomy. Abiraterone acetate was approved by Health Canada in 2011 and indicated to be used in combination with prednisone for the treatment of patients with mCRPC who have previously been treated with docetaxel-based chemotherapy.[1] In May 2013, Abiraterone acetate was approved an expanded indication by Health Canada to be used in combination with prednisone for the treatment of patients with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy.[1] In November 2012, the European Medicines Agency (EMA) adopted a new indication for Abiraterone acetate to be "ZYTIGA is indicated with prednisone or prednisolone for: the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated".[4] In December 2012 expanded indication for abiraterone acetate was approved by the U. S. Food and Drug Administration to be used in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.[5] The recommended dose of abiraterone acetate is 1000 mg (four 250 mg tablets) administered orally once daily.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of Abiraterone acetate (Zytiga) in combination with prednisone on patient outcomes compared to standard therapies or placebo in patients with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC) who have failed on androgen deprivation therapy and 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 COU-AA-302 study was an international, multicenter, double-blind, placebo-controlled, phase III RCT.[2] COU-AA-302 evaluated the efficacy and safety of abiraterone acetate 1000 mg orally once daily plus prednisone compared to placebo once daily plus prednisone in patients with asymptomatic or mildly symptomatic mCRPC, as defined according to the Brief Pain Inventory–Short Form (BPI-SF) where asymptomatic patients had scores of 0 to 1 or mildly symptomatic patients had scores 2 to 3. Patients must have failed on androgen deprivation therapy, which generally includes an LHRH agonist or orchiectomy, and have not received prior chemotherapy. A total of 1088 patients were randomly assigned to receive treatment with abiraterone (n=546) or placebo (n=542). Baseline characteristics were generally well balanced across treatment groups, patients had an ECOG performance status of 0 (76%) or 1 (24%). Ninety-five (95%) of study population were Caucasians. Patients with prior use of chemotherapy or ketoconazole were excluded from the study. The co-primary efficacy endpoints were overall survival (OS) and radiographic progression-free survival (rPFS). All 1088 patients except 6 received at least one dose of study drug, 1088 and 1082 patients were evaluated for efficacy and safety outcomes, respectively.

At the time of the second interim (20 December 2011), there were 333 deaths: 147 deaths (27%) in the abiraterone group and 186 deaths (34%) in the placebo group. The median OS was not reached in the abiraterone group and was 27.2 months in the placebo group (hazard ratio (HR) = 0.75, 95% confidence interval (CI) 0.61 to 0.93, p=0.0097), this analysis did not reach prespecified boundary for significance (p= 0.0005). The study was unblinded and crossover of patients in the placebo group to abiraterone treatment happened after the second interim analysis based on Independent Data Monitoring Committee (IDMC) recommendations. Results of the third interim analysis were similar to those of second interim analysis with HR = 0.79 and 95% CI 0.66 to 0.96, p= 0.0151, also this analysis did not reach prespecified boundary for significance (p= 0.0034). However, these results may be confounded because of the crossover.

At the time of the second interim (20 December 2011), the median rPFS was 16.5 months in the abiraterone group and 8.3 months in the placebo group (HR=0.53, 95% CI 0.45-0.62, p<0.0001).

At the time of the second interim (20 December 2011), the median time to PSA progression was 11.1 months in the abiraterone group and 5.6 months in the placebo group (HR=0.49, 95% CI 0.42-0.57, p<0.0001). The proportion of patients that achieved a ≥50% reduction in PSA levels from baseline was 61.5% in the

abiraterone group and 23.8% in the placebo group (p<0.0001). At the time of the first interim analysis (20 December 2010), more patients in the abiraterone group (36%) achieved objective response versus 16% in the placebo group, Relative Risk= 2.27, 95% CI 1.59-3.25, p<0.0001. Abiraterone also resulted in a significantly delay in time to opiate use when compared to prednisone alone (not reached vs. 23.7 months, respectively. HR: 0.69, 95% CI, 0.57 to 0.83; P<0.001).

Time to functional status decline of 10 points or more in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) global score was used as a proxy to measure the worsening of QOL. The median time to FACT-P degradation was 12.65 months in the abiraterone group and 8.31 months in the placebo group (HR=0.78, 95% CI 0.66-0.92, p=0.0028). While that of Total Outcome Index was 13.86 months in the abiraterone group and 9.26 months in the placebo group (HR=0.75, 95% CI 0.63-0.88, p=0.0006), and that of PCS was 11.10 months in the abiraterone group and 5.78 months in the placebo group (HR=0.70, 95% CI 0.60-0.83, p<0.0001), and that of Physical Well Being was 14.78 months in the abiraterone group and 11.07 months in the placebo group (HR=0.76, 95% CI 0.64-0.90, p=0.002), and that of Social/Family Well Being was 18.40 months in the abiraterone group and 16.59 months in the placebo group (HR=0.94, 95% CI 0.78-1.14, p=0.528), and that of Emotional Well Being was 22.11 months in the abiraterone group and 14.16 months in the placebo group (HR=0.71, 95% CI 0.59-0.87, p=0.0008), and that of Functional Well Being was 13.34 months in the abiraterone group and 8.35 months in the placebo group (HR=0.76, 95% CI 0.64-0.90, p=0.0012).

Adverse events (AEs) that occurred more commonly in the abiraterone group compared to the placebo group included Fatigue, arthralgia, and peripheral edema.

Serious adverse events (SAEs) that occurred more commonly in the abiraterone group compared to the placebo group included infections and infestations, nervous system disorders, renal and urinary disorders, gastrointestinal disorders, general disorders and administration site conditions, cardiac disorders, and metabolism and nutrition disorders. There were more AEs leading to discontinuation in the abiraterone group (10.1%) compared to the placebo group (9.1%). Twenty fatal AEs (3.7%) occurred in the abiraterone group and 12 fatal AEs (2.2%) occurred in the placebo group.

Potential limitations in the COU-AA-302 study include the involvement of the sponsor's staff in the design, monitoring, analyses (after unblinding), and publication of the study, OS one of the co-primary endpoints did not reach prespecified boundary for significance, results of the third interim analysis were potentially confounded by crossover, also interpretation of statistical significance based on interim analyses for subgroup analysis and secondary outcomes should be cautioned due to inflated Type I error rates. In addition, only patients with ECOG performance status of 0 and 1 were included limiting the generalizability of the study findings.

Table 1. Key efficacy and safety outcomes from the COU-AA-302 study based on 2nd interim analysis

	Abiraterone + Prednisone	Prednisone Alone
Efficacy Outcomes	N= 546	N= 542
Overall Survival		
Median (months)	NR	27.2
Hazard Ratio (95% CI)	0.75 (0.61, 0.93)	
P-value	0.01*	

	Abiraterone + Prednisone	Prednisone Alone
Efficacy Outcomes	N= 546	N= 542
Radiographic Progression-Free Survival		
Median (months)	16.5	8.3
Hazard Ratio (95% CI)	0.53 (0.45, 0.62)	
P-value	<0.001	
Time to PSA Progression		
Median (months)	11.1	5.6
Hazard Ratio (95% CI)	0.49 (0.42, 0.57)	
P-value	<0.001	
PSA Response†		
% of Patients with decline of ≥50% in PSA level	62	24
Relative Risk (95% CI)	2.59 (2.19, 3.05)	
P-value	<0.001	
Median time (months)to functional-status decline measured‡		
FACT-P total score	12.7	8.3
Hazard Ratio (95% CI)	0.78 (0.66, 0.92)	
P-value	0.003	
Objective response rate§		
Subjects with measurable disease at baseline	220	218
Complete response, n (%)	24 (10.9)	8 (3.7)
Partial response, n (%)	54 (24.5)	26 (11.9)
Non-Responder, n (%)	142 (64.5)	184 (84.4)
Relative Risk (95% CI)	2.27 (1.59, 3.25)	
P-value	<0.0001	
Saftey Outcome	(N= 546)	(N= 542)
Safety, n (%)		
Fatal AEs	20 (4)	12 (2)
SAEs	178 (33)	142 (26)
AEs leading to discontinuation	55 (10)	49 (9)
Grade 3 or 4 adverse event	258 (48)	225 (42)
Any AEs	537 (99)	524 (97)
AE=adverse event; **CI**=confidence interval; **FACT-P**=Functional Assessment of Cancer Therapy-Prostate; **PSA**=prostate-specific antigen; **RECIST**= Response Evaluation Criteria in Solid Tumors; **SAE**=serious adverse event		

Source: Ryan 2013,[2] EPAR Assessment report[6]

Cut-off date: December 20, 2011

*The prespecified boundary for significance (P≤0.0005) was not reached for the overall survival at the observed number of events (333 deaths).

†Modified PCWG2 criteria was used to measure the decline of 50% or more in the PSA level.

‡Time to Functional status decline was defined as the months from randomization to the first date a patient has a decrease of 10 points or more on FACT-P score.

§Objective response rate results by RECIST criteria were ascertained in patients with measurable disease at baseline and based on independent.

2.1.4 Comparison with Other Literature

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

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

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

Patient Advocacy Group Input

The following patient advocacy groups provided input on abiraterone acetate for the treatment of patients with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC) after failure of ADT and who have not received prior chemotherapy: Prostate Cancer Canada and Canadian Cancer Survivor Network. From a patient perspective, recurrence of cancer or treatment failure is of great concern. About half of the respondents felt that there are needs in their current therapies that are not being met. Respondents were willing to tolerate side effects if the treatment improved the quality of life and prolonged survivability. The majority of respondents who have experience using abiraterone reported that abiraterone improved their quality of life and was effective in treating their prostate cancer. Although there were adverse effects reported by those who took abiraterone, survey respondents reported that because it halted disease progression and provided for better control of symptoms, there was a willingness among most advanced prostate cancer patients to tolerate most side effects. As such, there is a necessity to make abiraterone available or more affordable.

PAG Input

Input on abiraterone (Zytiga) for mCRPC was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified that abiraterone as an oral drug already available on the market, with relatively well-tolerated profile and easily used in the community as enablers. PAG noted that the use of abiraterone in this group of patients would be a new standard of care, where optimal management has not been defined. Barriers to implementation identified include 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 requested clarification on how abiraterone and docetaxel would fit in the treatment algorithm for mCRPC.

2.2 Interpretation and Guidance

Prostate cancer is the most commonly diagnosed cancer in men in Canada with 26, 500 new cases and the third leading cause of cancer death in 2012. The majority of patients who are started on androgen ablative therapy will develop progression to castrate

resistance and can potentially be candidates for a well tolerated effective treatment. Currently, patients with mCRPC but with no or minimal symptoms are often observed closely without intervention as there have been no studies that have demonstrated improvement in overall survival with either secondary hormonal interventions or chemotherapy. Low dose prednisone is sometimes recommended for this group of patients with only a minority of patients experiencing benefit. Prostate cancer patients with this stage of disease are often seen and managed by urologists.

The systematic review identified only one unique randomized controlled trial of abiraterone acetate in patients with metastatic CRPC who are asymptomatic or minimally symptomatic. The study incorporated two co-primary endpoints including overall survival and radiographic progression free survival and compared abiraterone acetate and prednisone versus placebo and prednisone.

The results of the COU-AA-302 demonstrated an improvement in overall survival and radiographic progression free survival in favour of abiraterone. At the 2nd planned interim analysis, the mOS was not yet reached for patients on abiraterone and was 27.2 months in the placebo group, HR=0.75 (0.61 to 0.93 p=.01) although the prespecified boundary for significance (P≤0.0005) was not reached for the overall survival at the observed number of events (333 deaths). The other co-primary endpoint of radiographic progression free survival was 16.5 months for the abiraterone group and 8.3 months in the placebo group (HR=0.53, 0.45-0.62 p<0.0001).

Significant improvements in time to PSA progression (11.1 vs 5.6 months), PSA response as defined by a ≥50% decrease in PSA (61.5% vs 23.8%), objective tumour responses (36% vs. 16%) as well as patient reported outcomes favoured those on abiraterone. Specifically, there was a reduced risk of average pain intensity progression (HR=0.82 p=0.049) and deterioration of most quality of life domains as measured by FACT-P.
In general, abiraterone was well tolerated with the most common adverse events being fatigue, back pain, arthralgias, nausea and constipation which were all observed in the placebo arm. Adverse events of special interest related to mineralocorticoid-associated events such as fluid retention, hypokalemia, and hypertension were more commonly seen in the abiraterone group (66% versus 50%). Treatment related adverse events leading to treatment discontinuation was similar between the abiraterone and placebo arms (10% vs. 9%) except for those discontinuations due hepatotoxicity (2.2% vs. 0.2%).
In summary, the results of the COU-AA-302 study demonstrated the efficacy and safety of abiraterone acetate and prednisone in patients with mCRPC with minimal or no symptoms.

In the pre-chemotherapy setting of mCRPC, treatment options are limited to secondary hormonal therapies such as anti-androgens, ketoconazole or low dose prednisone, all of which have not been shown to improve survival. The demonstrated efficacy of abiraterone in this setting potentially fills a void in which there is significant clinical need.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to the use of abiraterone acetate in the treatment of asymptomatic or minimally symptomatic mCRPC based on one high-quality randomized, placebo-controlled trial that demonstrated a clinically and statistically significant benefit in radiographic progression-free survival for abiraterone acetate compared with prednisone. Several secondary endpoints including quality of life were also

demonstrated to be statistically significant and clinically meaningful in favour of the abiraterone group.

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

- The COU-AA-302 study did not meet its prespecified boundary for significance for the co-primary endpoint of overall survival observed at the time of the second and third interim analysis and that the recommendations by the independent data monitoring committee of unblinding and crossover of patients after the second interim analysis from placebo to abiraterone may attenuate any future observed survival benefit. Although the improvement in overall survival was not statistically significant, the results of both the second and third interim analysis favoured the abiraterone arm.
- Abiraterone acetate given with prednisone is a well-tolerated oral regimen which appears to provide a clinically meaningful improvement in survival as well as delaying radiographic progressions in patients with few or no symptoms from metastatic CRPC who may otherwise receive prednisone only or be observed without intervention.
- Although adverse events leading to treatment discontinuation were similar between the two groups, the adverse event profiles were higher with abiraterone acetate than with prednisone including treatment emergent serious adverse events.
- The role of abiraterone acetate remains undefined in patients with CRPC without metastasis.
- The repeated use of abiraterone in mCRPC patients post-docetaxel who have received abiraterone pre-chemotherapy is also 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.

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 clear evidence that one treatment modality is superior in efficacy. However, despite ablative treatment, some patients develop recurrent disease as evidenced by a biochemical recurrence (elevation in PSA) with or without metastases. Standard first-line therapy for recurrence remains androgen deprivation therapy. The majority of patients initially respond to androgen deprivation therapy but almost all eventually go on to develop 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 viscera. For patients with only biochemical 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 an anti-androgen such as bicalutamide or an androgen synthesis inhibitor such as ketoconazole can be used.[7] If patients are combined androgen blockade, anti-androgen withdrawal is often done and low dose prednisone can be considered. In general, early chemotherapy with docetaxel is not recommended for those without metastatic disease outside the context of a clinical trial.[3] In general, there has been no widely accepted standard of care for this population as no phase 3 study has demonstrated improved survival. Importantly, patients with non-metastatic CRPC were not included in the COU-AA-302 study.

For those with mCRPC who are asymptomatic or minimally symptomatic, secondary hormonal maneuvers are often used although again, no survival benefit has been demonstrated. Chemotherapy with docetaxel has previously been recommended for those with a good performance status.

Treatment for Symptomatic CRPC

When secondary hormonal therapies fail, suitable patients are treated with docetaxel chemotherapy. In two large randomized phase 3 studies,[8,9] docetaxel significantly improved overall survival by over 2 months, had a PSA response rate of approximately 50% and also improved quality of life. Docetaxel was approved by Health Canada in 2004 for treatment of

mCRPC. Although effective, docetaxel is a palliative treatment and eventually all patients develop progressive disease.

For patients who have progressed on docetaxel, recent data supports the use of both chemotherapy such as cabazitaxel or alternatively additional 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.[10] Both enzalutatmide,[11] an androgen receptor antagonist and abiraterone acetate,[12] 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 2 years with the approval of a number of new agents which have demonstrated survival benefits in the post docetaxel 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. However, treatment of non-metastatic CRPC and asymptomatic or minimally symptomatic mCRPC remains a clinical void although only recent data suggests that androgen synthesis inhibition may provide clinical benefit.

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 at this stage of disease. The COU-AA-302 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 a ECOG performance status of 0 or 1. Patients with only PSA progression and stable metastatic disease had to meet the definition of PSA progression based on the PSA criteria of the Prostate Cancer Clinical Trials Working Group 2 for study entry

Other Patient Populations in Whom the Drug May Be Used

Abiraterone with prednisone has been shown to be effective in the POST-chemotherapy setting for mCRPC. Currently, insufficient evidence exists for the use of abiraterone in non-metastatic CRPC or at even earlier; hormone-sensitive settings but ongoing studies are evaluating abiraterone in earlier settings of the prostate cancer.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups provided two separate submissions on abiraterone acetate for asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer ("mCRPC") patients who have failed androgen deprivation therapy (ADT) and have not received prior chemotherapy, and their input is summarized below.

- Canadian Cancer Survivor Network ("CCSN")
- Prostate Cancer Canada ("PCC")

The CCSN conducted an online survey, which was publicized on CCSN's website (survivornet.ca), on Twitter and on Facebook. The survey was also published in two CCSN e-letters and circulated to approximately 100 prostate cancer support groups and to CCSN's Prostate Cancer Advisory Council.

- The survey was completed by 16 advanced prostate cancer patients and caregivers.

The PCC conducted an anonymous and confidential online survey. The survey had a combination of multiple choice, rating and open-ended questions.

- 101 people responded to the survey, and 59 completed the survey. Of the total number of respondents, nine (9) were caregivers to someone with prostate cancer, 90 had been diagnosed with prostate cancer, and 2 did not respond.

- 76 respondents identified the stage of their disease: 27 were in the metastatic/advanced stage, 15 had localized prostate cancer, 29 were in remission, and 5 did not know or hadn't been told. 13 respondents had experience with abiraterone.

- Of the total number of respondents who answered the survey, 42 were from Ontario, 17 were from Alberta, 11 were from Quebec, 9 were from Nova Scotia, 2 were from Manitoba, 2 were from New Brunswick, 1 was from Newfoundland/Labrador, and 1 was from the Northwest Territories.

From a patient perspective, recurrence of cancer or treatment failure is of great concern. About half of the respondents felt that there are needs in their current therapies that are not being met. Respondents were willing to tolerate side effects if the treatment improved the quality of life and prolonged survival. The majority of respondents who have experience using abiraterone reported that abiraterone improved their quality of life and was effective in treating their prostate cancer. Although there were adverse effects reported by those who took abiraterone, survey respondents reported that because it halted disease progression and provided for better control of symptoms, there was a willingness among most advanced prostate cancer patients to tolerate most side effects. Symptoms having greatest impact on daily living and quality of life included fatigue, urinary frequency and pain.

Please see below for a summary of specific input received from the patient advocacy groups. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar.

4.1 Condition and Current Therapy Information

4.1.1 Experiences patients have with mCRPC

The majority of metastatic respondents identified urinary function, sexual dysfunction and fatigue as problematic symptoms.

Among the people who self-identified as having metastatic/advanced prostate cancer, fatigue was cited as the symptom of greatest severity, with close to half of respondents describing it as moderate, a very small number described it as severe, and the remainder as mild or as not a problem.

When asked what symptoms or problems they experienced with advanced prostate cancer that affected their day-to-day living and quality of life, survey respondents from the CCSN survey replied as follows:

- Sexual dysfunction: 94%
- Fatigue: 75%
- Pain: 56%
- Living with uncertainty: 50%
- Urinary incontinence: 50%
- Weight loss, lack of appetite: 44%
- Not sleeping at night or restlessness: 25%
- Anxiety, panic attacks or depression: 25%
- Fractures or fear of fracture: 19%
- Feeling isolated or lonely: 6%

In addition to the above symptoms and problems, respondents also added the negative impact of joint issues, and fear of death.

Comments included, "*I am also experiencing joint issues, apparently a side effect of extended use of anti-androgens pre- and post-radiation*."

Another respondent stated, "*I need to urinate two to six times a night. I am afraid of death. I am tired all the time and have lost a lot of weight*."

Survey respondents then rated their top five symptoms that are the most important to control as follows:

- Fatigue: 69%
- Pain: 56%
- Urinary incontinence: 44%
- Sexual dysfuyction: 38%
- Living with uncertainty: 38%

One respondent stated that fecal incontinence was the top symptom and very difficult to deal with.

When asked about the impact of the disease on the ability to perform daily activities, the activities with which performance was associated with the greatest difficulty were (in order of most impacted to least impacted): sexual intimacy, work, travel and exercise. Other comments about the impacts of the disease concerned: libido, hormone therapy side effects, and the ongoing search for new treatments in the face of rising PSA. One metastatic respondent stated: "*Loss of libido due to hormone therapy is my biggest challenge inpartner relationship*", and another respondent stated, "*There are a lot of issues that affect sex. The degree of ED, effectivenness of 'aids', dgeree of libido, partners libido etc*". When speaking about prostate cancer treatments, a respondent stated: "*Radiation and hormone treatment have affected my body and cognitive ability*".

From a patient perspective, patients are both physically and psychologically impacted by living with advanced prostate cancer. As such, advanced prostate cancer patients are eager to access new therapies that might promote healing and halt disease progression.

4.1.2 Patients' Experiences with Current Therapy for mCRPC

Respondents included treatments that ranged from surgery, to radiation, to chemotherapy (e.g., docetaxel (Taxotere), abiraterone acetate (Zytiga), enzalutamide (Xtandi)), to hormone therapy. For men in advanced stages of prostate cancer, there was a greater propensity to mention hormone related treatments including specifically Casodex and Zoladex.

Based on the CCSN survey, respondents reported common side effects of current therapies as follows:

Side effects	Percentage of Respondents
Diarrhea	42%
Nausea and vomiting	42%
Anemia	25%
Risk of infection	18%
Other (weight gain; loss of appetite; pain; fatigue; constipation)	25%

Respondents also reported the following side effects as most difficult to deal with:

Side effects	Percentage of Respondents
Diarrhea	27%
Nausea and vomiting	27%
Anemia	18%
Other (weight gain; pain)	18%

The majority of respondents to both CCSN and PCC survey did not have issues accessing treatment, while a small number did. Reasons given for access issues included limited availability in patient's community, financial hardship due to cost, travel costs associated with getting treatment and supplies or issues with administration. Respondents provided the following statements:

> "*Current therapy is accessible and funded in Ontario. One hundred miles for treatment, tests and appointments along with $12 for parking and expensive lunches adds up when living on government pension only*."

> "*No issues in accessing my current therapy, but it does create a certain amount of fincancial concern because in my own personal situation, I am 337 km from the hospital where I receive treatment and based on the current gas costs and having to travel once a week for a period of time and then less frequently plus the cost of meals, parking, etc., and being on a disability pension, does create additional stress related to the whole situation.*"

Respondents also indicated a lack of education on the part of their physician about available treatment options: "*General lack of knowledge of Canadian doctors with Prostate Cancer 101, latest scanning methods, and latest treatments that are commonly*

known and applied in the US"; "*My initial Urologist was not proactive in treatment when my prostate cancer returned after a radical prostatectomy in 2001. I had to pursue my own treatment program and changed Doctors to a more proactive man.*"

About half of respondents report that there are needs in their current therapies that are not being met. These include:

> "*Prostate pain seems to be constant even with the current hormone-blocking therapy I am on.*"
>
> "*It is likely that I will develop resistance to Xtandi and will need to seek additional medical therapy. I still have my prostate gland and have not had any radiation. I will resist having chemotherapy with docetaxol for as long as possible, It will be important than any additional treatments be covered by my provincial health care plan.*"
>
> "*No significant improvement to date.*"
>
> "*Ability to keep on with treatment until symptoms are stopped.*"
>
> "*All the medications have side effects that are hard to deal with. Also, I would like something that would slow progression.*"

Advanced prostate cancer patients reported that they are eager to access new therapies that might promote healing and halt disease progression.

4.1.3 Impact of mCRPC and Current Therapy on Caregivers

The survey reflected an array of responses showing how strongly the diagnosis of prostate cancer affects partners and families. Several respondents indicated that emotional stress was of the greatest impact: "*Difficulty in coping with extra care and needs. Emotional impact*"; "*Increased stress and worry*" and "*internal stress for all family*".

Both respondents and their caregivers also indicated that sexual function impacted their lives together: "*not able to have sexual relations, but that was a tradeoff we made together. It is better to be alive and able to do most things together, than be dead*"; "*my loss of libido and ED are a challenge for my healthy partner*"; "*Reduced sex drive and any interest in sex is greatly depleted. However, we continue to be romantic in our own way and well recognize that without the regimen that I am on, I may not be here to enjoy the other parts of life, grandkids, your daughter`s wedding, nature, etc.*"

Respondents noted that it affected almost all aspects of life. Some of the key responses include;

> "*It impacts every aspect of normal life from: helping with special meal preparation; providing support through the stress of the cancer journey; sexual realtionship; travel capability; added stress; disruption in sleep; attendance at key medical appointments and meetings*".
>
> "Your life becomes the same as the person with the disease. Your schedule becomes their schedule. You are always there to provide support. Because of the disease and its effects, you take on many new roles in your life."

"Seeing your loved one experience the pain that they have as a result of the cancer. Trying to keep a positive outlook on days when things don't seem as positive as one would like. Keeping up everyone's spirits. Staying hopeful. Trusting that one day there will be a 'CURE.' Thank you to all the people that dedicate their time and effort in trying to find the magic answer."

"Financial. Not able to plan ahead. Staying on top of treatments, possible effects, medications, scheduling, etc."

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Abiraterone

Respondents that have not used abiraterone expect that a new drug would have a positive impact on reducing disease progression and increasing survival. Respondents indicated that this would be "very important" to them. In terms of what side effects would be tolerated for a new drug, respondents were willing to tolerate side effects if the treatment improved the quality of life and prolonged the survival rate.

According to the CCSN survey, half (8) of respondents stated they had no experience with Zytiga. Expectations for a new drug included:

- Maintain quality of life: 100%
- Delay onset of symptoms: 100%
- Delay need for chemotherapy: 64%
- Reduce side effects from current medications or treatments: 64%
- Easier to use: 55%

Respondents included the following comments:

"I would like to be able to benefit from a new treatment that would improve my quality of life and help me live longer."

"Any drug that could make chemotherapy unnecessary would be a welcome alternative."

"If the drug acted positively on my prostate tumour to reduce the pain factor, it would give me a much better quality of life."

The majority of respondents who are currently on abiraterone reported that it improved their quality of life and was effective in treating their prostate cancer (i.e., control symptom, reduce side effects compared to other treatments, halt disease progression). Although there were adverse effects reported by those who took abiraterone, survey respondents reported that because it halted disease progression and provided for better control of symptoms, there was a willingness among most advanced prostate cancer patients to tolerate most side effects.

According to the PCC survey, ten people indicated the side effects of abiraterone that they felt were tolerable, and a few noted that they were similar to the side effects they experienced while on hormonal therapy. The most commonly mentioned included fatigue, which was deemed to be a tolerable side effect four times, and hot flashes, mentioned

three times. Other examples of tolerable side effects included: mood swings, night sweats, cognitive impairment and a reduction in potassium. Three respondents mentioned that they did not experience side effects, one respondent had been on it for two years, one for only three days, and one declined to indicate. One caregiver responded on behalf of her husband with a description of the negative impact it had on their lives: "*Totally wiped him out, had no energy, no appetite, felt terrible*".

Based on the survey conducted by the CCSN, the following adverse effects that were reported while taking abiraterone were:

- Fatigue: 50%
- Diarrhea: 33%
- Hot flashes: 33%

Other side effects included loss of appetite and hot flashes. The respondents also commented on which side effects were acceptable and which were not, as follows:

- Fatigue: 57% of respondents said that fatigue was acceptable, 25% not acceptable.
- Diarrhea: 67% acceptable, 33% not acceptable.
- Hot flashes: 100% acceptable.

Although there were adverse effects reported by those who took Zytiga, a majority of survey respondents (57%) reported that Zytiga halted disease progression and 100% reported being able to better control symptoms. There was a willingness among most advanced prostate cancer patients to tolerate most side effects.

4.3 Additional Information

PCC noted that the question about patient expectations for new drugs, what kinds of improvements in condition would be adequate compared with previous treatments, or asking about the gap it was expected to fill are not questions that are well suited for patients with no experience of the drug in question.

It is PCC opinion that these questions lead to unrealistic expectations: patients with no experience of the drug would like it to work better, or even perfectly, and have no side effects. Questions about the risks associated with the drug, and the benefits it might have would be better addressed by the pharmaceutical company producing the drug, as they would have done extensive research on niches that need to be filled. An alternative would be to ask these questions of patients who have experience of the drug, and who have an understanding of its risk versus its benefits.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

Input on abiraterone (Zytiga) for mCRPC was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

PAG identified that abiraterone as an oral drug already available on the market, with relatively well-tolerated profile and easily used in the community as enablers.

PAG noted that the use of abiraterone in this group of patients would be a new standard of care, where optimal management has not been defined. Barriers to implementation identified include 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 requested clarification on how abiraterone and docetaxel would fit in the treatment algorithm for mCRPC.

Please see below for details on the individual parameters.

5.1 Factors Related to Comparators

PAG identified that there is no standard approach to treating patients for asymptomatic or mildly symptomatic mCRPC and who have not undergone chemotherapy with castrate-resistant prostate cancer. The most common approaches are anti-androgen therapy with LHRH, corticosteroid therapy alone, or monitor patients until patient experiences significant increases in PSA levels and symptoms. Abiraterone is indicated to be used with prednisone.

5.2 Factors Related to Patient Population

PAG expressed concerns on appropriate use of abiraterone since the majority of patients with mCRPC are not seen by physicians in the cancer system but by urologists. PAG noted that a large patient population exists, resulting in a significant budget impact.

As abiraterone is already funded for second-line post docetaxel, PAG had concerns with indication creep where patients/physicians may want to use abiraterone instead of docetaxel, given that abiraterone is a relatively well tolerated oral therapy not requiring clinic visits for administration.

PAG is requesting clarification on the treatment algorithm for mCRPC: if a patient uses abiraterone for asymptomatic disease and then docetaxel for disease progression, is retreatment with abiraterone after docetaxel still applicable? PAG also noted an upcoming pCODR review for mCRPC patients, which could also impact the treatment algorithm.

5.3 Factors Related to Accessibility

As an oral agent, abiraterone can be delivered to patients more easily than intravenous therapy in both rural and urban settings. As such, PAG identified the ease in accessibility of treatment for patients as an enabler.

However, PAG noted that in some jurisdictions, oral medications are not covered in the same way as intravenous cancer medications, which may limit accessibility of treatment to patients. For these jurisdictions, patients would first require an application to their pharmacare program, and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

5.4 Factors Related to Dosing

See 5.2.

5.5 Factors Related to Implementation Costs

PAG noted that abiraterone is already funded and is a well-tolerated oral therapy administered in the community. This is an enabler to implementation.

PAG noted the barrier to implementation would be the potentially large budget impact since some of these patients who are asymptomatic or mildly symptomatic are not receiving any treatment and that treatment is continuous until disease progression. The delay in time to disease progression and symptoms is significant for patients' quality of life and may delay the impact of resources required to deliver downstream treatments.

5.6 Other Factors

None identified.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of abiraterone acetate (Zytiga) in combination with prednisone on patient outcomes compared to standard therapies or placebo in patients with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC) who have failed on androgen deprivation therapy and have not received prior chemotherapy (see Table 1 in Section 6.2.1 for outcomes of interest and comparators). Note: No supplemental questions were addressed in this review.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished double-blind RCTs	Patients with asymptomatic or mildly symptomatic mCRPC who have failed on ADT and have not received prior chemotherapy.	Abiraterone 1000 mg QD orally + prednisone	Antiandrogens Other hormonal therapies (e.g. steroids, ketoconazole, estrogen therapies) Placebo **all above treatments administered with or without prednisone	OS PFS QoL ORR CBR TTP PRO SAE AE WDAE PSA response Pain response Time to pain progression Time to PSA progression Skeletal-related events Bone metastases Biomarker data

ADT=androgen deprivation therapy; **AE**=adverse events; **CBR**=clinical benefit rate; **mCRPC**=metastatic castration-resistant prostate cancer; **ORR**=objective response rate; **OS**=overall survival; **PFS**=progression-free survival; **PRO**= patient-reported outcome measures; **PSA**=prostate-specific antigen; **QD**=once daily; **QoL**=health related quality of life; **RCT**=randomized controlled trial; **SAE**=serious adverse event; **TTP**=time to progression; **WDAE**=withdrawal due to adverse events

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

6.2.2 Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 3) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was abiraterone acetate (Zytiga).

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 September 5, 2013.

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

6.2.3 Study Selection

Two members of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.
Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

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

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

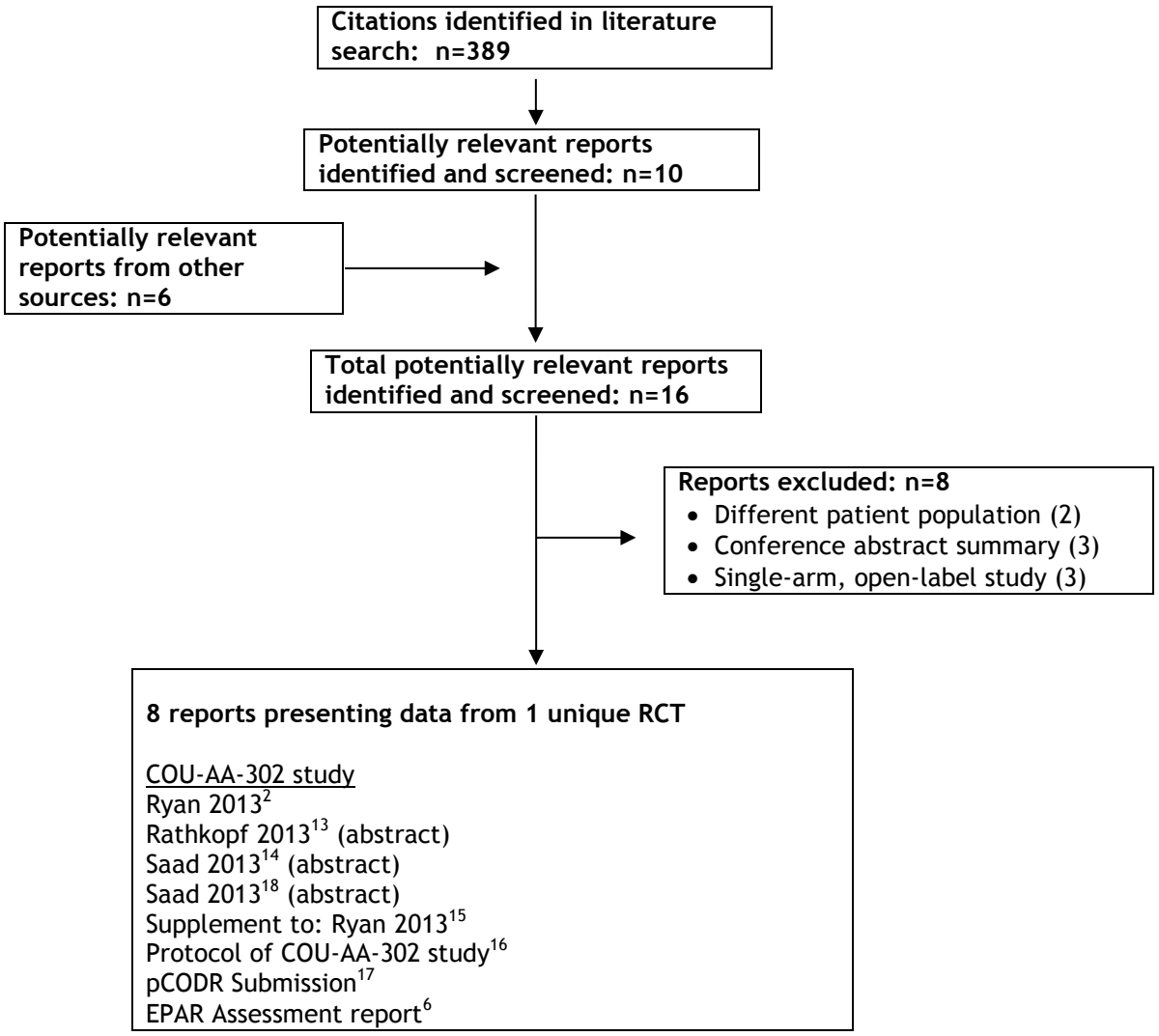
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions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

6.3 Results

6.3.1 Literature Search Results

Of the 15 potentially relevant reports identified, 8 reports were included in the pCODR systematic review[2,6,13-18] and 8 reports were excluded. Reports were excluded because they were for different patient population,[19,20] conference abstract[21-23] of the main study, and single-arm open-label studies.[24-26] No FDA report for this indication was available.

Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



No FDA report for this indication was available

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of the COU-AA-302 Trial[2,6,15,27]

Trial Design	Key Inclusion and Exclusion Criteria	Intervention and Comparator	Outcomes
Multinational*, DB, placebo-controlled, phase 3 RCT Randomization period: April 2009-June 2010 Method of randomization: centrally using an interactive voice recognition system Randomization was performed at a 1:1 (abiraterone acetate plus prednisone : placebo plus prednisone) ratio and stratified by: • ECOG performance status (0 vs. 1) Clinical cut-off date for first and second interim analyses were December 20, 2010 and December 20, 2011, respectively Funded by: by Janssen Research and Development, formerly Cougar Biotechnology	**Inclusion criteria** Patients 18 years or older with mCRPC Medical or surgical castration with serum testosterone level <50 ng/dL at screening Documented prostate cancer progression by PSA Previous anti-androgen therapy and progression after withdrawal ECOG performance status 0 or 1 BPI-SF scores of 0 to 1 (asymptomatic) or 2 to 3 (mildly symptomatic) Adequate haematological, renal and liver function that met predefined criteria Estimated life expectancy ≥6 months **Exclusion criteria** Prior use of cytotoxic chemotherapy or biologic therapy for the treatment of CRPC Known brain, liver, or visceral organ metastasis Prior therapy with ketoconazole lasting more than 7 days for prostate cancer Use of opiate analgesics	Abiraterone Acetate 1000 mg, orally QD plus prednisone 5 mg BID Placebo, orally QD plus prednisone 5 mg BID	**Primary** • Overall survival • Radiographic progression-free survival **Secondary** • Time to opiate use for cancer pain • Time to initiation of cytotoxic chemotherapy • Time to a decline in ECOG performance status by at least 1 grade • Time to PSA progression • PSA response rate • Objective response rate • QoL • Time to pain progression • Time to analgesic progression • Duration of response in patients with measurable disease • Safety

Trial Design	Key Inclusion and Exclusion Criteria	Intervention and Comparator	Outcomes
	including codeine and dextropropoxyphene, for cancer-related pain currently or anytime within 4 weeks of Cycle 1 Day 1		
BID=twice daily; **BPI-SF**=Brief Pain Inventory-Short Form; **DB**=double-blind; **ECOG**=Eastern Cooperative Oncology Group; **mCRPC**=metastatic castration-resistant prostate cancer; **PSA**=prostate-specific antigen; **QD**=once daily; **QoL**=quality of life; **RCT**=randomized controlled trial; **RECIST**= Response Evaluation Criteria in Solid Tumors			

*EPAR Assessment report[6] mentioned that 151 study sites participated in the study; supplement to Ryan 2013[15] reported that 12 countries (including Canada) were participating in COU-AA-302 Trial.

a) Trials

One phase III, double-blind, placebo-controlled RCT was included in this review (see Table 2). COU-AA-302 study was designed to evaluate the efficacy and safety of oral abiraterone acetate in patients with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC), as defined according to the Brief Pain Inventory–Short Form (BPI-SF) where asymptomatic patients had scores of 0 to 1 or mildly symptomatic patients had scores 2 to 3. Patients must have also failed on androgen deprivation therapy (ADT), which generally includes an LHRH agonist or orchiectomy, and have not received prior chemotherapy. This study was conducted at 151 centers across 12 countries including Canada, and was sponsored by the manufacturer.
Patients were randomized at a 1:1 ratio to orally receive treatment with either abiraterone acetate (1000 mg daily) or placebo. Randomization was stratified by baseline ECOG performance score. Patients were enrolled from April 2009 through June 2010 and randomized to a study treatment centrally using an Interactive Web/Voice Response System. Blinding was obtained using placebo capsules that were matched in size, color (white to off-white), and shape (oval) to abiraterone acetate tablets.[16] After the second interim analysis and due to the significant advantage for patients in one arm of the study compared with the other arm, the IDMC unanimously recommended unbinding the study and allowing cross-over of subjects from placebo to abiraterone.

The COU-AA-302 study was powered to evaluate treatment efficacy using the co-primary end points OS and rPFS. Only one analysis was planned for the co-primary rPFS endpoint after 378 progression-free events which would provide 91% power in detecting a median rPFS of 4 months for the placebo group versus 6 months for the abiraterone group (HR=0.667) (α=0.01). For the co-primary end point of overall survival, 773 death events were required to have a power of 85% to detect a hazard ratio of 0.80 (α=0.04), assuming a median survival of 27.5 months in the abiraterone acetate plus prednisone group (will be referred to as abiraterone group) and 22.0 months in the placebo plus prednisone group (will be referred to as placebo group), the final analysis was to be performed when 773 deaths occurred, with an interim analysis performed when 116 (15%), 311 (40%), and 425 (55%) deaths occurred. O'Brien–Fleming boundaries as implemented by the Lan–DeMets alpha spending method was used to incorporate the group-sequential design by including 3 interim analyses and one final analysis for the overall survival end point, where the alpha level considered were <0.0001, 0.0005, 0.0034, and 0.0400 for the first Interim analysis, second Interim analysis, third Interim analysis, and final analysis, respectively.

b) Populations

The intention-to-treat (ITT) population (n=1088) in the COU-AA-302 trial was defined as all randomly assigned patients, regardless of whether they received study medication. Of the 1088 randomized patients, 546 patients were assigned to receive abiraterone acetate plus prednisone (from now on will be referred to as abiraterone) and 542 patients were assigned to receive placebo plus prednisone (from now on will be referred to as placebo). Of the randomized subjects, 4 patients and 2 patients did not receive their allocated intervention in the abiraterone group and placebo group respectively. Safety analyses were assessed for all randomized patients who received any study drug. A summary of the study population and patient disposition in the COU-AA-302 trial is presented in Figure 1.

Baseline demographics and disease characteristics were generally balanced between the 2 treatment groups (Table 3). The median age was 71(range 44-95) years for abiraterone group and 70 (range 44-90) for placebo group. Seventy-six percent (76%) and 24% of subjects had an ECOG performance status grade 0 and grade 1 at baseline, respectively.[1] Ninety-five (95%) of study population were Caucasians. Twenty-five percent (25%) and 26% of subjects had metastatic disease (M1) at initial diagnosis in the abiraterone group and placebo group, respectively. Eighty three percent (83%) of subjects in the abiraterone group and 80% of subjects in the placebo group had bone metastases. At study entry median baseline PSA concentrations were 42.01 and 37.74 ng/mL, median LDH concentrations were 187 and 184 IU/L, and median hemoglobin concentrations were 13.0 and 13.1 g/dL for the abiraterone and placebo groups, respectively. Forty-seven percent (47%) and 45% had prior prostate cancer-related surgery, and 52% and 56% had prior prostate cancer radiotherapy in the abiraterone group and placebo group, respectively.

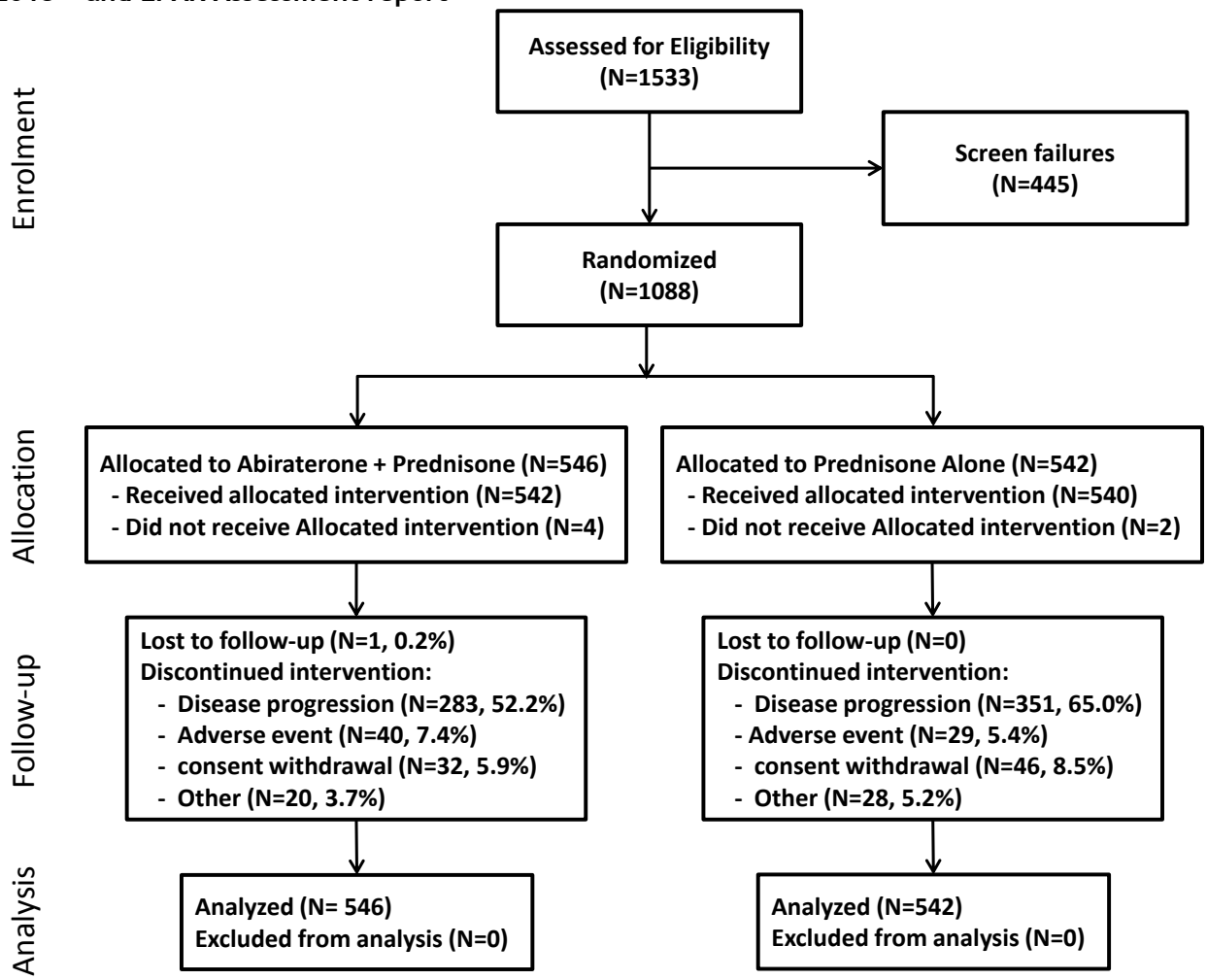
Table 3. Baseline patient demographics and clinical characteristics in COU-AA-302 Trial[1, 6,15,]

	Abiraterone + Prednisone (N= 546)	Prednisone Alone (N= 542)
Age, years		
Median (range)	71 (44, 95)	70 (44, 90)
Mean (SD)	70.5 (8.80)	70.1 (8.72)
Race, N (%)		
White	520 (95.4)	510 (94.4)
Black	15 (2.8)	13 (2.4)
Asian	4 (0.7)	9 (1.7)
Other	6 (1.1)	6 (1.1)
Metastasis Stage at Diagnosis, N (%)		
N	542	541
M0	239 (44.1)	230 (42.5)
M1, M1a, M1b, M1c	135 (24.9)	142 (26.2)
MX	75 (13.8)	88 (16.3)
Unknown	91 (16.8)	75 (13.9)
Not Applicable	2 (0.4)	6 (1.1)
Screening BPI-SF pain score (worst pain over last 24 hours)		
N	532	522
0–1 N (%)	353 (66)	336 (64)
2–3 N (%)	169 (32)	170 (33)
≥4 N (%)	10 (2)	16 (3)
Median	0.0	0.0

	Abiraterone + Prednisone (N= 546)	Prednisone Alone (N= 542)
Range	0–10	0–9
Total Gleason score at diagnosis		
N	488	508
<7 N (%)	65 (13.3)	64 (12.6)
7 N (%)	160 (32.8)	190 (37.4)
>7 N (%)	263 (53.9)	254 (50.0)
PSA at initial diagnosis (ng/mL)		
N	470	454
Mean (SD)	174.01 (540.433)	219.69 (888.783)
Median (range)	22.3 (0.4, 5036.0)	21.0 (0.3, 9726.3)
Previous cancer therapy		
N	544	542
Surgery N (%)	256 (47)	244 (45)
Radiotherapy N (%)	283 (52)	303 (56)
Hormonal N (%)	544 (100)	542 (100)
Other N (%)	82 (15)	63 (12)
Extent of Disease at study entry, N (%)		
N	544	542
Bone	452 (83.1)	432 (79.7)
Bone only	274 (50.4)	267 (49.3)
>10 bone metastases	264 (49)	253 (47)
Soft tissue or node	267 (49.1)	271 (50.0)
Bone, Soft Tissue, or Node	544 (100.0)	542 (100.0)
Other	4 (0.7)	7 (1.3)
Time from initial diagnosis to first dose (years)		
N	542	540
Mean (SD)	6.7 (4.85)	6.5 (4.77)
Median (range)	5.5 (0, 28.0)	5.1 (0, 28.0)
Time from LHRH to first dose (months)		
N	530	526
Median (range)	40.4 (1.6, 225.6)	40.8 (1.9, 260.9)
Baseline PSA (ng/ml)		
N	546	539
Median (range)	42.0 (0.0, 3927.4)	37.7 (0.7, 6606.4)
Baseline alkaline phosphatase (IU/l)		
N	546	539
Median (range)	93.0 (32, 1927)	90.0 (21, 3056)
Baseline lactate dehydrogenase (U/l)		
N	543	536
Median (range)	187.0 (60, 871)	184.0 (87, 781)
BPI-SF=Brief Pain Inventory-Short Form; **LHRH**=luteinizing hormone–releasing hormone; **PSA**=prostate-specific antigen		

Source: supplement to Ryan 2013,[15] EPAR Assessment report,[6] pCODR Submission[17] (Health Canada Module 2.7.4)

Figure 1. Patient disposition in the COU-AA-302 Trial study adapted from supplement to Ryan 2013[15] and EPAR Assessment report[6]



c) Interventions

Patients received abiraterone acetate 1000 mg orally once daily as four 250 mg tablets or matched placebo tablets, taken at least 1 hour before a meal or 2 hours after a meal. All patients received 5-mg prednisone twice daily which was not required to be taken at the same time as study treatment. In case study drug dose is changed prednisone dose will remain unchanged and prednisone dose was omitted and not be made up in case it was missed. Patients experiencing a Grade 3 or greater toxicity, study treatment were interrupted until the toxicity decreased to Grade 1 or lower (grades based upon the CTCAE, version 3.0). Once the toxicity resolved to ≤grade 1, study treatment could be resumed at a reduced dose. Patients experiencing grade 4 toxicity or experiencing sustained toxicity that do not return to ≤grade 1 after appropriate medical management and two dose level reductions were required to discontinue study treatment. Concurrent treatment with LHRH analogue was mandatory for patients who did not undergo orchiectomy. Concurrent administration

of other anticancer treatment except LHRH agonists was prohibited during study treatment Phase. Treatment was continued until confirmed radiographic progression of disease and/or unequivocal clinical progression, sustained side effects, withdrawal of patient consent, initiation of new anticancer treatment, or death. Crossovers were not permitted between the two treatment groups up until the second interim analysis, after which crossover was permitted from placebo. After discontinuation of study treatment patients were permitted to use other antineoplastic treatments, where 44% of subjects in the abiraterone group and 60% of subjects in the placebo group received antineoplastic agents administered as subsequent therapy Table 4 presents a summary of these agents.

Table 4. Antineoplastic agents administered as subsequent therapy for prostate Cancer prior to the clinical cut-off for the 2nd interim analysis (20 December 2011)[15]

	Abiraterone + Prednisone (N= 546) N(%)	Prednisone Alone (N= 542) N(%)
Number of patients with selected subsequent therapy for prostate cancer	242 (44)	327 (60)
Docetaxel	207 (38)	287 (53)
Cabazitaxel	45 (8)	52 (10)
Ketoconazole	39 (7)	63 (12)
Sipuleucel-T	27 (5)	24 (4)
Abiraterone acetate	26 (5)	54 (10)
≥2 Therapies	78 (14)	122 (23)
≥3 Therapies	21 (4)	28 (5)

Source: Supplement to Ryan 2013[15]

At the time of the second interim analysis, 166 (30.6%) patients were receiving study drug in the abiraterone group compared with 86 (15.9%) patients in the placebo group. The median time on treatment was 13.8 months in the abiraterone group and 8.3 months in the placebo group, while the median follow-up time was 22.2 months. Compliance level of abiraterone or placebo exceeded [redacted]% in [redacted]% of subjects in both treatment group, whereas Compliance level of prednisone exceeded [redacted]% in more than [redacted]% in both treatment groups.[17] *(Non-disclosable clinical information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed*)

d) Patient Disposition

All randomly assigned patients except 6 (4 patients in the abiraterone group and 2 patients in the placebo group) in the COU-AA-302 study (ITT population) received study medication. Of the 1088 randomized patients, 546 patients were assigned to receive abiraterone and 542 patients were assigned to receive placebo.

As of the clinical cut-off for the second interim analysis on December 20, 2011, 166 (30.6%) patients randomized to abiraterone remained on treatment, while 86 (15.9%) patients randomized to placebo remained on treatment. The primary reason for discontinuation from study drug was disease progression in both arms (52% abiraterone vs. 65% placebo). Other reasons for discontinuation from study drug included adverse events (7.4% abiraterone vs. 5.4% placebo), withdrawal of consent (5.9% abiraterone vs. 8.5% placebo) or other (3.7% abiraterone vs. 5.2% placebo). Only one patient in the

abiraterone group was lost to follow-up. A summary of the patient disposition in the COU-AA-302 trial is presented in Table 5.

Table 5. Patient Disposition prior to the clinical cut-off for the 2nd interim analysis (20 December 2011)[1,6]

	Abiraterone + Prednisone	Prednisone Alone
Randomized	546	542
Received allocated intervention	542	540
Discontinued treatment (%)	376 (69.4%)	454 (84.1%)
Disease progression	283 (52.2%)	351 (65.0%)
Adverse Event	40 (7.4%)	29 (5.4%)
Consent withdrawal	32 (5.9%)	46 (8.5%)
Other	20 (3.7%)	28 (5.2%)
Lost to follow-up	1 (0.2%)	0

e) Limitations/Sources of Bias

Potential limitations in the COU-AA-302 study include:

- The study design, monitoring, analyses (after unblinding), and publication were overseen by the sponsor. In addition, after the first interim analysis, radiographic progression-free survival was assessed by an investigator.
- The trial population was composed of patients with an ECOG status of 0 (76% of patients) or 1 (24% of patients), with no patients enrolled with an ECOG status >1. This limits the generalizability of results to patients with a poorer performance status.
- Overall survival which is one of the co-primary endpoints did not reach prespecified boundary for significance at second and third interim analysis, and no final analysis available yet.
- Potential confounding effect of crossover and variation of compliance to study protocol could have impacted the beneficial effects of abiraterone, where crossover from placebo to abiraterone took place after the second interim analysis based on the recommendation of the IDMC.
- There were substantial discontinuations by the time of 2nd interim analysis (70% vs 84%, abiraterone vs. placebo), primarily due to disease progression and the majority of patients who discontinued therapy received subsequent chemical treatments (59% vs. 67%, abiraterone vs. placebo.) Of those who discontinued, docetaxel was received by [redacted]% and [redacted]% in abiraterone and placebo groups, respectively, where docetaxel is a chemotherapy that was not allowed in the treatment phase, also [redacted]% of the patients in the abiraterone group and [redacted]% of those in the placebo group of those who discontinued treatment received abiraterone acetate after treatment discontinuation. Hence, the estimation of treatment effects could be confounded, because the subsequent treatments received were incomparable between the two arms, also, those patients who were not responsive to the study drug might have benefit from the subsequent treatments. On the other hand, these differential treatments could also lead to a biased estimation of the risk of harms attributable to abiraterone. *(Non-disclosable clinical information*

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

- In subgroup analysis (of OS and rPFS) and secondary outcome (time to PSA progression and PSA response rate), a p-value less than 0.05 or confidence interval does not include one, does not indicated statistical significance, as the interpretation of statistical significance based on interim analyses should be cautioned due to inflated Type I error rates and different alpha level required to claim statistical significance which was not done. Also it is not uncommon that results could show statistical significance at interim analysis but this significance disappeared and became non-significant later on at the completion of the trial.
- Study COU-AA-302 did not include patients with moderate or severe symptomatic mCRPC who are chemotherapy naive or CRPC patients without metastasis therefore generalizability to these populations is unknown. Also, the repeated use of abiraterone in mCRPC patients post-docetaxel who have received abiraterone pre-chemotherapy was not specifically evaluated in the COU-AA-302 study.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The co-primary efficacy endpoints in the COU-AA-302 study were overall survival (OS) and radiographic progression-free survival (rPFS). OS was defined as the time from randomization to death from any cause whereas; rPFS was defined as the time from randomization to the occurrence of one of the following: progression of disease by bone scanning according to the criteria adapted from the Prostate Cancer Working Group (PCWG2) Consensus; or Progression of soft tissue lesions as measured by computed tomography (CT) or magnetic resonance imaging (MRI) as defined according to modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria; or death from any cause. OS and rPFS data were analyzed in the ITT population, which included all randomized patients. rPFS co-primary endpoint was powered at 91% to detect a hazard ratio of 0.667 (α=0.01) with 378 progression-free events. The co-primary endpoint OS was powered at 85% to detect a hazard ratio of 0.80 (α=0.04) with 773 events, but after the second interim analysis (after 333 deaths 43% of total death events) and due to the significant advantage for patients in one arm of the study compared with the other arm, the IDMC unanimously recommended unbinding the study and allowing cross-over of subjects from placebo to abiraterone. Secondary outcomes included time to PSA progression, PSA response, quality of life (QoL), Objective response rate (ORR) and safety. QoL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire.

Safety analyses were assessed for all randomized patients who received any study drug and occurred at each study visit and between 15 and 28 days after treatment discontinuation. Adverse events were classified by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 3.0) and monitored by the IDMC.

A summary of efficacy and safety outcomes from the COU-AA-302 study are presented in Table 6 and Table 7.

Table 6. Summary of efficacy outcomes from the COU-AA-302 study based on 2nd interim analysis

	Abiraterone + Prednisone (N= 546)	Prednisone Alone (N= 542)
Overall Survival		
Median (months)	NR	27.2
Hazard Ratio (95% CI)	0.75 (0.61, 0.93)	
P-value	0.01*	
Radiographic Progression-Free Survival		
Median (months)	16.5	8.3
Hazard Ratio (95% CI)	0.53 (0.45, 0.62)	
P-value	<0.001	
Time to PSA Progression		
Median (months)	11.1	5.6
Hazard Ratio (95% CI)	0.49 (0.42, 0.57)	
P-value	<0.001	
PSA Response†		
% of Patients with decline of ≥50% in PSA level	62	24
Relative Risk (95% CI)	2.59 (2.19, 3.05)	
P-value	<0.001	
Median time (months)to functional-status decline measured‡		
FACT-P total score	12.7	8.3
Hazard Ratio (95% CI)	0.78 (0.66, 0.92)	
P-value	0.003	
Objective response rate§		
Subjects with measurable disease at baseline	220	218
Complete response, n (%)	24 (10.9)	8 (3.7)
Partial response, n (%)	54 (24.5)	26 (11.9)
Non-Responder, n (%)	142 (64.5)	184 (84.4)
Relative Risk (95% CI)	2.27 (1.59, 3.25)	
P-value	<0.0001	
CI=confidence interval; **FACT-P**=Functional Assessment of Cancer Therapy-Prostate; **PSA**=prostate-specific antigen; **RECIST**= Response Evaluation Criteria in Solid Tumors		

Source: Ryan 2013,[2] EPAR Assessment report[6]
Cut-off date: December 20, 2011
*The prespecified boundary for significance (P≤0.0005) was not reached for the overall survival at the observed number of events (333 deaths).
†Modified PCWG2 criteria was used to measure the decline of 50% or more in the PSA level.
‡Time to Functional status decline was defined as the months from randomization to the first date a patient has a decrease of 10 points or more on FACT-P score.
§Objective response rate results by RECIST criteria were ascertained in patients with measurable disease at baseline and based on independent

Table 7. Summary of safety outcomes from the COU-AA-302 study

n (%)	Abiraterone + Prednisone (N= 546)	Prednisone Alone (N= 542)
Safety, n (%)		
Fatal AEs	20 (4)	12 (2)
SAEs	178 (33)	142 (26)
AEs leading to discontinuation	55 (10)	49 (9)
Grade 3 or 4 adverse event	258 (48)	225 (42)
Any AEs	537 (99)	524 (97)
AE=adverse event; **SAE**=serious adverse event		

Source: Ryan 2013,[2] EPAR Assessment report[6]

Efficacy Outcomes

a) Overall Survival (OS)

One of the co-primary end points in the COU-AA-302 study was OS, which was defined as the time from randomization to death from any cause. Log-rank test was used to evaluate overall survival, with stratification according to ECOG performance-status score. Distribution curve, median and 95% confidence interval were estimated using the Kaplan-Meier method. The study was unblinded and crossover of patients in the placebo group to abiraterone treatment happened after the second interim analysis.

At the time of the first interim OS analysis (20 December 2010) 209 deaths had occurred, but the median OS was not reached in either arm of treatment.

At the time of the second interim (20 December 2011) OS analysis median follow-up was 22.2 months at which 333 deaths had occurred, 147 deaths (27%) in the abiraterone group and 186 deaths (34%) in the placebo group, the median OS was not reached in the abiraterone group and was 27.2 months in the placebo group (hazard ratio (HR) = 0.75, 95% confidence interval (CI) 0.61 to 0.93, p=0.0097). This analysis did not reach prespecified boundary for significance (p= 0.0005). Results are presented in Table 8 and Figure 2. (Source: EPAR Assessment report).[6]

At the time of the third interim (22 May 2012), 434 deaths had occurred, 200 deaths (36.6%) in the abiraterone group and 234 deaths (43.2%) in the placebo group, the median OS was 35.3 months in the abiraterone group and 30.1 months in the placebo group (HR = 0.79, 95% CI 0.66 to 0.96, p=0.0151). This analysis did not reach prespecified boundary for significance (p= 0.0034). Results are presented in Table 8. (Source: EPAR Assessment report).[6]

The expected OS benefit did not reach the prespecified statistical significance level even at the 3rd interim analysis.

Table 8. Overall survival in the COU-AA-302 study at the second interim and third interim analysis. (ITT)[*]

Overall survival	Second interim Analysis		Third interim Analysis[†]	
	AA + Pred (N= 546)	**Pred Alone (N= 542)**	**AA + Pred (N= 546)**	**Pred Alone (N= 542)**
Event, n (%)	147 (26.9)	186 (34.3)	200 (36.6)	234 (43.2)
Censored, n (%)	399 (73.1)	356 (65.7)	346 (63.4)	308 (56.8)
Overall survival (months)				
25th percentile (95% CI)	21.19 (19.15, 24.38)	18.76 (17.84, 20.47)	21.29 (19.15, 23.33)	18.86 (17.81, 20,60)
Median (95% CI)	NE (NE, NE)	27.24 (25.95, NE)	35.29 (31.24, 35.29)	30.13 (27.30, 34.10)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	35.29 (NE, NE)	34.69 (34.10, NE)
Range	(0.0+, 30.0+)	(0.0+, 30.8+)	(0.0+, 35.3)	(0.0+, 35.7+)
6-month event-free rate	0.980	0.972	0.980	0.972
12-month event-free rate	0.912	0.901	0.807	0.901
18-month event-free rate	0.807	0.778	0.694	0.778
24-month event-free rate	0.707	0.600	0.570	0.628
30-month event-free rate	0.616	0.458	0.570	0.521
36-month event-free rate	0.000	0.000	0.000	0.146
P-value[‡]	0.0097[§]		0.0151[§]	
Hazard ratio (95% CI)	0.75 (0.61, 0.93)		0.79 (0.66, 0.96)	

AA= abiraterone acetate; **CI**=confidence interval; **NE** = not estimable; **Pred**= Prednisone

Source: EPAR Assessment report[6]

Note: + = censored observation

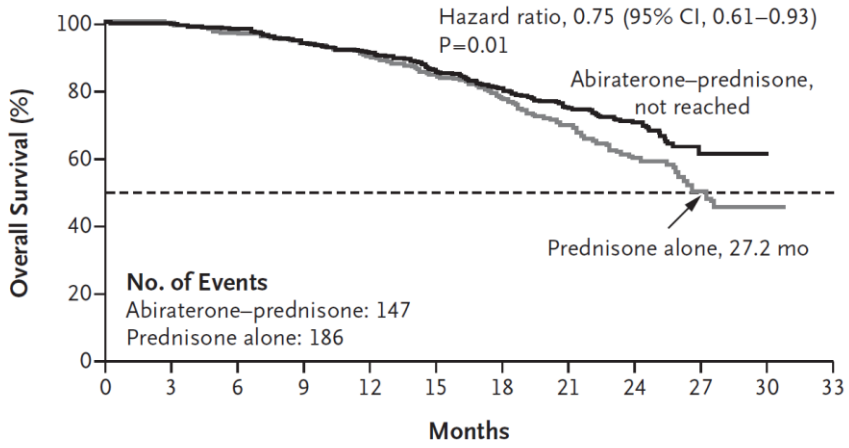
* Second interim analysis (cut-off date: 20 Dec 2011) after 333 deaths and third interim analysis (cut-off date: 22 May 2012) after 434 deaths. The median OS was not reached in either arm of treatment at time of the first interim OS analysis (20 December 2010 - 209 events)

†In February 2012 the data and safety monitoring committee unanimously recommended unblinding the study and crossover of patients in the prednisone-alone group to abiraterone treatment. At the time of unblinding, statisticians who were employees of the sponsor performed the analyses.

‡Analyses were performed with the use of a log-rank test stratified by the baseline score on the Eastern Cooperative Oncology Group Performance Status score (0 or 1)

§The prespecified boundary for significance P≤0.0005 and P≤0.0034 was not reached for the overall survival at the second and third interim analysis respectively.

Figure 2. Kaplan-Meier estimates of overall survival in the COU-AA-302 study at the 2nd interim analysis (cut-off date: 20 Dec 2011) after 333 deaths. Adapted from Ryan 2013[2]



No. at Risk

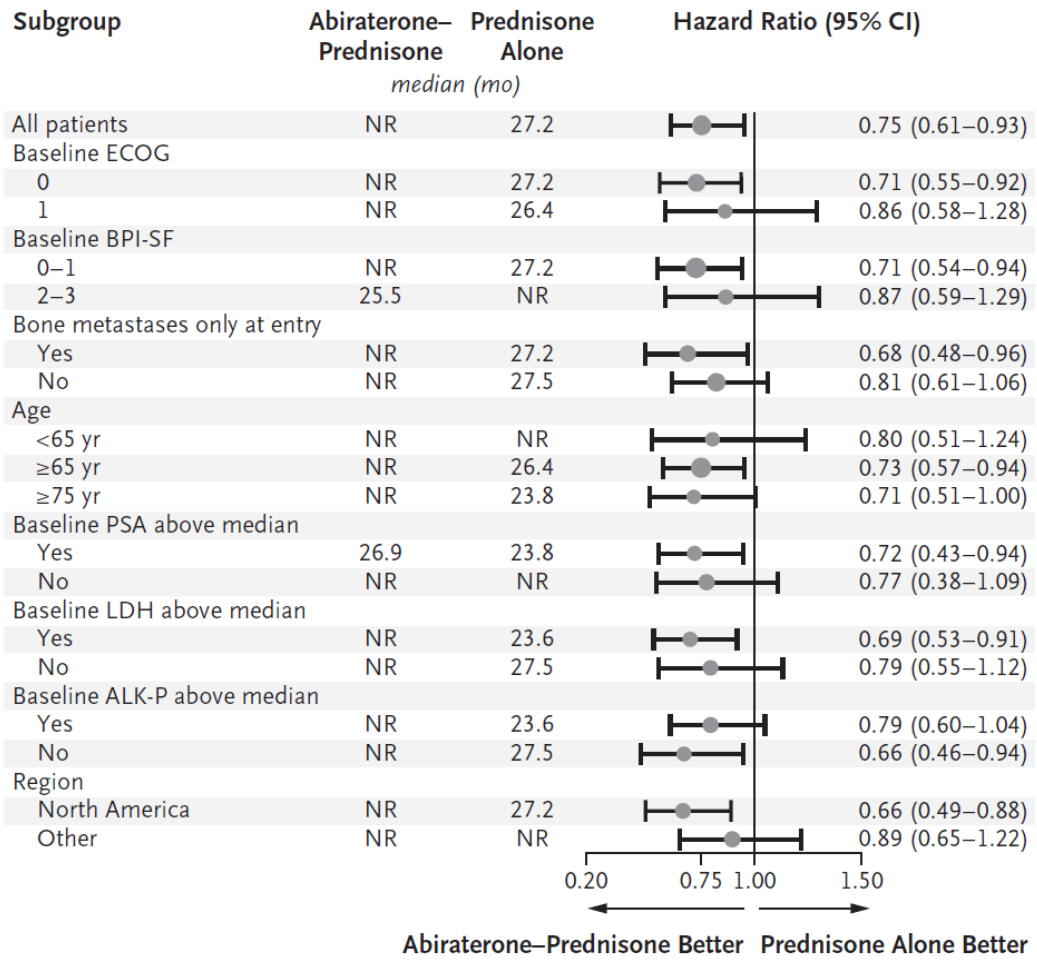
AA + prednisone	546	538	524	503	482	452	412	258	120	27	0	0
Prednisone alone	542	534	509	493	465	437	387	237	106	25	2	0

AA= Abiraterone Acetate

Subgroup analyses at the time of the second interim (20 December 2011) showed that all Hazard Ratios were less than 1.0) (Figure 3). However, no conclusion can be made as if abiraterone is more beneficial than placebo in these subgroup analyses.

In an abstract by Saad et al.[14] which reported the results when the median follow-up for OS was 27.1 month, it was found that prior use of bone-targeted therapies (BTT) had no impact on OS (HR=0.92; 95% CI: 0.75, 1.12; p=0.409). However, in another abstract by Saad et al.[18] which reported the results when the median follow-up was 27.1 month, it was found that the use of concomitant BTT for treatment of bone metastases was associated with improved OS (HR=0.754; 95% CI: 0.604, 0.940; p=0.012).

Figure 3. Subgroup analysis of overall survival in the COU-AA-302 study at the 2nd interim analysis (cut-off date: 20 Dec 2011) after 333 deaths. Adapted from Ryan 2013[2]



b) Radiographic Progression-Free Survival (rPFS)

One of the co-primary end points in the COU-AA-302 study was rPFS, which was defined as the time interval from the date of randomization to the first date of radiographic progression or death due to any cause. Radiographic disease progression was defined by the appearance of two or more new bone lesions on bone scan as per PCWG2 criteria or by soft tissue lesions by CT or MRI using modified RECIST criteria. log-rank test was used to evaluate overall survival, with stratification according to ECOG performance-status score. Distribution curve, median and 95% confidence interval were estimated using the Kaplan-Meier method. At the time of the first interim analysis radiographic progression was evaluated by an independent review, after that radiographic progression was assessed by an investigator.

At the time of the first interim rPFS analysis (20 December 2010) 401 subjects had radiographic disease progression or died 150 subjects (28%) in the abiraterone and 251 subjects (46%) in the placebo group, the median rPFS was not reached in the abiraterone group and was 8.3 months in the placebo group, (HR = 0.43, 95% CI 0.35 to 0.52, p<0.0001) the study met its prespecified significance level of 0.01. Results are presented in Table 9 and Figure 4. (Source: EPAR Assessment report).[6]

At the time of the second interim (20 December 2011), 607 radiographic disease progression or died had occurred, this analysis was consistent with the first interim analysis, showing a median rPFS of 16.5 months in the abiraterone group and 8.3

months in the placebo group (HR=0.53, 95% CI 0.45-0.62, p<0.0001). Results are presented in Table 9. (Source: EPAR Assessment report).[6]

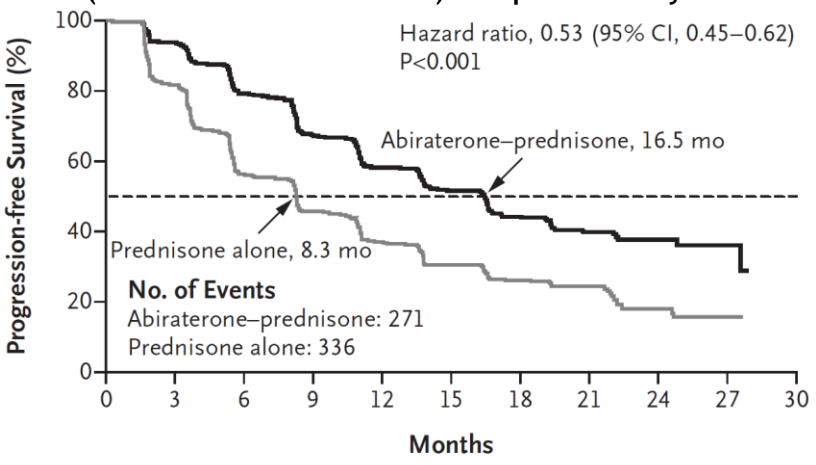
At the time of the third interim (22 May 2012) after unblinding the study and crossover of patients in the placebo group to abiraterone treatment happened, Hazard ratio and P-value were similar to that of the second interim analysis. (Source: pCODR Submission).[17]

Table 9. Radiographic progression-free survival first interim and Second Interim analysis in the COU-AA-302 study*

rPFS	First interim Analysis		Second interim Analysis	
	Abiraterone plus Prednisone (N= 546)	**Prednisone Alone (N= 542)**	**Abiraterone plus Prednisone (N= 546)**	**Prednisone Alone (N= 542)**
Event, n (%)	150 (27.5)	251 (46.3)	271 (49.6)	336 (62.0)
Censored, n (%)	396 (72.5)	291 (53.7)	275 (50.4)	206 (38.0)
Time to event (months)				
25th percentile (95% CI)	8.28 (8.02, 9.49)	3.65 (3.52, 4.04)	8.15 (7.03, 8.28)	3.61 (3.48, 3.75)
Median (95% CI)	NE (11.66, NE)	8.28 (8.12, 8.54)	16.46 (13.80, 16.79)	8.25 (8.05, 9.43)
75th percentile (95% CI)	NE (NE, NE)	NE (13.63, NE)	NE (27.60, NE)	19.32 (16.39, 22.21)
Range	(0.0+, 17.7+)	(0.0+, 16.6+)	(0.0+, 27.9+)	(0.0+, 27.7+)
6-month event-free rate	0.799	0.579	0.794	0.564
12-month event-free rate	0.557	0.34	0.583	0.371
18-month event-free rate	0.507	0.254	0.444	0.262
24-month event-free rate	-	-	0.377	0.181
30-month event-free rate	-	-	0.289	0.155
P-value†	< 0.0001		< 0.0001‡	
Hazard ratio (95% CI)	0.425 (0.347, 0.522)		0.530 (0.451, 0.623)‡	
CI=confidence interval; **NE** = not estimable				

Source: EPAR Assessment report[6]
Note: + = censored observation
*At first interim an independent review of radiographic progression free survival was undertaken cut-off date: 20 Dec 2010. At second Interim analysis radiographic progression free survival was assessed by an investigator cut-off date: 20 Dec 2011.
†Analyses were performed with the use of a log-rank test stratified by the baseline score on the Eastern Cooperative Oncology Group Performance Status score (0 or 1)
‡At the third interim analysis (cut-off date: 22 May 2012) which was undertaken after unblinding the study and crossover of patients in the prednisone-alone group to abiraterone treatment median time to progression, Hazard ratio and P-value were similar to that of the second interim analysis.

Figure 4. Kaplan-Meier estimates of radiographic progression-free survival in the COU-AA-302 study at the 2nd interim analysis (cut-off date: 20 Dec 2011). Adapted from Ryan 2013[2]

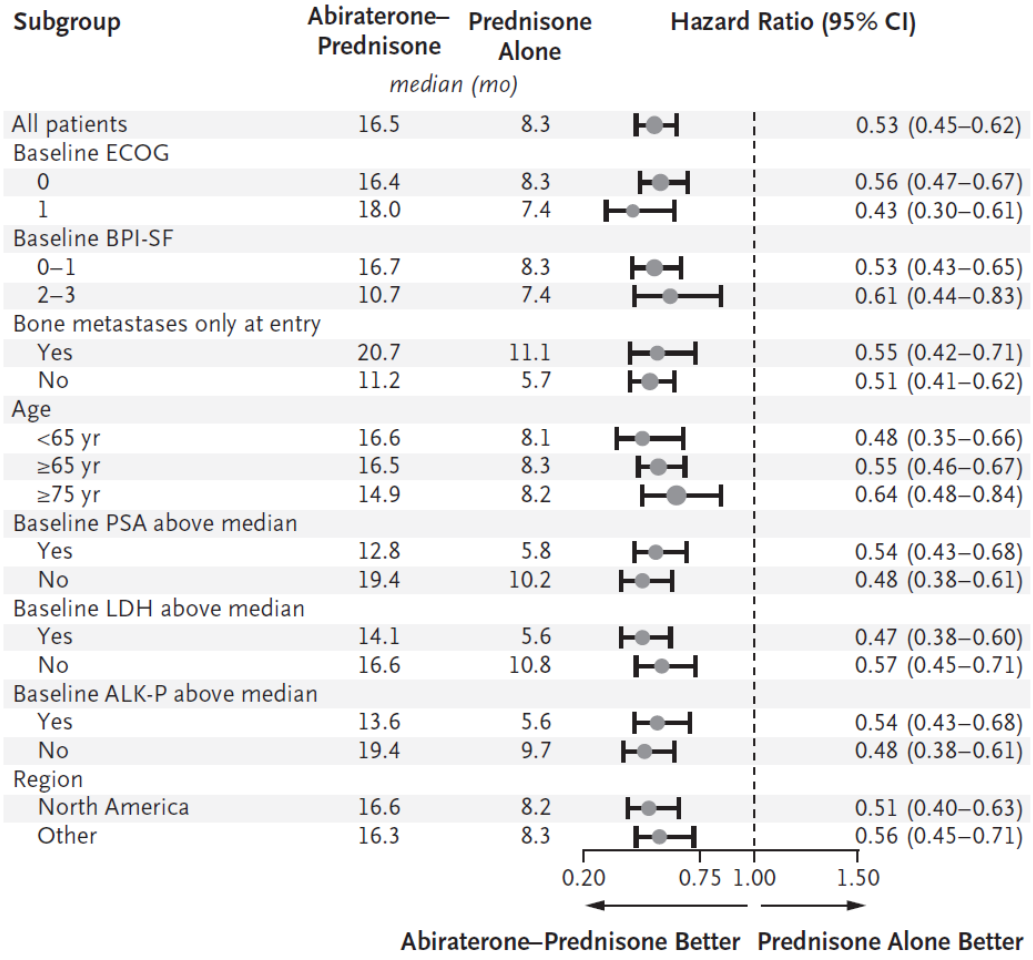


No. at Risk											
AA + pred	546	485	389	311	240	195	155	85	38	9	0
Pred alone	542	406	244	177	133	100	80	37	14	1	0

AA= Abiraterone Acetate; **Pred**= Prednisone

Subgroup analyses at the time of the second interim (20 December 2011) showed consistent rPFS benefit of abiraterone acetate across all subgroups (all HR<1.0) (Figure 5). However, no conclusion can be made as if abiraterone is more beneficial than placebo in these subgroup analyses.

Figure 5. Subgroup analysis of radiographic progression-free survival in the COU-AA-302 study at the 2nd interim analysis (cut-off date: 20 Dec 2011). Adapted from Ryan 2013[2]



c) Time to PSA Progression and PSA Response

Time to PSA progression was defined as the time interval from randomization to the date of the PSA progression as defined in the PCWG2 criteria. A log-rank test was used to evaluate overall survival, with stratification according to ECOG performance-status score. Distribution curve, median and 95% confidence interval were estimated using the Kaplan-Meier method.

At the time of the first interim analysis (20 December 2010), 191 subjects (35.0%) in the abiraterone group had PSA progression with median time to PSA progression was 13.8 months versus 306 subjects (56.5%) in the placebo group with median time to PSA progression was 5.6 months, HR=0.40, 95% CI (0.33-0.48), p<0.0001, Results are presented in Table 10. (Source: EPAR Assessment report).[6]

At the time of the second interim analysis (20 December 2011), 339 subjects (62.1%) in the abiraterone group had PSA progression with median time to PSA progression was 11.1 months versus 381 subjects (70.3%) in the placebo group with median time to PSA progression was 5.6 months, HR=0.49, 95% CI (0.42-0.57), p<0.0001. Results are presented in Table 10; Kaplan-Meier curves of time to PSA progression are shown in Figure 6. (Source: EPAR Assessment report,[6] Ryan 2013[2])

Table 10. Time to PSA Progression Analysis, first interim and Second Interim analysis in the COU-AA-302 study, ITT

Time to PSA Progression	AA + Pred n (%)	AA + Pred Median mo (95% CI)	Pred alone n (%)	Pred alone Median mo (95% CI)	Hazard Ratio (95% CI)	P value
Interim 2 (CCO 20 Dec 2011)	339 (62.1)	11.07 (8.51, 11.24)	381 (70.3)	5.55 (5.39, 5.59)	0.488* (0.420, 0.568)	<0.0001†
Interim 1 (CCO 20 Dec 2010)	191 (35.0)	13.8 (11.1, NE)	306 (56.5)	5.6 (5.3, 5.6)	0.398* (0.3303, 0.4790)	<0.0001†

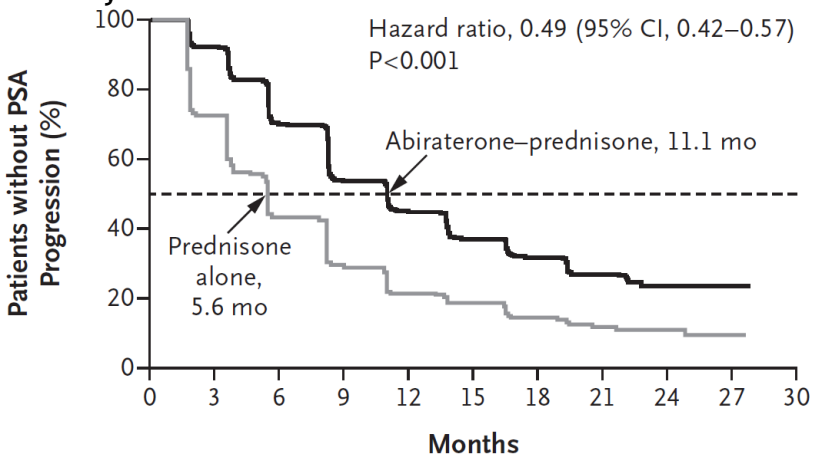
AA= abiraterone acetate; **CCO**=clinical cutoff; **CI**=confidance interval, **ITT**=intent to treat; **Pred=** Prednisone

Source: EPAR Assessment report[6]

*Hazard ratio <1 favors Abiraterone Acetate

†Analyses were performed with the use of a log-rank test stratified by the baseline score on the Eastern Cooperative Oncology Group Performance Status score (0 or 1).

Figure 6. Kaplan-Meier estimates of time to PSA progression according to PCWG2 criteria in the COU-AA-302 study at the 2nd interim analysis (cut-off date: 20 Dec 2011). Adapted from Ryan 2013[2]



No. at Risk

AA + pred	546	472	337	241	189	145	116	63	21	6	0
Pred alone	542	335	169	106	71	57	39	15	11	1	0

AA= Abiraterone Acetate; **PCWGE2**=Prostate Cancer Clinical Trials Working Group 2; **Pred=** Prednisone; **PSA**=prostate-specific antigen

PSA response rate was defined as proportion of patients achieving ≥50% reduction in PSA levels from baseline according to PCWG2 criteria. At the time of the second interim analysis (20 December 2011), A confirmed PSA response was observed in 336 subjects (61.5%) in the abiraterone group and 129 subjects (23.8%) in the placebo group, Relative Risk= 2.59, 95% CI (2.19, 3.05), p<0.0001. Results are presented in Table 11. (Source: pCODR Submission[17] (Health Canada Module 2.7.3), Ryan 2013[2])

Table 11. PSA Response Rate Based on PCWG2 Criteria from the COU-AA-302 study

Objective response rate	Abiraterone + Prednisone (N= 546)	Prednisone Alone (N= 542)
Subjects with PSA Response, n (%)	374 (68.5%)	156 (28.8%)
Confirmed, n (%)	336 (61.5%)	129 (23.8%)
Unconfirmed, n (%)	38 (7.0%)	27 (5.0%)
Relative Risk (95% CI)*	2.59 (2.19, 3.05)	
P-value†	<0.0001	
CI=confidence interval; **PCWG2**=Prostate Cancer Working Group		

Source: pCODR Submission[17] (Health Canada Module 2.7.3)
*Relative Risk is based on confirmed response. Relative Risk > 1 favors Abiraterone Acetate
†p-value is based on confirmed response from Chi-squared test

d) Objective Response Rate

Objective response rate (ORR) was defined as proportion of patients with measurable disease achieving complete response (CR) or partial response (PR) according to modified RECIST criteria (in order to be considered targeted lesion baseline lymph node size must be ≥2cm).

At the time of the first interim analysis (20 December 2010), ORR were assessed by independent review, the proportion of subjects with measurable disease at baseline who had achieved objective response (CR or PR) was 36% in the abiraterone group and 16% in the placebo group, Relative Risk= 2.27, 95% CI (1.59, 3.25), p<0.0001. Results are presented in Table 12. (Source: EPAR Assessment report,[6] Ryan 2013[2])

Table 12. Objective response rate in patients with measurable disease (RECIST) from the COU-AA-302 study*

Objective response rate	Abiraterone + Prednisone (N= 546)	Prednisone Alone (N= 542)
Subjects with measurable disease at baseline	220	218
Objective response, n (%)	78 (35.5)	34 (15.6)
Complete response, n (%)	24 (10.9)	8 (3.7)
Partial response, n (%)	54 (24.5)	26 (11.9)
Non-Responder, n (%)	142 (64.5)	184 (84.4)
Stable disease	61%	69%
Progressive disease	2%	15%
Relative Risk (95% CI)†	2.27 (1.59, 3.25)	
P-value‡	<0.0001	
CI=confidence interval; **RECIST**= Response Evaluation Criteria in Solid Tumors		

Source: Ryan 2013,[2] EPAR Assessment report[6]
* Objective response rate results by RECIST criteria were ascertained in patients with measurable disease at baseline and based on independent review
† Relative Risk is based on objective response; Relative Risk > 1 favors Abiraterone Acetate
‡p-value is from Chi-squared test

e) Patient-Reported Outcomes

Study subjects completed Brief Pain Inventory-Short Form (BPI-SF) and Functional Assessment of Cancer Therapy-Prostate (FACT-P) assessment instruments during their treatment period. Data from the 20 December 2011 clinical cut-off was used to perform the analyses.

e.1. Brief Pain Inventory

Self-assessment of pain experienced during the study was assessed by BPI-SF. The time to average pain intensity progression was defined as the time interval from randomization to the first date a subject experienced an increase of ≥30% from baseline in the average of BPI-SF pain intensity item scores (items 3 [worst], 4 [least], 5 [average], and 6 [right now]) observed at 2 consecutive evaluations ≥4 weeks apart without a decrease in analgesic usage score. Rating scale for items 3, 4, 5 of BPI-SF ranges from 0 = no pain to 10 =pain as bad as you could imagine, lower score indicates lower pain severity.

For every assessment, the cumulative compliance rate for completion of the BPI-SF was 95% or greater for both treatment groups. When compared with placebo, treatment with abiraterone significantly reduced the risk of average pain intensity progression by 18% (HR=0.82, 95% CI= (0.67, 0.999), p=0.0490). The median time to average pain intensity progression in the abiraterone group was 26.7 months versus 18.4 months in the placebo group. Median time to opiate use for cancer-related pain was significantly delayed with abiraterone when compared to prednisone alone (not reached vs. 23.7 months, respectively; HR: 0.69, 95% CI: 0.57 to 0.83; P<0.001)

e.2. Quality of Life

Quality of life was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. The FACT-P is a multidimensional, self-reported instrument used to assess health related quality of life (HRQoL) in men with prostate cancer, it consists of FACT-G (general) a 27 core items to assess patient function in four domains (physical, social/family, emotional, functional well-being) which measures general HRQoL in cancer patients, and supplemented by a 12-item prostate cancer subscale (PCS) to assess prostate cancer-specific quality of life. Each item is rated on a Likert type scale from 0 to 4; these rating are then combined to produce subscale scores for each domain in addition to a global score. Higher overall scores indicate better HRQoL. Range of FACT-P total score is from 0 to 156. A clinically meaningful change was estimated to be 6 to 10 for FACT-P total score.[28]
In the COU-AA-302 time to functional status decline was defined as the months from randomization to the first date a patient has a decrease of 10 points or more on FACT-P score.

At any given assessment, the cumulative compliance rate for completion of the FACT-P instrument was 95% for both treatment groups. When compared with placebo, treatment with abiraterone prolonged the time to FACT-P (Total Score) degradation by 22% (HR=0.78, 95% CI= (0.66, 0.92), p=0.0028). The median time to degradation FACT-P (Total Score) in the abiraterone group was 12.7 months versus 8.3 months in the placebo group. In all FACT-P categories except Social/Family Well Being there seem to be significant decreases in the median time to degradation for subjects in the abiraterone group when compared with the placebo group. Detailed results are shown in Table 13.

Even though results of median time to degradation FACT-P (Total Score) and almost all FACT-P categories might seems significantly better for abiraterone when compared with placebo group, however the interpretation of statistical significance based on

interim analyses should be cautioned due to inflated Type I error rates and different alpha level required to claim statistical significance which was not done.

Table 13. Functional Assessment of Cancer Therapy-Prostate scores from the COU-AA-302 study

FACT-P Subscale	Median (95% CI) Time to Degradation (months)*		Hazard ratio (95% CI)	p-value
	Abiraterone + Prednisone	Prednisone Alone		
FACT-P (Total Score)	12.65 (11.07, 14.00)	8.31 (7.39, 10.61)	0.778 (0.659, 0.918)	0.0028
Total Outcome Index†	13.86 (11.99, 16.49)	9.26 (8.31, 11.07)	0.745 (0.630, 0.882)	0.0006
PCS	11.10 (8.64, 13.80)	5.78 (5.49, 8.31)	0.703 (0.598, 0.827)	< 0.0001
FACT–G	16.56 (13.86, 19.35)	11.07 (8.51, 14.75)	0.758 (0.634, 0.906)	0.0023
Physical Well Being	14.78 (13.63, 16.82)	11.07 (9.10, 13.80)	0.759 (0.637, 0.904)	0.002
Social/Family Well Being	18.40 (13.83, NE)	16.59 (11.07, NE)	0.940 (0.775, 1.139)	0.5283
Emotional Well Being	22.11 (17.35, NE)	14.16 (13.34, 19.45)	0.714 (0.586, 0.869)	0.0008
Functional Well Being	13.34 (11.01, 15.74)	8.35 (7.39, 10.12)	0.760 (0.644, 0.898)	0.0012
FACT-G=Functional Assessment of Cancer Therapy-General; **FACT-P**=Functional Assessment of Cancer Therapy-Prostate; **PCS=** Prostate Cancer Scale				

Source: EPAR Assessment report[6]

*Time to Functional status decline was defined as the months from randomization to the first date a patient has a decrease of 10 points or more on FACT-P score.

†Trial Outcome Index is based on the functional and physical well-being subscales of the FACT-G and the PCS.

Harms Outcomes

The safety analysis population consisted of 1082 patients and safety assessments were performed continuously throughout the study and up to 30 days after the last dose of study medication. Adverse events were classified using the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 and monitored by the IDMC.

At the time of the second interim analysis, the median time on treatment was 13.8 months in the abiraterone group and 8.3 months in the placebo group. Overall, the rates of adverse events were similar in the abiraterone and placebo groups.

All data reported in the harms section are as of the 20 December 2011 data cut-off date.

a) Dose modifications

Ninety-three point five percent (93.5%) of subjects in the abiraterone group and 98.1% of subjects in the placebo group had no dose reductions, the most frequently reported reason for dose reduction was 'Restart dosing'. Eighty-one (81%) of subjects in the abiraterone group and 88% of subjects in the placebo group had no dose interruption. Most dose modifications were due to adverse events or toxicity. Detailed results are presented in Table 14.

Table 14. Dose modifications of abiraterone acetate plus Prednisone or Prednisone alone from the COU-AA-302 study

	Abiraterone + Prednisone (N= 542)	Prednisone Alone (N= 540)
Number of Dose Reductions, n (%)		
0	507 (93.5)	530 (98.1)
1	25 (4.6)	10 (1.9)
2	10 (1.8)	0
Reason for Dose Reduction, n (%)	35 (6.5)	10 (1.9)
Adverse event or toxicity	5 (0.9)	1 (0.2)
Serious Adverse Event or Hospitalization	0	0
Restart Dosing	29 (5.4)	8 (1.5)
Other	1 (0.2)	1 (0.2)
Number of Dose Interruption, n (%)		
0	439 (81.0)	475 (88.0)
1	71 (13.1)	50 (9.3)
2	24 (4.4)	12 (2.2)
3	5 (0.9)	2 (0.4)
>3	3 (0.6)	1 (0.2)
Reason for Dose Interpretation, n (%)	103 (19.0)	65 (12.0)
Adverse event or toxicity	71 (13.1)	35 (6.5)
Serious Adverse Event or Hospitalization	34 (6.3)	26 (4.8)
Other	12 (2.2)	12 (2.2)

Source: EPAR Assessment report[6]

b) Summary of Adverse Events

Treatment-emergent adverse events were reported in 99.1% of subjects in the abiraterone group and in 97% of subjects in the placebo group.

Higher rates of Grade 3-4 treatment-emergent adverse events (TEAEs) (48% vs. 42%), serious TEAEs (33% vs. 26%), TEAEs leading to treatment discontinuation (10% vs. 9%), TEAEs leading to death (4% vs. 2%), and all deaths within 30 days of last dose (3.3% vs. 1.5%) were reported in the abiraterone group than those in the placebo group. Results are summarized in table 15.

Table 15. Summary of adverse events from the COU-AA-302 study

Adverse Events, n (%)	Abiraterone + Prednisone (N= 542)	Prednisone Alone (N= 540)
Treatment-Emergent Adverse Events (TEAEs)	537 (99.1)	524 (97.0)
Drug-related	424 (78.2)	413 (76.5)
Grade 3-4 TEAEs	258 (47.6)	225 (41.7)
Drug-related	122 (22.5)	91 (16.9)
Serious TEAEs	178 (32.8)	142 (26.3)
Drug-related	59 (10.9)	54 (10.0)
Grade 3-4	150 (27.7)	117 (21.7)
Drug-related Grade 3-4	53 (9.8)	39 (7.2)

Adverse Events, n (%)	Abiraterone + Prednisone (N= 542)	Prednisone Alone (N= 540)
TEAEs Leading to Treatment Discontinuation	55 (10.1)	49 (9.1)
Drug-related	29 (5.4)	23 (4.3)
TEAEs Leading to Death	20 (3.7)	12 (2.2)
Drug-related	5 (0.9)	4 (0.7)
All deaths within 30d of last dose	18 (3.3)	8 (1.5)
Underlying Disease	7 (1.3)	3 (0.6)
Other	10 (1.8)	4 (0.7)
Unknown	1 (0.2)	1 (0.2)

Source: EPAR Assessment report[6]

c) Serious Adverse Events

Treatment-emergent serious adverse events (TESAEs) were more commonly reported in the abiraterone group (32.8%) than in the placebo group (26.3%). Higher rates in TESAEs in the abiraterone group than in the placebo group in all terms except in musculoskeletal and connective tissue disorders, and in respiratory, thoracic and mediastinal disorders. Results are summarized in table 16.

Table 16. Serious Adverse Events Reported in at Least 1% of Subjects from the COU-AA-302 study

Serious Adverse Events, n (%)	Abiraterone + Prednisone (N= 542)	Prednisone Alone (N= 540)
Total number of subjects with a treatment-emergent serious adverse event	178 (32.8)	142 (26.3)
Infections and infestations	45 (8.3)	31 (5.7)
Nervous system disorders	30 (5.5)	13 (2.4)
Renal and urinary disorders	27 (5.0)	25 (4.6)
Musculoskeletal and connective tissue disorders	14 (2.6)	18 (3.3)
Gastrointestinal disorders	16 (3.0)	13 (2.4)
General disorders and administration site conditions	13 (2.4)	12 (2.2)
Cardiac disorders	29 (5.4)	14 (2.6)
Metabolism and nutrition disorders	13 (2.4)	6 (1.1)
Respiratory, thoracic and mediastinal disorders	15 (2.8)	21 (3.9)
Blood and lymphatic system disorders	7 (1.3)	7 (1.3)

Source: EPAR Assessment report[6]

d) Treatment-Emergent Adverse Events of Special Interest

Adverse events of special interest with abiraterone treatment include the mineralocorticoid-associated events of fluid retention/edema, hypokalemia, hypertension, cardiac disorders, and hepatotoxicity (ALT and AST). Higher rates of adverse events of special interest were reported in the abiraterone group (66%) than in the placebo group (50%).

Fluid retention/oedema adverse events were reported in 28% of subjects in the abiraterone group and 24% of subjects in the placebo group. Most Fluid retention/oedema AEs were Grade 1 or 2.

Hypokalaemia events were reported in 17% of subjects in the abiraterone group and 13% of subjects in the placebo group. Most Hypokalaemia AEs were Grade 1 or 2.

Hypertension events were reported in 22% of subjects in the abiraterone group and 13% of subjects in the placebo group. Grade 3 or 4 hypertensive events were reported in 4% of subjects in the abiraterone group and 3% of subjects in the placebo group.

Hepatotoxicity adverse events reported as LFT were reported more in the abiraterone group when compared with the placebo group. Where ALT increases were reported in 12% in the abiraterone group versus 5% in the placebo group and for AST 11% versus 5%. Treatment discontinuations due to adverse events of hepatotoxicity were reported in 2.2% of subjects in the abiraterone group versus 0.2% in the placebo group. Higher percentage of patients (1.1%) in the abiraterone group reported hepatotoxicity SAEs than in the placebo group (0.6%).[6]
Nineteen percent (19%) of subjects in the abiraterone group and 16% of subjects in the placebo group reported cardiac disorders events. Arrhythmias was reported in 14% in the abiraterone group versus 12% in the placebo group, ischaemic heart disease was reported in 4% in the abiraterone group versus 3% in the placebo group, cardiac disorders for other causes was reported in 3% in each treatment group, and cardiac failure was reported in 2% in the abiraterone group versus 0.4% in the placebo group.[6] Results are summarized in table 17.

Table 17. Treatment-Emergent Adverse Events of Special Interest from the COU-AA-302 study

Adverse Event, n (%)	Abiraterone + Prednisone (N = 542)		Prednisone Alone (N = 540)	
	Grade 1-4	Grade 3 or 4	Grade 1-4	Grade 3 or 4
Total number of subjects with a treatment-emergent serious adverse event of special interest	360 (66.4)		272 (50.4)	
Fluid retention or edema	150 (28)	4 (<1)	127 (24)	9 (2)
Hypokalemia	91 (17)	13 (2)	68 (13)	10 (2)
Hypertension	118 (22)	21 (4)	71 (13)	16 (3)
Cardiac disorder*	102 (19)	31 (6)	84 (16)	18 (3)
Atrial fibrillation	22 (4)	7 (1)	26 (5)	5 (<1)
ALT increased	63 (12)	29 (5)	27 (5)	4 (<1)
AST increased	58 (11)	16 (3)	26 (5)	5 (<1)

Source: Ryan 2013[2]
*Cardiac disorders included ischemic heart disease, myocardial infarction, supraventricular tachyarrhythmia, ventricular tachyarrhythmia, cardiac failure, and possible arrhythmia-related investigations, signs, and symptoms.

e) Treatment-Emergent Adverse Events

The most frequently reported AEs, reported in ≥15% of subjects in either the abiraterone or placebo group were: fatigue (39% versus 34%), back pain (32% in each treatment group), arthralgia (28% versus 24%), nausea (22% in each treatment group), constipation (23% versus 19%), hot flush (22% versus 18%), diarrhea (22%

versus 18%), bone pain (20% versus 19%), Muscle spasm (14% versus 20%), Pain in extremity (17% versus 16%), cough (17% versus 14%), fluid retention or edema (28% vs. 24%), hypokalemia (17% vs. 13%), hypertension (22% vs. 13%), and cardiac disorder (19% vs. 16%). Results are summarized in Table 18 below.

Grade 3 or 4 AEs were reported in 48% of subjects in the abiraterone group versus 42% in the placebo group. The most frequently reported Grade 3 or 4 AEs were hypertension 4% in the abiraterone group versus 3% in the placebo group, back pain 3% in the abiraterone group versus 4%in the placebo group, alanine aminotransferase increased 5.4% in the abiraterone group versus 0.7% in the placebo group, and aspartate aminotransferase increased 3.0% in the abiraterone group versus 0.9% in the placebo group.[6]

Table 18. Treatment-Emergent Adverse Events of grades 1 to 4 Reported in at Least 15% of Subjects in Any treatment Group in the COU-AA-302 study

Adverse Event, n (%)	Abiraterone + Prednisone (N = 542)	Prednisone Alone (N = 540)
Fatigue	212 (39)	185 (34)
Back pain	173 (32)	173 (32)
Arthralgia	154 (28)	129 (24)
Nausea	120 (22)	118 (22)
Constipation	125 (23)	103 (19)
Hot flush	121 (22)	98 (18)
Diarrhea	117 (22)	96 (18)
Bone pain	106 (20)	103 (19)
Muscle spasm	75 (14)	110 (20)
Pain in extremity	90 (17)	85 (16)
Cough	94 (17)	73 (14)
Fluid retention or edema	150 (28)	127 (24)
Hypokalemia	91 (17)	68 (13)
Hypertension	118 (22)	71 (13)
Cardiac disorder	102 (19)	84 (16)

Source: Ryan 2013[2]

f) Adverse event leading to death

Deaths due to adverse events occurred in 20 patients (3.7%) in the abiraterone group and 12 patients (2.2%) in the placebo group (see Table 19). Five (0.9%) of these deaths in the abiraterone group and 4 (0.7%) in the placebo group were considered drug-related. The most common adverse events leading to death were general disorders, including disease infections including pneumonia and respiratory tract infection.

Table 19. Adverse event leading to death

Adverse Event, n (%)	Abiraterone + Prednisone (N= 542)	Prednisone Alone (N= 540)
Total no. subjects with a treatment-emergent adverse event leading to death	20 (3.7)	12 (2.2)

Source: Ryan 2013[2]

6.4 Ongoing Trials

At present, no relevant ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review

8 ABOUT THIS DOCUMENT

This Final 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 Abiraterone acetate for Metastatic Castration-Resistant Prostate Cancer in patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. The manufacturer, as the primary data owner, did not agree to the disclosure of some Clinical information, therefore, this information was redacted from this publicly available Guidance Report.

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

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

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **Embase** 1974 to 2013 July 25**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

#	Searches	Results
1	(Zytiga* or abiraterone or cb-7630 or cb7630 or CB-7598 or CB7598).ti,ot,ab,sh,rn,hw,nm.	1642
2	(154229-18-2 or EM5OCB9YJ6 or 154229-19-3 or G819A456D0).rn,nm.	1119
3	or/1-2	1656
4	3 use pmez	450
5	*abiraterone/	93
6	*abiraterone acetate/	199
7	(Zytiga* or abiraterone or cb-7630 or cb7630 or CB-7598 or CB7598).ti,ab.	1024
8	or/5-7	1051
9	8 use oemezd	652
10	4 or 9	1102
11	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	463988
12	Randomized Controlled Trial/	734318
13	Randomized Controlled Trials as Topic/	130506
14	"Randomized Controlled Trial (topic)"/	36062
15	Controlled Clinical Trial/	491617
16	Controlled Clinical Trials as Topic/	7110
17	"Controlled Clinical Trial (topic)"/	1976
18	Randomization/	143415
19	Random Allocation/	143415
20	Double-Blind Method/	247818
21	Double Blind Procedure/	119050
22	Double-Blind Studies/	205505

23	Single-Blind Method/	36928
24	Single Blind Procedure/	17953
25	Single-Blind Studies/	36928
26	Placebos/	268262
27	Placebo/	235004
28	Control Groups/	47953
29	Control Group/	47953
30	(random* or sham or placebo*).ti,ab,hw.	2186343
31	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	387121
32	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	774
33	(control* adj3 (study or studies or trial*)).ti,ab.	684151
34	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.	60652
35	allocated.ti,ab,hw.	83103
36	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	47639
37	or/11-36	2749653
38	10 and 37	382
39	Androstenols/ae, ct, to, po use pmez	36
40	*abiraterone/ae, ct or *abiraterone acetate/ae, ct	113
41	39 or 40	149
42	10 and 41	134
43	exp *drug toxicity/	69700
44	exp *drug hypersensitivity/	46477
45	*abnormalities, drug-induced/	44274
46	exp *postoperative complications/	348347
47	exp *intraoperative complications/	21025
48	exp *adverse drug reaction/	178437
49	exp *drug safety/	11832
50	exp *side effect/	48218
51	exp *postoperative complication/	348347

52	exp *peroperative complication/	21025
53	"side effects (drug)"/	0
54	"side effects (treatment)"/	0
55	(safe or safety).ti.	199198
56	side effect*.ti.	29638
57	(adverse or undesirable or harm* or toxic or injurious or risk or risks or reaction* or toxic or toxicit* or toxologic* or complication* or noxious or tolerability or poison* or teratogen* or intoxication or warning*).ti.	1644258
58	((drug or chemically) adj induced).ti.	26233
59	or/43-58	2420779
60	10 and 59	35
61	42 or 60	168
62	38 or 61	444
63	limit 62 to english language	414
64	remove duplicates from 63	330

2. Literature search via PubMed

Search	Add to builder	Query	Items found	Time
#1	Add	Search **(Zytiga* OR abiraterone OR cb-7630 OR cb7630 OR CB-7598 OR CB7598 OR 154229-18-2 OR EM5OCB9YJ6 OR 154229-19-3 OR G819A456D0) AND publisher[sb]**	24	13:08:10

3. Cochrane Central Register of Controlled Trials (Central)

Issue 6 of 12, June 2013

There are 6 results from 704315 records for your search on 'Zytiga* OR abiraterone OR cb-7630 OR cb7630 OR CB-7598 OR CB7598 in title abstract keywords in Trials'

4. Grey Literature search via:

Clinical trial registries:

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

Ontario Institute for Cancer. Ontario Cancer trials
http://www.ontario.canadiancancertrials.ca/

Search terms: Zytiga or abiraterone

Select international agencies including:

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

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

Search terms: Zytiga or abiraterone

Conference abstracts:

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

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

Search terms: Zytiga or abiraterone / last 5 years

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