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Title	Use of abiraterone acetate in the management of castration-resistant prostate cancer: a population-based cost-effectiveness study in Quebec
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Reviewer 1	Dr. Waseem Sharieff MD PhD
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General comments (author response in bold)	The authors address important questions – what is the effect of abiraterone on survival in metastatic castrate resistant prostate cancer (mCRPC) and what is its cost effectiveness? They did a retrospective cohort study using Quebec's public healthcare administrative databases to compare survival of mCRPC patients treated with abiraterone (with or without chemotherapy) to a historical cohort of similar patients treated without abiraterone. There was small but significant survival benefit in favour of abiraterone; this was not significant after adjusting for covariates. They also looked at drug costs using administrative databases, and calculated incremental cost per life year gained. They concluded that abiraterone in post chemotherapy setting was cost effective. The manuscript is well written. The paper could be improved by separating the economic component which could be another paper on its own. As it now stands, the paper has several limitations which could be improved by following standard critical appraisal checklists for observational studies and economic evaluations. **Thank you the reviewer for these comments. The initial manuscript has been separated into two manuscripts entitled:** **1) Impact of abiraterone acetate in the post-docetaxel setting on the survival of metastatic castration-resistant prostate cancer patients: a population-based study in Quebec;** **and** **2) Use of abiraterone acetate in the management of castration-resistant prostate cancer: a population-based cost-effectiveness study in Quebec.** 1. The objective statement 'to characterize the pattern of use of abiraterone in Quebec…' is vague. The authors may frame it as a research question, for example to examine the effect of abiraterone on survival in mCRCPC patients, in comparison to a historical cohort who did not receive abiraterone. Similarly, they could say, 'to estimate the incremental cost per life year gained associated with the use of abiraterone, compared to historical controls'. **Thank you the reviewer for these comments.** **The objectives were revised as follows:** **1)1st manuscript: "Our objective was to characterize the pattern of use of abiraterone in Quebec since its availability in 2012, and to evaluate survival in patients receiving abiraterone post-docetaxel or as "exception patients" using a retrospective observational cohort from the Quebec public healthcare administrative database."** **2) 2nd manuscript: The study objective was to perform a real-life cost-effectiveness analysis of abiraterone in the post-docetaxel setting compared to historical controls, from the perspective of the Quebec healthcare system. Only drug costs were considered in this analysis.** 2. The authors should consider defining all variables including justification for selecting the covariates. How was arrhythmias defined? It was a significant negative prognostic factor. Was it a terminal event, e.g., ventricular tachycardia? **1st manuscript : The justification was mentioned in page 5, paragraph 2, Covariates section : "Comorbidities identified included cardiovascular disease (CVD) and chronic diseases, such as diabetes, hypertension, dyslipidemia, which are known factors associated with increased CVD risk and associated mortality. These were defined as follows: 1) diagnostics or treatment for chronic diseases (diabetes: ICD-9 code 250 or by the use of insulin or hypoglycemic agents, dyslipidemia: ICD-9 code 272 or by the use of lipid lowering drugs and hypertension: ICD-9 code 401 - 404 or by the use of thiazides, ACE inhibitors without furosemide, calcium channel blockers, or β-blockers without other markers of coronary artery disease) 2) cardiovascular events: coronary heart disease: ICD-9: 410-414, ICD-10: 122-125, a medical procedure (coronary artery bypass grafting, angiography, or angioplasty) or use of oral nitrate; cerebrovascular disease: ICD-9 codes 430-438 or medical procedures; chronic heart failure: ICD-9 codes: 398.91, 402, 428 or a prescription of furosemide with digoxin, ACEI, spironolactone or β-blockers; and arrhythmia: diagnosis (ICD-9 code 426-427), a medical procedure using a pacemaker and the use of drugs for cardiac arrhythmias (amiodarone, digoxin, quinidine, disopyramide, flecainamide, mexiletine, procainamide, propafenone, or sotalol) [16]. In addition, the overall health status was estimated by a modified patient's Von Korff Chronic Disease Score (CDS) [17] at index date. Having received medication used to prevent skeletal-related events due to bone metastases, also called bone-targeted therapy (denosumab or zoledronic acid) and palliative radiotherapy prior or during the study period were**

	considered as covariates." **2nd manuscript, Covariate section, pages 4 and 5: "Comorbidities identified included cardiovascular disease (CVD) and chronic diseases, such as diabetes, hypertension, dyslipidemia, which are known factors associated with increased CVD risk and associated mortality. The definition of these covariates is available in the footnotes of the Table 1. In addition, the overall health status was estimated by a modified patient's Von Korff Chronic Disease Score (CDS) [14] at index date. Having received medication used to prevent skeletal-related events due to bone metastases, also called bone-targeted therapy (denosumab or zoledronic acid) and palliative radiotherapy prior or during the study period were considered as covariates."** 3. The authors should consider adding a flow chart showing how many patients were identified, how many were included/excluded, and how many were analyzable. **A flow-chart was included in each one of the manuscripts.** 4. Sample size is fixed by the nature of study design. Power calculations should be included. **2nd manuscript: In paragraph 1 of page 7, the statistical power calculation was described as follow: ''A statistical power calculation was performed to assess the number needed to achieve a statistical power of 80% based on an alpha of 5% and the proportion of patients in each group of 34% in abiraterone post-docetaxel and 66% in chemotherapy only group. A total of 298 events (deaths) would be required in both groups for an HR of 0.72, or 134 events for an HR of 0.60. In our cohort the number of deaths was 181 (141 and 40 in the chemotherapy only and abiraterone post-chemotherapy group, respectively).''** 5. Table 1 and 2 contain descriptive data which are not statistically compared. Given non-randomized nature of these data, appropriate statistical tests could be performed. **1st manuscript : The Statistical analysis section (page 4 and 5) was completed with univariate and multivariate tests : '' T-tests and chi-square tests were applied to assess differences in patient characteristics (treatments and comorbidities), abiraterone treatment duration and days of hospitalization (all causes and PC-related) between groups. Quantile regression was performed to assess the impact of prior docetaxel exposure on the median days of PCa-related hospitalization, adjusted for several covariates (described below) [12, 13]. …. The Cox proportional hazards model was used to estimate the hazard ratio (HR) of prior docetaxel exposure, adjusted for several covariates, which respected the proportional hazards assumption. In addition, the direct adjusted survival function was used to estimate the survival curves, as well as the adjusted median and mean survivals, of the average patient in each of the abiraterone groups [15]. This method estimates the direct adjusted survival function by averaging the predicted survival functions for each combination of covariates. '' In addition, the corresponding p-values were mentioned in Tables 1 and 2.** **2nd manuscript: Similarly, as in manuscript 1.** 6. There could be some interdependence among covariates. How was that analyzed? **1st manuscript: Palliative radiation was found to have an interaction with abiraterone groups and age groups, which also did not respect the proportional hazards assumption of the Cox model. This was considered as stratification factor in both Cox and quantile regression analyses. In text this was specified in page 7, paragraph 2 : '' The proportional hazards assumption was respected for all variables except for palliative radiation which was used as stratification factor.''** **2nd manuscript: Similarly, to the 1st manuscript an interaction was found between bone-targeted therapies and exposure group (chemotherapy alone vs abiraterone post-docetaxel). This was considered as stratification factor in both Cox and quantile regression analyses. In text this was specified in page 8, paragraph 1 : ''An interaction was detected between bone target therapies and abiraterone exposure and age group, consequently the bone targeted therapy was used as stratification factor in the Cox analysis.''** 7. Were tests for interaction conducted? **Please refer to answers provided at point 6.** 8. Given the relative small sample size, the number of co-variates appears large. **A stepwise analysis was performed in both manuscripts 1 and 2 for multivariate analyses, yet the same factors were found statistically significant as in the full analyses (data not showed). The complete analyses were preferred by the authors to be presented in these manuscripts.** 9. For cost effectiveness analysis, the authors need to outline their assumptions, and they should state whose perspective they took in costing the interventions (provider, patient or societal). **2nd Manuscript : At paragraph 2 of page 3, the perspective of the study was added as follows: ''The study objective was to perform a real-life cost-effectiveness analysis of abiraterone in the post-docetaxel setting compared to historical controls, from the perspective of the Quebec healthcare system. Only drug costs were considered in this analysis.''** 10. Costing is typically done by multiplying unit price with volume of utilization. It appears that costs were directly computed from reimbursement data. Although, the authors present utilization data, it does not include nursing and pharmacy dispensing times, which might not have been captured in their cost data. They should comment on this in the discussion. **We agree with the reviewer's comment, yet in this case, both methods (multiplying unit price with**

	volume of utilization or summing the cost unit of all prescriptions by each patient) give similar results. Yet, the direct calculation using individual costs allowed to estimate the 95%CI as well. As only drug costs were taken into calculation, this was added in the objective. Because of the words' limit no comment was added in the discussion section. 11. Authors should consider including cost of radiotherapy. There appears to be significant reduction in palliative radiotherapy in the abiraterone groups. When this cost is included, ICER would further lean in favour of abiraterone. Also, this finding implies that pain symptoms were reduced, and thus quality of life was improved. Under this assumption, quality adjusted life years could be incorporated in the cost effectiveness analyses. **2nd manuscript: In the cost-effectiveness study of abiraterone, the percentage of patients receiving palliative radiation was similar between groups: 28.3% in chemotherapy only group and 25.3% in abiraterone post-docetaxel group (p-value=0.5839). Unfortunately, the RAMQ databases does not include quality of life information. This was discussed in page 8 paragraph 3 and page 9, paragraph 1. Yet, the percentage of patients receiving bone-targeted therapies in the abiraterone post-docetaxel group was higher than in the chemotherapy only group (58.6% vs 86.9%; p-value <0.0001). This was accounted in the costs calculation. Finally, we have performed an additional analysis on the median days of hospitalization. The results are discussed as follow: "Quality of life and other secondary measures of efficacy were not available in our claims-based cohort study, therefore, these were not taken into account by our study. Yet, our results suggest that the use of abiraterone might reduce the hospitalization days, which may favor the the ICER of abiraterone, however we cannot directly extrapolate the reduction of hospitalization days on quality of life." (page 8, paragraph 3) and "Yet, an important decrease in PCa-related hospitalizations were noted in abiraterone post-docetaxel group, that might decrease the difference in the total costs, and consequently the ICER." (page 9 paragraph 1)** 12. Time span for the cost effectiveness analysis should be for the entire life time. Restricted it to the duration of the study, underestimates gain in life years. **2nd manuscript: A 60-month cost-effectiveness analysis was performed. As the life expectancy in this population of metastatic castration-resistant prostate cancer in the post-docetaxel setting is extremely low, a lifetime analysis was not considered appropriate.** 13. The authors should include sensitivity analyses. **A sensitivity analysis was performed and presented in Table 5 of the 2nd manuscript.** 14. Table 1 shows 'diagnosed metastasis' prevalence of 94.8% in chemotherapy group and 87.1% in abiraterone group. Should this not be 100% in both groups? **1st manuscript: In Results section, page 6, paragraph 1 was mentioned: "Although we expected that 100% of patients should have metastatic disease, only 82.8% of "exception patients" had a diagnosis of metastasis, vs 95.7% in the abiraterone post-docetaxel group." This is explained by the fact that in the Quebec healthcare system, specifically the RAMQ databases, the diagnosis codes are not mandatory for physicians' payment claims.** 15. Tables 1 and 2 could be improved by putting demographic and comorbidity data in a single table, and medication and hospitalization data in another table. **Thank you for this suggestion. Tables 1 and 2 were revised accordingly in both manuscripts.** 16. Authors should consider graphical presentation for data presented in Tables 3-5. **The table presentations provide more details than the graphical representation, as such the authors considered the tables presentation.** 17. In the discussion, the authors compare their results to others and merely quote references. They should consider adding the actual results of others in comparison with their own along with references. **In manuscript 1, the 2nd paragraph in page 8 was added to address this comments. Yet, due to the words' limit, in manuscript 1, the results of other studies were grouped as: "Results of recent studies are comparable to our real-life ICER results, suggesting that abiraterone is cost-effective in clinical practice, when considering a willingness-to-pay threshold of $100K." (page 8, paragraph 3 in manuscript 2).** 18. The authors should discuss their limitations in a separate paragraph. **The limitations are now discussed in separate paragraphs (1st manuscript - pages 8 and 9; 2nd manuscript pages 8 and 9).** 19. Overall, I feel this is an important study with interesting results. However, it needs further work. Cost effectiveness is done after establishing 'effectiveness'. With the current data, I am afraid effectiveness can not be established as hazard ratios crossed unity. Thus, ICER based on such hazard ratios would include scenarios where abiraterone could be more costly and less effective, i.e., cost ineffective rather than cost effective. The authors should also note that funding decisions on cancer drugs are not solely based on some ICER threshold. The paper should reflect this. **Thank you for this comments. The 2nd manuscript was revised accordingly.**
Reviewer 2	Dr. Kirk A. Keegan MD MPH
Institution	Department of Urologic Surgery, Vanderbilt University School of Medicine, Nashville, TN
General comments (author	The authors have provided a well-written manuscript that describes the incremental cost

response in bold)	effectiveness of use of abiraterone in advanced prostate cancer in Quebec. This is an important clinical question. The manuscript would benefit from discussing the limitations of their findings with regard to its overall generalizability outside of Quebec. **Due to the words' limit, no other comment was done on the generalizability outside of Quebec. However, it is well known that cost and economic evaluation are less generalizable, and that the generalizability is limited to similar healthcare systems.** Moreover, the abstract would benefit from a description that dollars represents Canadian dollars. **The abstract was modified accordingly.**