Abiraterone vs. docetaxel for metastatic hormone-sensitive prostate cancer: A microsimulation model

Amanda E. Hird, MD1,2; Diana E. Magee, MD, MPH2,3; Douglas C. Cheung, MD2,3; Rano Matta, MD1,2; Girish S. Kulkarni, MD, PhD, FRCSC2,3; Robert K. Nam, MD, MSc, FRCSC1,2

1 Division of Urology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; 2 Institute for Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada; 3 Division of Urology, Princess Margaret Hospital, University Health Network, Toronto, ON, Canada

Funding: Ajmera Family Chair in Urologic Oncology

Cite as: Can Urol Assoc J 2020 March 30; Epub ahead of print. http://dx.doi.org/10.5489/cuaj.6234

Published online March 30, 2020

***

Abstract

Introduction: Our aim was to determine whether androgen-deprivation therapy (ADT) with abiraterone acetate (AA) or ADT with docetaxel chemotherapy (DC) resulted in improved quality-adjusted life years (QALYs) among men with de novo metastatic castration-sensitive prostate cancer (mCSPC) and the cost-effectiveness of the preferred strategy using decision analytic techniques.

Methods: A microsimulation model with a lifetime time horizon was constructed. Our primary outcome was QALYs. Secondary outcomes included cost, incremental cost-effectiveness ratio (ICER), unadjusted overall survival (OS), rates of second- and third-line therapy, and adverse events. A systematic literature review was used to generate probabilities and utilities to populate the model. The base case was a 65-year-old patient with de novo mCSPC.

Results: A total of 100 000 microsimulations were generated. Initial AA resulted in a gain of 0.45 QALYs compared to DC (3.36 vs. 2.91 QALYs) with an ICER of $276 251.84 per QALY gained with initial AA therapy. Median crude OS was 51 months with AA and 48 months with DC. Overall, 46.6% and 42.6% of patients received second-line therapy and 8.7% and 7.9% patients received third-line therapy in the AA and DC groups, respectively. Grade 3/4 adverse events were experienced in 17.6% of patients receiving initial AA and 22.3% of patients receiving initial DC.
Conclusions: Although ADT with AA results in a gain in QALYs and crude OS compared to DC, AA therapy is not a cost-effective treatment strategy to apply uniformly to all patients. The availability of AA as a generic medication may help to close this gap. The ultimate choice should be based on patient and tumor factors.

Introduction
Prostate cancer is the most commonly diagnosed cancer among men in Canada and approximately 8% present with metastatic disease\(^1\). Traditionally, androgen deprivation therapy (ADT) alone has been the initial treatment of choice in the setting of metastatic disease. However, recent well-conducted randomized controlled trials (RCTs) suggest that the addition of chemotherapy and non-steroidal anti-androgen agents improve survival outcomes when given to men with locally advanced or metastatic castrate sensitive disease\(^2\)\(^-\)\(^4\). Based on two high quality randomized trials (CHAARTED: docetaxel\(^3\) and LATITUDE: abiraterone acetate\(^5\), we now have evidence for the utility of: 1) Chemotherapy with ADT; and 2) Anti-androgen therapy with ADT for castrate sensitive de-novo metastatic prostate cancer (mCSPC).

However, the two treatment pathways have not been compared head to head to determine which agent should be used first, and this issue remains controversial\(^6\). Given its associated toxicity, chemotherapy may be more advantageous to administer earlier on in the disease when the patients’ performance status is, theoretically, at its highest. Initial chemotherapy does not preclude subsequent abiraterone use if castrate resistance develops and studies have shown benefit of anti-androgen therapy after chemotherapy among men with castrate resistant disease\(^7\). On the other hand, abiraterone acetate is easier to administer (oral pill) and has a lower associated toxicity profile when compared to chemotherapy\(^8\). Studies have shown its effectiveness prior to chemotherapy in men with castrate resistant disease\(^9\). However, abiraterone can induce neuroendocrine differentiation and although very rare, this disease transformation is associated with poor survival\(^10\). Furthermore, abiraterone therapy is associated with a significant increase in cost by more than $100,000 CAD when used prior to chemotherapy\(^11\).

In the absence of a direct comparative trial, the aim of this study was to develop a decision model to determine whether long-term ADT combined with upfront chemotherapy (docetaxel)(DC) or long-term ADT with upfront additional anti-androgen therapy (abiraterone acetate)(AA) results in improved quality adjusted life years (QALY) among adult men with mCSPC.
Methods

The model
We constructed a microsimulation model using TreeAgePro Healthcare 2018 (TreeAge Software Inc., Williamstown, MA) to compare treatment strategies for men with newly diagnosed mCSPC. Two management arms were modelled: 1) ADT with initial DC; and 2) ADT with initial AA and prednisone. Our primary outcome was QALY. Secondary outcomes included overall survival (OS), rates of use of second- and third-line therapy, and rates of adverse therapy-related events. If AA demonstrated superiority over DC with regards to QALY, an incremental cost effectiveness ratio (ICER) would be calculated to determine the incremental cost associated with a gain of one quality adjusted life year \( ^{12} \). This model was developed from a healthcare payer perspective with a lifetime time horizon. The Markov cycle length was three months to mimic the follow-up interval used in clinical practice for patients with metastatic prostate cancer. Within cycle correction with a 1.5% discount rate was used to account for bias arising from discrete-time Markov models \( ^{13,14} \).

Base case
The base case was a 65-year-old patient with de novo mCSPC who was a candidate for either DC or AA therapy. Modelled patients represented a cohort of patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, with radiographic evidence of metastatic disease. This was in concordance with the randomized clinical trials whose data was used to populate this decision model \( ^{3,5,8,15} \).

Markov states
Our Markov diagram is presented in Figure 1. The base case patient could enter one of two initial treatment states: ADT with AA (and prednisone) or ADT with DC. Patients in the ADT with AA arm were modelled to receive continuous ADT with AA. Patients in the ADT with DC arm were modelled to received continuous ADT with six cycles of DC (75mg/msq every 3 weeks for 6 cycles). In each state, patients could experience treatment-associated complications, treatment-related death, and disease progression, while accounting for the competing risk of other cause mortality. Costs and disutilities were populated based on values reported in the literature, adjusted for cycle length and were tolled as appropriate for one cycle length.

After each instance of disease progression, simulated patients could proceed with a subsequent line of therapy (second- or third- line therapy) or receive palliative care. Probabilities of proceeding to DC (if AA was received initially) and probability of proceeding to AA (if DC was received initially) were based on the rate of proceeding to an equivalent secondary therapy in randomized trials.
Assumptions

We assumed patients who did not experience an adverse event, death, or progression completed therapy without treatment interruptions or dose adjustments. We assumed patients who did not complete initial chemotherapy or at least three months of abiraterone did not derive any survival benefit from therapy and were modelled to proceed to second line therapy or palliative care. All patients who received DC initially received AA as second line therapy. Conversely, all patients who received AA initially, received DC as second line therapy. Third line therapy was modelled as proportion of patients receiving cabazitaxel and its associated costs and treatment toxicities.

Chemotherapy-related adverse events were defined as at least grade three and above with respect to severity using the Clavien-Dindo classification and the Common Terminology Criteria for Adverse Events. We assumed that there were no long-term treatment-related complications after the primary treatment phase (i.e. all utilities returned to baseline after the three-month treatment cycle). Although the cost of a hospital admission and emergency department visit was the same for patients on chemotherapy and abiraterone, the variability was modelled in the distribution of inpatient versus outpatient treatment of complications based on Phase IV Ontario-based population data. The cost and distribution of hospitalizations and emergency department visits were not modified based on previous chemotherapy exposure as it has been shown that reasons for visits to hospital is similar between these two groups of patients.

Data sources

A comprehensive MEDLINE literature search was completed to determine model probabilities and utilities. A manual search of the reference lists from our identified studies, meta-analyses, and review articles was performed to ensure important articles were not missed. With the presence of multiple randomized trials in this disease space, all with slightly different inclusion criteria and patient demographics, comparability between groups is paramount and must be carefully adjusted for in the analysis. Thus, in order to achieve balance between arms, weighted averages between trials were used. When incorporating progression rates among patients from the STAMPEDE trial, rates among patients with metastatic disease were used. If there were multiple datapoints obtained for a given probability, we used a weighted-average approach to combine estimates. RCT data were preferentially used when available. Rates taken from time to event analyses were converted into quarterly probabilities assuming an exponential distribution (Table 1).

Utilities were obtained using the Tufts-New England Medical Center Cost Effectiveness Analysis registry (http://www.tufts-nemc.org/cearegistry/data/default.asp) and using a manual search of published urology decision models with a reference of 1 for perfect health and 0 for death (Table 2).

Disutilities are penalties applied to the baseline health state to reflect short term decreases in patients’ quality of life. We applied transitional penalties to account for the inconvenience of
procedures and potential short-term complications. These penalties were subtracted from the
given health state’s baseline utility.

Cost data was obtained using a combination of published literature sources and using the
Canadian Institute for Health Information (CIHI) Patient Cost Estimator (PCE) to estimate the
average cost of hospital services nationally, by jurisdiction, and by patient age group (Table 3).
The cost of a standard hospital stay is derived by the total inpatient costs divided by the total
number of weighted cases within that jurisdiction. Canada-wide estimates were used and limited

Validation
Sensitivity analyses were completed for all variables across a range of plausible values and
scenarios. The model was presented to content experts in modelling and urologic oncology to
assess the face validity of our results. External validity was assessed by comparing outcomes
from our model to published literature that was not used in the construction of our decision
analysis.

Results
A total of 100,000 microsimulations were completed. Overall, 4.9% of patients in the AA group
discontinued primary therapy due to adverse events compared to 13.7% of patients who received
initial DC. From the AA group, 46.6% went onto receive subsequent DC and 8.7% received third
line therapy. From the DC group, 42.6% went onto received subsequent AA and 7.9% received
third line therapy. Overall, 93.3% experienced a cancer-related death in the AA group compared
to 94.2% in the DC group.

Survival outcomes
The AA pathway was preferred with an estimated survival of 3.36 quality adjusted life years
(QALYs) versus 2.91 QALYs in the DC pathway (incremental gain of 0.45 QALYs with initial
AA). Unadjusted median OS was 4.25 years (51 months) with initial AA versus 4.00 years (48
months) with initial DC. A survival curve at 60 months was generated (Figure 2) with a visible
separation of curves at the 40-month mark in favour of initial AA.

Adverse events
Overall, 17.6% experienced AA-induced adverse events among patients receiving initial AA
compared to 22.3% among simulated patients receiving initial DC. Overall, 0.5% experienced
treatment-related death with initial DC versus 1% with initial AA.

Cost
Average cost of prostate cancer treatment was $188,815.07 with initial AA therapy
compared to $64,501.75 with initial DC. This resulted in an ICER of $276,251.84 per QALY
($124,313.32/0.45 QALYs) gained with initial AA therapy.
Sensitivity analyses
One-way sensitivity analyses were completed on all variables as part of our model validation (Table 4). None of the thresholds that altered the treatment decision were reached, suggesting that initial AA is the preferred pathway. Similarly, tornado analysis demonstrated that the most sensitive variables were receiving second line therapy and adverse events although none were decision altering or reduced the ICER to below $200,000/QALY (Figure 3).

Recently, AA has been approved for generic production. This was estimated to be $2,370.09 per month based on pharmacy costing data. The model was re-run with this modified cost and generated an overall estimated cost of therapy of $124,094.10 for patients receiving initial AA, corresponding to an ICER of $149,022.09 per QALY gained. In order to contextualize different potential costs of AA (including current and projected generic costs), a deterministic sensitivity analysis comparing three-monthly costs of AA with their corresponding ICER is presented in Figure 4. To bring the willingness to pay (WTP) threshold (WTP per QALY gained) to less than $100,000 CAD, the monthly cost of AA would have to be less than approximately $1,750 CAD (or $5,250 CAD over three months).

Validation: External
External validity was assessed by comparing event counts and time to events generated by the model to published series that were not included in its development. Cancer-related deaths occurred in 88% of patients treated with AA and 91% of patients treated with chemotherapy. This is consistent with the proportion of cancer-related deaths reported in the GETUG-AFU trial (82%, with cause of death unknown in 10% of the population)\(^ {15} \). By setting probability of AA and DC therapy to zero (thus modeling survival with third line and palliative therapy only), estimated survival was 12 months, which is consistent with two recently published Phase III studies evaluating cabazitaxel in the post-DC setting\(^ {17,18} \). Furthermore, unadjusted OS for this cohort is similar to Phase IV population-level survival analyses after introduction of abiraterone and enzalutamide estimating an OS of 40 months among patients with mCRPC\(^ {16} \) compared to 48-51 months in this study of patients with de-novo mCSPC. Overall cost of care for a patient with mCRPC was an estimated $144,350 USD\(^ {19} \), similar to what was estimated by our model analysis.

Discussion
We performed a decision analysis investigating initial ADT in combination with DC versus ADT in combination with AA for men with de-novo mCSPC. A total of 100,000 microsimulations were generated. Initial AA resulted in a gain of 0.45 QALYs compared to DC (3.36 versus 2.91 QALYs). Median crude OS was 51 months with AA and 48 months with DC. Graphically, 5-year overall survival with both therapies was similar (Figure 2) although survival for simulated patients in the initial AA group appeared to separate from the DC group around the 40-month mark in favour of AA. Average cost of prostate cancer treatment was $188,815.07 with initial
AA therapy compared to $64,501.75 with initial DC. Incremental cost effectiveness of AA over DC was $276,251.84 per QALY gained. Sensitivity analysis estimating the ICER with the reduced cost of AA in Canada was $149,022.09 per QALY gained.

The choice of either DC or AA with initial ADT therapy for men with de-novo mCSPC is based on two landmark clinical trials. The CHAARTED trial showed that 6 cycles of single agent intravenous chemotherapy (docetaxel) with ADT significantly improved median overall survival by 13 months when given at the time of metastatic prostate cancer diagnosis compared to ADT alone (57.6 months versus 44.0 months, HR 0.61 [95%CI 0.47-0.80], p<0.001)3. Subsequently, a double-blind placebo controlled randomized trial investigated the utility of abiraterone with ADT upfront in men with de novo mCSPC 5. The LATITUDE study demonstrated a significant improvement in overall survival with upfront abiraterone with ADT compared to ADT alone (HR=0.62, 95% CI 0.51-0.76, p<0.001)5. While both therapies have clearly established their effectiveness in this population3,5,8,15, the optimal sequence to employing each therapy is not well defined.

Answering this clinical question using a randomized clinical trial would be expensive and difficult to perform. A recent network meta-analysis6 completed an indirect comparison of the two interventions using pooled data from five randomized trials3-5,8,15 and found a non-significant improvement in OS with AA (HR 0.84, 95%CI: 0.67-1.06). This method of analysis however fails to model downstream treatment pathways, including second- and third-line therapy as well as quality of life and cost parameters. Decision models, however, account for these factors and are an accepted tool used to guide clinical decision making in the field of urologic oncology, including in prostate cancer20 and recurrent high grade non-muscle invasive bladder cancer21. This model was built using randomized data and in the absence of a direct comparative trial provides the best guidance to date regarding optimal management of this patient population.

Traditionally, an accepted WTP threshold per QALY gained is approximately $50,000 USD22. However, this threshold is somewhat arbitrary and may vary depending on the clinical and societal context22. One report stated that a WTP threshold of two to three times the per capita annual income (i.e. a U.S. threshold of $110,000 to $160,000 per QALY today) may be more appropriate22. Furthermore, a review on WTP thresholds for oncology drugs reported that they were often in the range of $100,000 to $150,000 per QALY gained23. A review of ICERs that influence government recommendations regarding cancer screening initiatives revealed that an ICER value of $61,600 USD per QALY yielded a high sensitivity of 90% and specificity of 85% for a positive recommendation24. The present study revealed a WTP threshold of $276,251.84 CAD per QALY gained with initial AA and ADT compared with DC and ADT. This is outside of the accepted WTP threshold suggesting that although AA demonstrates some survival benefits, it is not cost-effective. As demonstrated in Figure 4, the future availability of generic AA and the potential equivalence of 250 mg per day dosing when combined with a low-fat meal may further increase the potential cost savings associated with AA25. This may facilitate reaching
a more economically feasible ICER to enable integration of this agent earlier in the disease trajectory into an economically constrained system (although it remains at the upper limits of cost-effectiveness).

Alternatively, identifying which patients derive the most benefit from initial AA may help to guide treatment selection. While no effectiveness thresholds were crossed for the model probabilities within their respective plausible clinical ranges (Table 4, Figure 3), the probabilities that came closest were those pertaining to likelihood of second line therapy. Phase IV population-level evidence analyzing rates of second line therapy after DC and AA may be used in the future to guide treatment selection. While there may be difference between the preferred agent based on disease-specific and demographic subgroups, unfortunately, we were not able to model this in the current study given that progression-free survival rates stratified by specific high-risk criteria (for example, presence or absence of visceral metastasis, high versus low volume disease), were reported by some but not all trials. Therefore, this represents a pragmatic analysis that can be applied to a broad group of patients. There are limitations to the current study. The probabilities used to generate this model were largely taken from randomized patient data therefore may not be representative of all patients presenting with de-novo mCSPC. Inclusion criteria and patient demographics were slightly different between trials; however, we attempted to achieve similarity between groups by using weighted averages for progression outcomes for the AA and DC trials. Furthermore, the included studies used slightly differing definitions of progression. Specifically, the placebo-controlled LATITUDE trial reported radiographic progression free survival whereas CHAARTED defined time to progression as radiographic or metastatic symptom progression-free survival, which may impact trial comparability. In addition, while AA was the first non-steroidal anti-androgen agent to have published level 1 clinical trial evidence supporting its use in the setting of mCSPC, the utility of other agents (such as enzalutamide, darolutamide, or apalutamide) may impact the anticipated efficacy and incremental cost. The ENZAMET trial and anticipated ARCHES trial investigate enzalutamide while the TITAN trial compares apalutamide to placebo in the setting of mCSPC. A decision analysis comparing AA and enzalutamide in the setting of metastatic castrate resistant prostate cancer suggested that enzalutamide was a more cost-effective option. Although beyond the scope of this project, comparison of AA to enzalutamide and to apalutamide in the setting of mCSPC is warranted. Lastly, the proportion of patients receiving second line therapy is reflective of the numbers directly reported in clinical trials and may not be representative of what is seen in clinical practice.

The strengths of this study include the use of best practice modeling techniques that realistically depict the disease and surveillance pathways for this population. The model accurately portrays the follow-up and surveillance patterns used in clinical practice, which increases the model’s generalizability. Furthermore, we were able to model many simulated patients and our results were found to be both internally and externally valid. Specific rates of
AA-related complications were adapted from Ontario-based Phase IV population level data and the cost of such complications were adapted from systemic therapy-related adverse events averaged across all primary cancer sites. Cost of therapy data was directly derived from published Canadian literature.

**Conclusions**

While AA resulted in a marginal increase in QALYs gained over DC when combined with ADT as initial therapy in men with de-novo mCSPC, this study shows that this gain is not cost effective with an estimated WTP threshold over $270,000 CAD. The price of generic AA and the potential use of reduced dose AA may alter the treatment landscape in favor of novel anti-androgen agents in the future. The utility of other non-steroidal anti-androgen agents in this setting with differing cost and side effect profiles may also alter treatment selection.
References


Figures and Tables

**Fig. 1.** State transition diagram. Second-line therapy after abiraterone: docetaxel; Second-line therapy after docetaxel: abiraterone; third-line therapy: cabazitaxel. Markov cycle length: 3 months. ADT: androgen-deprivation therapy.
Fig. 2. Kaplan-Meier survival curve comparing initial treatment with androgen-deprivation therapy plus abiraterone acetate (AA) vs. androgen-deprivation therapy plus docetaxel chemotherapy (DC) among simulated men with metastatic castrate-sensitive prostate cancer. OS: overall survival.

Fig. 3. Tornado diagram of incremental cost effectiveness ratio (ICER) of androgen-deprivation therapy (ADT) with abiraterone acetate (AA) vs. ADT with docetaxel chemotherapy (DC). Generated using 10 000 microsimulations. Blue: low; Red: high.
**Fig. 4.** Deterministic sensitivity analysis showing the incremental cost effectiveness ratio (ICER) of abiraterone acetate (AA) vs. docetaxel chemotherapy (DC) (blue). Graph shows the ICER (y-axis) based on the three-month cost of AA (x-axis) in Canadian dollars. Conventional willingness to pay (WTP) thresholds of $50,000, $100,000, and $150,000 are shown (black). Model-estimated current cost of AA: $11,927.07 (per three months) (red). Model-estimated cost of generic AA: $7,110.27 (per three months) (red).
Estimated cost of generic AA
ICER: $149,022.09

Current cost of AA
ICER: $276,251.84
Table 1. Model probabilities

<table>
<thead>
<tr>
<th>Probability</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality on AA</td>
<td>0.01 (range 0.009–0.01)</td>
<td>Fizazi et al, 2017; James et al, 2017</td>
</tr>
<tr>
<td>Incremental adverse event on AA</td>
<td>15% over 30.4 months (range 14–15%)</td>
<td>Fizazi et al, 2017; James et al, 2017</td>
</tr>
<tr>
<td>Complete AA</td>
<td>0.98</td>
<td>Fizazi et al, 2017</td>
</tr>
<tr>
<td>Progression-free survival on AA</td>
<td>50% at 45.9 months (range 33.2–54.0)</td>
<td>Fizazi et al, 2017; James et al, 2017</td>
</tr>
<tr>
<td>Progression-free survival if discontinued AA</td>
<td>50% at 13.0 months (range 11.9–14.8)</td>
<td>Fizazi et al, 2017; James et al, 2017</td>
</tr>
<tr>
<td>Second-line therapy after AA</td>
<td>0.503 (range 0.476–0.536)</td>
<td>Fizazi et al, 2017</td>
</tr>
<tr>
<td>Mortality on DC</td>
<td>0.0045 (range 0.003–0.006)</td>
<td>Sweeney et al, 2015; James et al, 2016</td>
</tr>
<tr>
<td>Incremental adverse event on DC</td>
<td>0.232 (range 0.16–0.46)</td>
<td>Sweeney et al, 2015; James et al, 2016</td>
</tr>
<tr>
<td>Complete DC</td>
<td>0.81 (range 0.77–0.86)</td>
<td>Sweeney et al, 2015; James et al, 2016</td>
</tr>
<tr>
<td>Progression-free survival after DC</td>
<td>50% at 29.7 months (range 22.9–33.0)</td>
<td>Sweeney et al, 2015; Gravis et al, 2016</td>
</tr>
<tr>
<td>Progression-free survival without DC</td>
<td>50% at 18.3 months (range 15.3–19.8)</td>
<td>Sweeney et al, 2015; Gravis et al, 2016</td>
</tr>
<tr>
<td>Second-line therapy after DC</td>
<td>0.456 (range 0.441–0.536)</td>
<td>Sweeney et al, 2015; James et al, 2016</td>
</tr>
<tr>
<td>Progression-free survival on second-line therapy</td>
<td>AA: 50% at 8.3 months (range 5.0–8.5)</td>
<td>Cicero et al, 2017; Scher et al., 2012;</td>
</tr>
<tr>
<td></td>
<td>DC: 50% at 7.6 months (range 4.0–7.6)</td>
<td>Petrioli et al, 2015; Azad et al, 2014;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mezynski et al, 2012; Suzman et al, 2014;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>De Bono et al, 2017; Fizazi et al, 2017;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oudard et al, 2017</td>
</tr>
<tr>
<td>Progression-free survival if did not complete</td>
<td>AA: 50% at 3.0 months (range 3.0–6.6)</td>
<td>Scher et al, 2012; Fizazi et al</td>
</tr>
<tr>
<td>complete second-line therapy</td>
<td>DC: 50% at 3.0 months (range 3.0–6.6)</td>
<td></td>
</tr>
<tr>
<td>Probability of receiving third-line therapy</td>
<td>19% over 14.4 months (range 19–42%)</td>
<td>Scher et al 2012</td>
</tr>
</tbody>
</table>
Mortality on third-line therapy | 0.05 (0.002–0.05) | De Bono et al, 2010; Bracarda et al, 2014; Eisenberger et al
Adverse event on third-line therapy | 0.592 (0.305–0.689) | Bracarda et al, 2014; Eisenberger et al; Saad et al, 2016
Progression-free survival on third-line | 50% at 2.8 months (range 2.6–5.5) | De Bono et al, 2010; Petrioli et al, 2015; Al Nakouzi et al, 2015; Wissing et al, 2015; Sonpavde et al, 2015; Caffo et al; Pezaro et al; Saad et al
Median survival with palliation | 50% at 13 months (range 5.6–14.5) | Scher et al, 2012; Eisenberger et al; Krishnan et al, 2014

‡Weighted average of the referenced trials. ‡Metastasis-only subgroup from the STAMPEDE-ABI trial used to generate progression-free survival. §Proportion of patients receiving chemotherapy, immunotherapy, or enzalutamide after progression in the LATITUDE trial (n=158/314). †Proportion of patients receiving non-steroidal, anti-androgen, non-docetaxel chemotherapy, or immunotherapy after progression in the CHAARTED trial (n=213/397). *Time to progression after stopping second line DC not available. Assumed to be the same as time to progression after stopping second-line AA. AA: abiraterone acetate; DC: docetaxel chemotherapy
### Table 2. Model utilities

<table>
<thead>
<tr>
<th>Utilities</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>On AA</td>
<td>0.76* (range 0.63–0.84)</td>
<td>Krahn et al, 2003&lt;sup&gt;48&lt;/sup&gt;; Stewart et al, 2005&lt;sup&gt;49&lt;/sup&gt;; Collins et al, 2007&lt;sup&gt;50&lt;/sup&gt;; Volk et al, 2004&lt;sup&gt;51&lt;/sup&gt;; Hall et al, 2019&lt;sup&gt;52&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adverse event with AA</td>
<td>-0.11†</td>
<td>Sanyal et al, 2016&lt;sup&gt;53&lt;/sup&gt;; Yong et al, 2012&lt;sup&gt;54&lt;/sup&gt;</td>
</tr>
<tr>
<td>AA surveillance</td>
<td>0.76* (range 0.63–0.84)</td>
<td>Krahn et al, 2003&lt;sup&gt;48&lt;/sup&gt;; Stewart et al, 2005&lt;sup&gt;49&lt;/sup&gt;; Collins et al, 2007&lt;sup&gt;50&lt;/sup&gt;; Volk et al, 2004&lt;sup&gt;51&lt;/sup&gt;; Hall et al, 2019&lt;sup&gt;52&lt;/sup&gt;</td>
</tr>
<tr>
<td>On DC</td>
<td>0.64* (range 0.64–0.72)</td>
<td>Lloyd et al, 2015&lt;sup&gt;55&lt;/sup&gt;; Hall et al, 2019&lt;sup&gt;52&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adverse event with DC</td>
<td>-0.11</td>
<td>Sanyal et al, 2016&lt;sup&gt;53&lt;/sup&gt;; Yong et al, 2012&lt;sup&gt;54&lt;/sup&gt;</td>
</tr>
<tr>
<td>DC surveillance</td>
<td>0.68* (range 0.67–0.73)</td>
<td>Lloyd et al, 2015&lt;sup&gt;55&lt;/sup&gt;; Hall et al, 2019&lt;sup&gt;52&lt;/sup&gt;</td>
</tr>
<tr>
<td>On third-line therapy</td>
<td>0.55* (range 0.55–0.72)</td>
<td>Collins et al, 2007&lt;sup&gt;50&lt;/sup&gt;; Lloyd et al, 2015&lt;sup&gt;55&lt;/sup&gt;; Sandblom et al, 2004&lt;sup&gt;56&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adverse event on third-line therapy</td>
<td>-0.11</td>
<td>Sanyal et al, 2016&lt;sup&gt;53&lt;/sup&gt;; Yong et al, 2012&lt;sup&gt;54&lt;/sup&gt;</td>
</tr>
<tr>
<td>Third-line therapy surveillance</td>
<td>0.55* (range 0.55–0.72)</td>
<td>Collins et al, 2007&lt;sup&gt;50&lt;/sup&gt;; Lloyd et al, 2015&lt;sup&gt;55&lt;/sup&gt;; Sandblom et al, 2004&lt;sup&gt;56&lt;/sup&gt;</td>
</tr>
<tr>
<td>Palliation</td>
<td>0.46</td>
<td>Sandblom et al, 2004&lt;sup&gt;56&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Utilities calculated using weighted averages of the value from identified studies. †Utility on androgen deprivation therapy alone. ‡Disutility of adverse AA event applied from chemotherapy literature. AA: abiraterone acetate; DC: docetaxel chemotherapy.
Table 3. Model costs

<table>
<thead>
<tr>
<th>Event</th>
<th>Cost per patient month</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT</td>
<td>$371</td>
<td>Dragonir et al, 2014&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>On AA</td>
<td>$3975.69 (range $2370.09–3975.69)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Dragonir et al, 2014&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>ER visits for AA</td>
<td>129 events per 5143 person-months</td>
<td>Wallis et al, 2018&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hospitalizations for AA</td>
<td>108 events per 5143 person-months</td>
<td>Wallis et al, 2018&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>AA adverse event requiring inpatient treatment</td>
<td>$7099 (range $5574–7099)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>CIHI PCE (<a href="https://www.cihi.ca/en/patient-cost-estimator">https://www.cihi.ca/en/patient-cost-estimator</a>)</td>
</tr>
<tr>
<td>AA surveillance</td>
<td>$3975.69 (range $2370.09–3975.69)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Dragonir et al, 2014&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>On DC</td>
<td>$1300.35</td>
<td>Dragonir et al, 2014&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>ER visits for DC</td>
<td>703 events per 11436 person-months</td>
<td>Wallis et al, 2018&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hospitalizations for DC</td>
<td>490 events per 11436 person-months</td>
<td>Wallis et al, 2018&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chemotherapy adverse event requiring outpatient treatment</td>
<td>$2056 (range $1848–2056)</td>
<td>CIHI PCE (<a href="https://www.cihi.ca/en/patient-cost-estimator">https://www.cihi.ca/en/patient-cost-estimator</a>)&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>DC surveillance</td>
<td>$526.35</td>
<td>Dragonir et al, 2014&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>On third-line therapy</td>
<td>$9166.35</td>
<td>Dragonir et al, 2014&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adverse event on third-line therapy</td>
<td>$7099 (range $5679–7099)</td>
<td>CIHI PCE (<a href="https://www.cihi.ca/en/patient-cost-estimator">https://www.cihi.ca/en/patient-cost-estimator</a>)</td>
</tr>
<tr>
<td>Third-line therapy surveillance</td>
<td>$155.35</td>
<td>Dragonir et al, 2014&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Palliation</td>
<td>$3671</td>
<td>Krahn et al, 2014&lt;sup&gt;57&lt;/sup&gt;; Sanyal et al, 2016&lt;sup&gt;53&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>‡</sup>Range generated using estimated cost of generic abiraterone. <sup>†</sup>Cost of an abiraterone related treatment complication assumed to be the same as a chemotherapy related treatment complication. AA: abiraterone acetate; ADT: androgen-deprivation therapy; CIHI PCE: Canadian Institute for Health Information Patient Cost Estimator; DC: docetaxel chemotherapy; HCP: healthcare professional; ER: emergency room.
Table 4. Clinically important sensitivity analyses for average effectiveness

<table>
<thead>
<tr>
<th>Probability</th>
<th>Value (Clinical range)</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of adverse DC event</td>
<td>0.23 (0.16–0.46)</td>
<td>NR</td>
</tr>
<tr>
<td>Probability of adverse AA event</td>
<td>0.15 (0.14–0.15)</td>
<td>NR</td>
</tr>
<tr>
<td>Probability of completing DC</td>
<td>0.81 (0.77–0.86)</td>
<td>NR</td>
</tr>
<tr>
<td>Probability of completing AA</td>
<td>0.98</td>
<td>NR</td>
</tr>
<tr>
<td>Probability of death on AA</td>
<td>0.01 (0.009–0.01)</td>
<td>NR</td>
</tr>
<tr>
<td>Probability of death on DC</td>
<td>0.0045 (0.003–0.006)</td>
<td>NR</td>
</tr>
<tr>
<td>Probability of second line therapy after AA</td>
<td>0.50</td>
<td>NR</td>
</tr>
<tr>
<td>Probability of second line therapy after DC</td>
<td>0.46 (0.44–0.54)</td>
<td>NR</td>
</tr>
<tr>
<td>Starting age</td>
<td>65 years (40–100)</td>
<td>NR</td>
</tr>
<tr>
<td>Utility on AA</td>
<td>0.76 (0.63–0.84)</td>
<td>NR</td>
</tr>
<tr>
<td>Utility on DC</td>
<td>0.64 (0.64–0.72)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Sensitivity analyses generated using 10 000 microsimulations. AA: abiraterone acetate; DC: docetaxel chemotherapy; NR: not reached.