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New therapeutic options in metastatic castration-resistant prostate cancer: Can cost-effectiveness analysis help in treatment decisions?

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Abstract

Objective: To evaluate the cost-effectiveness of abiraterone, cabazitaxel, and enzalutamide compared to placebo for treatment of metastatic castration-resistant prostate cancer.

Material and methods: A decision-tree model compared three treatment options for metastatic castration-resistant prostate cancer patients over 18 months from a societal perspective in 2012 USD. Chance nodes included baseline pain as a severity indicator, significant adverse effects (neutropenia, cardiac events, or seizures), and survival. Probabilities, survival rates, and health utilities were from clinical trials (COU-AA, TROPIC, and AFFIRM) and other published studies. Survival of enzalutamide was adjusted to match placebo groups across trials. Probabilistic sensitivity analyses, acceptability curves and net benefit calculations were performed.

Results: Abiraterone was the most cost-effective of the treatments ($123.4 K/quality-adjusted life year) compared to placebo, enzalutamide was $437.6 K/quality-adjusted life year compared to abiraterone, and cabazitaxel was $351.9 K/quality-adjusted life year compared to enzalutamide. Enzalutamide and cabazitaxel were not cost-effective compared to placebo at $154.3 K/quality-adjusted life year and $163.2 K/quality-adjusted life year, respectively. Acceptability curves showed abiraterone was cost-effective 29.3% of the time with a willingness to pay threshold of $100 K. The model was sensitive to changes in cost of the drugs, life expectancy, and survival rate. Sensitivity analysis shows that enzalutamide can become the most cost-effective option if the price of the medication decreased by 26% and other drug costs remained the same.

Conclusion: Based on the cost-effective analysis, and survival adjustments necessary to match placebo groups, we would recommend abiraterone for treatment of metastatic castration-resistant prostate cancer despite not quite falling under the usually accepted willingness to pay threshold. Further analysis should examine comparative survival across the three drugs.

Keywords

Prostate cancer, cost effectiveness, androgen inhibition, castrate resistant, decision making

Introduction

Prostate cancer is the most commonly diagnosed cancer in males, with 241,740 new cases in 2012.[1] Although most patients have localized cancer, some develop metastatic disease and become refractory to androgen deprivation therapy, resulting in metastatic castration-resistant prostate cancer (mCRPC).[2]

Since 2010, three new drug treatments have been approved as options for patients with mCRPC, who have previously received docetaxel. Cabaxitaxel (Jevtana®), a chemotherapy agent approved in June 2010, showed median survival of 15.1 months compared to 12.7 months on mitoxantrone (Novantrone®) but

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also demonstrated significant risk of grade III/IV neutropenia.[3] Abiraterone (Zytiga®), a non-chemotherapeutic CYP17 inhibitor approved in April 2011, showed median survival of 14.8 months compared to 10.9 months on prednisone alone but also increased the risk of grade III/IV cardiac events.[4] Enzalutamide (Xtandi®), an androgen receptor inhibitor approved in August 2012, showed 18-month median survival compared to 13.6 months on prednisone alone, but reported five cases of seizure including one case of status epilepticus.[5] Cost-effectiveness analysis (CEA) is a useful method to evaluate comparative effectiveness among treatments along with their relative costs.

Although all three new drug treatments improve survival compared to placebo, there is no clear survival advantage across the three treatments.[3–5] Although cabazitaxel clinical trials show slightly higher survival compared to its placebo than does abiraterone compared with its comparator, it is also associated with the most severe side effects.[3] Enzalutamide likely does not have significant survival advantage over abiraterone and cabazitaxel, given its comparatively healthier control group, but its use does not require the concurrent use of prednisone and has an equal or better side effect profile.[5] There is currently no clinical trial or CEA comparing survival and cost across all three treatments, although one paper compared the cost-effectiveness of cabazitaxel and abiraterone.[6] A CEA can add valuable information to help physicians and health care systems to make appropriate treatment decisions.

The purpose of this study is to evaluate the comparative cost-effectiveness of the three new treatment options vs placebo (prednisone only) for patients with mCRPC following docetaxel treatment failure from a US societal perspective.

Methods

A decision-tree model was used to compare the cost-effectiveness of four treatment options: placebo (prednisone alone), abiraterone given with prednisone, enzalutamide given with optional prednisone, and cabazitaxel given with prednisone for mCRPC patients who failed docetaxel. The inputs for the model are based on three published phase III randomized clinical trials: AFFIRM,[5] comparing enzalutamide plus an optional prednisone to prednisone alone, COU-AA-301,[4] comparing abiraterone plus prednisone to prednisone alone, and TROPIC,[3] comparing cabazitaxel plus prednisone to mitoxantrone plus prednisone. The inclusion criteria for our model were similar to those in the three studies: men with mCRPC and an Eastern Cooperative Oncology Group (ECOG) functional status score of 0 to 2 with disease progression despite prior docetaxel treatment. The main outcome of the CEA is incremental cost per quality-adjusted life year (QALYs). The model has chance node branches for baseline pain and grade III/IV side effects and survival rates at 18 months. Ranges were obtained from a Monte Carlo simulation using a beta distribution for probabilities and utilities, and a gamma distribution for costs. A model time-horizon of 18 months was used for costs and outcomes and to model lifetime survival. No discounting was used due to the short time-horizon (Figure 1).

Probabilities

In our model, the first chance node in all treatment arms divides patients into two groups based on the presence or absence of baseline (before treatment) pain greater than 4 on the BPI-SF pain scale or base line pain based on the McGill Melzack pain scale to account for the cost and disutility associated with pain. Clinically relevant grade III/IV adverse effects include: neutropenia (82%) for cabazitaxel, cardiac events (3.2%) for abiraterone, seizures (0.6%) and diarrhea (1.1%) for enzalutamide, and grade III/IV bone pain (7.4%) for the prednisone alone groups. Rates for each treatment option's adverse events were from their respective clinical trials.[3–5] We used mean expected survival at 18 months to enable comparison of survival across the three treatment groups at a consistent time point and provide a model for the calculation of lifetime survival used in our analysis (Tables 1–3).

Costs

Costs were in 2012 US dollars and were estimated by modeling utilization of treatment resources based on literature estimates and verified by clinical expert opinion. Costs of physician visits, procedures, and tests were from the Medicare fee schedule using Current Procedural Terminology (CPT) codes. Drug average wholesale prices (AWP) minus 17% for contract pricing were from Redbook.[7] Hospitalizations and procedure costs were estimated from Healthcare Cost and Utilization Project (HCUP) national data.[8] Charges were reduced to costs using the Medicare cost-to-charge ratio (0.45).[9] Total costs were calculated by multiplying resource utilization by the average cost per unit to reflect the cost of treatment for each arm (Tables 1–3).

The most important and resource intensive Grade III/IV adverse effects were modeled for each treatment arm. Cabazitaxel-related neutropenia treatment includes hospitalization for 9% of patients who developed grade III/IV neutropenia[3] and 2-week prophylactic G-CSF treatment in all patients for a median of six cabazitaxel treatment cycles.[10] Grade III/IV cardiac

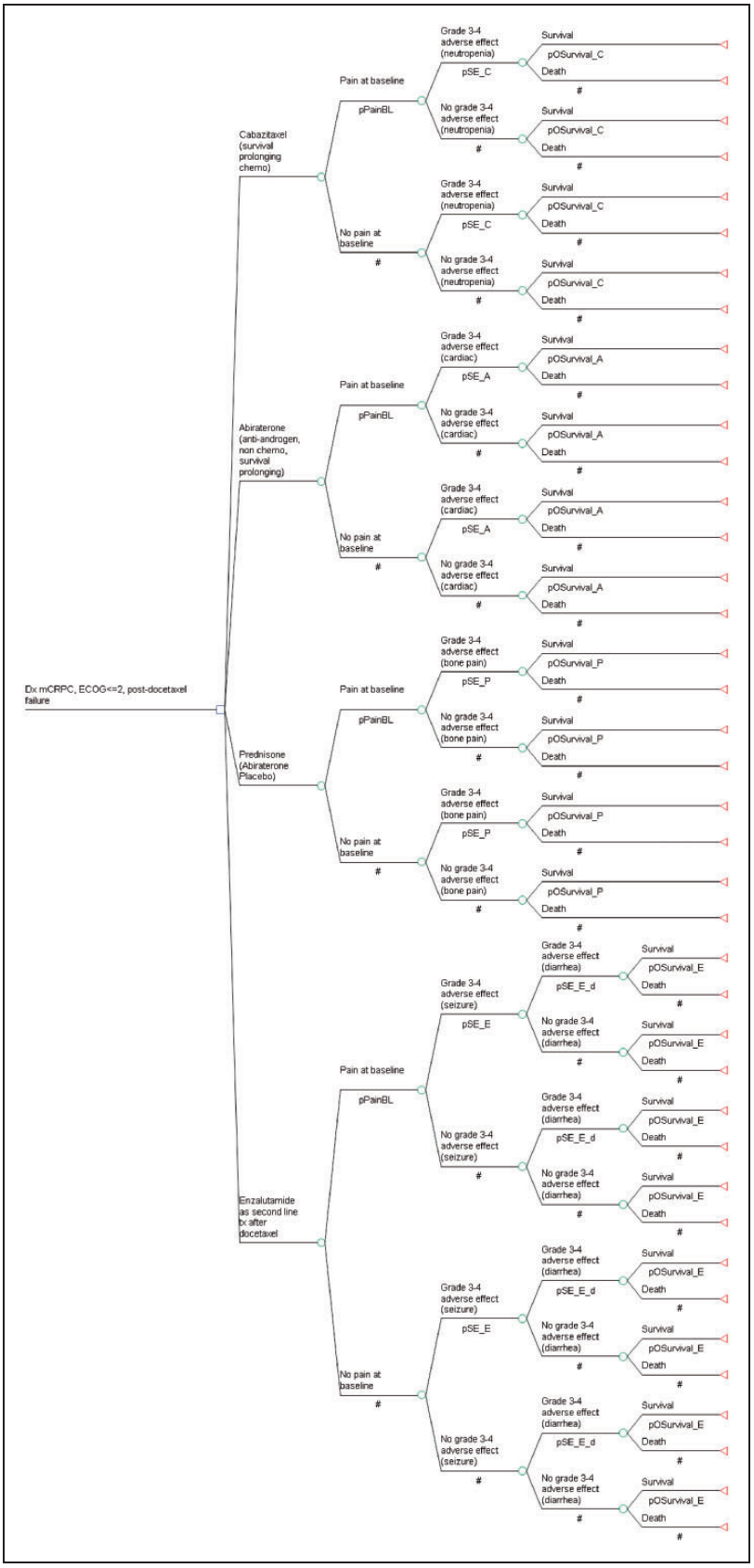

Figure 1. Decision tree used in model.

events associated with abiraterone are dysrhythmias and cardiac arrest/ventricular fibrillation and included initial hospitalization costs and at least five outpatient physician follow-ups during the treatment cycle. Seizures occurred in 5 (0.6%) patients of the enzalutamide population and of that four were assumed to be self-limiting needing only neurology consultation with EEG, CT, and MRI scans while for the one case of status epilepticus we estimated required emergency transport and hospitalization.[5] We estimated one month of seizure medication treatment for this patient as well. Additionally, we assumed that 50% of enzalutamide patients were on prednisone. Patients on prednisone only (placebo) who experienced baseline pain greater than 4 on the BPI-SF scale (45% of the patients in the prednisone only group) were treated with 15 weekly palliative radiation sessions. For patients with baseline pain in the three treatment arms, we assumed only half were treated with palliative radiation (22.5% of patients in each of the treatment groups). Bone pain treatment was applied to patients on prednisone alone with grade III/IV bone pain. Bone pain treatments included bisphosphonates, opioids, prophylactic stool softener/stimulant combination and acetaminophen usage daily, as needed. Finally, end-of-life hospitalization costs were given to patients that died within the 18 months time period for inclusion of cost data in our model.

Overall survival and life expectancy

Life expectancy was modeled using data from the Kaplan-Meier overall survival curves within each of the three clinical trials. A declining exponential approximation of life expectancy (DEALE) method was applied to the survival curves to determine life expectancy based on the 18-month trial data.[15] This method is accurate when survival is short as for this analysis. Placebo median overall survival was much longer in the enzalutamide trial (3.072 years) compared to the abiraterone trial (1.917 years), indicating the placebo group and also likely the treatment group was healthier in the enzalutamide trial than in the abiraterone trial. The comparative groups (mitoxantrone and placebo plus prednisone respectively) in the cabazitaxel and abiraterone trials were similar so a single placebo group was used in the CEA model for comparison against all treatments. In addition, when comparing average baseline pain scores across the three trials, the AFFIRM (enzalutamide) trial had lower average baseline pain scores than the other two studies; although the measurement of baseline pain had some variation across trials. Baseline pain scores are a significant indicator of survival in all three trials, providing further evidence that the population was healthier in the enzalutamide study than in the other two studies. Therefore, we adjusted the placebo group and treatment group survival curves in the enzalutamide trial downward to make survival data comparable with that of the abiraterone and cabazitaxel trials comparative groups. Although the indicator of pain reported was somewhat different across the three trials, we assumed the reported pain results indicated group differences. To adjust, we calculated the difference in survival at each point between the Kaplan Meier placebo survival curves from the enzalutamide and abiraterone trials. We then used the difference at each respective time point to adjust down the enzalutamide treatment survival curve. The survival of each treatment was compared with the same placebo group survival to make the treatment groups comparable (Table 4).

Utilities are used in cost-effective analysis to adjust life expectancy downward for poorer health states using patient preferences for different health states on a scale with 0 representing death and 1 perfect health. We obtained our utility scores for different health states

Table 1. Variables used in the decision model.

Variable	Value	Range/distribution	Reference
Pain at baseline – All	0.4500	(0.3375,0.5675)/Beta distribution	3
Side-effects (bone pain) – placebo	0.0740	(0.0555,0.0925)/Beta distribution	4
Side-effects (cardiac events) – abiraterone	0.0319	(0.0239,0.0399)/Beta distribution	4
Side-effects (seizures) – enzalutamide	0.0063	(0.0047,0.0078)/Beta distribution	5
Side-effects (diarrhea) – enzalutamide	0.0113	(0.0084,0.0141)/Beta distribution	5
Side-effects (neutropenia) – cabazitaxel	0.8167	(0.6125,1)/Beta distribution	3
Overall survival at 18 months placebo	0.2398	(0.1799,0.2998)/Beta distribution	4
Overall survival at 18 months abiraterone	0.3558	(0.2668,0.4447)/Beta distribution	4
Overall survival at 18 months enzalutamide	0.3680	(0.2760,0.4600)/Beta distribution	5
Overall survival at 18 months cabazitaxel	0.3923	(0.2943,0.4904)/Beta distribution	3

Table 2. Costs used in the decision model.

Cost variable	Cost (in 2012 USD)	Range/distribution	Factors included	Reference
Drug costs – placebo	$325	($162, $649) Gamma distribution	Prednisone costs are minimal. It is used with every treatment. Oncology doctor visits for 4 cycles[a]	4,12
Drug costs – abiraterone	$47,557	($23,779, $95,114) Gamma distribution	Abiraterone LFT monitoring (every 2 weeks for the first 3 months and monthly thereafter), monthly K+monitoring and oncology doctor visits for 8 cycles[a]	4,7,12
Drug costs – enzalutamide	$62,266	($31,123, $124,531) Gamma distribution	Oncology doctor visits for 8 cycles.[a] Only 50% of patients received prednisone	5,7,12
Drug costs – cabazitaxel	$51,707	($25,853, $103,413) Gamma distribution	Cabazitaxel infusion, lab monitoring, and follow up doctors visits for 8 cycles[a]	4,7,12
Grade 3/4 cardiac events – abiraterone	$13,241	($6,620, $26,481) Gamma distribution	Weighted average costs for dysrhythmia (80%) and cardiac arrest (20%) hospitalizations and 5 EKGs	4,8,12
Grade 3/4 seizure – enzalutamide	$3,386	($1,693, $6,772) Gamma distribution	Average cost of 4 episodes of self-limiting seizures and 1 episode of status epilepticus requiring hospitalization	5,7,12
Grade 3/4 neutropenia – cabazitaxel	$20,777	($10,389, $41,554) Gamma distribution	Two weeks of G-CSF treatment per cycle for all grade 3/4 neutropenia patients for 6 cycles[a], one hospitalization for 9% of the grade 3/4 neutropenia patients and doctors visits	3,7,8,12,13
Grade 0–2 neutropenia – cabazitaxel	$18,701	($9,350, $37,401) Gamma distribution	Two weeks of G-CSF treatment per cycle for all patients for 6 cycles[a]	3,7
Grade 3/4 bone pain – placebo	$11,061	($5,531, $22,122) Gamma distribution	Daily bisphosphonates, morphine, docusate sodium, and acetaminophen for 10.9 months[b]	4,7
Radiation for baseline pain – abiraterone, enzalutamide, cabazitaxel	$1,920	($960, $3,839) Gamma distribution	One course of radiation therapy with 15 treatments given to 50% of the patients with baseline pain in the treatment groups	11
Radiation for baseline pain – placebo	$3,802	($1,901, $7,604) Gamma distribution	One course of radiation therapy with 15 treatments given to all patients with baseline pain in the placebo group	11
Death associated hospitalization – all groups	$105,335	($52,667, $210,670) Gamma distribution	Average cost of last hospitalization for severe-side effects (neutropenia and cardiac events) for an average stay of 22 days	8,14

[a]Reported median cycle numbers were used.
[b]Reported median survival for placebo group.

from the literature and adjusted survival calculations using the lowest score applicable to patients represented by each model arm.[11,16,20,21] This means that if a patient was to experience a grade III/IV side effect such as neutropenia in addition to having baseline pain then the utility assigned to that arm would be the lower of the two if the treatment duration was the same. If treatment duration was short, such as for the seizure health state, then that utility was given for that time period (one month in this case), and the lowest next utility given for the remainder of time experienced.

QALYs are the gold standard outcome for life expectancy in CEA and are calculated by multiplying the corresponding utilities by life expectancies. We compared two alternative treatments using the formula for the incremental cost-effectiveness ratio (ICER): $(Cost_{Drug1} - Cost_{Drug2})/(QALYs_{Drug1} - QALYs_{Drug2})$. If there are more than two treatment options then each treatment option is compared to the next lowest cost treatment option. We also compared each treatment with placebo to better understand each drug's value over no treatment.

Sensitivity analysis

One-way sensitivity analyses were performed by varying each model input within a clinically plausible range. Probabilistic sensitivity analysis was also performed using a 1000-iteration Monte Carlo simulation. We used gamma distributions for costs, normal distributions for life expectancy, and beta distributions for probabilities and utilities. Based on the Monte Carlo simulation of all variable distributions, we examined model result robustness by calculating an acceptability curve which gives us the number of times in percent a given treatment is cost-effective at different willingness to pay (WTP) thresholds. This indicates the uncertainty concerning the cost-effectiveness of each of the three interventions in the presence of one another.[1] Net monetary benefit was also calculated:

Table 3. Utilities used in the decision model.

Utility variable	Utility	Range/distribution	Utility measure	Reference
BonePain	0.43	(0.3225, 0.5375) Beta distribution	HUI	11
uCardiac	0.51	(0.3825, 0.6375) Beta distribution	EQ-5D	17
uPain	0.55	(0.4125, 0.6875) Beta distribution	QWB	11
uNeutropenia	0.57	(0.4298, 0.7163) Beta distribution	SG	16
uSeizure	0.58	(0.4313, 0.7188) Beta distribution	GOS	18
uNoRadiation	0.62	(0.4650, 0.7750) Beta distribution	QWB	19
uMetastaticDisease	0.62	(0.4650. 0.7750) Beta distribution	QWB	19
uRadiation	0.67	(0.5025, 0.8375) Beta distribution	QWB	19
uNoPain	0.69	(0.5175, 0.8625) Beta distribution	QWB	19

Table 4. Life expectancies (years) used in the decision model.

	Placebo	Abiraterone	Enzalutamide (adjusted)	Enzalutamide (unadjusted)	Cabazitaxel
LE_death[a]	0.753	0.809	0.804	0.735	0.843
Range/distribution	(0.5648, 0.9413) Normal distribution	(0.6068, 1.0113) Normal distribution	(0.6026, 1.0044) Normal distribution	N/A[c]	(0.6323, 1.0538) Normal distribution
LE_survival[b]	1.917	2.64	2.6974	3.8355	2.768
Range/distribution	(1.4378, 2.3963) Normal distribution	(1.9800, 3.3000) Normal distribution	(2.0231, 3.3718) Normal distribution	N/A[c]	(2.0760, 3.4600) Normal distribution
LE overall[d]	1.021	1.47	1.50	N/A[c]	1.593

[a]Life expectancy of those who died before the end of the 18 month study period.
[b]Life expectancy of those who survived beyond the 18 month study period.
[c]Not available because unadjusted value.
[d]Overall life expectancy all patients within the given treatment arm.

NMB = (Effect * WTP) − Cost. Any value greater than zero is a cost-effective option.

Results

In the base case model, the least expensive strategy was prednisone alone ($82,929), followed by abiraterone ($116,700), then enzalutamide ($129,769), and then cabazitaxel ($136,979) with the highest cost. The treatment options followed the same increasing pattern for quality-adjusted life expectancies, from 0.43 to 0.76 QALYs. Abiraterone had an ICER of $123.4 K/QALY when compared to the next lowest cost treatment, prednisone alone. The ICER for enzalutamide when compared to the next lowest treatment, abiraterone, is $437.6 K/QALY. Cabazitaxel had an ICER of $351.9 K/QALY when compared to the next lowest treatment, enzalutamide. Of the three treatments, none fell under the generally accepted WTP threshold of 100 K although abiraterone was within 24%. When compared to prednisone alone, enzalutamide had an ICER of $154.3 K/QALY and cabazitaxel had an ICER of $163.2 K/QALY, which is significantly above the usual $100 K WTP threshold. Of the three treatments abiraterone was the most cost-effective both compared with the other treatments and against placebo (Table 5).

Sensitivity analysis

Two-way sensitivity analysis. The cost-effectiveness model is robust to most of the variables in the decision tree. The model was sensitive to variables that affect the cost and life expectancy of abiraterone and adjusted life expectancy of enzalutamide. When both probability of survival and corresponding life expectancy are changed in a two-way sensitivity analysis, Abiraterone compared to placebo falls below $100 K/QALY; when the probability of survival is 0.37, life expectancies of survival (LES) is 2.68 years and of those who died (LED) becomes 0.88 years.

In contrast, enzalutamide compared to placebo falls below $100 K/QALY when the probability of survival is 0.41 and corresponding LES is 2.96 years and of LED is 0.8016 years. Enzalutamide compared to placebo falls below $120 K/QALY (Abiraterone's ICER) when the probability of survival is 0.39, LES is 2.84 years and LED becomes 0.8025 years. When the cost of the abiraterone drug and its monitoring ($47,557, [range = $23,779, $95,114]) goes below $41,150, then the ICER for abiraterone compared to placebo falls below the $100 K/QALY threshold. Additionally, when the cost of the enzalutamide drug and follow-up ($62,266 [range = $31,133, $124,532]) goes below $45,143 (26% decrease) then the ICER for enzalutamide compared to placebo falls below the $100 K/QALY threshold.

Monte Carlo simulation. The acceptability curve from the probabilistic sensitivity analysis showed that with a WTP threshold of $100 K, abiraterone is cost-effective 29.3% of the time, enzalutamide 20.9% of the time, and cabazitaxel 16.1% of the time. Cabazitaxel is not cost-effective throughout the WTP range of $0–$200 K. Net monetary benefits were calculated using a WTP threshold of $100 K and showed all negative values at that threshold with abiraterone over placebo (−$6770) being the least negative.

Discussion

Our cost effectiveness study demonstrated that abiraterone treatment is the most cost-effective of the three treatment options when compared to placebo and compared to the other treatments when enzalutamide survival is adjusted to match the other trials placebo group survival. Enzalutamide is not cost-effective and is extended dominated by the combination of abiraterone and cabazitaxel. Using the current WTP threshold in the US of $100 K, none of the three treatment ICERs fell below the upper limit of the threshold although abiraterone was within 24% of being cost-effective and is the most cost-effective treatment over prednisone alone.[22–24] The cost of abiraterone when reduced by 14% would cause abiraterone's ICER when compared to placebo (prednisone alone) to fall below $100 K/QALY. This small change would make abiraterone strictly cost-effective based on the

Table 5. Cost-effectiveness analysis – results.

Strategy	Total cost ($)	Total effect (QALYs)	Incremental cost ($)	Incremental eff (QALYs)	ICER ($/QALY)
Placebo	$82,929	0.43	0	0	0
Abiraterone	$116,700	0.70	$33,770	0.27	$123,430
Enzalutamide[a]	$129,769	0.73	$13,069	0.03	$437,623
Cabazitaxel	$136,979	0.76	$20,279	0.06	$351,865

QALY: quality-adjusted life year.
[a]Enzalutamide shows extended dominance so cabazitaxel is compared to abiraterone.

threshold and is feasible given the variability in current drug pricing.

As previously mentioned, we adjusted enzalutamide placebo survival curves to make survival and life expectancy comparable with abiraterone and cabazitaxel due to the differences in the survival of the placebo/comparative groups of their study populations. Without these adjustments enzalutamide's ICER would be $33,532/QALY when compared to placebo, making it the most cost-effective option and well below the $100 K/QALY threshold. However, it is important to compare the CEA across all the relevant treatment options, and survival adjustments are therefore necessary for comparable comparisons across the other two treatment options. Therefore, abiraterone remains the most cost-effective treatment option.

Our model had several weaknesses. First, we were unable to account for all the possible side effects of each treatment but focused on the most clinically important or costly. Second, we adjusted survival based on differences in placebo/comparator group survivals and used a single placebo comparator for all comparison; but it is important to note that cabazitaxel had mitoxantrone for its comparator rather than a placebo although mitoxantrone had no survival benefit in that trial so acted like a placebo group. Therefore, our assumption to use prednisone as the placebo group across all treatments is likely accurate. We did our best to adjust the survival curves in the enzalutamide trial based on the differences in their placebo groups because there are no head-to-head trials. Therefore, we think it is appropriate to adjust parameters across trials so that we can make a comparison across these treatments that will be useful to clinicians and healthcare decision makers. Finally, we used a variety of sources to determine costs and utilities. This approach and these data sources are the best available and are commonly used in modeled CEA studies. Our sensitivity analysis shows that drugs can fall below the ICER threshold by reductions in their prices, or if survival improves. In addition, we demonstrate that survival needs greater improvement for enzalutamide than for abiraterone in order to reach cost-effectiveness; re-emphaasizing the CE preference for abiraterone over enzalutamide. We think it is important to conduct CEA analysis across treatments rather than each compared to only against a placebo.

Another difference in the three regimens is the optional use of prednisone with enzalutamide as compared to its mandatory use with abiraterone and cabazitaxel.[3–5] Our model took into account the additional cost savings associated with lower prednisone use, however, we did not model any adverse events related to low dose prednisone use because we consider these to be minor in this population. Clinically, the use of prednisone has been a standard of therapy along with androgen synthesis inhibitors to alleviate the symptoms associated with increased mineralocorticoid levels with these agents. Enzalutamide rather is an androgen receptor signaling inhibitor and does not directly inhibit androgen production and prednisone is not a requirement in therapy, although its use was allowed in the clinical trial.[5] Abiraterone, although requiring frequent liver function and electrolyte monitoring, is the least costly in terms of drug cost alone. Enzalutamide was the most costly in terms of drug cost, but there were case reports of seizure in clinical trials that may affect its use. Cabazataxel is not cost-effective in our analysis, and this is partly due to the frequent and costly neutropenia side effects associated with its use but also due to its high drug cost. Because enzalutamide and abiraterone have different side-effect profiles, for patients with existing cardiac symptoms that want to avoid the cardiac side effects of the more cost-effective option, abiraterone, patients might be helped by enzalutamide as a secondary treatment option. Therefore, it might be wise to have both drugs on a drug formulary.

CEA analysis can help providers and patients weigh the cost versus benefit of a given treatment when multiple options exist. Our study is the first study that compares all of the treatment options for mCRPC post docetaxel while adjusting for differences in placebo group survival across the clinical trials. In the case of mCRPC, the three treatments have similar survival outcomes, after adjustment to match placebo group survivals. These three treatment options also have different adverse event utilities and overall costs associated with both the drug treatment and the treatment of their adverse events. Future value for these drugs is to determine their clinical benefit in chemo-naïve patients and some trials are ongoing for this. The results of our study can be useful in setting funding priorities for programs that are competing for scarce resources by making comparisons across all available treatment options.

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