Cost-effectiveness analysis of metformin with enzalutamide in the metastatic castrate-resistant prostate cancer setting

Jordan Hill, MD,[1] Mike Paulden, PhD,[2] Christopher McCabe, PhD,[2] Scott A. North, MD,[3] Peter Venner, MD,[3] Nawaid Usmani, MD[1]

[1]Department of Radiation Oncology, University of Alberta, Edmonton, Alberta, Canada
[2]Department of Health Economics, University of Alberta, Edmonton, Alberta, Canada
[3]Department of Medical Oncology, University of Alberta, Edmonton, Alberta, Canada

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Introduction: *Enzalutamide (Enza) is an effective treatment for metastatic castrate-resistant prostate cancer (mCPRC). However, Enza is not cost-effective (CE) at willingness to pay (WTP) thresholds from $0-$125 000/ quality adjusted life years (QALYs) and is therefore a strain on valuable health care dollars. Metformin (Met) is inexpensive (~$8.00/month) and is thought to improve prostate cancer specific and overall survival compared to those not taking Met. We hypothesized that there must be an added effect Met could provide that would make Enza CE thereby alleviating this financial strain on government health care budgets.*

Materials and methods: *We constructed a Markov model and performed a threshold analysis to narrow in on the added effect needed to make such a combination therapy cost-effective at various WTP thresholds.*

Results: *At a WTP threshold of $50 000/QALY Enza + Met is unlikely to be CE unless it increases Enza's efficacy by more than 30%. At a WTP threshold of $100 000, Enza + Met could be CE barring Met adds 18.73% to the efficacy of Enza.*

Conclusions: *Enza + Met is unlikely to be CE at WTP thresholds less than $100 000/QALY; these results make sense because a therapy that is not CE at these WTP thresholds by itself is unlikely to be CE with an adjuvant therapy that keep a patient on such a treatment for even longer. Finally, our model suggests that the mCRPC setting is not the optimal place to trial adding Met as the relative costs are high and utility values low.*

Key Words: enzalutamide, metformin, cost-effectiveness, metastatic castrate-resistant prostate cancer

Introduction

Every year there are approximately 1,276,106 new cases of prostate cancer globally making prostate cancer the second most commonly diagnosed malignancy among men. Many of these cases progress and metastasize leading to approximately 358,989 deaths worldwide each year.[1] Not surprisingly, the economic burden of prostate cancer is significant; in 2000 Grover et. al estimated that in Canada alone, the economic burden could reach as high as $9.76 billion for a cohort of 5.8 million men aged 40-80 over their respective lifespans, which would be a gross underestimate of the total costs for a similar cohort in 2017 given the relatively newer and modernized treatments.[2]

Compared to the rest of the prostate cancer population, patients with metastatic prostate cancer have a much shorter life expectancy and often endure significant health-related events that can be devastating to their quality of life and burdensome to the national health budget.[3] Hormone therapy (HT) is currently used as first-line treatment for patients

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Address correspondence to Dr. Nawaid Usmani, Department of Oncology, University of Alberta, Cross Cancer Institute, 11560 University Avenue, Edmonton, AB T6G 1Z2 Canada

with metastatic disease, with the intent of lowering testosterone levels in the body to less than 50 ng per deciliter (1.7 nmoL per liter), otherwise known as medical castration.[4] Eventually even with HT, tumor growth despite medical castration develops and is known as metastatic castrate-resistant prostate cancer (mCRPC).[5]

Several new therapies have changed the landscape of prostate cancer treatment, primarily due to their effectiveness as first-line therapies in patients with mCRPC. Enza is one of those medications that has garnered much of the attention,[6] but is quite expensive (~$3449/month) and was estimated to cost $125,424 per quality adjusted life year (QALY) gained.[7] At such a price, Enza is well over the willingness to pay threshold of $50 000/QALY which has been used for decades as the commonest measuring stick for new medical therapies entering the market.[8] As such, Enza is at risk of diminishing available public health resources in other areas of the health sector.

Metformin (Met) is relatively less expensive (~$7.56/month) and has been used for decades to treat patients with non-insulin dependent diabetes. Two recent large population-based studies of prostate cancer have demonstrated that diabetics taking Met had improved prostate cancer specific survival and overall survival compared with those not taking Met.[9,10] Furthermore, anti-neoplastic properties have been observed in several laboratory models and may relate to attenuation of hyperinsulinemia and direct actions of metformin on neoplastic cells, whereby inhibition of oxidative phosphorylation in cancer cells causes energetic stress.[11-13]

The results from these trials, combined with Met's relative low cost, have made it an appealing theoretical adjuvant therapy for Enza and other first-line agents like abiraterone (Abi). Currently, there are several ongoing trials investigating the impact of adding Met as an adjuvant therapy to Enza or Abi on overall survival in patients with mCRPC although it is not currently used as such.[14-16] Met + Enza might be more effective when compared to the efficacy of Enza alone, however, we will not know exactly how much more effective until the results from these ongoing results are reported. Additionally, Enza will eventually come off patent and it is expected to lead to a significant price drop, which one should also improve the cost-effectiveness of Enza + Met.[17] As a result, our group was interested in determining the exact post-patent cost for Enza combined with a certain hypothetical increase in efficacy with a Met adjuvant that would combine to make Enza a cost-effective therapy at a WTP threshold of $50 000.

The results of our model will ultimately determine whether or not adding Met to Enza in the mCRPC setting makes sense from a cost-effectiveness standpoint. This analysis is important to the researchers of these ongoing trials, but also to the providers that pay for these oncologic treatments. They may also be of particular interest to those running trials using Met at earlier stages in the prostate spectrum. A cost-effectiveness analysis of Enza compared to Enza + Met from a Canadian perspective is given here. We performed a stochastic threshold analysis whereby we inputted multiple theoretical post-patent costs for Enza combined with theoretical increases to efficacy with a Met adjuvant in order to determine an exact cost and added effect needed to make Enza + Met cost effective at several different WTP thresholds including the WTP threshold of $50 000/QALY.

Materials and methods

A Markov model was chosen in order to capture the estimated treatment benefit and associated costs for a theoretical group of men starting on first-line therapy following a diagnosis of mCRPC. This particular model simulates health-related events (disease progression, toxicities, etc.) that a hypothetical mCRPC cohort might experience from diagnosis to the time of death. Patients move to and from several health states and accrue diverse costs while they use health care resources to control the burden of disease associated with each health state they enter throughout the treatment process. Additionally, the model accounts for the hypothetical years of perfect health added with treatment and are reported as QALYs.

Model structure

The overall design of the model was constructed by clinicians both trained and experienced in the management of patients with mCRPC. The aforementioned clinicians are comprised of medical and radiation oncologists based in Canada. The design, along with assumptions made, were discussed and approved by health economists and statisticians.

The model design is shown in Figure 1. The clinical pathway closely follows the Alberta Health Services (AHS) guidelines for treatment of mCRPC.[18] Patients enter the model at the time of diagnosis of mCRPC. Our cohort is immediately started on Enza as first-line therapy for mCRPC (or a hypothetical combination of Enza + Met in the adjuvant arm). Abi is not entered as a first-line option, although our analyses suggest that it would have similar results to the model shown here (data not shown). Patients remain in this health state

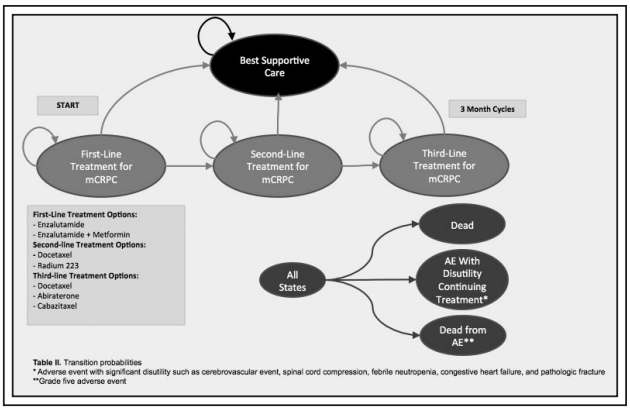

Figure 1. Markov model design.

until disease progression occurs, or a severe adverse event (AE) occurs necessitating discontinuation of treatment and palliation, or a minor AE requiring a dose reduction, or until a patient dies from disease progression, a grade five AE, or from natural causes. Upon leaving the first-line therapy health state patients can move onto second-line therapy, best-supportive care (BSC), or death. All subsequent treatments and health states are listed in Figure 1.

Transition probabilities are identical in all health states beyond first-line treatment on both arms of the model (Enza alone versus Enza + Met); this strategy was intentional as Met was shown to have minimal benefit in all-cause mortality after 24-30 months of use.[10] Met was only modeled with a benefit in the first-line setting, as including a theoretical benefit for Enza + Met beyond the first-line setting could potentially exaggerate the cost-effectiveness of Met in this model.

Transition probabilities

The transition probabilities used within our model are summarized in Table 1.[6,19-30] First-line transition probabilities are derived from results of the PREVAIL trial as this study is currently used to justify using Enza as first-line treatment in chemo-naive mCRPC patients in Canada. All subsequent transition probabilities are derived from the ALSYMPCA, TAX 327, COU-AA-302, TROPIC, and other studies listed below in Table 1. BSC after first-line treatment was determined by using the placebo values of the AFFIRM trial. Finally, BSC following second and third-line treatments were derived using expert elicitation, with the assumption that patients would survive half as long as the earlier best supportive care state, with a large degree of uncertainty.

Costs

The costs included within our model are summarized in Table 1.[6,7,24-26,29,31-34] All costs reported are 3 month costs. All costs were adjusted for inflation using STATSCAN's consumer price index table for health care costs. Our model accounts for oncologic medications, medical castration, bone therapy (bisphosphonates and or denosumab), ambulatory (physician and nursing fees, imaging, blood work, and radiation therapy), emergency department, analgesics, and hospitalization costs. All pharmacy costs are Canadian prices, but some of the non-pharmacological costs were taken from a US study. In these circumstances, all American costs were changed into Canadian values using the Bank of Canada's website on December 14, 2016 at a conversion rate of $1.31 Canadian dollars for every US dollar. Additionally, for any drugs requiring body surface area (BSA) for dosing, we used a BSA of 1.9 m^2.

Hospitalization costs were derived using toxicity data from the PREVAIL, COU-AA-302, ALSYMPCA, TAX 327, and TROPIC trials. Any grade three AE or higher was assumed to result in a hospitalization. For each type of hospitalization we used the Canadian Institute of Health Informations database to calculate the average hospitalization cost. The total costs were added and then divided by the number of months each of the above trials ran for to get a total cost for the entire non-placebo cohort. We then divided the total cost by the number of non-placebo patients to get a total cost per patient per month cost. This final cost was then multiplied by three to get a 3 month cost per patient.

Utility values

The utility values and disutility value used within our model are also summarized in Table 1.[35-38] All utility values are annual values. We included a disutility value for patients experiencing a cerebrovascular accident as a toxicity due to treatment. This strategy was intentionally chosen because unlike other adverse events, often, cerebrovascular accidents leave patients with irreversible complications which affects their own perception of their health. Additionally, we assumed that all BSC states had the same utility value, despite the fact that patients enter best supportive after having received different treatment lines; it is unlikely that patients perception of their health is identical irrespective of which of the available treatment regimens they received, however, no study has identified different utility values for specific lines of treatment.

TABLE 1. **Transition probabilities, Costs (3 month values) and utilities**

Parameter	Base-case estimate	Distribution	Distribution	Source parameters
First-line treatment (enzalutamide)				
Staying on enzalutamide	1- Tp's (~0.94)	Fixed	N/A	PREVAIL[6,19,20,21]
Dead from AE	0.0036	Beta	$\alpha = 3.1, \beta = 868.9$	PREVAIL[6]
Dose reduction	0.0017	Beta	$\alpha = 1.5, \beta = 870.5$	PREVAIL[6,22]
BSC	0.0080	Beta	$\alpha = 6.9, \beta = 865.1$	PREVAIL[6,19,20,21]
BSC with CVA	0.0006	Beta	$\alpha = 0.5, \beta = 871.5$	PREVAIL[6]
Docetaxel	0.0440	Beta	$\alpha = 38.6, \beta = 833.4$	PREVAIL[6,19,20,21]
Radium 223	0.0020	Beta	$\alpha = 1.3, \beta = 870.7$	PREVAIL[6,19,20,21]
With metformin (15% hypothetical added effect)				
Staying on enzalutamide	1- Tp's (~0.96)	Fixed	N/A	Assumption
Dead from AE	0.0036	Beta	$\alpha = 3.1, \beta = 868.9$	Assumption
Dose reduction	0.0017	Beta	$\alpha = 1.5, \beta = 870.5$	Assumption
BSC	0.0040	Beta	$\alpha = 3.5, \beta = 868.5$	Assumption
BSC with CVA	0.0006	Beta	$\alpha = 0.5, \beta = 871.5$	Assumption
Docetaxel	0.0250	Beta	$\alpha = 21.8, \beta = 850.2$	Assumption
Radium 223	0.0008	Beta	$\alpha = 0.7, \beta = 871.3$	Assumption
With metformin (10% hypothetical added effect)				
Staying on enzalutamide	1-Tp's (~0.95)	Fixed	N/A	Assumption
Dead from AE	0.0036	Beta	$\alpha = 3.1, \beta = 868.9$	Assumption
Dose reduction	0.0017	Beta	$\alpha = 1.5, \beta = 870.5$	Assumption
BSC	0.0054	Beta	$\alpha = 4.7, \beta = 867.3$	Assumption
BSC with CVA	0.0006	Beta	$\alpha = 0.5, \beta = 871.5$	Assumption
Docetaxel	0.0300	Beta	$\alpha = 26.2, \beta = 845.8$	Assumption
Radium 223	0.0010	Beta	$\alpha = 0.9, \beta = 871.1$	Assumption
With metformin (5% hypothetical added effect)				
Staying on enzalutamide	1-Tp's (~0.949)	Fixed	N/A	Assumption
Dead from AE	0.0036	Beta	$\alpha = 3.1, \beta = 868.9$	Assumption
Dose reduction	0.0017	Beta	$\alpha = 1.5, \beta = 870.5$	Assumption
BSC	0.0065	Beta	$\alpha = 5.7, \beta = 866.3$	Assumption
BSC with CVA	0.0006	Beta	$\alpha = 0.5, \beta = 871.5$	Assumption
Docetaxel	0.0370	Beta	$\alpha = 32.3, \beta = 839.7$	Assumption
Radium 223	0.0012	Beta	$\alpha = 1.0, \beta = 871.0$	Assumption
Second-line treatment (docetaxel)				
BSC	1-Tp's	Fixed	N/A	Assumption
Staying on docetaxel	0.50	Beta	$\alpha = 132.5, \beta = 132.5$	de Bono et al[20,23,24]
Cabazitaxel	0.140	Beta	$\alpha = 37.1, \beta = 227.9$	de Bono et al[20,23,24]
Enzalutamide	0.160	Beta	$\alpha = 42.4, \beta = 222.6$	de Bono et al[20,23,24]
Dead (from either AE or disease progression)	0.0030	Beta	$\alpha = 1.0, \beta = 334.0$	TAX 327[24]
Second-line treatment (radium 223)				
Receive second injection and then to BSC	1-Tp's (~0.978)	Beta	N/A	Assumption
BSC (did not receive second injection)	0.0220	Beta	$\alpha = 13.2, \beta = 586.8$	ASLYMPCA[25]
Dead (from either AE or disease progression)	0.0002	Beta	$\alpha = 0.1, \beta = 599.9$	ASLYMPCA[25]

TABLE 1 (Cont'd). **Transition probabilities, Costs (3 month values) and utilities**

Parameter	Base-case estimate	Distribution	Distribution parameters	Source
Third-line treatment (cabazitaxel)				
BSC	1-Tp's (~0.40)	Beta	N/A	Assumption
Dead (from either AE or disease progression)	0.005	Beta	$\alpha = 1.8, \beta = 369.2$	TROPIC[26]
Staying on cabazitaxel	0.595	Beta	$\alpha = 52.36, \beta = 35.64$	Caffo et al[27]
Third-line treatment (abiraterone)				
BSC	1-Tp's (~0.540)	Fixed	N/A	Assumption
Staying on abiraterone	0.460	Beta	$\alpha = 17.48, \beta = 20.5$	Loriot et al[28]
Dead (from either AE or disease progression)	0.002	Beta	$\alpha = 1.1, \beta = 540.9$	COU-AA-302[29]
BSC following first-line therapy				
Continuing BSC	1-Tp's	Fixed	N/A	Assumption
Dead	0.502	Beta	$\alpha = 200.3, \beta = 198.7$	AFFIRM[30]
BSC following second-line therapy				
Continuing BSC	1- TP's	Fixed	N/A	Expert elicitation
Dead	0.250	Beta	$\alpha = 17.2, \beta = 22.8$	Expert elicitation
BSC following third-line therapy				
Continuing BSC	1- TP's	Fixed	N/A	Expert elicitation
Dead	0.125	Beta	$\alpha = 2.5, \beta = 17.5$	Expert elicitation
Parameter	**Mean**	**Standard**	**Distribution**	**Source deviation**
Pharmacological costs				
Enzalutamide (160 mg/day)	$10 347	N/A	Fixed	PCODR[7]
Metformin (1000 mg/day)	$35	N/A	Fixed	ACFP price comparison[31]
Abiraterone (1000 mg/day)	$10 344	N/A	Fixed	PCODR[32]
Docetaxel (75 mg/m^2 q 21 days)	$2322	N/A	Fixed	Dragomir et al[33]
Radium 223 (3 injections)	$16 920	N/A	Fixed	Toronto General
Hospital pharmacy price quote				
Cabazitaxel (25 mg/m^2 q day 1, 21)	$25 380	N/A	Fixed	Dragomir et al[33]
Dexamethasone (8 mg IV q 21 days)	$14.07	N/A	Fixed	Dragomir et al[33]
Prednisone (10 mg/day)	$4.02	N/A	Fixed	Dragomir et al[33]
Medical castration	$1056	16	Beta	Dragomir et al[33]
Bone therapy	$1578	36	Beta	Dragomir et al[33]
Analgesics pre-docetaxel	$79	$362	Beta	Mehra et al[34]
Analgesics post-docetaxel	$227	$900	Beta	Mehra et al[34]
Non- pharmacological costs				
Ambulatory costs pre-docetaxel	$4477	$6176	Beta	Mehra et al[34]
Ambulatory costs post-docetaxel	$5750	$8550	Beta	Mehra et al[34]
Emergency costs pre-docetaxel	$83	$362	Beta	Mehra et al[34]
Emergency costs post-docetaxel	$239	$645	Beta	Mehra et al[34]
Hospitalization costs enzalutamide	$100	N/A	Fixed	PREVAIL[6]
Hospitalization costs abiraterone	$138.93	N/A	Fixed	COU-AA-302[29]
Hospitalization costs docetaxel	$738.60	N/A	Fixed	TAX 327[24]
Hospitalization costs radium 223	$369.30	N/A	Fixed	ASLYMPCA[25]
Hospitalization costs cabazitaxel	$1135	N/A	Fixed	TROPIC[26]

TABLE 1 (Cont'd). **Transition probabilities, Costs (3 month values) and utilities**

Parameter	Base-case estimate	Distribution	Distribution parameters	Source
Utility values				
First-line treatment	0.83	0.018	Beta	Lloyd et al[35]
Second-line treatment pre-chemo	0.70	0.02	Beta	Lloyd et al[35]
Chemotherapy	0.66	0.02	Beta	Diels et al[36]
Post-chemotherapy	0.6	0.03	Beta	Diels et al[36]
BSC	0.5	0.02	Beta	Vicente et al[37]
Cerebrovascular accident disutility	- 0.15	0.05	Beta	Davies et al[38]

AE = adverse event; BSC = best supportive care; BSC with CVA = best supportive care with cerebrovascular accident

WTP per QALY	Theoretical post-patent 3-month cost of enzalutamide										
	$0	$1 000	$2 000	$3 000	$4 000	$5 000	$6 000	$7 000	$8 000	$9 000	$10 344
$50 000	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
$60 000	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
$70 000	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
$80 000	1.30%	10.80%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
$90 000	0.47%	0.71%	1.36%	14.01%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
$100 000	0.29%	0.36%	0.48%	0.71%	1.42%	18.73%	N/A	N/A	N/A	N/A	N/A
$110 000	0.21%	0.24%	0.29%	0.36%	0.48%	0.73%	1.48%	25.51%	N/A	N/A	N/A
$120 000	0.16%	0.18%	0.21%	0.24%	0.29%	0.37%	0.49%	0.75%	1.55%	N/A	N/A
$130 000	0.13%	0.15%	0.16%	0.18%	0.21%	0.24%	0.30%	0.37%	0.50%	0.76%	2.63%
$140 000	0.11%	0.12%	0.13%	0.15%	0.16%	0.18%	0.21%	0.25%	0.30%	0.38%	0.58%
$150 000	0.10%	0.11%	0.11%	0.12%	0.13%	0.15%	0.17%	0.19%	0.21%	0.25%	0.32%

Table 2a. Efficacy increase necessary for enzalutamide and metformin to be cost-effective at various combinations of the willingness-to-pay (WTP) per quality-adjusted life year (QALY) threshold and the theoretical post-patent 3-month cost of enzalutamide. 'N/A' refers to combinations for which enzalutamide and metformin is not cost-effective for any efficacy increase less than or equal to 30%.

WTP per QALY	Efficacy increase to enzalutamide when used in combination with metformin										
	0%	1%	2%	3%	4%	5%	6%	7%	8%	9%	10%
$50 000	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
$60 000	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
$70 000	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
$80 000	N/A	N/A	$382	$623	$746	$821	$872	$911	$941	$965	$985
$90 000	N/A	$1 622	$2 340	$2 581	$2 703	$2 778	$2 829	$2 868	$2 897	$2 921	$2 941
$100 000	N/A	$3 579	$4 297	$4 538	$4 661	$4 736	$4 787	$4 824	$4 853	$4 877	$4 897
$110 000	N/A	$5 535	$6 255	$6 496	$6 619	$6 693	$6 744	$6 781	$6 810	$6 833	$6 852
$120 000	N/A	$7 491	$8 213	$8 455	$8 577	$8 651	$8 701	$8 738	$8 766	$8 789	$8 808
$130 000	N/A	$9,448	$10 170	$10 412	$10 534	$10 608	$10 658	$10 695	$10 723	$10 745	$10 763
$140 000	N/A	$11 404	$12 128	$12 370	$12 492	$12 565	$12 616	$12 651	$12 679	$12 701	$12 719
$150 000	N/A	$13 360	$14 085	$14 328	$14 450	$14 523	$14 573	$14 608	$14 635	$14 656	$14 674

Table 2b. Theoretical post-patent 3-month cost of enzalutamide necessary for enzalutamide and metformin to be cost-effective at various combinations of the willingness-to-pay (WTP) per quality-adjusted life year (QALY) threshold and the efficacy increase to enzalutamide when used in combination with metformin. 'N/A' refers to combinations for which enzalutamide and metformin is not cost-effective for any positive theoretical post-patent 3-month cost of enzalutamide.

Results

At our baseline value of added effect for Enza + Met (15%), there was an increase in expected lifetime costs per patient by $17 736 compared to Enza alone. Additionally, it improves the expected effectiveness of treatment by 0.24 QALYs compared to Enza alone. The incremental cost-effectiveness ratio is $75 013/QALY. Accounting for parameter uncertainty, adding Met to Enza has a 68.4% probability of being cost-effective at a WTP of $100 000/QALY.

We also performed two distinct probabilistic threshold analysis; the first probabilistic threshold analysis was designed to narrow in on the exact added effect Met would need to add to Enza in order to make such a combination therapy CE at various WTP thresholds from $50 000- $150 000/QALY and at various possible post-patent costs of $0-$10 344 (current cost). The results of this probabilistic threshold analysis are reported below in Table 2a. The second probabilistic threshold analysis calculates an exact post-patent price that would be cost effective at various hypothetical amounts of added efficacy (0%-10%) with Met, at various WTP thresholds mentioned previously. The results of the second probabilistic threshold analysis are reported in Table 2b.

Conclusions

Our results demonstrate, that price is a less important variable, because it is the same on both arms of the Markov model. In other words, if one drops the price of Enza, then the price drops on both competing model arms neutralizing any benefit of dropping the price. It is therefore the theoretical added effect inputs that become more important if a theoretical treatment of Enza + Met is to be CE compared to Enza alone. There are no combinations of increased efficacy from 0%-30% with a price of Enza between $0-$10 344 that is CE at WTP thresholds below $70 000/QALY. These results correlate with the fact that the health state with or without Enza + Met is already extremely expensive due to the costs of medical castration, bone therapy (bisphosphonates and or denosumab), ambulatory fees (physician and nursing fees, imaging, blood work, and radiation therapy), emergency visits, analgesics, and hospitalizations. In fact, the non-pharmacological costs while taking Enza are equal and in some instances more costly then Enza itself. This suggests that while the price of Enza is perhaps too high for the QALY return, that there is also an additional problem in that the health state's other costs are also far too expensive relative to the additional health provided to the health care system. It is even less likely that these non-pharmacological costs will be reduced in the future than the price of Enza; these costs reflect the need for frequent expensive tests, health care follow up, and other medical supports and directly correlate to the severity of the mCRPC health state. These results, although less encouraging than were originally assumed, actually make sense, because Enza is not CE at these WTP thresholds by itself and is therefore unlikely to be CE with a theoretical adjuvant therapy that would hold a patient on such a treatment and in a health state for even longer unless there is a very significant increase in added efficacy (at least above 30% compared to Enza alone).

The first combination that is theoretically possible is at a WTP threshold of $80 000/QALY; here it would require a price for Enza of approximately $0 per 3 month cycle and an added effect of 1.3% in order to be CE. This possibility is not helpful because no pharmaceutical companies would be expected to produce a drug and distribute it for free. Additionally, at a WTP threshold of $90 000/QALY, it would require a price for Enza of approximately $3000 per 3 month cycle and an added effect of 14%. This combinations, although possible, is unlikely as it requires a price drop of 70% and a very hefty increase to efficacy compared to Enza alone.

Perhaps the most interesting portion to analyze within this model is the data for a WTP threshold of $100 000/QALY, which many believe to be a more realistic WTP threshold for modern oncologic treatments.[39] If the price of Enza could be cut to just under half of its' current price down to $5000, one would also need to add 18.73% to Enza's efficacy to make Enza + Met CE at a WTP of $100 000/QALY. An 18.73% is difficult to understand without an example as to what such an increase would mean in the real world; the landmark study for Enza was the PREVAIL trial and in that trial, there were 872 patients on the Enza arm. At 36 months time there was still 367/872 patients still on Enza in the PREVAIL trial. Now imagine an equivalent yet hypothetical study with Enza + Met; such a trial would also have to include 872 patients on an Enza + Met arm. However, instead of 367/872 patients still on treatment at 36 months one would have to have 523/872 patients, of a hypothetical cohort, still on treatment at 36 months. From both a price and effectiveness standpoint this combination is still at best a theoretical possibility; firstly, it is unlikely that the price could drop by 50% following the expiration of Enza's patent particularly given the fact that Canada pays far less for Enza than in other countries. Secondly, it is unlikely that Met could add 18.73% to the effectiveness of Enza, because that is well over the reported prostate cancer specific mortality benefits seen at 30 months

time for those taking Met versus those not taking Met in certain retrospective studies.[10]

Additionally, at any WTP of $130 000, no added benefit is needed and the price doesn't need to drop to make the theoretical combination therapy of Enza + Met CE. This makes sense, given that the CE of Enza alone was around $125 424/QALY gained. In other words, any added effect for Enza at a minimal addition of price by adding Met (only $35 extra per month) will be CE given that Enza alone is CE at a WTP threshold of $125 424/QALY.

In coming months or years the results of ongoing trials comparing Enza alone to Enza + Met will be published and the results will transform the hypothetical inputs of our model into real data. However, the threshold analysis from our model suggests that Enza + Met will have to add a significant amount of efficacy compared to Enza alone in order to be CE at WTP thresholds of $100 000 or less. Additionally, one would have to see a significant price drop in Enza following the expiration of its' patent. Meaning that a positive result in these trials, might actually be a detrimental result from a CE perspective. As a result, perhaps the most important conclusions from our model is that new therapies such as Met, may actually be best given as an adjuvant therapy at an earlier stage of diagnosis for prostate cancer patients. Whether or not the Met is best used concurrent or sequentially with treatments earlier on in the prostate cancer disease spectrum is yet to be determined. However, the literature seems to demonstrate that Met is most effective during the first 6 months of its' use and could therefore be added concurrently and early on with treatments such as prostatectomy, external beam radiotherapy, brachytherapy, and hormone therapy.[10] At an earlier stage of diagnosis, the costs are relatively small and the utility gains are relatively higher compared to the mCRPC setting, taking the pressure off of a new therapy to add to the efficacy of current treatments used at earlier stages of disease while optimizing CE results. □

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