Supplementary Handout for EE505: Cost-Effectiveness Analysis of Contemporary Advanced Prostate Cancer Management: A Markov Model for the Canadian Context

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1 Full List of Trials Used

Table 1: List of trials, treatments, and health states used

Trial	Treatments	Health States	Sources
AFFIRM	Enzalutamide post docetaxel	mCPRC	42
ARAMIS	Darolutamide	nmCRPC	14
ARANOTE	Darolutamide	low-risk mCSPC	40
		high-risk mCSPC	
ARASENS	Darolutamide and docetaxel	low-risk mCSPC	44
		high-risk mCSPC	
COU-AA-301	Abiraterone post docetaxel	mCRPC	6
COU-AA-302	Abiraterone	mCRPC	37
EMBARK	Enzalutamide	nmCSPC	15
	ADT alone	nmCSPC	
ENZAMET	Enzalutamide	low-risk mCSPC	49
		high-risk mCSPC	
	Enzalutamide and docetaxel	low-risk mCSPC	
		high-risk mCSPC	
	Docetaxel	high-risk mCSPC	
	ADT alone	low-risk mCSPC	
		high-risk mCSPC	
FIRSTANA	Docetaxel	mCRPC	31
GETUG-AFU 15	Docetaxel	high-risk mCSPC	17
	ADT alone	high-risk mCSPC	
PEACE-1	Abiraterone and docetaxel	low-risk mCSPC	13
		high-risk mCSPC	
	Docetaxel	high-risk mCSPC	
PRESIDE	Docetaxel	mCRPC	30
PREVAIL	Enzalutamide	mCRPC	4
PROSELICA	Cabazitaxel post docetaxel	mCRPC	12
PROSPER	Enzalutamide	nmCRPC	20
SPARTAN	Apalutamide	nmCRPC	45
STAMPEDE	Abiraterone	low-risk mCSPC	19
		high-risk mCSPC	
		nmCRPC	2
	ADT alone	low-risk mCSPC	19
		high-risk mCSPC	
TITAN	Apalutamide	low-risk mCSPC	9
		high-risk mHPSC	
TROPIC	Cabazitaxel post docetaxel	mCRPC	7
Jikei University nmCRPC Docetaxel Trial	Docetaxel	nmCRPC	21

2 State Transition Diagrams

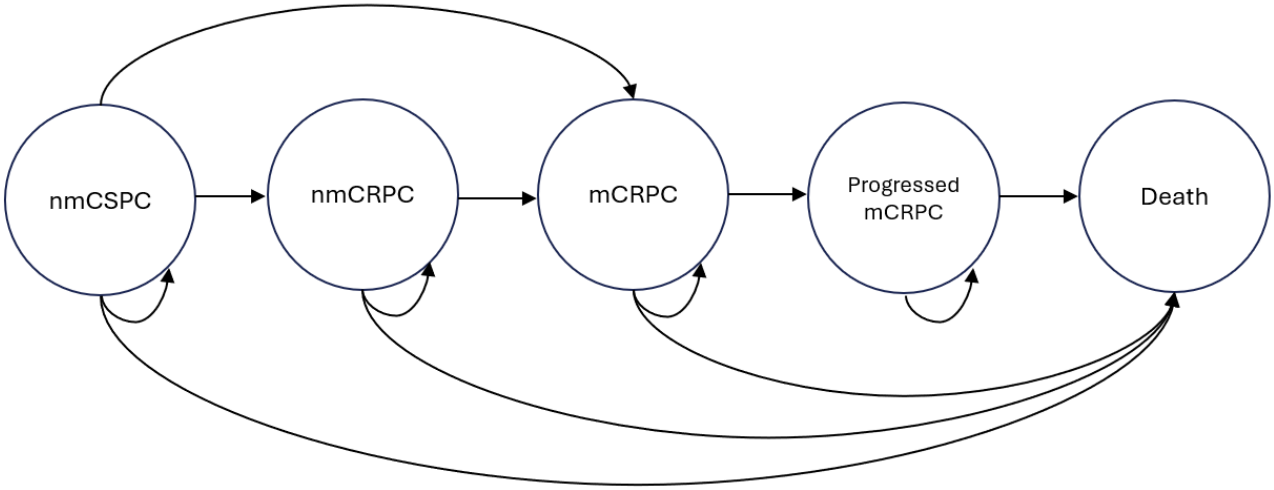


Figure 1: State transition diagram for nmCSPC-starting patients

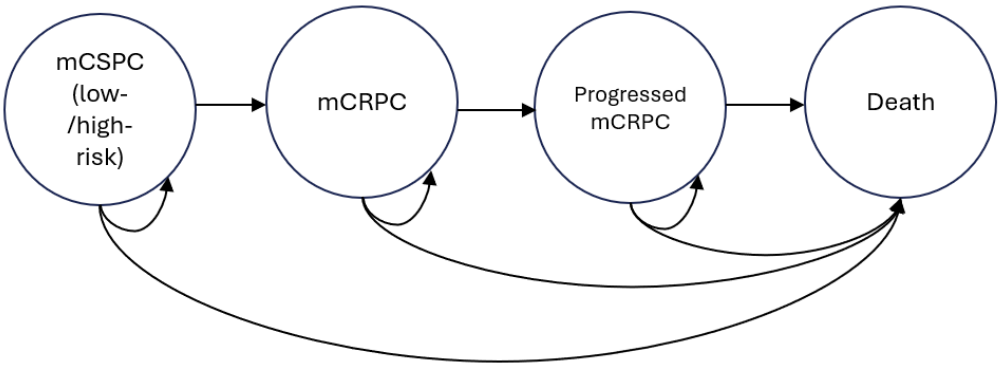


Figure 2: State transition diagram for low-risk mCSPC and high-risk mCSPC-starting patients

3 Full List of Treatment Sequences

3.1 nmCSPC start

Note: All treatments are in combination with ADT.

Table 2: List of treatment sequences: nmCSPC start

nmCSPC treatment	nmCRPC treatment	mCRPC treatment	Compact name	SGAA Use
ADT	abiraterone	docetaxel	(ADT,abi,doce)	early
ADT	abiraterone	docetaxel then cabazitaxel (2nd line)	(ADT,abi,doce then caba)	early
ADT	apalutamide	docetaxel	(ADT,apa,doce)	early
ADT	apalutamide	docetaxel then cabazitaxel (2nd line)	(ADT,apa,doce then caba)	early
ADT	darolutamide	docetaxel	(ADT,daro,doce)	early
ADT	darolutamide	docetaxel then cabazitaxel (2nd line)	(ADT,daro,doce then caba)	early
ADT	docetaxel	abiraterone	(ADT,doce,abi)	late
ADT	docetaxel	docetaxel	(ADT,doce,doce)	none
ADT	docetaxel	docetaxel then abiraterone (2nd line)	(ADT,doce,doce then abi)	late
ADT	docetaxel	docetaxel then cabazitaxel (2nd line)	(ADT, doce,doce then caba)	none
ADT	docetaxel	docetaxel then enzalutamide (2nd line)	(ADT, doce, doce then enza)	late
ADT	docetaxel	enzalutamide	(ADT,doce,enza)	late
ADT	enzalutamide	docetaxel	(ADT,enza,doce)	early
ADT	enzalutamide	docetaxel then cabazitaxel (2nd line)	(ADT,enza,doce then caba)	early
enzalutamide	docetaxel	docetaxel	(enza,doce,doce)	early
enzalutamide	docetaxel	docetaxel then cabazitaxel (2nd line)	(enza,doce,doce then caba)	early

3.2 low-risk mCSPC start

Note: All treatments are in combination with ADT.

Table 3: List of treatment sequences: low-risk mCSPC start

mCSPC treatment	mCRPC treatment	Compact name	SGAA Use
abiraterone	docetaxel	(abi,doce)	early
abiraterone	docetaxel then cabazitaxel (2nd line)	(abi, doce then caba)	early
ADT	abiraterone	(ADT,abi)	late
ADT	docetaxel	(ADT,doce)	none
ADT	docetaxel then abiraterone (2nd line)	(ADT,doce then abi)	late
ADT	docetaxel then cabazitaxel (2nd line)	(ADT,doce then caba)	none
ADT	docetaxel then enzalutamide (2nd line)	(ADT,doce then enza)	late
ADT	enzalutamide	(ADT,enza)	late
apalutamide	docetaxel	(apa,doce)	early
apalutamide	docetaxel then cabazitaxel (2nd line)	(apa,doce then caba)	early
darolutamide	docetaxel	(daro,doce)	early
darolutamide	docetaxel then cabazitaxel (2nd line)	(daro,doce then caba)	early
abiraterone & docetaxel	docetaxel	(doce+abi,doce)	early
abiraterone & docetaxel	docetaxel then cabazitaxel (2nd line)	(doce+abi,doce then caba)	early
darolutamide & docetaxel	docetaxel	(doce+daro,doce)	early
darolutamide & docetaxel	docetaxel then cabazitaxel (2nd line)	(doce+daro,doce then caba)	early
enzalutamide & docetaxel	docetaxel	(doce+enza,doce)	early
enzalutamide & docetaxel	docetaxel then cabazitaxel (2nd line)	(doce+enza,doce then caba)	early
enzalutamide	docetaxel	(enza,doce)	early
enzalutamide	docetaxel then cabazitaxel (2nd line)	(enza,doce then caba)	early

3.3 high-risk mCSPC start

Note: All treatments are in combination with ADT.

Table 4: List of treatment sequences: high-risk mCSPC start

mCSPC treatment	mCRPC treatment	Compact name	SGAA Use
abiraterone	docetaxel	(abi,doce)	early
abi	docetaxel then cabazitaxel (2nd line)	(abi, doce then caba)	early
ADT	abiraterone	(ADT,abi)	late
ADT	docetaxel	(ADT,doce)	none
ADT	docetaxel then abiraterone (2nd line)	(ADT,doce then abi)	late
ADT	docetaxel then cabazitaxel (2nd line)	(ADT,doce then caba)	none
ADT	docetaxel then enzalutamide (2nd line)	(ADT,doce then enza)	late
ADT	enzalutamide	(ADT,enza)	late
apalutamide	docetaxel	(apa,doce)	early
apalutamide	docetaxel then cabazitaxel (2nd line)	(apa,doce then caba)	early
darolutamide	docetaxel	(daro,doce)	early
darolutamide	docetaxel then cabazitaxel (2nd line)	(daro,doce then caba)	early
docetaxel	abiraterone	(doce,abi)	late
docetaxel	docetaxel	(doce,doce)	none
docetaxel	docetaxel then abiraterone	(doce,doce then abi)	late
docetaxel	docetaxel then cabazitaxel	(doce,doce then caba)	none
docetaxel	docetaxel then enzalutamide	(doce,doce then enza)	late
docetaxel	enzalutamide	(doce,enza)	late
abiraterone & docetaxel	docetaxel	(doce+abi,doce)	early
abiraterone & docetaxel	docetaxel then cabazitaxel (2nd line)	(doce+abi,doce then caba)	early
darolutamide & docetaxel	docetaxel	(doce+daro,doce)	early
darolutamide & docetaxel	docetaxel then cabazitaxel (2nd line)	(doce+daro,doce then caba)	early
enzalutamide & docetaxel	docetaxel	(doce+enza,doce)	early
enzalutamide & docetaxel	docetaxel then cabazitaxel (2nd line)	(doce+enza,doce then caba)	early
enzalutamide	docetaxel	(enza,doce)	early
enzalutamide	docetaxel then cabazitaxel (2nd line)	(enza,doce then caba)	early

4 Utility and Cost Tables

Table 5: Monthly direct drug and related costs

Treatment	Cost (C$)	Source
ADT	322	[1;3]
Abiraterone	919	[1]
Apalutamide	3401	[1]
Cabazitaxel	4134	[22]
Darolutamide	3401	[1]
Docetaxel	103	[3]
Enzalutamide	3401	[1]
Non-IV management	92	[3]
IV management	455	[3]
End-of-life	1,449	[10]

Note: End-of-life costs apply to the last 12 months (or fewer) of life in the progressed mCRPC stage

We report state-specific utility values, where utility ranges from 0 at death to 1 at ideal health. Due to concerns about accurately separating pre- and post-progression events and values (see Section 5 of this handout), we chose not to apply disutility adjustments to specific treatments or adverse events. Also note that although we could not find specific utility values for the nmCRPC state, we interpolated nmCRPC utility from our mCSPC and mCRPC utility values using FACT-P quality-of-life questionnaire results[25].

Table 6: State specific utility values

Health state	Utility value	Source
nmCSPC	0.95	[24]
mCSPC (low- & high-risk)	0.85	[27]
nmCRPC	0.8	[25;27;51]
mCRPC	0.75	[51]
Progressed mCRPC	0.6	[51]

5 Novel Parameter Estimation Algorithm

Our goal of modeling treatments in sequence introduces a new statistical challenge that we tackle with a novel parameter estimation algorithm. This section features a limited technical overview of the problem and our solution, and is geared toward statistically-oriented readers. We aim to provide a more robust discussion of the algorithm in a future methodological companion article.

To demonstrate the issue, suppose we wish to model a treatment sequence of treatment X followed by treatment Y. Suppose we use data from trial T_X that investigates treatment X within mCSPC, and data from trial T_Y that investigates treatment Y within mCRPC. Since patients in T_X received some follow-up in mCRPC which was not Y, we need to separate T_X outcomes between events that occurred in mCSPC and those that occurred in mCRPC, so that we can remove the latter. However, we cannot tell which events in T_X happened pre- or post-progression to mCPRC, leading to a so-called "parameter identification problem".

We found only a few relevant works that address this identification problem[1]. The first is Li, Litvin, and Manski (2023)[26] , who use a global search optimization algorithm to overcome an identification problem in trial reporting, and the second is a 2018 presentation document by Eldon Spackman[47], where the author outlines our specific identification problem and offers the suggestion of using optimization or simulation approaches. Although neither work offers a comprehensive solution for our needs, we build upon the optimization approach to construct a novel parameter estimation algorithm.

Briefly, the algorithm conducts a grid search over feasible sets of model parameters (i.e. state transition probabilities). First, the algorithm generates asymptotic PFS and OS survival curves for each feasible combination of parameters and then chooses the parameter values whose simulated survival curves have minimal error from the actual trial survival curves.

Although it does not fully solve the identification problem, this algorithm provides a robust, flexible, and computationally efficient way to choose the model parameters which best fit the trial evidence. In every survival curve analyzed for this article, the algorithm delivered a lower or comparable mean squared error than fitting using Weibull and Lognormal functions.

[1]Majer et al. (2022)[29] also appear to approach the problem of estimating three transition parameters from PFS and OS curves, but their solution appears to partly rely on "visual inspection" of goodness-of-fit, which we found undesirable. Similarly, Pahuta et al. (2019)[32] examine time-homogeneous processes, which is too restrictive for our setting.

6 Sensitivity Results: Equal SGAA drug prices

We find that if the direct drug costs of apalutamide, darolutamide, and enzalutamide were lowered to those of abiraterone (based on Canadian price levels), then each of these drugs would become most cost-effective for different starting states. Specifically, we examine the case where all four SGAAs have a monthly direct drug cost of C$919. We present concise cost-effectiveness results in the table below. Note that early SGAA use is still the most cost-effective choice for all patient groups, but now abiraterone is not uniformly leading. Instead, enzalutamide is best for nmCSPC and low-risk mCSPC, darolutamide is best for high-risk mCSPC with a CET of C$50K per QALY, and apalutamide is best for high-risk mCSPC with a CET of C$100K per QALY. This sensitivity analysis confirms that abiraterone is most cost-effective in the main results primarily due to its substantially lower cost and not due to a superior clinical benefit. Moreover, this analysis shows that lowering the price of SGAAs to abiraterone's level strengthens the case for early SGAA use. Lower enzalutamide prices solidify the early SGAA use advantage in low-risk mCSPC and cause nmCSPC SGAA use (instead of nmCRPC SGAA use) to become the most cost-effective choice, even at a CET of C$50K per QALY.

Table 7: Most cost-effective sequences with equal SGAA prices

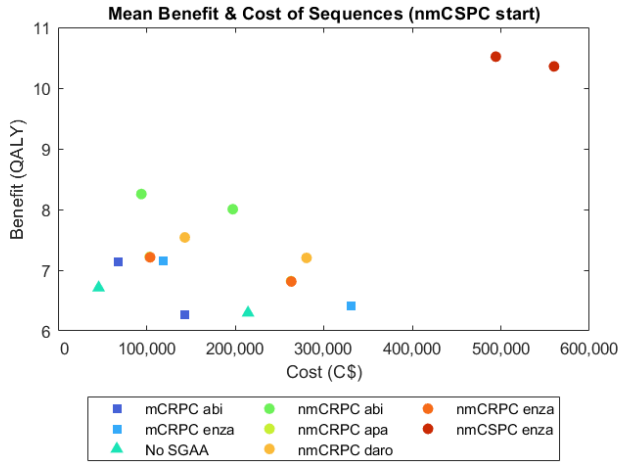
Starting Health State	Cost Effectiveness Threshold	Rank	Mean NHB (QALY)	Treatment Sequence (nmCSPC, nmCRPC, mCRPC)* or (mCSPC, mCRPC)†	SGAA Use
nmCSPC	C$50K per QALY	1	7.00	(enza, doce, doce)*	early
		2	6.37	(ADT, abi, doce)*	early
		3	6.06	(ADT, daro, doce)*	early
	C$100K per QALY	1	8.76	(enza, doce, doce)*	early
		2	7.94	(enza, doce, doce then caba)*	early
		3	7.31	(ADT, abi, doce)*	early
low-risk mCSPC	C$50K per QALY	1	4.78	(enza, doce)†	early
		2	4.49	(abi, doce)†	early
		3	4.47	(ADT, doce)†	none
	C$100K per QALY	1	6.17	(enza, doce)†	early
		2	5.90	(abi, doce)†	early
		3	5.36	(apa, doce)†	none
High-risk mCSPC	C$50K per QALY	1	4.28	(daro & doce, doce)†	early
		2	4.12	(apa, doce)†	early
		3	3.59	(abi, doce)†	early
	C$100K per QALY	1	5.36	(apa, doce)†	early
		2	5.04	(daro & doce, doce)†	early
		3	4.60	(abi, doce)†	early

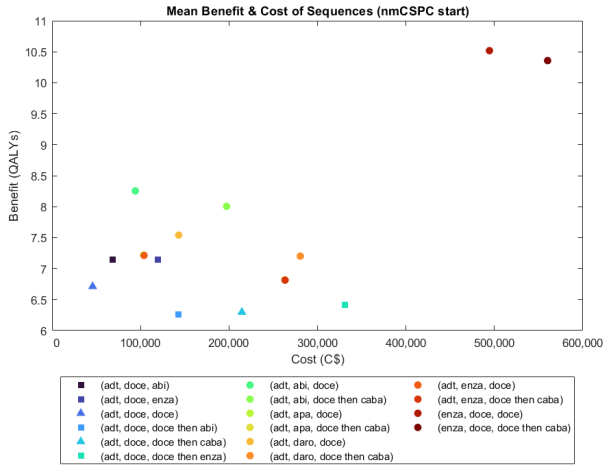
7 Supplementary Graphs: Individual treatment sequences

This section shows benefit-cost scatter plots and acceptability curve graphs for individual treatment sequences next to the regular grouped plots and graphs seen on the poster.

7.1 nmCSPC start

Figure 3: Benefit-cost plot (QALY) for nmCSPC-starting patients



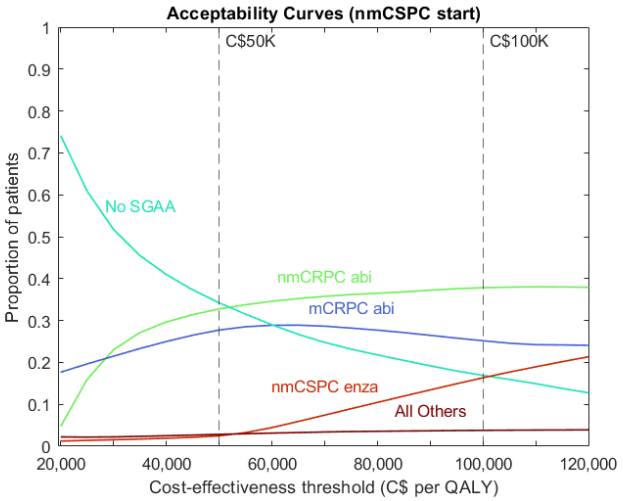


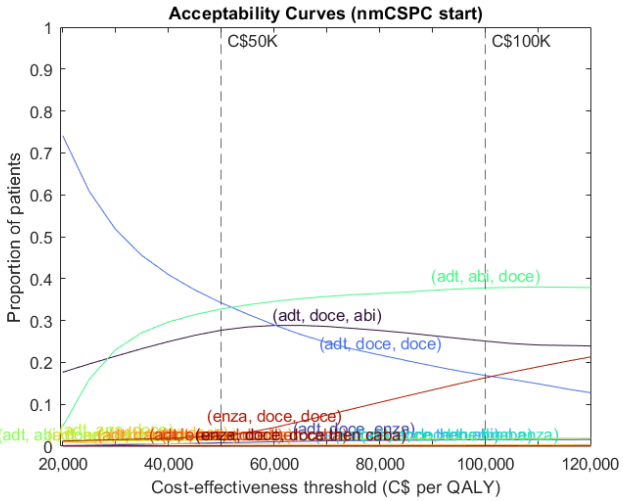
i) grouped treatment sequences

ii) ungrouped treatment sequences

Note: Circles: early SGAA use. Squares: Late SGAA use. Triangles: No SGAA use.

Figure 4: Acceptability curves of NHB in QALYs for nmCSPC-starting patients



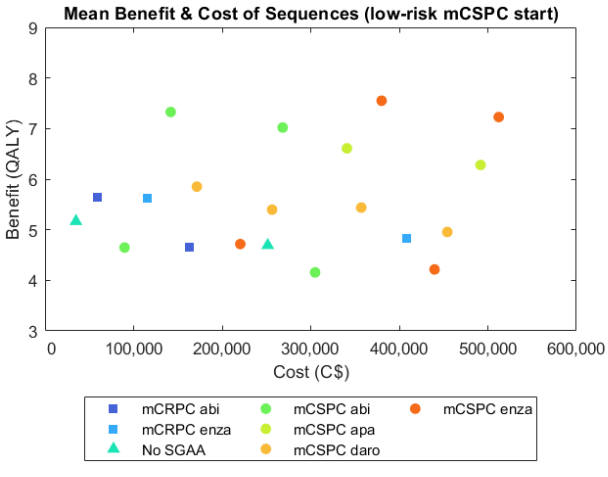


i) grouped treatment sequences

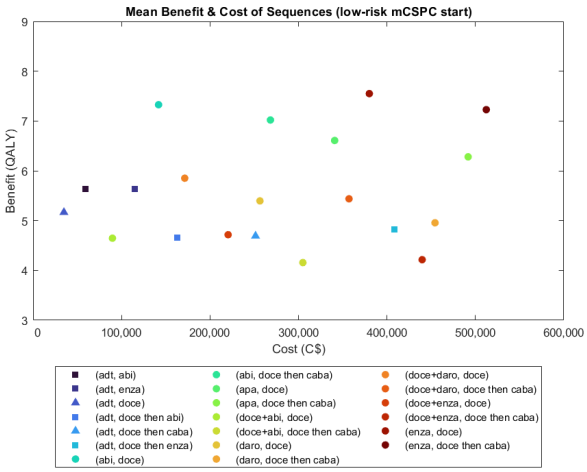
ii) ungrouped treatment sequences

7.2 low-risk mCSPC start

Figure 5: Benefit-cost plot (QALY) for low-risk mCSPC-starting patients



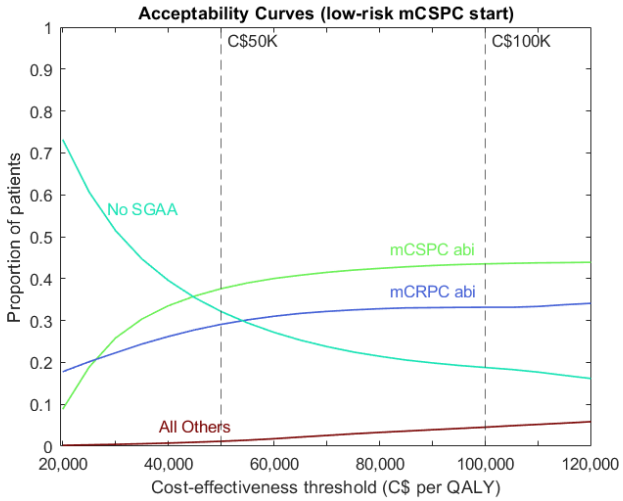
i) grouped treatment sequences



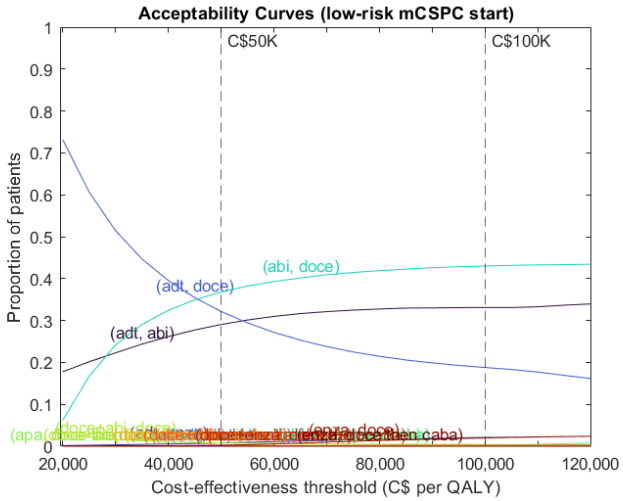
ii) ungrouped treatment sequences

Note: Circles: early SGAA use. Squares: Late SGAA use. Triangles: No SGAA use.

Figure 6: Acceptability curve graphs: low-risk mCSPC-starting patients



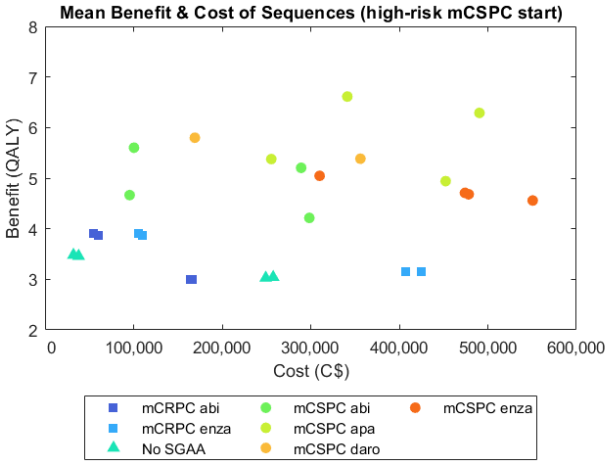
i) grouped treatment sequences



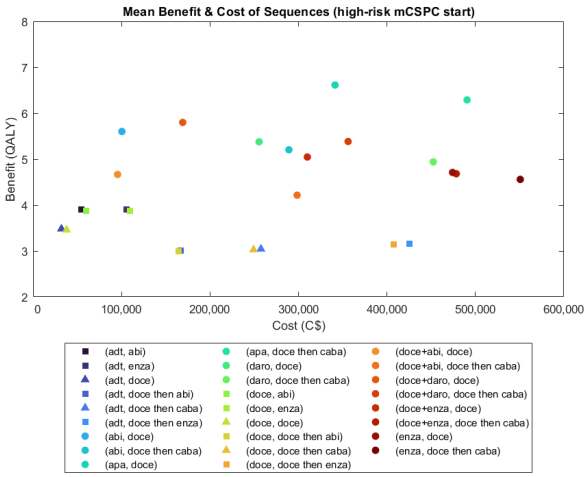
ii) ungrouped treatment sequences

7.3 high-risk mCSPC start

Figure 7: Benefit-cost plot (QALY) for high-risk mCSPC-starting patients



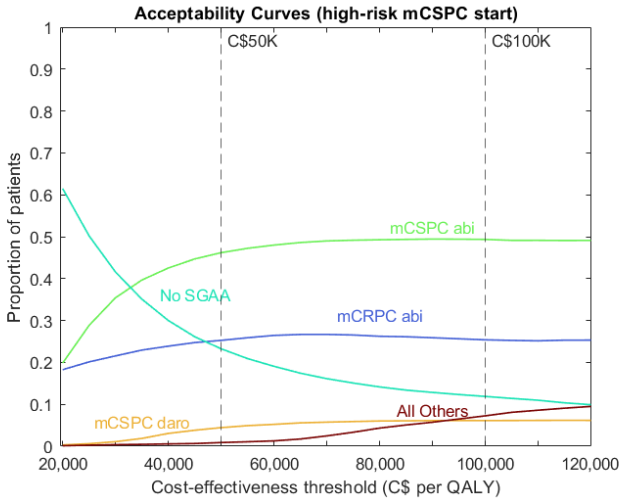
i) grouped treatment sequences



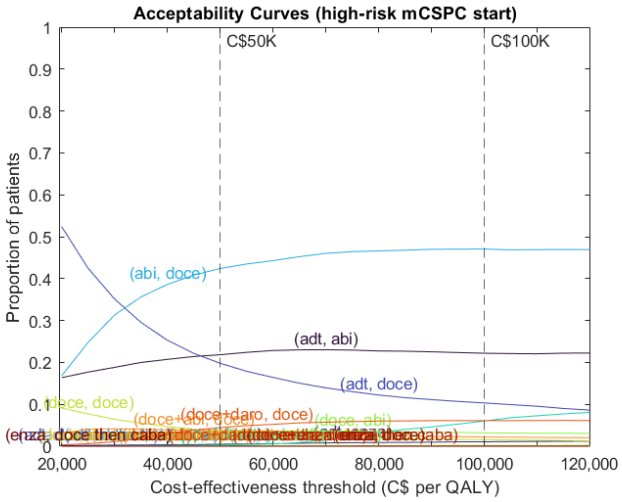
ii) ungrouped treatment sequences

Note: Circles: early SGAA use. Squares: Late SGAA use. Triangles: No SGAA use.

Figure 8: Acceptability curve graphs: high-risk mCSPC-starting patients



i) grouped treatment sequences



ii) ungrouped treatment sequences

8 Supplementary Tables: Best mean outcomes in LYs

This section shows the tables shown in the graphs as well as supplementary analogous tables with benefit and net health benefit measured in LYs. These results reflect the wider pattern that our results are robust to patient/payer preferences between measuring health in terms of QALYs or LYs.

Note: NHB = Net Health Benefit. CET = Cost-effectiveness threshold, similar interpretation to willingness-to-pay (WTP).

8.1 nmCSPC start

Table 8: Best mean outcomes for nmCSPC (QALY)

Outcome	Benefit (QALY)	Cost (C$)	NHB (QALY)	Treatment Sequence (nmCSPC,nmCRPC,mCRPC)
Benefit	10.55	495,406	N/A	(enza, doce, doce)
NHB @ CET of C$50K per QALY	8.26	94,438	6.37	(ADT, abi, doce)
NHB @ CET of C$100K per QALY	8.26	94,438	7.31	(ADT, abi, doce)

Table 9: Best mean outcomes for nmCSPC (LY)

Outcome	Benefit (LY)	Cost (C$)	NHB (LY)	Treatment Sequence (nmCSPC,nmCRPC,mCRPC)
Benefit	11.39	495,406	N/A	(enza, doce, doce)
NHB @ CET of C$50K per LY	9.64	94,438	7.75	(ADT, abi, doce)
NHB @ CET of C$100K per LY	9.64	94,438	8.69	(ADT, abi, doce)

8.2 low-risk mCSPC start

Table 10: Best mean outcomes for low-risk mCSPC (QALY)

Outcome	Benefit (QALY)	Cost (C$)	NHB (QALY)	Treatment Sequence (mCSPC,mCRPC)
Benefit	7.55	380,237	N/A	(enza, doce)
NHB @ CET of C$50K per QALY	7.32	141,717	4.49	(abi, doce)
NHB @ CET of C$100K per QALY	7.32	141,717	5.90	(abi, doce)

Table 11: Best mean outcomes for low-risk mCSPC (LY)

Outcome	Benefit (LY)	Cost (C$)	NHB (LY)	Treatment Sequence (mCSPC,mCRPC)
Benefit	9.30	380,237	N/A	(enza, doce)
NHB @ CET of C$50K per LY	9.01	141,717	6.17	(abi, doce)
NHB @ CET of C$100K per LY	9.01	141,717	7.59	(abi, doce)

8.3 high-risk mCSPC start

Table 12: Best mean outcomes for high-risk mCSPC (QALY)

Outcome	Benefit (QALY)	Cost (C$)	NHB (QALY)	Treatment Sequence (mCSPC,mCRPC)
Benefit	6.61	341,307	N/A	(apa, doce)
NHB @ CET of C$50K per QALY	5.60	100,448	3.59	(abi, doce)
NHB @ CET of C$100K per QALY	5.60	100,448	4.60	(abi, doce)

Table 13: Best mean outcomes for high-risk mCSPC (LY)

Outcome	Benefit (LY)	Cost (C$)	NHB (LY)	Treatment Sequence (mCSPC,mCRPC)
Benefit	8.18	341,307	N/A	(apa, doce)
NHB @ CET of C$50K per LY	7.08	100,448	4.60	(abi, doce)
NHB @ CET of C$100K per LY	7.08	100,448	5.07	(abi, doce)

References

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