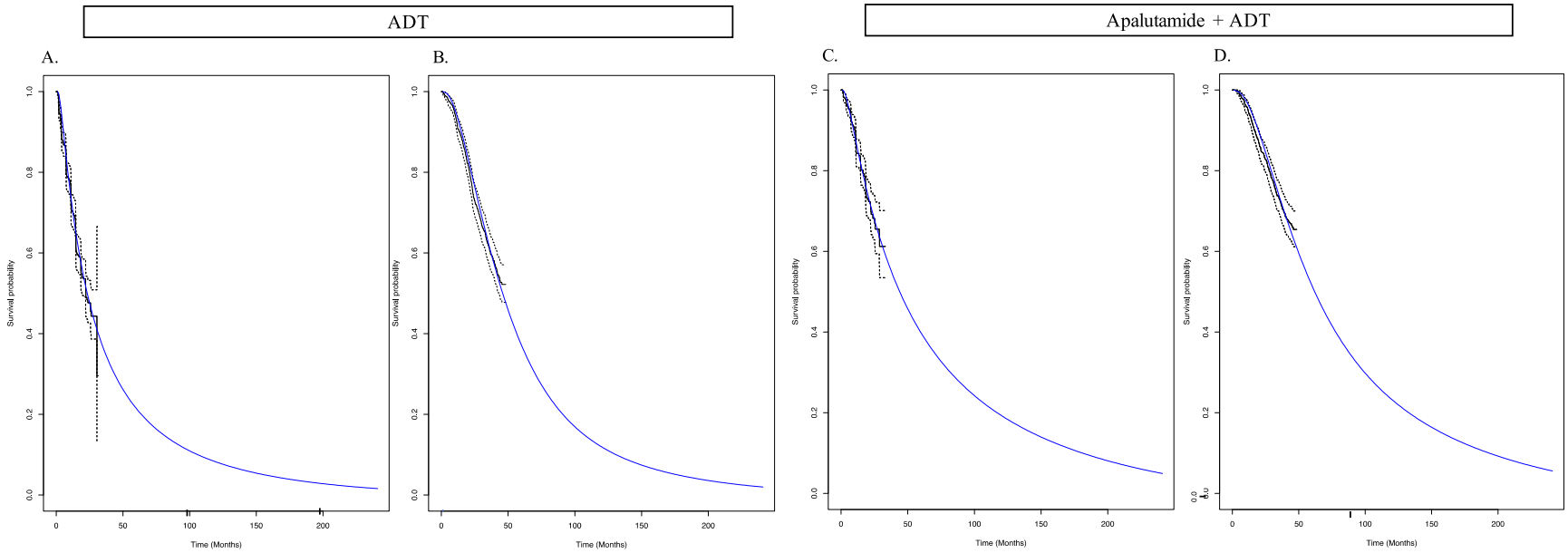
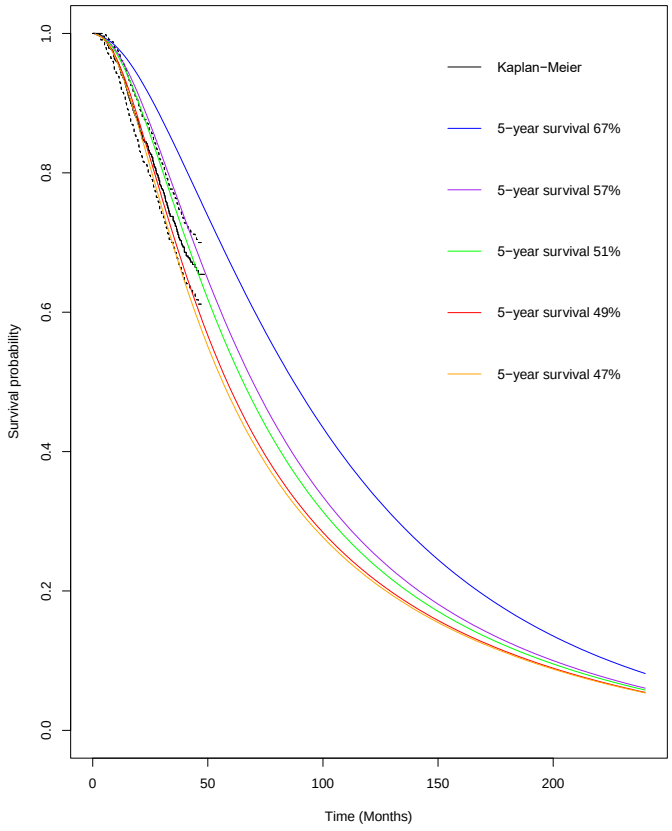
APPENDIX

Supplementary Fig. 1. Model calibration to observed progression and survival estimates. Graphical representation of modeled progression (PF to PD) and overall survival for treatment strategy of ADT alone and apalutamide+ADT, relative to observed progression-free survival (ADT ***[A]***, apalutamide+ADT ***[C]***) and overall survival (ADT ***[B]***, apalutamide+ADT ***[D]***) Kaplan-Meier curves from the TITAN trial for each treatment strategy. ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio, mCRPC: metastatic castration-sensitive prostate cancer; OS: overall survival; PD: progressive-disease; PF: progression-free.



Supplementary Fig. 2. Scenario analysis by variations in expected mortality following treatment with apalutamide and ADT. Scenario of alternative survival expectations following treatment with apalutamide+ADT as modeled by an exponential distribution for the transition of progressive disease to the death health state. Re-created Kaplan-Meier OS curve from the TITAN trial depicted in black, with 95% confidence intervals represented by the dotted-lines. Model-derived survival outcomes demonstrated in colored lined, with varying 5-year survival rates. Accompanying table demonstrates analyses details with expected 5-year survival rates and ICER, as compared to ADT alone. ADT: androgen-deprivation therapy; ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life-years.



Extrapolated 5-year Survival (%)	ICER
67%	$104,904/QALY
57%	$134,635/QALY
51%	$164,700/QALY
49%	$177,155/QALY
47%	$185,092/QALY

Supplementary Table 1. Data variables for model input			
Variable	**Base value**	**95% confidence interval**	**Reference**
Progression estimates (log-normal distribution)			
ADT			Chi 2019[1]
PF to PD			
Mean of logs	3.139	2.995, 3.282	
Standard deviation of logs	1.274	1.153, 1.407	
Apalutamide + ADT			Chi 2019[1]
PF to PD			
Mean of logs	3.842	3.613, 4.071	
Standard deviation of logs	1.292	1.121, 1.488	
Survival estimates (exponential distribution)			
ADT			Chi 2020[2]
PD to death			
Rate	0.048	0.038, 0.059	
Apalutamide + ADT			Chi 2020[2]
PD to death			
Rate	0.060	0.052, 0.066	
Probability of events			
Subsequent treatment post-ADT[1]			Chi 2020[2]
Abiraterone	0.215	-	
Bicalutamide	0.116	-	
Docetaxel	0.272	-	
Enzalutamide	0.077	-	
Subsequent treatment post-apalatumide + ADT[1]		-	
Abiraterone	0.145	-	
Bicalutamide	0.114	-	
Docetaxel	0.268	-	
Enzalutamide	0.065		
Probability of grade 3 or 4 AE – ADT[2]	0.417	-	Chi 2020[2]
Fall	0.009	-	
Fracture	0.008	-	
Seizure	0	-	
Rash	0.009	-	
Probability of grade 3 or 4 AE – Apalutamide + ADT[2]	0.494	-	
Fall	0.013	-	
Fracture	0.034	-	
Seizure	0.002	-	

Supplementary Table 1. Data variables for model input			
Variable	**Base value**	**95% confidence interval**	**Reference**
Rash	0.063		
Health state utility			
Progression-free as mCSPC[3]			
ADT	0.80	0.71–0.83	Chi 2018, Hall 2019, Sathianathen 2019, Lloyd 2015[3-6]
Apalutamide + ADT	0.80	0.71–0.83	
Progressive disease to mCRPC[4]			
ADT	0.63	0.63–0.83	
Apalutamide + ADT	0.63	0.63–0.83	
Disutility for AE of Interest			
Fall	-0.069	–	Doyle 2008[7] Matza 2014[8] Nafees 2008[9] NICE 2010[10]
Fracture	-0.090	–	
Rash	-0.032	–	
Seizure	-0.040	–	
Costs per month (2020 Canadian dollars)			
Apalutamide[5]	3240.76	2430.23–3240.76	pCODR 2018[11]
ADT[5]	303.20	–	pCODR 2018[11]
Abiraterone[5]	3512.42	878.10–3512.42	pCODR 2013[12]
Bicalutamide[5]	36.30	–	pCODR 2018[11]
Docetaxel[5]	32.50	32.50–42.07	OCC
Enzalutamide[5]	3514.63	1735.76–3514.63	pCODR 2013[12]
Physician visit[6]	81.52	–	SOB 2018
CT thorax[7]	81.52	–	SOB 2018
CT abdomen[7]	99.53	–	SOB 2018
CT pelvis[7]	99.53	–	SOB 2018
End-of-life care[8]	11 935.50	0–29 838.75	Bekelman 2016 [13]

Supplementary Table 1. Data variables for model input			
Variable	**Base value**	**95% confidence interval**	**Reference**
Hospitalization for fall[9]	6143.56	321.57–29,962.37	OCCI CAT[14]
Hospitalization for fracture[9]	7302.24	2597.08–11 368.35	OCCI CAT[14]
Hospitalization for seizure[9]	8299.63	891.21–42 208.66	OCCI CAT[14]

Data variables for progression/survival estimates, probabilities of events, health state utilities/disutilities, and included costs for both the base-case analysis. Transition probabilities modeled from log-normal parametric distributions and exponential distributions.
[1]Probabilities of subsequent treatment derived from reported rates from the TITAN trial.
[2]Probabilies of AE derived from reported rates for each treatment strategy from the TITAN trial.
[3]Health state utility of baseline mCSPC patients derived from published literature. As disutilities were applied for treatment-related AE, as reported in the TITAN trial, the health state utility was equal between patients treated with ADT and apalutamide with ADT. The range of health state utility estimates for patients with mCSPC, were based upon the published literature.
[4]Health state utility derived from the reported literature of symptomatic mCRPC patients. The ranges of health state utility estimates were based upon health utility estimates for asymptomatic (highest) mCRPC patients to those who require cytotoxic chemotherapy (lowest).
[5]Cycle costs for treatment. The ranges are derived from the cost of clinically-plausible dose reductions for apalutamide, abiraterone and enzalutamide. For docetaxel, the cost range is derived from the cost of treatment for individuals with a body surface area ranging from $1.7m^2$ to $2.2m^2$. All treatment costs were derived from reported list prices from pan-Canadian Oncology Drug Reviews (pCODR), except for docetaxel for which the price was derived from the local institutional price. [6]Physician visits costs (as per the OHIP schedule of benefits, retrieved from *http://www.health.gov.on.ca/en/pro/programs/ohip/sob/*) were incorporated into the model per cycle (monthly). [7]Routine imaging costs with CT of chest, abdomen, and pelvis (as per OHIP schedule of benefits, retrieved from: *http://www.health.gov.on.ca/en/pro/programs/ohip/sob/*) were incorporated into the model every 3 months. [8]End-of-life care costs were included as a terminal cost upon transition to the death health state. The base-case value is the cost associated with a length-of-stay of 6 days, as per the mean length-of-stay in the published literature. The range of costs is derived from a hospital length-of-stay of 0–14 days. [9]Hospitalization costs for each of the AE of interest were included, as reported in the Ontario Case Costing Initiative cost analysis tool based upon the direct patient costs (i.e., those related to provision of care), for typical cases over the age of 65. ADT: androgen-deprivation therapy; AE: adverse events; CAT: Cost Analysis Tool; CT: computed tomography; mCSPC: metastatic castration-sensitive prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; PF: progression-free; PD: progressive-disease; OCCI: Ontario Case Costing Initiative; OHIP: Ontario Health Insurance Plan.

Supplementary Table 2. Scenario analysis with price reductions in apalutamide drug costs			
Scenario	**Incremental cost ($)**	**Incremental effectiveness (QALY)**	**ICER**
25% price reduction (cycle cost=$2430.58)	167 419	1.33	$125 879/QALY
50% price reduction (cycle cost=$1620.38)	116 464	1.33	$87 567/QALY
75% price reduction (cycle cost=$810.90)	67 562	1.33	$50 798/QALY

Scenario analysis with price reductions to apalutamide drug costs of 25%, 50% and 75%, per cycle. ADT: androgen-deprivation therapy; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.

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